SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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División de Nuevas Creaciones

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SOLICITUD

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ENTRADA EN FASE NACIONAL:

21. **EXPEDIENTE No.** 06-128811

54. **TITULO** INHIBIDORES DE CINASA HETEROCICLICOS FUSIONADOS

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

DOMICILIO PRINCETON NEW JERSEY ESTADOS UNIDOS DE AMERICA

74. **APODERADO** JUAN PABLO CADENA SARMIENTO

22. **SANTAFE DE BOGOTA, D.C.**

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

1 SOLICITUD DE:

☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.

☒ Capítulo I. ☐ Capítulo II.

2 SOLICITANTE (71)	Nombre: **BRISTOL – MYERS SQUIBB COMPANY** Dirección: P.O. Box 4000, Route 206 and Provinceline Road, Princeton, NJ 08543-4000, Estados Unidos de América Nacionalidad o Domicilio: Estados Unidos Lugar de Constitución: Estados Unidos Teléfono: Fax: E-mail	**IDENTIFICACION** C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual_____ Número _____
3 REPRESENTANTE O APODERADO	Nombre: JUAN PABLO CADENA SARMIENTO Dirección: Cra. 7 No. 71-21, Torre B, Piso 4 Teléfono: 744-2200 Fax: 742-2200 E-mail:	**IDENTIFICACION** C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual_____ Número 80.410.337 TP 57492
4 INVENTOR (ES) (72)	**Nombre:** Robert M. BORZILLERI, Zhong CHEN, Tram N. HUYNH, Wayne VACCARO, Xiao-Tao CHEN, Kyoung S. KIM, Zhen-Wei CAI **Dirección:** 222 Riverwoods Drive, New Hope, Pennsylvania 18938 (US); 30 Kingston Terrace, Princeton, New Jersey 08540 (US); 26 Manley Road, Pennington, New Jersey 08534 (US); 1706 Westover Road, Yardley, Pennsylvania 19067 (US); 3708 Powder Horn Drive, Furlong, Pennsylvania 18925 (US); 252 Forest Lane, North Brunwick, Nueva Jersey 08902 (US); 36 Hills Drive, Belle Mead, New Jersey 08502 (US), (Respectivamente) **Nacionalidad o Domicilio:** Estados Unidos de América (Respectivamente)	

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6 Título (54): INHIBIDORES DE CINASA HETEROCICLICOS FUSIONADOS

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

2020-F06 (01-11-15)

10 **ANEXOS**

- [x] Comprobante de pago de la tasa de presentación de la solicitud. $463.000
- [x] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso. Fotocopia autenticada
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Traducción de la solicitud internacional al castellano. (Resu men, descripción, reivindicaciones, dibujos)
- [ ] Copia del examen preliminar efectuado por la IPEA.
- [ ] Traducción del examen preliminar efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
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- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12x12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [x] Otros - Documentos PCT
  Tarjeta de Propietarios

11 **FIGURA CARACTERÍSTICA:**

12 Solicito la concesión de la patente,

NOMBRE: JUAN PABLO CADENA SARMIENTO

FIRMA:

C.C. 80.410.337 de Usaquén T.P. 57492 del C.S.J.

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DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
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C O N C E P T O

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	463,000.00
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SON: CUATROCIENTOS SESENTA Y TRES MIL PESOS

RESPONSABLE : _____

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

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PATENTE [X] PCT/US2005/022682 MODELO DE UTILIDAD [ ] DISEÑO INDUSTRIAL [ ]

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DOMICILIO PRINCETON NEW JERSEY ESTADOS UNIDOS DE AMERICA

APODERADO JUAN PABLO CADENA SARMIENTO

TITULO INHIBIDORES DE CINASA HETEROCICLICOS FUSIONADOS

CLASIFICACION

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PRORROGA CAMBIO DE NOMBRE

TRASPASO A

INVENTOR (ES) ROBERT M BORZILLERI ZHONG CHEN TRAM N HUYNH WAYNE VACCARO XIAO TAO CHEN

OTROS KYOUNG S KIM ZHEN-WEI CAI

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(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)*: BORZILLERI, Robert M. [US/US]; 222 Riverwoods Drive, New Hope, Pennsylvania 18938 (US). CHEN, Zhong [CN/US]; 30 Kingston Terrace, Princeton, New Jersey 08540 (US). HUYNH, Tram N. [US/US]; 26 Manley Road, Pennington, New Jersey 08534 (US). VACCARO, Wayne [US/US]; 1706 Westover Road, Yardley, Pennsylvania 19067 (US). CHEN, Xiao Tao [US/US]; 3708 Powder Horn Drive, Furlong, Pennsylvania 18925 (US). KIM, Kyoung S. [US/US]; 252 Forest Lane, North Brunwick, New Jersey 08902 (US). CAI, Zhen-Wei [US/US]; 36 Hills Drive, Belle Mead, New Jersey 08502 (US).

(74) Agents: GIBBONS, Maureen et al.; Bristol-Myers Squibb Company, P.O. Box 4000, Princeton, New Jersey 08543-4000 (US).

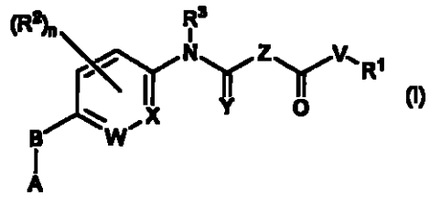
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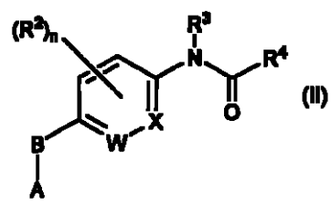
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: FUSED HETEROCYCLIC KINASE INHIBITORS



(I)



(II)

(57) Abstract: In general, the instant invention comprises compounds of Formulas (I) and (II) including pharmaceutically acceptable salts thereof. The compounds of the invention are useful as protein kinase inhibitors and therefore are useful for treating cancer and other protein kinase mediated diseases.

WO 2006/004636 A2

FUSED HETEROCYCLIC KINASE INHIBITORS

RELATED APPLICATIONS

This application claims priority benefit under Title 35 § 119(e) of United States Provisional Application Nos. 60/583,459, filed June 28, 2004, and 60/612,563, filed September 23, 2004, the contents of which are herein incorporated by reference.

FIELD OF INVENTION

This invention relates to compounds that inhibit the protein tyrosine kinase activity of growth factor receptors such as c-Met, thereby making them useful as anti-cancer agents. The pharmaceutical compositions that comprise these compounds are also useful in the treatment of diseases, other than cancer, which are associated with signal transduction pathways operating through growth factor and anti-angiogenesis receptors such as c-Met.

BACKGROUND

Hepatocyte growth factor (HGF), also known as scatter factor (SF), because of its ability to disrupt colony formation *in vitro*, is a mesenchymally derived cytokine known to induce multiple pleiotropic responses in normal and neoplastic cells (Sonnenberg et al., *J. Cell Biol.* 123:223-235, 1993; Matsumato et al., *Crit. Rev. Oncog.* 3:27-54,1992; and Stoker et al., *Nature* 327:239-242, 1987). These responses are known to include proliferation in both epithelial and endothelial cells, dissociation of epithelial colonies into individual cells, stimulation of motility (motogenesis) of epithelial cells, cell survival, induction of cellular morphogenesis (Montesano et al., *Cell* 67:901-908, 1991), and promotion of invasion (Stella et al., *Int. J. Biochem. Cell Biol.* 12:1357-62, 1999 and Stuart et al., *Int. J. Exp. Path.* 81:17-30, 2000), all critical processes underlying metastasis. HGF has also been reported to promote angiogenesis (Bussolino et al., *J. Cell Biol.* 119:629-641, 1992). In addition, HGF plays a critical role in tissue regeneration, wound healing, and normal embryonic processes, all of which are dependent on both cell motility and proliferation.

HGF initiates these physiological processes through high affinity binding to its cognate receptor, the Met protein tyrosine kinase receptor, an identified

protooncogene (Park et al., *Proc. Natl. Acad. Sci. USA* 84:6379-83, 1987 and Bottaro et al., *Science* 251:802-4, 1991). The mature form of Met consists of a highly glycosylated external α-subunit as well as a β-subunit with a large extracellular domain, a transmembrane segment and a cytoplasmic tyrosine kinase domain. Ligand engagement induces Met dimerization that results in an autophosphorylated activated receptor. Activation of Met promotes signal transduction cascades as defined by transphosphorylation of key cytoplasmic tyrosine residues responsible for recruiting multiple effector proteins (Furge et al., *Oncogene* 19:5582-9, 2000). These include the p85 subunit of the PI3-kinase, phospholipase Cγ (Gaul et al., *Oncogene* 19:1509-18, 2000), Grb2 and Shc adaptor proteins, the protein phosphatase SHP2 and Gab1. The latter adapter has emerged as the major downstream docking molecule that becomes tyrosine phosphorylated in response to ligand occupancy (Schaeper et al., *J. Cell Biol.* 149:1419-32, 2000; Bardelli, et al., *Oncogene* 18:1139-46, 1999 and Sachs et al., *J. Cell Biol.* 150:1375-84, 2000). Activation of other signaling molecules has been reported in HGF stimulated cells, most notably Ras, MAP kinases, STATs, ERK-1, -2 and FAK (Tanimura et al., *Oncogene* 17:57-65,1998; Lai et al., *J. Biol. Chem.* 275:7474-80 2000 and Furge et al., *Oncogene* 19:5582-9, 2000). The role of many of these signaling molecules has been well established in cell proliferation.

Met, also referred to as hepatocyte growth factor receptor (HGFR), is expressed predominantly in epithelial cells but has also been identified in endothelial cells, myoblasts, hematopoietic cells and motor neurons. Overexpression of HGF and activation of Met has been associated with the onset and progression in a number of different tumor types as well as in the promotion of metastatic disease. Initial evidence linking Met to cancer has been supported by the identification of kinase domain missense mutations, which predisposes individuals to papillary renal carcinomas (PRC) and hepatocellular carcinomas (HCC) (Lubensky et al., *Amer. J. Pathology*, 155:517-26, 1999). Mutated forms of Met have also been identified in ovarian cancer, childhood HCC, gastric carcinoma, head and neck squamous cell carcinoma, non-small cell lung carcinoma, colorectal metastasis (Christensen et al., *Cancer Res.*, 63:7345-55, 2003; Lee et al., *Oncogene*, 19:4947-53, 2000 and Direnzo et al., *Clin. Cancer Res.*, 1:147-54, 1995). In addition, further evidence supporting the role of the Met in cancer is based on the overexpression of HGF and Met receptor in

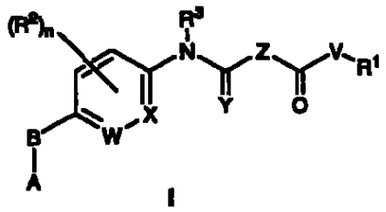
various tumors including thyroid, ovarian and pancreatic carcinomas. It has also been demonstrated to be amplified in liver metastases of colorectal carcinomas (Rong et al. *Cancer Res.* 55:1963-1970, 1995; Rong et al., *Cancer Res.* 53:5355-5360, 1993; Kenworthy et al., *Br. J. Cancer* 66:243-247, 1992 and Scarpino et al. *J. Pathology* 189:570-575, 1999). TPR-Met (an activated form similar to BCR/Abl in CML) has been described and identified in human gastric carcinoma (PNAS 88:4892-6, 1991). In patients with invasive breast carcinoma and in a recent study in non small cell lung cancer patients, expression of either the receptor or ligand is a predictor of decreased survival, further linking Met to tumor progression (Camp et al., *Cancer* 86:2259-65 1999 and Masuya et al., *Br. J. Cancer,* 90:1555-62, 2004). In general, most human tumors and tumor cell lines of mesenchymal origin inappropriately express HGFR and/or HGF.

Numerous experimental data support the role of HGF and Met in tumor invasion, growth, survival and progression ultimately leading to metastases. Preclinically, transgenic expression of HGF results in a metastatic phenotype (Takayama et al., *PNAS*, 94:701-6, 1997) and an amplified/overexpressed Met spontaneously transforms NIH-3T3 cells (Cooper et al., *EMBO J.*, 5:2623-8, 1986).

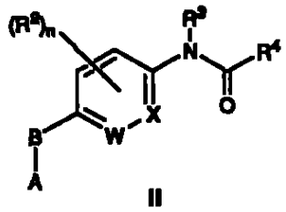
Biological agents, such as ribozymes, antibodies and antisense RNA targeting either HGF or Met have been shown to inhibit tumorogenesis (Stabile et al., *Gene Therapy*, 11:325-35, 2004, Jiang et al., *Clin. Cancer Res*, 9:4274-81, 2003 and Genentech US 6,214,344, 2001). Thus, selective, small molecule kinase modulators targeting Met are expected to have therapeutic potential for the treatment of cancers in which Met receptor activation plays a critical role in the development and progression of primary tumors and secondary metastases. HGF is also known to regulate angiogenesis, a process critical in tumor growth and dissemination. Therefore, there is a potential for this class of modulators to impact angiogenesis-dependent diseases as well that may include among others, diabetic retinopathy, macular degeneration, obesity and inflammatory disease such as rheumatoid arthritis.

SUMMARY

The present invention is directed to compounds having the following Formulas I and II:



I



II

including pharmaceutically acceptable salts, enantiomers, diastereomers, and solvates thereof, wherein:

R^1 is H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, arylalkyl, substituted arylalkyl, aryl, substituted aryl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, heteroaryl, substituted heteroaryl, heterocyclo, substituted heterocyclo, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, or substituted heterocycloalkyl;

each R^2 is independently, H, halogen, cyano, NO_2, OR^5, NR^6R^7, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclo, substituted heterocyclo, aryalkyl, substituted arylalkyl, heterocycloalkyl, or substituted heterocycloalkyl;

B is O, NR^8, S, SO, SO_2, CR^9R^{10};

V is NR^{11} or $-(CR^{47}R^{48})_p-$;

W or X are independently C or N;

Y is O, S, or NR^{12};

Z is $-CR^{13}R^{14}-$, $-(CR^{13}R^{14})_mNR^{15}-$;

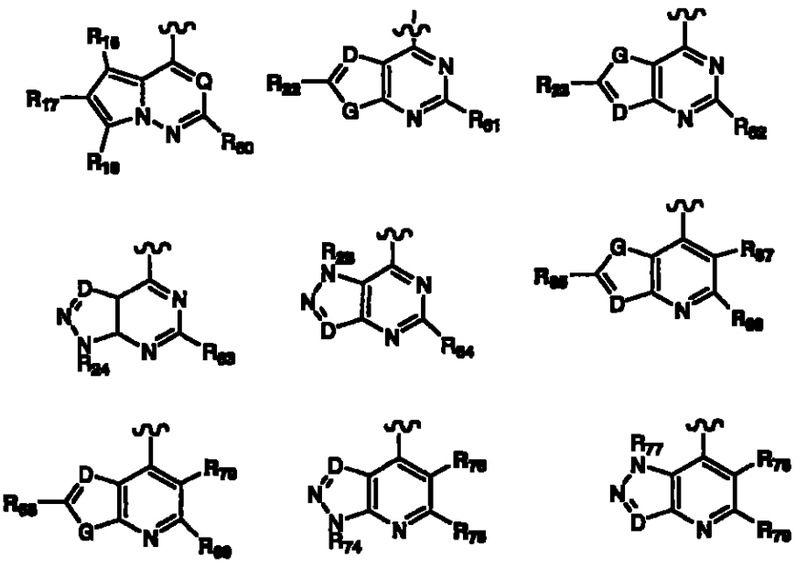
l is 0 to 4;

m is 0 to 2;

n is 0 to 4;

p is 0 to 4, provided that if p is 0, R^1 is not phenyl;

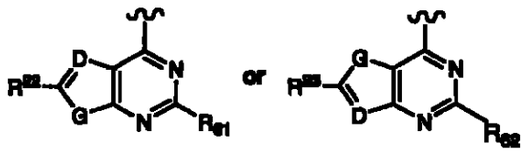
A is:



Q is CR^{19};

D is CR^{20} or N;

G is S, O or NR^{21}, provided that if A is



and G is S, R^4 is not a substituted phenyl group;

R^3, R^5, R^6, R^7, R^8, R^{11} and R^{15} are each independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, or substituted heterocycloalkyl;

R^4 is aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, or substituted heterocycloalkyl;

R^9 and R^{10} are independently H, halogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, or substituted heterocycloalkyl;

R^{12} is H, alkyl, substituted alkyl, CN, NO_2 or SO_2NH_2;

R^{13}, R^{14}, R^{15}, R^{47} and R^{48} are independently H, halogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclo, substituted heterocyclo or taken together to form a carbocyclic or heterocyclic ring of 3 to 8 atoms;

R^{16}, R^{17}, R^{18}, R^{20}, R^{22}, R^{23}, R^{60}, R^{61}, R^{62}, R^{63}, R^{64}, R^{65}, R^{66}, R^{67}, R^{68}, R^{69}, R^{70}, R^{75}, R^{76}, R^{78}, and R^{79}, are independently H, halogen, NO_2, cyano, OR^{26}, $NR^{27}R^{28}$, CO_2R^{29}, $C(O)NR^{30}R^{31}$, SO_2R^{32}, $SO_2NR^{33}R^{34}$, $NR^{35}SO_2R^{36}$, $NR^{37}C(O)R^{38}$, $NR^{39}CO_2R^{40}$, $-CO(CH_2)_1R^{41}$; $-CONH(CH_2)_1R^{42}$, alkylaminoalkyl, alkylaminoalkynyl, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_7 cycloalkyl, substituted C_3 to C_7 cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, hydroxyalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, arylalkyl, substituted arylalkyl, heterocycloalkyl, or substituted heterocycloalkyl;

R^{19} is H or cyano;

R^{21} and R^{24} are independently H, C_1 to C_6 alkyl or substituted C_1 to C_6 alkyl;

R^{25}, R^{74} and R^{77} are independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heterocycloalkyl, or substituted heterocycloalkyl

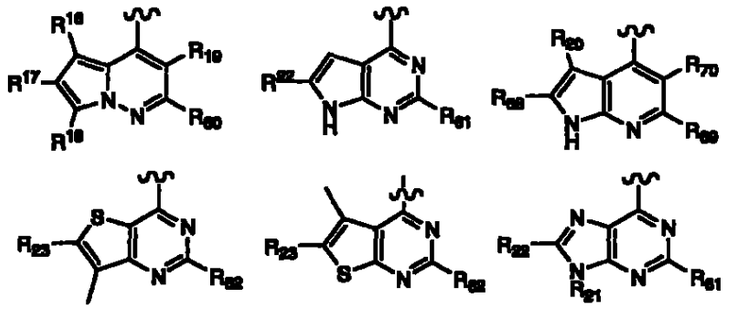
R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, R^{33}, R^{34}, R^{35}, R^{36}, R^{37}, R^{38}, R^{39}, R^{40}, R^{41}, and R^{42} are independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heterocycloalkyl, or substituted heterocycloalkyl.

In some embodiments of the present invention, R^1 is an optionally substituted C_{1-6} alkyl, alkenyl, alkynyl, optionally substituted C_{3-7} cycloalkyl, C_{3-7} eterocycloalkyl, optionally substituted phenyl, optionally substituted biphenyl, or a C_5 to C_{11} optionally substituted monocyclic or bicyclic heteroaryl. Preferably, R^1 is phenyl, optionally substituted with at least one of Cl, F, OCH_3, C_{1-4} alkyl, alkenyl, alkynyl, CN, hydroxy, amido, phenoxy, CH_2CN, benzyl, $NHCO_2CH_3$; biphenyl, pyridyl, azepanyl, pyrazolyl, thiazolyl, indolyl, indazolyl, indenyl, cyclopropyl, isopropyl, phenylethyl, aminoalkyl, benzyl, amidoalkyl, morpholine, and furanylmethyl.

In some embodiments of the present invention, R^2 is H, alkoxy, halo, methyl, haloalky or CN.

In some embodiments of the present invention, R^4 is an optionally substituted phenyl, an optionally substituted pyridyl, an optionally substituted pyrrolidinyl, an optionally substituted pyridyl-N-oxy, or an optionally substituted pyridinone, wherein said substituent is selected, for example, from hydroxyl, halo, C_1 to C_4alkyl, C_3 to C_7 cycloalkyl, CN, alkylthio, alkoxy, phenyl, amino, heterocycloalkyl, aminoalkylamino and alkylaminoalkoxy. In some embodiments of the present invention, the substituent is F, Br, Cl, methyl, pentyl, methoxy, phenyl, morpholinyl, NH_2, or $NHCHNH_2$.

According to some embodiments of the present invention, A is one of the following:



According to one embodiment of the present invention, R^{19} is H or CN and R^{16}, R^{17}, and R^{18} are independently H, C_1 to C_4 alkyl, C_1 to C_4 alkoxy, or $-C(O)_2R^{29}$ wherein R^{29} is C_1 to C_4 alkyl.

According to one embodiment of the present invention, $R^{22}$and R^{61} are H.

According to another embodiment of the present invention, R^{68}, R^{69} and R^{70} are H; R^{20} is C_1 to C_4 alkyl; alkenyl; alkynyl; C_3 to C_6 heterocycloaryl; $-CO(CH_2)_1R^{41}$, wherein R^{41} is C_1 to C_4 alkyl; haloalkyl; amino; alkylamino; C_5 to C_7 heterocycloalkyl; C_5 to C_7 heteroaryl; or $C(O)_2R^{29}$ wherein R^{29} is ethyl; CN; alkoxy; phenylmethyl; alkylaminoalkynyl; alkylaminoalkyl, hydroxyalkyl; or methoxyalkyl.

According to one embodiment of the present invention, Y is O or S.

According to one embodiment of the present invention, B is O.

In some embodiments of the present invention, Z is $-CR^{13}R^{14}$ or NR^{15} wherein R^{13}, R^{14}, and R^{15} are each H or R^{13} and R^{14} together with the carbon to which they are attached form a cyclopropyl.

The present invention is also directed to pharmaceutical compositions comprising therapeutically effective amounts of a compound of Formula I or II, or a salt or solvate thereof, together with a pharmaceutically acceptable carrier.

The present invention also provides methods for the treatment of cancer comprising administering to a patient in need thereof a pharmaceutically effective amount of a compound of Formula I or II or a salt or solvate thereof, optionally including administering to the patient at least one additional anticancer agent.

DESCRIPTION

The present invention provides for compounds of Formulas I and II defined above, pharmaceutical compositions employing such compounds, methods of making and methods of using such compounds.

Listed below are definitions of various terms used to describe the compounds of the instant invention. These definitions apply to the terms as they are used throughout the specification (unless they are otherwise limited in specific instances) either individually or as part of a larger group.

The term "alkyl" herein alone or as part of another group refers to a monovalent alkane (hydrocarbon) derived radical containing from 1 to 12 carbon atoms unless otherwise defined. Preferred alkyl groups have from 1 to 6 carbon atoms. An alkyl group is an optionally substituted straight, branched or cyclic saturated hydrocarbon group. Alkyl groups may be substituted at any available point of attachment. An alkyl group substituted with another alkyl group is also referred to as a "branched alkyl group". Exemplary alkyl groups include methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl, dodecyl, and the like. Exemplary substituents include but are not limited to one or more of the following groups: alkyl, aryl, halo (such as F, Cl, Br, I), haloalkyl (such as CCl_3 or CF_3), alkoxy, alkylthio, hydroxy, carboxy (-COOH), alkyloxycarbonyl (-C(O)R), alkylcarbonyloxy (-OCOR), amino ($-NH_2$), carbamoyl (-NHCOOR- or -OCONHR-), urea (-NHCONHR-) or thiol (-SH). In some preferred embodiments of the present

invention, alkyl groups are substituted with, for example, amino, heterocycloalkyl, such as morpholine, piperazine, piperidine, azetidine,hydroxyl, methoxy, or heteroaryl groups such as pyrrolidine,

The term "alkenyl" herein alone or as part of another group refers to a hydrocarbon radical straight, branched or cyclic containing from 2 to 12 carbon atoms and at least one carbon to carbon double bond. Alkenyl groups may also be substituted at any available point of attachment. Exemplary substituents for alkenyl groups include those listed above for alkyl groups, and especially include C_3 to C_7 cycloalkyl groups such as cyclopropyl, cyclopentyl and cyclohexyl, which may be further substituted with, for example, amino, oxo, hydroxyl, etc.

The term "alkynyl" herein alone or as part of another group refers to a hydrocarbon radical straight, branched or cyclic containing from 2 to 12 carbon atoms and at least one carbon to carbon triple bond. Alkynyl groups may also be substituted at any available point of attachment. Exemplary substituents for alkenyl groups include those listed above for alkyl groups such as amino, alkylamino, etc.

The numbers in the subscript after the symbol "C" define the number of carbon atoms a particular group can contain. For example "C_1 to C_6 alkyl" means a straight or branched saturated carbon chain having from one to six carbon atoms; examples include methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, t-butyl, n-pentyl, sec-pentyl, isopentyl, and n-hexyl. Depending on the context, "C_1 to C_6 alkyl" can also refer to C_1 to C_6 alkylene which bridges two groups; examples include propane-1,3-diyl, butane-1,4-diyl, 2-methyl-butane-1,4-diyl, etc. "C_2 to C_6 alkyenyl means a straight or branched carbon chain having at least one carbon-carbon double bond, and having from two to six carbon atoms; examples include ethenyl, propenyl, isopropenyl, butenyl, isobutenyl, pentenyl, and hexenyl. Depending on the context, "C_2 to C_6 alkenyl" can also refer to C_2 to C_6 alkenediyl which bridges two groups; examples include ethylene-1,2-diyl (vinylene), 2-methyl-2-butene-1,4-diyl, 2-hexene-1,6-diyl, etc. "C_2 to C_6 alkynyl" means a straight or branched carbon chain having at least one carbon-carbon triple bond, and from two to six carbon atoms; examples include ethynyl, propynyl, butynyl, and hexynyl.

The terms "alkoxy" or "alkylthio" herein alone or as part of another group denote an alkyl group as described above bonded through an oxygen linkage (-O-) or a sulfur linkage (-S-), respectively.

The term "alkoxycarbonyl" herein alone or as part of another group denotes an alkoxy group bonded through a carbonyl group. An alkoxycarbonyl radical is represented by the formula: -C(O)OR, where the R group is a straight or branched C_{1-6} alkyl group, cycloalkyl, aryl, or heteroaryl.

The term "alkylcarbonyl" herein alone or as part of another group refers to an alkyl group bonded through a carbonyl group or –C(O)R.

The term "alkylcarbonyloxy" herein alone or as part of another group denotes an alkylcarbonyl group bonded through an oxygen linkage.

The term "arylalkyl" herein alone or as part of another group denotes an aromatic ring bonded through an alkyl group (such as benzyl) as described above.

The term "aryl" herein alone or as part of another group refers to monocyclic or bicyclic aromatic rings, *e.g.* phenyl, substituted phenyl and the like, as well as groups which are fused, *e.g.*, napthyl, phenanthrenyl and the like. An aryl group thus contains at least one ring having at least 6 atoms, with up to five such rings being present, containing up to 22 atoms therein, with alternating (resonating) double bonds between adjacent carbon atoms or suitable heteroatoms. Aryl groups may optionally be substituted with one or more groups including, but not limited to halogen, such as Br, F, or Cl, alkyl, such as methyl, ethyl, propyl, alkoxy, such as methoxy or ethoxy, hydroxy, carboxy, carbamoyl, alkyloxycarbonyl, nitro, alkenyloxy, trifluoromethyl, amino, cycloalkyl, aryl, heteroaryl, cyano, alkyl $S(O)_m$ (m=O, 1, 2), or thiol.

The term "amino" herein alone or as part of another group refers to $-NH_2$. An "amino" may optionally be substituted with one or two substituents, which may be the same or different, such as alkyl, aryl, arylalkyl, alkenyl, alkynyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, thioalkyl. carbonyl or carboxyl. These substituents may be further substituted with a carboxylic acid, any of the alkyl or aryl substituents set out herein. In some embodiments, the amino groups are substituted with carboxyl or carbonyl to form *N*-acyl or *N*-carbamoyl derivatives.

The term "cycloalkyl" herein alone or as part of another group refers to fully saturated and partially unsaturated hydrocarbon rings of 3 to 9, preferably 3 to 7 carbon atoms. Further, a cycloalkyl may be substituted. A substituted cycloalkyl refers to such rings having one, two, or three substituents, selected from the group consisting of halo, alkyl, substituted alkyl, alkenyl, alkynyl, nitro, cyano, oxo (=O), hydroxy, alkoxy, thioalkyl, $-CO_2H$, $-C(=O)H$, CO_2-alkyl, $-C(=O)$alkyl, keto, =*N*-OH, =*N*-O-alkyl, aryl, heteroaryl, heterocyclo, a five or six membered ketal (*i.e.* 1,3-dioxolane or 1,3-dioxane), $-NR'R''$, $-C(=O)NR'R''$, $-CO_2NR'R''$, $-C(=O)NR'R''$, $-NR'CO_2R''$, $-NR'C(=O)R''$, $-SO_2NR'R''$, and $-NR'SO_2R''$, wherein each of R' and R" are independently selected from hydrogen, alkyl, substituted alkyl, and cycloalkyl, or R' and R" together form a heterocyclo or heteroaryl ring.

The term "heteroaryl" herein alone or as part of another group refers to substituted and unsubstituted aromatic 5 or 6 membered monocyclic groups, 9 or 10 membered bicyclic groups, and 11 to 14 membered tricyclic groups which have at least one heteroatom (O, S or N) in at least one of the rings. Each ring of the heteroaryl group containing a heteroatom can contain one or two oxygen or sulfur atoms and/or from one to four nitrogen atoms provided that the total number of heteroatoms in each ring is four or less and each ring has at least one carbon atom. The fused rings completing the bicyclic and tricyclic groups may contain only carbon atoms and may be saturated, partially saturated, or unsaturated. The nitrogen and sulfur atoms may optionally be oxidized and the nitrogen atoms may optionally be quaternized. Heteroaryl groups which are bicyclic or tricyclic must include at least one fully aromatic ring but the other fused ring or rings may be aromatic or non-aromatic. The heteroaryl group may be attached at any available nitrogen or carbon atom of any ring. The heteroaryl ring system may contain zero, one, two or three substituents selected from the group consisting of halo, alkyl, substituted alkyl, alkenyl, alkynyl, aryl, nitro, cyano, hydroxy, alkoxy, thioalkyl, $-CO_2H$, $-C(=O)H$, $-CO_2$-alkyl, $-C(=O)$alkyl, phenyl, benzyl, phenylethyl, phenyloxy, phenylthio, cycloalkyl, substituted cycloalkyl, heterocyclo, heteroaryl, $-NR'R''$, $-C(=O)NR'R''$, $-CO_2NR'R''$, $-C(=O)NR'R''$, $-NR'CO_2R''$, $-NR'C(=O)R''$, $-SO_2NR'R''$, and $-NR'SO_2R''$, wherein each of R' and R" is independently selected from hydrogen,

alkyl, substituted alkyl, and cycloalkyl, or R' and R" together form a heterocyclo or heteroaryl ring.

Exemplary monocyclic heteroaryl groups include pyrrolyl, pyrazolyl, pyrazolinyl, imidazolyl, oxazolyl, diazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, furanyl, thienyl, oxadiazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl and the like.

Exemplary bicyclic heteroaryl groups include indolyl, benzothiazolyl, benzodioxolyl, benzoxaxolyl, benzothienyl, quinolinyl, tetrahydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuranyl, chromonyl, coumarinyl, benzopyranyl, cinnolinyl, quinoxalinyl, indazolyl, pyrrolopyridyl, furopyridinyl, dihydroisoindolyl, tetrahydroquinolinyl and the like.

Exemplary tricyclic heteroaryl groups include carbazolyl, benzidolyl, phenanthrollinyl, acridinyl, phenanthridinyl, xanthenyl and the like.

The term "heterocycloalkyl" herein alone or as part of another group refers to a cycloalkyl group (nonaromatic) in which one of the carbon atoms in the ring is replaced by a heteroatom selected from O, S or N, and in which up to three additional carbon atoms may be replaced by said heteroatoms. The term "heterocycloalkyl" herein alone or as part of another group refers to a stable, saturated, or partially unsaturated monocyclic ring system containing 5 to 7 ring members of carbon atoms and other atoms selected from nitrogen, sulfur and/or oxygen. A heterocyclic ring may be a 5, 6 or 7-membered monocyclic ring and contain one, two, or three heteroatoms selected from nitrogen, oxygen and/or sulfur. The heterocyclic ring may be optionally substituted which means that the heterocyclic ring may be substituted at one or more substitutable ring positions by one or more groups independently selected from alkyl (preferably lower alkyl), heterocycloalkyl, heteroaryl, 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.

Examples of such heterocycloalkyl groups include piperazine, piperidine, morpholine, homomorpholine, thiomorpholine, pyrrolidine, and azetidine.

A heteroaryl or heterocycloalkyl group may also be an 8-11 membered bicyclic ring which consists of carbon atoms and contains one, two, or three heteroatoms selected from nitrogen, oxygen and/or sulfur. Some preferred bicyclic rings include benzodioxole, quinoxaline, indolyl, and quinolinyl. The term "optionally substituted" as it refers to "heteraryl" or heterocycloalkyl herein indicates that the heterocyclyl group 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.

The term "heteroatom" means O, S or N, selected on an independent basis. It should be noted that any heteroatom with unsatisfied valences is assumed to have the hydrogen atom to satisfy the valences.

The term "halogen" or "halo" refers to chlorine, bromine, fluorine or iodine selected on an independent basis.

The term "anticancer" agent includes any known agent that is useful for the treatment of cancer including 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, including as anti-VEGF antibodies such as Avastin, and small molecules such as ZD6474 and SU6668, vatalanib, BAY-43-9006, SU11248, CP-547632, and CEP-7055 are also included. Anti- Her2 antibodies from Genentech (such as Herceptin) may also be utilized.

Suitable EGFR inhibitors include gefitinib, erlotinib, and cetuximab. Pan Her inhibitors include canertinib, EKB-569, and GW-572016. Also included are Src inhibitors, dasatinib (BMS-354825) as well as Casodex® (bicalutamide, Astra Zeneca), Tamoxifen, MEK-1 kinase inhibitors, MAPK kinase inhibitors, PI3 inhibitors, and PDGF inhibitors, such as imatinib. Also included are anti-angiogenic and antivascular agents which, by interrupting blood flow to solid tumors, render cancer cells quiescent by depriving them of nutrition. Castration, which also renders androgen dependent carcinomas non-proliferative, may also be utilized. Also included are IGF1R inhibitors, inhibitors of non-receptor and receptor tyrosine kinases, and inhibitors of integrin signaling. Additional anticancer agents include microtubule-stabilizing agents such as paclitaxel (also known as Taxol®), docetaxel (also known as Taxotere®), 7-O-methylthiomethylpaclitaxel (disclosed in U.S. 5,646,176), 4-desacetyl-4-methylcarbonatepaclitaxel, 3'-*tert*-butyl-3'-N-*tert*-butyloxycarbonyl-4-deacetyl-3'-dephenyl-3'-N-debenzoyl-4-O-methoxycarbonyl-paclitaxel (disclosed in USSN 09/712,352 filed on November 14, 2000), 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 (disclosed in WO 99/02514), [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 (disclosed in USP 6,262,094) and derivatives thereof; and microtubule-disruptor agents. Also suitable are CDK inhibitors, an antiproliferative cell cycle inhibitor, epidophyllotoxin; an antineoplastic enzyme; a topoisomerase inhibitor; procarbazine; mitoxantrone; platinum coordination complexes such as cis-platin and carboplatin; biological response modifiers; growth inhibitors; antihormonal therapeutic agents; leucovorin; tegafur; and haematopoietic growth factors.

Additional cytotoxic agents include, melphalan, hexamethyl melamine, thiotepa, cytarabin, idatrexate, trimetrexate, dacarbazine, L-asparaginase, camptothecin, topotecan, bicalutamide, flutamide, leuprolide, pyridobenzoindole derivatives, interferons, and interleukins.

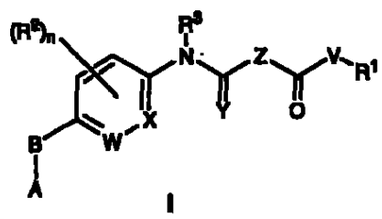
Pyridine-N-oxy refers to a pyridine ring having an oxygen substituted on the N atom of the pyridine ring.

When a functional group is termed "protected", this means that the group is in modified form to preclude undesired side reactions at the protected site. Suitable protecting groups for the compounds of the present invention will be recognized from the present application taking into account the level of skill in the art, and with reference to standard textbooks, such as Greene, T. W. et al., *Protective Groups in Organic Synthesis*, Wiley, N.Y. (1991).

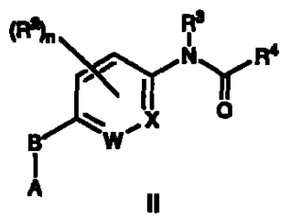
As used herein, the term "patient" encompasses all mammalian species.

The phrase "pharmaceutically acceptable salt(s)", as used herein, unless otherwise indicated, includes salts of acidic or basic groups which may be present in the compounds of formulas I and II. The compounds of formulas I and II that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds of formulas I and II are those that form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, acid citrate, tartrate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts.

The compounds of the present invention have the following Formula I or II:



I



II

including pharmaceutically acceptable salts thereof, wherein:

R^1 is H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, arylalkyl, substituted arylalkyl, aryl, substituted aryl, alkenyl, substituted alkenyl, alkynyl,

substituted alkynyl, heteroaryl, substituted heteroaryl, heterocyclo, substituted heterocyclo, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, or substituted heterocycloalkyl;

each R^2 is independently, H, halogen, cyano, NO_2, OR^5, NR^6R^7, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclo, substituted heterocyclo, aryalkyl, substituted arylalkyl, heterocycloalkyl, or substituted heterocycloalkyl;

B is O, NR^8, S, SO, SO_2, CR^9R^{10};

V is NR^{11} or $-(CR^{47}R^{48})_r-$;

W or X are independently C or N;

Y is O, S, or NR^{12};

Z is $-CR^{13}R^{14}-$, $-(CR^{13}R^{14})_mNR^{15}-$;

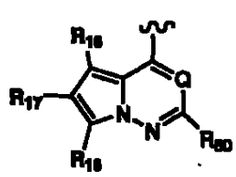
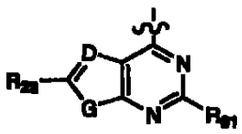
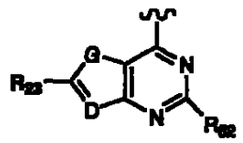
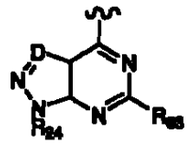
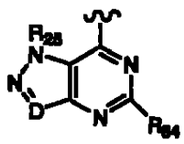
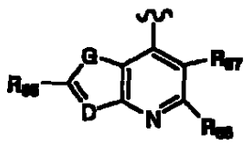
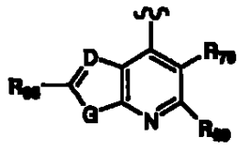
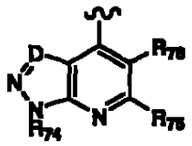
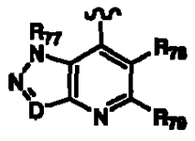
l is 0 to 4;

m is 0 to 2;

n is 0 to 4;

p is 0 to 4, provided that if p is 0, R^1 is not phenyl;

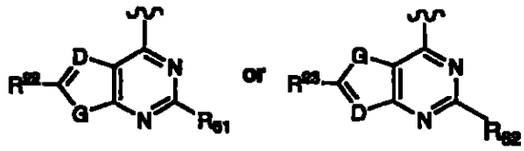
A is:

Q is CR^{19};

D is CR^{20} or N;

G is S, O or NR^{21}, provided that if A is



and G is S, R^4 is not a substituted phenyl group;

R^3, R^5, R^6, R^7, R^8, R^{11} and R^{15} are each independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, or substituted heterocycloalkyl;

R^4 is aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, or substituted heterocycloalkyl;

R^9 and R^{10} are independently H, halogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, or substituted heterocycloalkyl;

R^{12} is H, alkyl, substituted alkyl, CN, NO_2 or SO_2NH_2;

R^{13}, R^{14}, R^{15}, R^{47} and R^{48} are independently H, halogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclo, substituted heterocyclo or taken together to form a carbocyclic or heterocyclic ring of 3 to 8 atoms;

R^{16}, R^{17}, R^{18}, R^{20}, R^{22}, R^{23}, R^{60}, R^{61}, R^{62}, R^{63}, R^{64}, R^{65}, R^{66}, R^{67}, R^{68}, R^{69}, R^{70}, R^{75}, R^{76}, R^{78}, and R^{79}, are independently H, halogen, NO_2, cyano, OR^{26}, $NR^{27}R^{28}$, CO_2R^{29}, $C(O)NR^{30}R^{31}$, SO_2R^{32}, $SO_2NR^{33}R^{34}$, $NR^{35}SO_2R^{36}$, $NR^{37}C(O)R^{38}$, $NR^{39}CO_2R^{40}$, $-CO(CH_2)_tR^{41}$; $-CONH(CH_2)_tR^{42}$, alkylaminoalkyl, alkylaminoalkynyl, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_7 cycloalkyl, substituted C_3 to C_7 cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, hydroxyalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, arylalkyl, substituted arylalkyl, heterocycloalkyl, or substituted heterocycloalkyl;

R^{19} is H or cyano;

R^{21} and R^{24} are independently H, C_1 to C_6 alkyl or substituted C_1 to C_6 alkyl;

R^{25}, R^{74} and R^{77} are independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heterocycloalkyl, or substituted heterocycloalkyl

R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, R^{33}, R^{34}, R^{35}, R^{36}, R^{37}, R^{38}, R^{39}, R^{40}, R^{41}, and R^{42} are independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heterocycloalkyl, or substituted heterocycloalkyl.

The invention also provides a method for treating a proliferative disease, such as cancer, by administering to a patient in need of such treatment an effective amount of a compound of formula I or II, as defined above.

In another embodiment, the invention provides a method for treating a proliferative disease via modulation of Met kinase by administering to a patient in need of such treatment an effective amount of a compound of formula I or II, as defined above, in combination (simultaneously or sequentially) with at least one other anti-cancer agent. In a preferred embodiment, the proliferative disease is cancer.

The invention further provides pharmaceutical compositions comprising compounds having formula I or II together with a pharmaceutically acceptable carrier.

More specifically, the compounds of Formulas I and II are useful in the treatment of a variety of cancers, including, but not limited to, the following:

a) carcinoma, including that of the bladder, breast, colon, kidney, liver, lung, including small cell lung cancer, esophagus, gall bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin, including squamous cell carcinoma;

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

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

d) tumors of mesenchymal origin, including fibrosarcoma and rhabdomyosarcoma;

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

f) other tumors, including melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentosum, keratoctanthoma, thyroid follicular cancer and Kaposi's sarcoma.

Due to the key role protein 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 prostatic hyperplasia, familial adenomatosis polyposis, neuro-fibromatosis, atherosclerosis, pulmonary fibrosis, arthritis, psoriasis, glomerulonephritis, restenosis following angioplasty or vascular surgery, hypertrophic scar formation, inflammatory bowel disease, transplantation rejection, endotoxic shock, and fungal infections.

Compounds of Formulas I and II as modulators of apoptosis, will be useful in the treatment of cancer (including but not limited to those types mentioned herein above), viral infections (including but not limited to herpevirus, poxvirus, Epstein-Barr virus, Sindbis virus and adenovirus), prevention of AIDS development in HIV-infected individuals, autoimmune diseases (including but not limited to systemic lupus, erythematosus, autoimmune mediated glomerulonephritis, rheumatoid arthritis, psoriasis, inflammatory bowel disease, and autoimmune diabetes mellitus), neurodegenerative disorders (including but not limited to Alzheimer's disease, AIDS-related dementia, Parkinson's disease, amyotrophic lateral sclerosis, retinitis pigmentosa, spinal muscular atrophy and cerebellar degeneration), myelodysplastic syndromes, aplastic anemia, ischemic injury associated with myocardial infarctions, stroke and reperfusion injury, arrhythmia, atherosclerosis, toxin-induced or alcohol related liver diseases, hematological diseases (including but not limited to chronic anemia and aplastic anemia), degenerative diseases of the musculoskeletal system (including but not limited to osteoporosis and arthritis) aspirin-sensitive rhinosinusitis, cystic fibrosis, multiple sclerosis, kidney diseases and cancer pain.

Compounds of Formulas I and II may modulate the level of cellular RNA and DNA synthesis. These agents would therefore be useful in the treatment of viral infections (including but not limited to HIV, human papilloma virus, herpesvirus, poxvirus, Epstein-Barr virus, Sindbis virus and adenovirus).

Compounds of Formulas I and II may be useful in the chemoprevention of cancer. Chemoprevention is defined as inhibiting the development of invasive cancer by either blocking the initiating mutagenic event or by blocking the progression of pre-malignant cells that have already suffered an insult or inhibiting tumor relapse.

Compounds of Formulas I and II may also be useful in inhibiting tumor angiogenesis and metastasis.

Some compounds of the present invention have been found to inhibit protein kinases other than Met, such as those in the Trk family of protein kinases.

The compounds of this invention may also be useful in combination (administered together or sequentially) with known anti-cancer treatments such as radiation therapy or with cytostatic or cytotoxic agents, such as for example, but not limited to, DNA interactive agents, such as cisplatin or doxorubicin; topoisomerase II inhibitors, such as etoposide; topoisomerase I inhibitors such as CPT-11 or topotecan; tubulin interacting agents, such as paclitaxel, docetaxel or the epothilones (for example ixabepilone), either naturally occurring or synthetic; hormonal agents, such as tamoxifen; thymidilate synthase inhibitors, such as 5-fluorouracil; and anti-metabolites, such as methotrexate, other tyrosine kinase inhibitors such as Iressa and OSI-774; angiogenesis inhibitors; EGF inhibitors; VEGF inhibitors; CDK inhibitors; SRC inhibitors; c-Kit inhibitors; Her1/2 inhibitors and monoclonal antibodies directed against growth factor receptors such as erbitux (EGF) and herceptin (Her2).

The pharmaceutical compositions 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. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example,

microcrystalline cellulose, sodium crosscarmellose, corn starch, or alginic acid; binding agents, for example starch, gelatin, polyvinyl-pyrrolidone or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to mask the unpleasant taste of the drug or delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a water soluble taste masking material such as hydroxypropyl-methylcellulose or hydroxypropyl-cellulose, or a time delay material such as ethyl cellulose, cellulose acetate buryrate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water soluble carrier such as polyethyleneglycol or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethylene-oxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening

agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as butylated hydroxyanisol or alpha-tocopherol.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, for example soy bean lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavoring agents, preservatives and antioxidants.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, flavoring and coloring agents and antioxidant.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous solutions. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution.

The sterile injectable preparation may also be a sterile injectable oil-in-water microemulsion where the active ingredient is dissolved in the oily phase. For example, the active ingredient may be first dissolved in a mixture of soybean oil and lecithin. The oil solution then introduced into a water and glycerol mixture and processed to form a microemulsion.

The injectable solutions or microemulsions may be introduced into a patient's blood-stream by local bolus injection. Alternatively, it may be advantageous to administer the solution or microemulsion in such a way as to maintain a constant circulating concentration of the instant compound. In order to maintain such a constant concentration, a continuous intravenous delivery device may be utilized. An example of such a device is the Deltec CADD-PLUS.TM. model 5400 intravenous pump.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension for intramuscular and subcutaneous administration. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Compounds of Formulas I and II may also be administered in the form of a suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compound of Formula I are employed. (For purposes of this application, topical application shall include mouth washes and gargles.)

The compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles and delivery devices, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than

intermittent throughout the dosage regimen. Compounds of the present invention may also be delivered as a suppository employing bases such as cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

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.

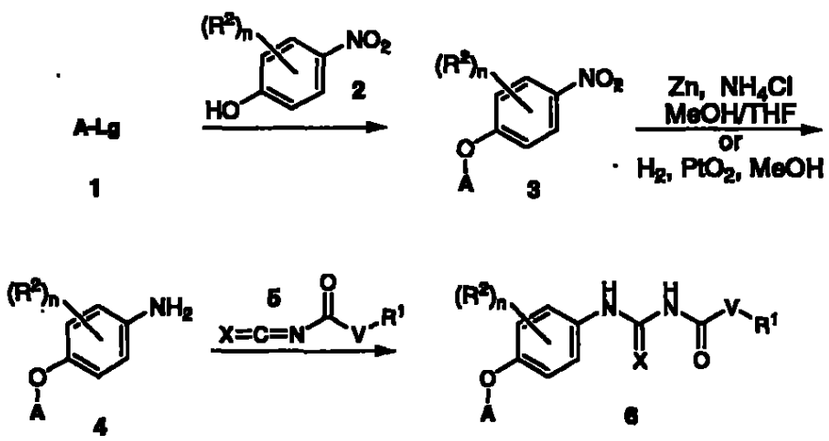
If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described above and the other pharmaceutically active agent or treatment within its approved dosage range. Compounds of Formulas I and II may also be administered sequentially with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

Certain compounds of Formulas I and II may generally be prepared according to the following Schemes 1-16. The compounds are synthesized readily using synthetic methods known to one skilled in the art. Tautomers and solvates (e.g., hydrates) of the compounds of Formulas I and II are also within the scope of the present invention. Methods of solvation are generally known in the art. Accordingly, the compounds of the instant invention may be in the free or hydrate form, and may be obtained by methods exemplified by the following schemes below.

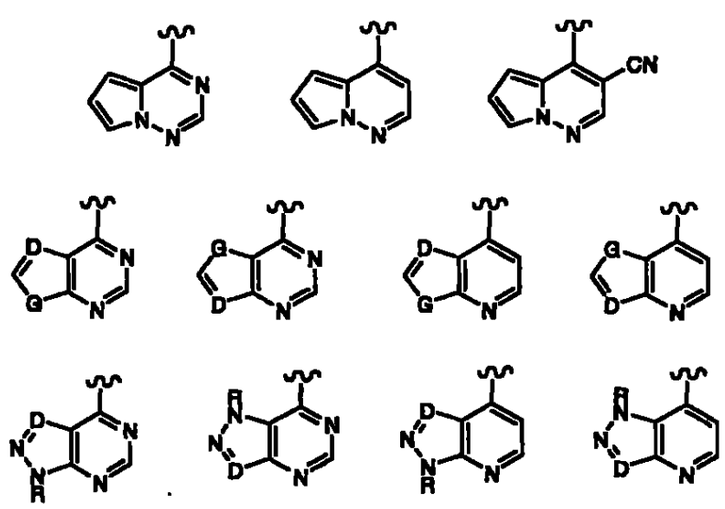
In general, the desired fused heterocycles can be prepared using the synthetic routes outlined in Schemes 1-3. The leaving group (Lg), such as a halogen (or triflate) of a heterocycle (A, whereby open positions may be optionally substituted) 1 can be displaced with a substituted phenol 2 to provide ether 3 (Scheme 1). Groups A-Lg can be prepared according to the general procedures outlined in, for example, Hunt, J. T. *et al.* WO 00/071129; Hunt, J. T. *et al. J. Med. Chem.* 2004, *47*, 4054-4059; Leftheris, K. *et al.* WO 02/040486; Mastalerz, H. *et al.* WO 03/042172; Dyckman, A. *et al.* WO 03/091229; Vite, G. D. *et al.* WO 04/054514; Salvati, M. E. *et al.* WO 03/082208; Thibault, C. *et al. Org. Lett.* 2003, *5*, 5023-5025; Zhang, Z. *et al. J. Org.*

Chem. **2002**, *67*, 2345-2347; Itoh, T. *et al. J. Heterocyclic Chem.* **1982**, *19*, 513-517; Tedder, M. E. *et al. Bioorg. Med. Chem. Lett.* **2004**, *14*, 3165-3168; Dorn, H. *et al. J. Prakt. Chem.* **1982**, *324*, 557; Sanghvi, Y. S. *et al. J. Med. Chem.* **1989**, *32*, 945-951; Temple, C. Jr. *et al. J. Org. Chem.* **1972**, *37*, 3601-3604; Hurst, J. *et al.* EP119774; Hurst, J. *et al.* EP151962; Ward, R. W. *et al.* EP152910; Luzzio, M. J. *et al.* WO 01/094353; Marx, M. A. *et al.* WO 03/000194; Boschelli, D. H. *et al.* WO 04/048386; He, M. *et al.* WO 05/021554; Barker, J. M. *et al. J. Chem. Res., Synopses* **1986**, *4*, 122-123, the disclosures of which are herein incorporated by reference. Reduction of the nitro group of intermediate **3** with, for example either zinc dust and ammonium chloride or Adam's catalyst (platinum(IV) oxide) under catalytic hydrogenation conditions can furnish the aniline **4**. Treatment of the aniline **4** with an isocyanate **5** (X = O) or isothiocyanate **5** (X = S) affords the desired acylurea or acylthiourea **6**, respectively.

SCHEME 1



A =



Lg = leaving group, such as a halogen

X = O or S

G is O, S, or NR^{21}

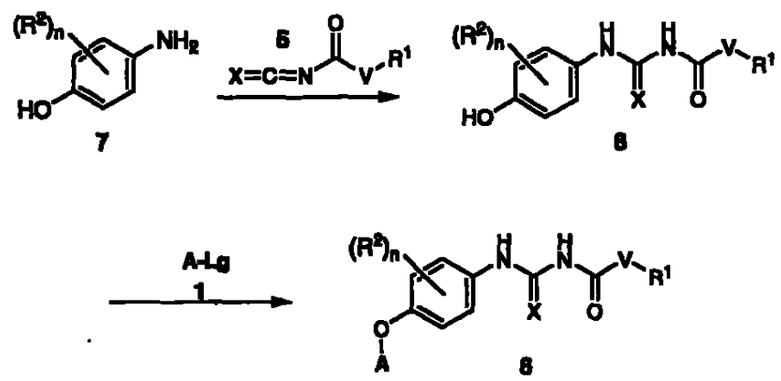
D is CR^{20} or N

V = as defined above

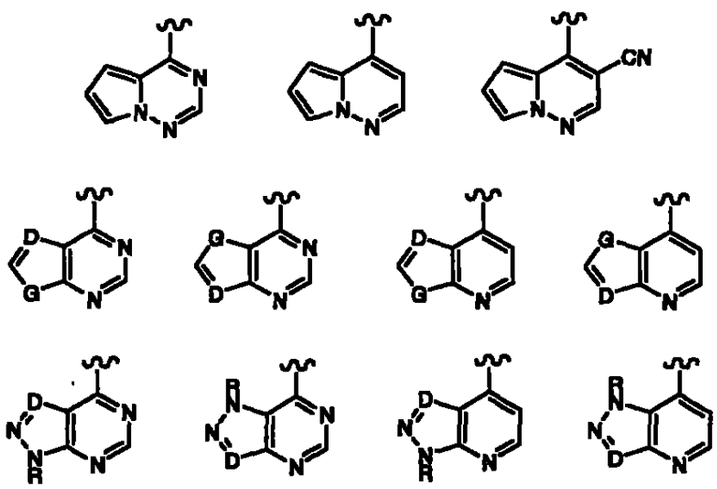
Alternatively, the appropriately substituted aniline 7 can be treated with an isocyanate 5 (X = O) or isothiocyanate 5 (X = S) to give the phenol 8 (Scheme 2).

Reaction of intermediate 8 with a heterocycle (A-Lg) 1 can provide the desired compound 6.

SCHEME 2



A =



Lg = leaving group, such as a halogen

X = O or S

G is O, S, or NR^{21}

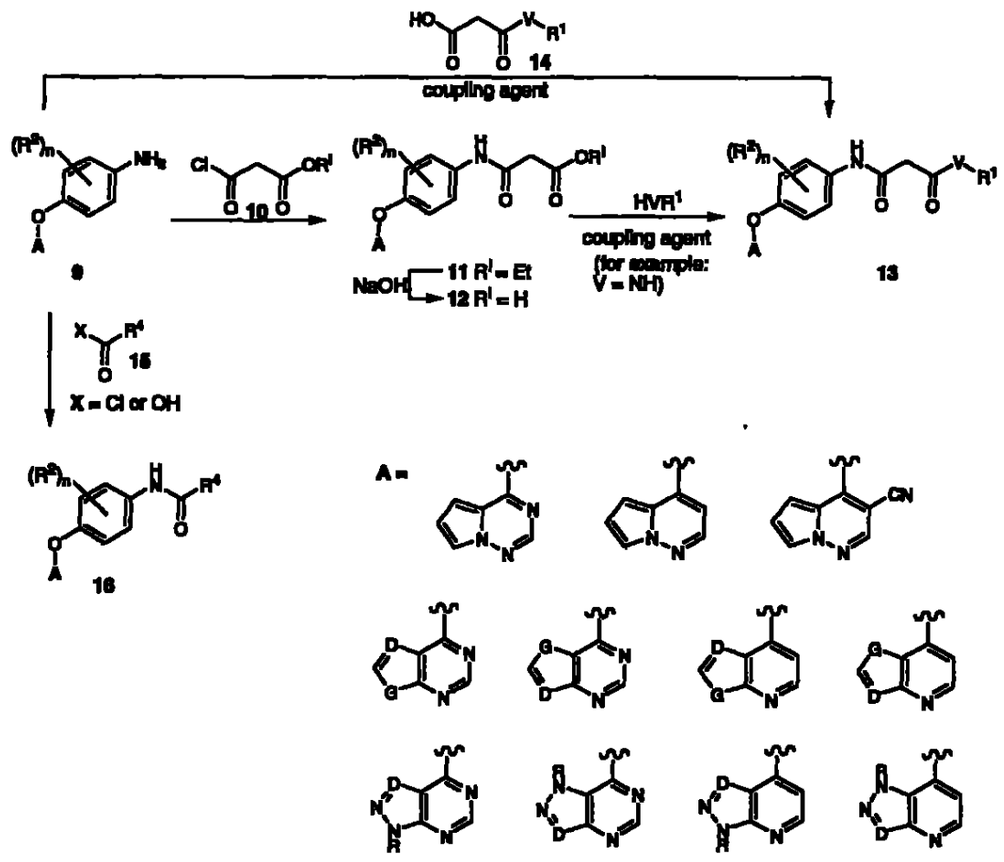
D is CR^{20} or N

V = as defined above

In general, amide derivatives described in the invention can be prepared using the chemistry outlined in Scheme 3. For example, aniline 9 (derived from Scheme 1)

can be acylated with compound **10** to provide amide **11**. Hydrolysis of the ester **11** with, for example sodium hydroxide can afford carboxylic acid **12**. Desired compound **13** can then be obtained from intermediate **12** using known amide-bond forming conditions. Alternatively, aniline **9** can be converted directly to compound **13** using carboxylic acid **14** and a coupling agent, such as benzotriazol-1-yloxytris(trimethylamino)phosphonium hexafluorophosphate, 1-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, or bromotripyrrolidinophosphonium hexafluorophosphate. Treatment of aniline **9** with an acid chloride **15** (X = Cl) or a carboxylic acid **15** (X = OH) and a coupling reagent can provide amides of the type **16**.

SCHEME 3



G is O, S, or NR^{21}

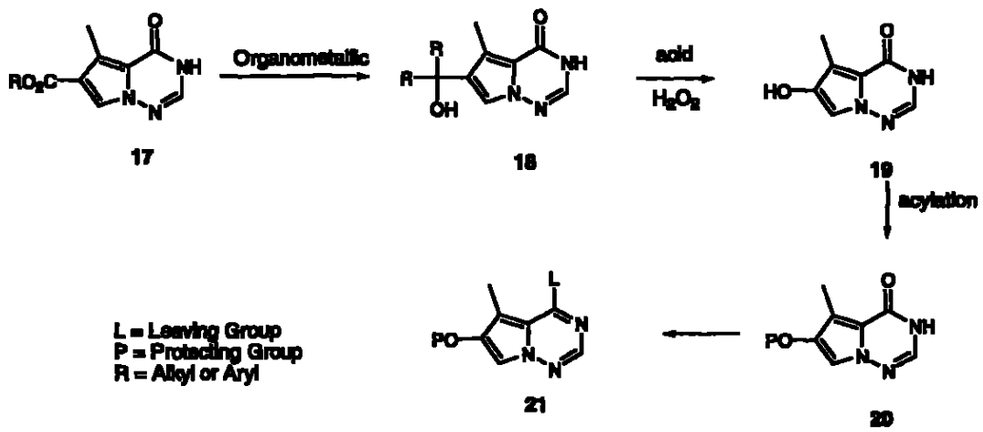
D is CR^{20} or N

V = as defined above

A substituted heterocyclic derivative, for example pyrrolotriazine compound **26a/b** (Scheme 5), can be prepared using the synthetic routes outlined in Schemes 4 and 5. Carboxylic esters, wherein R can be an alkyl or an aryl (such as phenyl) **17** can be contacted with no less than 2 equivalents of an alkyl or aryl organometallic agent such as a Grignard reagent, organolithium, organozinc, etc. to produce the tertiary alcohol **18** (Scheme 4). The reaction is generally performed in an ether solvent, such as tetrahydrofuran, dibutylether, or diethyl ether, or any other non-reactive solvent such as benzene, toluene, or hexane, for example. Tertiary alcohol **18** can be treated with a mixture of acid in the presence of hydrogen peroxide or organic peroxides such as *t*-butylhydroperoxide, cumenehydroperoxide to affect the rearrangement to hydroxypyrrolotriazine **19**. Almost any acid could be used as the catalyst for the oxidative rearrangement, the reaction has been demonstrated with organic acids, mineral acids, and Lewis acids. Some acids which have been used for this type of reaction include: *p*-toluenesulfonic acid, methansulfonic acid, formic acid, sulfuric acid, nitric acid, BF_3-OEt_2, trifluoroacetic acid, acidic zeolites, and acidic ion exchange resins. The concentration of the acid can be varied, the concentration and strength of the acid is used to control the kinetics of the reaction. The concentration of the peroxide can be varied from 30-50%. Any reducing agent which reacts to decompose hydrogen peroxide could be used in the quenching of this reaction, including, but not limited to sodium metabisulfite, sodium hydrogen sulfite, sodium thiosulfate, sodium hydrosulfite. A variety of bases can be used while quenching the reaction to control the pH. Hydroxypyrrolotriazine **19** can be reacted with a variety of acylating reagents, to furnish **20** (where, for example, P can be pivalate ester). Compound **20** can be contacted with an appropriate halogenating agent (for example, phosphorous oxychloride, $POCl_3$) to afford **21** (L = Cl). Other reagents can be used to accomplish this transformation besides $POCl_3$, including PCl_5, mixtures of PCl_5/$POCl_3$, $PhP(O)Cl_2$, $SOCl_2$. Usually an amine is used to catalyze the reaction, including Et_3N, $PhNMe_2$, DABCO, etc. Additionally, formamides such as, for example N,N-dimethylformamide and alkylamides such as *N*-methylpyrrolidinone can

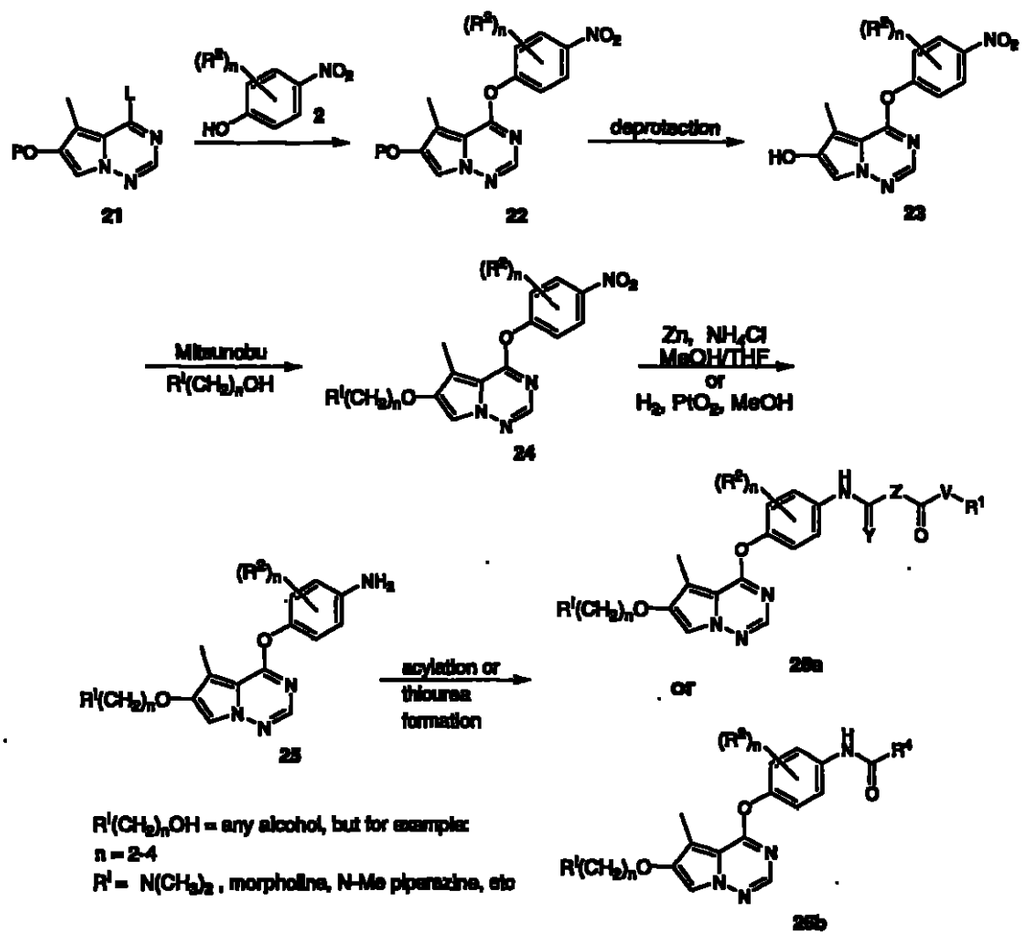
also be used to catalyze the reaction. The reaction can be run in any solvent inert to the haloginating agent, including benzene, toluene, THF, etc.

SCHEME 4



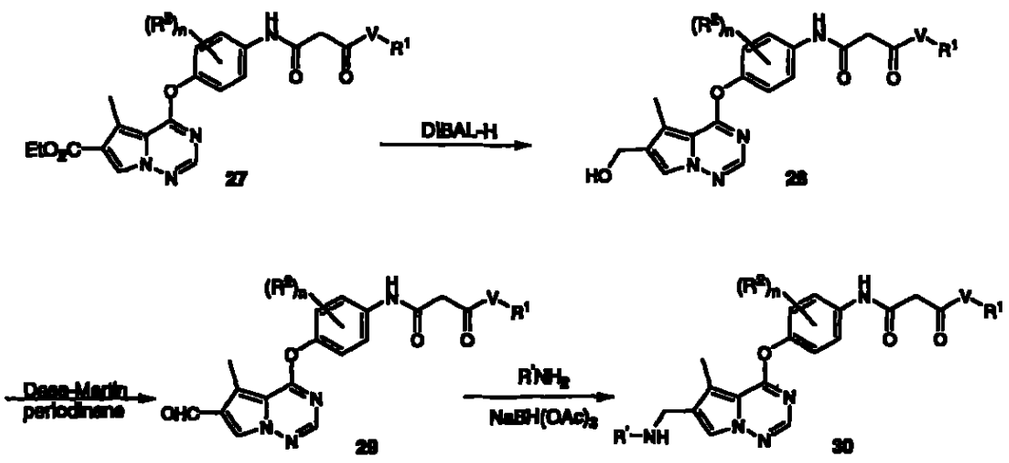
The appropriately protected imidate **21** (Scheme 5) can be treated with an optionally substituted phenol **2** to provide intermediate **22**. Phenol **23**, derived from deprotection of compound **22** (using sodium hydroxide in the case where P = pivalate) can be converted to ether **24** via a Mitsunobu reaction with an alcohol. Reduction of the nitro substituent of **24** using the same conditions described above in Scheme 1 can furnish the aniline **25**. Conversion of aniline **25** to the desired acylurea, acylthiourea or amide **26a/b** can be accomplished using chemistry previously described in Schemes 1 and 3.

SCHEME 5



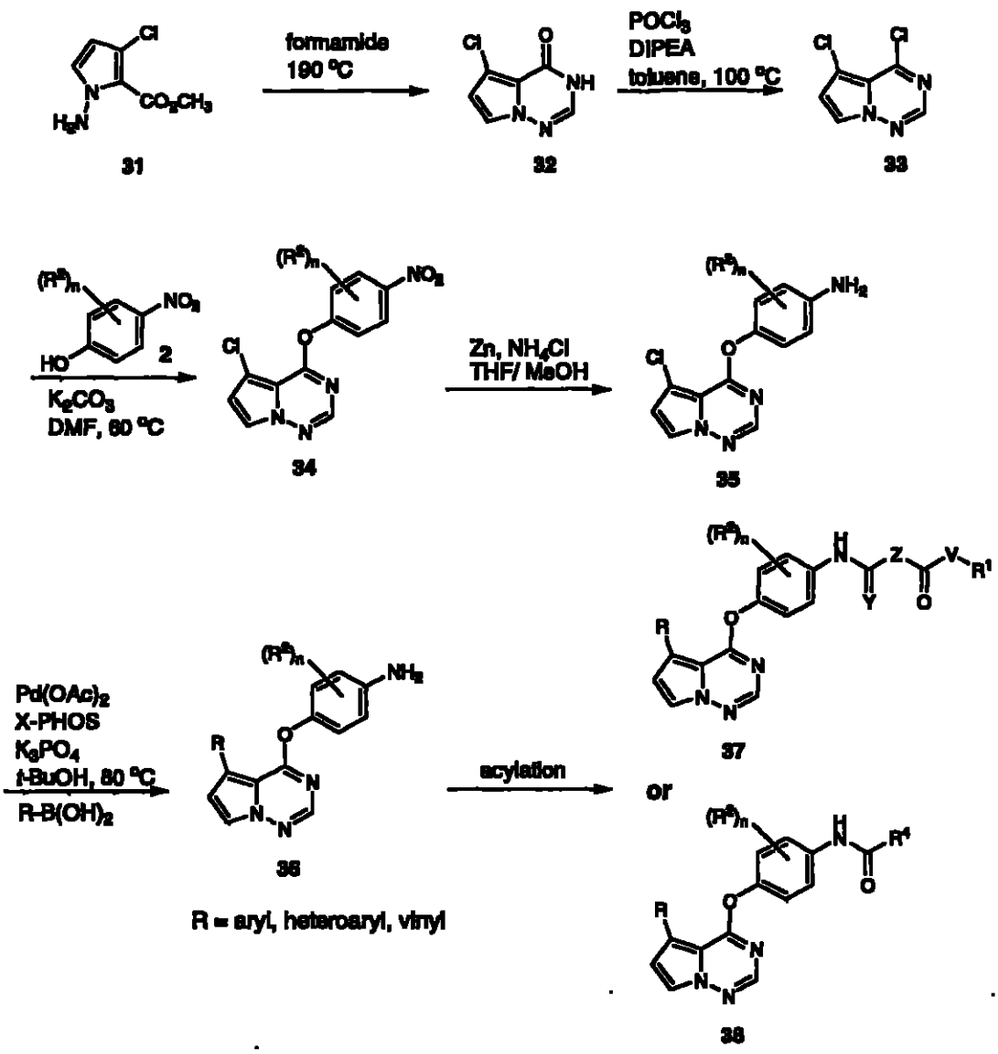
Amine compounds **30** can be prepared using the chemistry described in Scheme 6. Reduction of ester **27** with for example, diisobutylaluminum hydride (DIBAL-H) can provide alcohol **28**. Oxidation of compound **28** with for example Dess-Martin periodinane (1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1*H*)-one) can afford aldehyde **29**. Reductive amination of aldehyde **29** with an appropriately substituted amine in the presence of a reducing agent, such as sodium triacetoxyborohydride can furnish the desired amine **30**.

SCHEME 6



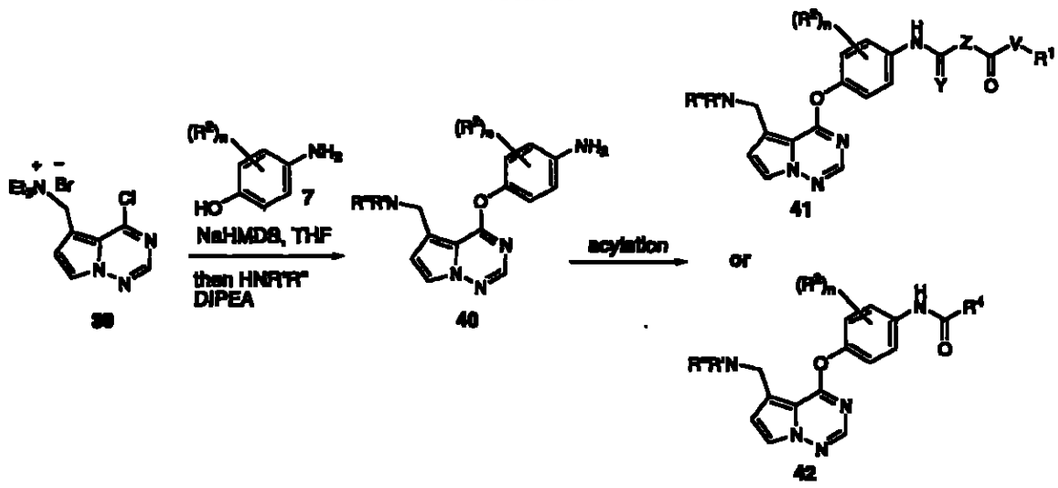
Various substituents, such as optionally substituted aryl, heteroaryl or vinyl groups can be introduced onto the 5-position of the pyrrolo[2,1-*f*][1,2,4]triazine ring using the chemistry outlined in Scheme 7. The aminopyrrole derivative **31** can be cyclized in the presence of formamide to produce 5-chloropyrrolo[2,1-*f*][1,2,4]triazin-4(3*H*)-one (**32**). Treatment of intermediate **32** with $POCl_3$ in the presence of a base, such as Hunig's base at elevated temperatures can afford 4,5-dichloropyrrolo[2,1-*f*][1,2,4]triazine (**33**). The coupling of an appropriately substituted phenol **2** with compound **33** in the presence of a base, such as potassium carbonate can provide intermediate **34**. The nitro group of **34** can be reduced using zinc dust and ammonium chloride to generate the aniline **35**. Palladium-mediated coupling reactions with various boronic acids can provide intermediate **36**, which can be converted to the desired compounds **37** or **38** using chemistry described above.

SCHEME 7



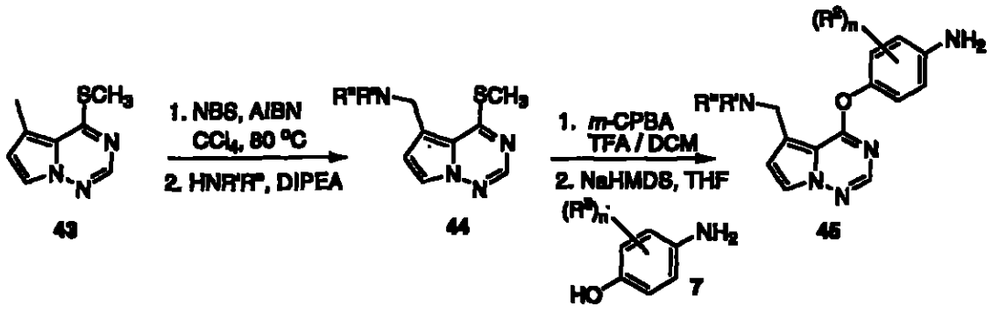
Substitution at the 5-position of the pyrrolo[2,1-*f*][1,2,4]triazine ring can also be accomplished by coupling the triethylammonium salt **39** with an appropriately substituted phenol **7** followed by treatment with an amine (HNR'R") in the presence of a base, such as Hunig's base to afford the aniline **40** (Scheme 8). Aniline **40** can be further processed as described previously to produce the desired compounds **41** or **42**.

SCHEME 8



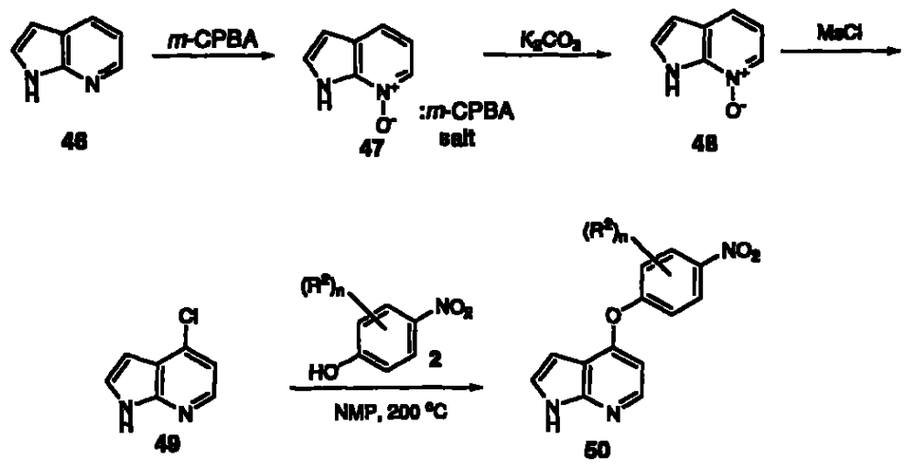
Alternatively, 5-methyl-4-(methylthio)pyrrolo[2,1-*f*][1,2,4]triazine (43) can be brominated with, for example *N*-bromosuccinimide (NBS) and 2, 2'-azobisisobutyronitrile (AIBN) in carbontetrachloride at elevated temperatures (Scheme 9). Treatment of the bromide intermediate with an amine (HNR'R") in the presence of a base, such as Hunig's base can provide intermediate 44. Oxidation of the thiomethyl group of 44 can be accomplished with, for example 3-chloroperbenzoic acid (*m*-CPBA). Treatment of the sulfone intermediate with the phenoxide generated from compound 7 and sodium bis(trimethylsilyl)amide (NaHMDS) can provide the aniline intermediate 45.

SCHEME 9



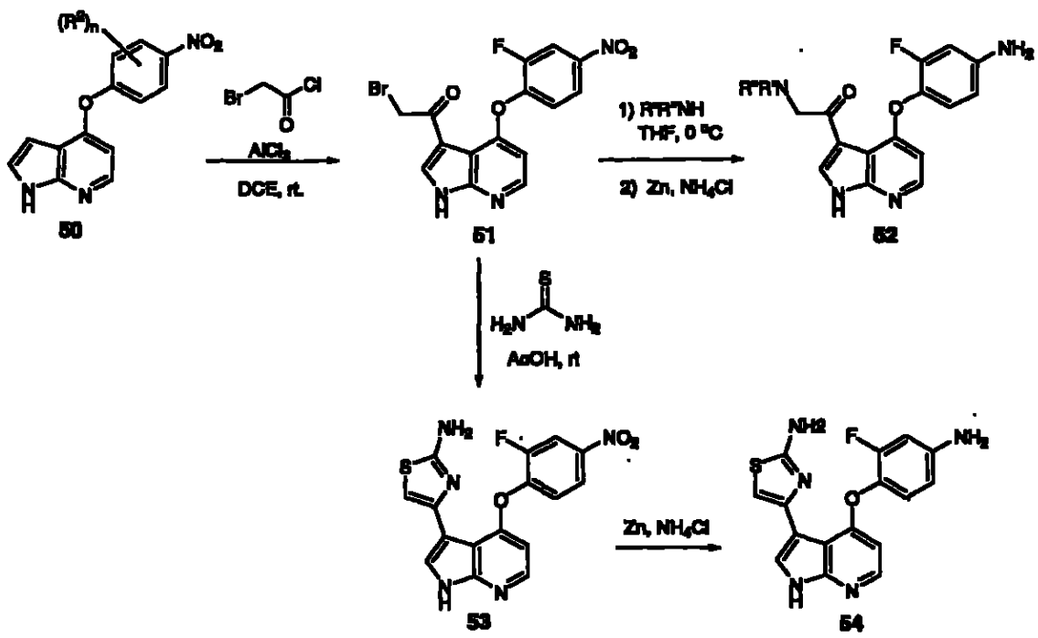
The pyrrolo[2,3-*b*]pyridine intermediate **50** can be prepared using chemistry outlined in Scheme 10. 4-Chloro-1*H*-pyrrolo[2,3-*b*]pyridine (**49**) can be obtained from commercially available 1*H*-pyrrolo[2,3-*b*]pyridine (**46**) using the synthetic sequence described by Thibault C. and coworkers (*Org. Lett.* **2003**, *5*, 5023-5025) which is illustrated in Scheme 10. Treatment of intermediate **49** with the phenol **2** at elevated temperatures can afford the key intermediate **50**, which can be converted to the desired compounds using chemistry described in Schemes 1 and 3.

SCHEME 10



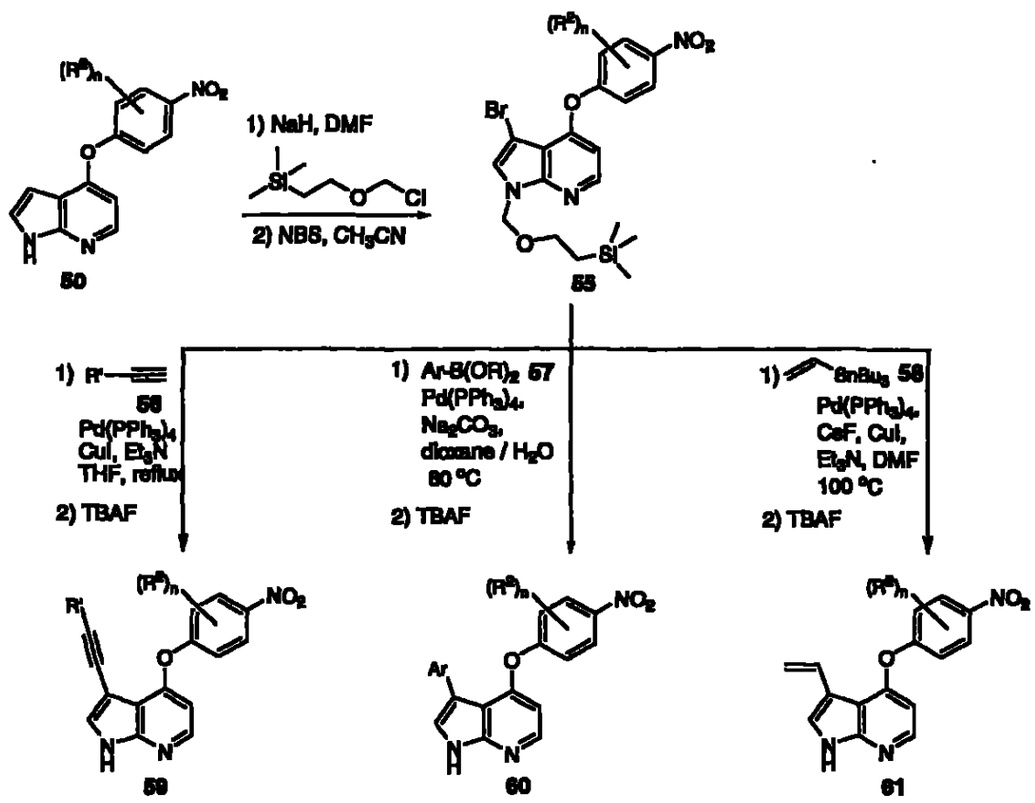
Incorporation of various substituents on the 3-position of the pyrrolo[2,3-*b*]pyridine ring can be accomplished using chemistry described in Schemes 11 and 12. For example, acylation of intermediate **50** with 2-bromoacetyl chloride in the presence of aluminum trichloride can provide compound **51** (Scheme 11). Treatment of intermediate **51** with an amine (R"R'NH) or thiourea, followed by subsequent reduction with zinc dust and ammonium chloride can provide the anilines **52** and **54**, respectively.

SCHEME 11



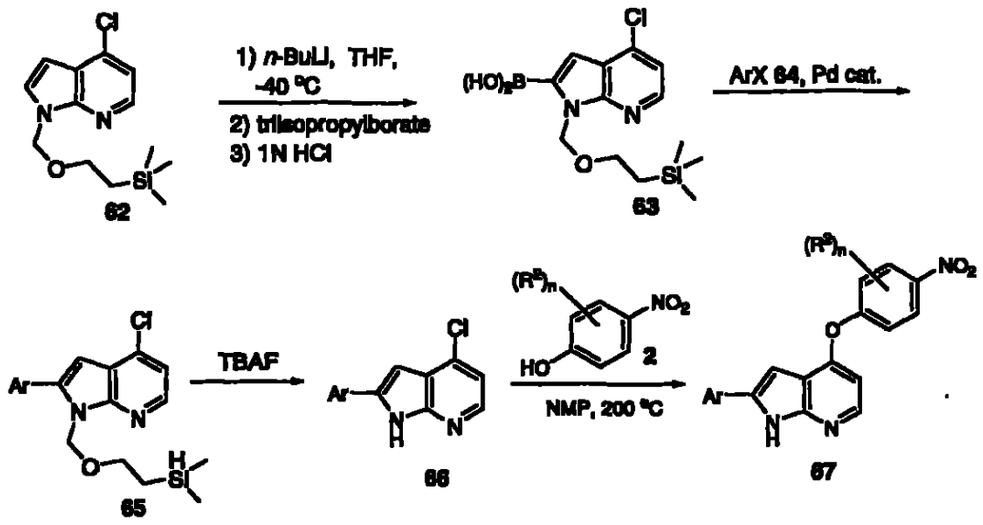
Alternatively, protection of compound **50** with, for example (2-(chloromethoxy)ethyl)trimethylsilane in the presence of a base, such as sodium hydride, followed by bromination with NBS can provide intermediate **55** (Scheme 12). The bromide **55** can then be treated with substituted alkynes **56**, arylboronates / arylboronic acids **57**, or vinylstannanes **58** in the presence of a palladium and/or copper catalyst to afford the intermediates **59-61**, respectively. Removal of the protecting group of **59-61** with tetrabutylammonium fluoride (TBAF) followed by reduction of the nitro groups can provide the corresponding aniline intermediates, which can be acylated using chemistry previously described in Schemes 1 and 3.

SCHEME 12



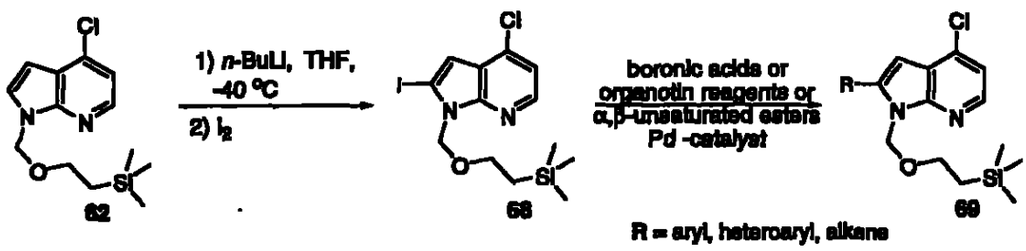
Incorporation of various substituents at the 2-position of the pyrrolo[2,3-*b*]pyridine nucleus can be accomplished using the chemistry outlined in Schemes 13 and 14. The protected azaindole derivative **62**, derived from compound **49** (Scheme 10) can be treated with *n*-butyllithium at low temperature followed by triisopropylborate (Scheme 13). The requisite intermediate can then be hydrolyzed to generate the boronic acid **63**. Coupling of the boronic acid **63** with various aryl or heteroaryl halides **64** can be accomplished using a palladium catalyst to furnish intermediate **65**. Removal of the protecting group of **65** with TBAF can afford compound **66**, which can be treated with phenol **2** at elevated temperature to provide the intermediate **67**. Compound **67** can be further modified to furnish the desired compounds using similar chemistry described above.

SCHEME 13



Alternatively, compound **62** can be converted to iodide **68** using chemistry described in Scheme 14. Intermediate **68** can be coupled with a variety of reagents, such boronic acids, organostannes or substituted olefins in the presence of a transition metal catalyst [i.e., $Pd(OAc)_2$ – *cf.* Chi, S. M. *et al. Tetrahedron Lett.* **2000**, 919-922] to give **69**. Intermediate **69** can be converted to the desired analogues using chemistry previously described.

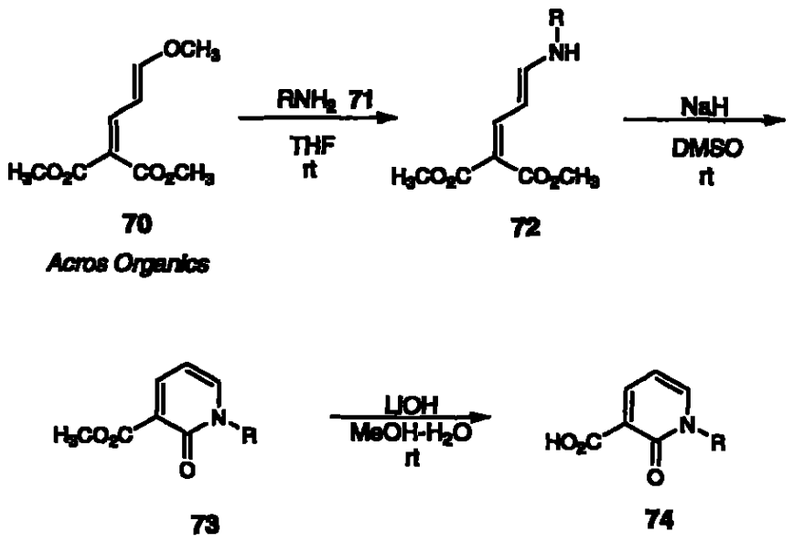
SCHEME 14



The pyridinone intermediate **74** can be obtained by a two step process beginning with commercially available (*E*)-dimethyl 2-(3-methoxyallylidene)malonate (**70**) (Scheme 15). Thus, treatment of compound **70** with an amine or aniline **71** at room temperature can provide intermediate **72**, which can then be cyclized in the

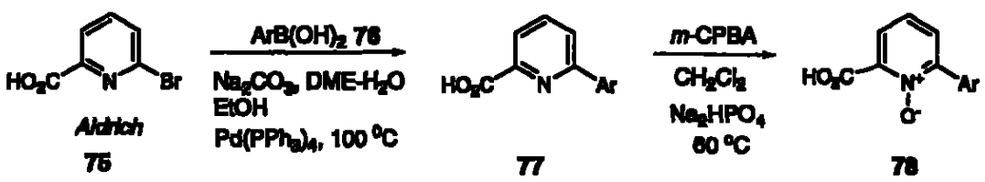
presence of a base, such as sodium hydride in dimethylsulfoxide to generate 73. Hydrolysis of intermediate 73 under basic conditions can provide the desired pyridinone intermediate 74, which can be coupled to various anilines as described in the aforementioned Schemes.

SCHEME 15



The pyridyl *N*-oxide intermediate 78 (Scheme 16) can be obtained by a two-step process in which the commercially available 6-bromopicolinic acid (75) is coupled with boronic acid or borinate 76 in the presence of a palladium(0) catalyst and sodium carbonate, followed by oxidation of the requisite intermediate 77 at elevated temperature. Intermediate 78 can then be coupled to various anilines as described in the aforementioned Schemes.

SCHEME 16



The following examples and preparations describe the manner and process of making and using the invention and are illustrative rather than limiting. It should be understood that there may be other embodiments which fall within the spirit and scope of the invention as defined by the claims appended hereto.

ASSAYS

The pharmacological properties of the compounds of this invention may be confirmed by a number of pharmacological assays. The exemplified pharmacological assays which follow have been carried out with the compounds according to the invention and/or their pharmaceutically acceptable salts.

Met Kinase assay

Reagents	Substrate Mix Final Concentration
Stock Solution	
Tris-HCl, (1M, pH 7.4)	20 mM
$MnCl_2$ (1M)	1 mM
DTT(1M)	1 mM
BSA (100 mg/ml)	0.1 mg/ml
$polyGlu_4$/tyr (10 mg/ml)	0.1 mg/mL
ATP (1mM)	1 μM
γ-ATP (10μCi/μl)	0.2 μCi/ml

Buffer	Enzyme mix
20ul 1M DTT	4ul GST/Met enzyme(3.2mg/ml) = 10ng/rxn
200ul 1M Tris-HCL, pH 7.4	qs 12ml Buffer
20ul 100mg/ml BSA	
qs 20ml H_20	

Incubation mixtures employed for the Met kinase assay contain the synthetic substrate polyGlu:Tyr, (4:1), ATP, ATP-γ-^{33}P and buffer containing Mn^{++} and/or Mg^{++}, DTT, BSA, and Tris buffer. Reactions are incubated for 60 minutes at 27°C and stopped by the addition of cold trichloroacetic acid (TCA) to a final concentration 4%. TCA precipitates are collected onto GF/C unifilter plates (Packard Instrument Co., Meriden, CT) using a Filtermate universal harvester (Packard Instrument Co., Meriden, CT) and the filters are quantitated using a TopCount 96-well liquid scintillation counter (Packard Instrument Co., Meriden, CT). Dose response curves

are generated to determine the concentration required to inhibit 50% of kinase activity (IC_{50}). Compounds are dissolved at 10 mM in dimethyl sulfoxide (DMSO) and evaluated at six concentrations, each in quadruplicate. The final concentration of DMSO in the assay is 1%. IC_{50} values are derived by non-linear regression analysis and have a coefficient of variance (SD/mean, n=6) = 16%.

The compounds of the invention inhibit the Met kinase enzyme with IC_{50} values between 0.01 to 100 μM. Preferred compounds have IC_{50} values less than 1.0μM, and more preferably, less than about 0.5 μM.

The following examples and preparations describe the manner and process of making and using the invention and are illustrative rather than limiting. It should be understood that there may be other embodiments which fall within the spirit and scope of the invention as defined by the claims appended hereto.

EXAMPLES

All reactions were carried out with continuous magnetic stirring under an atmosphere of dry nitrogen or argon. All evaporations and concentrations were carried out on a rotary evaporator under reduced pressure. Commercial reagents were used as received without additional purification. Solvents were commercial anhydrous grades and were used without further drying or purification. Flash chromatography was performed using silica gel (EMerck Kieselgel 60, 0.040-0.060 mm).

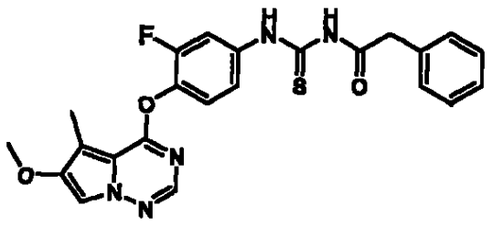
Analytical Reverse Phase (RP) HPLC was performed using a Phenomenex Luna C18 S5 4.6 mm × 50 mm column or a YMC S5 ODS 4.6 x 50 mm column. In each case a 4 min linear gradient (from 100% A: %0 B to 0% A: 100 % B) was used with the following mobile phase system: A = 90% H_2O/MeOH + 0.2% H_3PO_4; B = 90% MeOH/H_2O + 0.2% H_3PO_4 at flow rate = 4mL/min and detection at 220 nm.

Preparative Reverse Phase (RP) HPLC was performed with a linear gradient elution using H_2O/MeOH mixtures buffered with 0.1% trifluoroacetic acid and detection at 220 nm on one of the following columns: Shimadzu S5 ODS-VP 20 x 100 mm (flow rate = 9 mL/min), or YMC S10 ODS 50 x 500 mm (flow rate = 50 mL/min), or YMC S10 ODS 30 x 500 mm (flow rate = 20 mL/min).

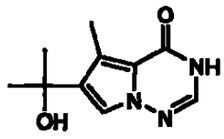
All final products were characterized by ^{1}H NMR, RP HPLC, electrospray ionization (ESI MS) or atmospheric pressure ionization (API MS) mass spectrometry. ^{1}H NMR spectra were obtained on either a 500 MHz JEOL or a 400 MHz Bruker instrument. ^{13}C NMR spectra were recorded at 100 or 125 MHz. Field strengths are expressed in units of δ (parts per million, ppm) relative to the solvent peaks, and peak multiplicities are designated as follows: s, singlet; d, doublet; dd, doublet of doublets; dm, doublet of multiplets; t, triplet; q, quartet; br s, broad singlet; m, multiplet.

The following abbreviations are used for commonly used reagents : Boc or BOC: *t*-butyl carbamate; Fmoc: 9*H*-fluorenylmethyl carbamate; NMM: *N*-methylmorpholine; Ms: methanesulfonyl; DIEA or DIPEA: diisopropylethylamine or Hunig's base; NMP: *N*-methylpyrrolidinone; BOP reagent: benzotriazol-1-yloxytris(trimethylamino)phosphonium hexafluorophosphate; DCC: 1,3-dicyclohexylcarbodiimide; EDCI: 1-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; RT: room temperature; t_R: retention time; h: hour(s); min: minute(s); PyBrOP: bromotripyrrolidinophosphonium hexafluorophosphate; TBTU: *O*-(1*H*-benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium tetrafluoroborate; DMAP: 4-*N*,*N*-dimethylaminopyridine; HOBt: hydroxybenzotriazole; HATU: *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate; DIBAL-H: diisobutylaluminum hydride; $Na(OAc)_3BH$: sodium triacetoxyborohydride; HOAc: acetic acid; TFA: trifluoroacetic acid; LiHMDS: lithium bis(trimethylsilyl)amide; *m*-CPBA: *m*-chloro: 3-chloroperbenzoic acid; AIBN: 2, 2'-azobisisobutyronitrile; DMSO: dimethyl sulfoxide; MeCN: acetonitrile; MeOH: methanol; EtOAc: ethyl acetate; DMF: dimethyl formamide; THF: tetrahydrofuran; DCE: 1,2-dichloroethane; Et_2O: diethyl ether.

EXAMPLE 1

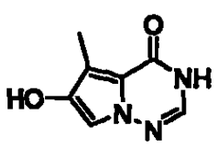


1-(3-Fluoro-4-(6-methoxy-5-methylpyrrolo[2,1-*f*][1,2,4] triazin-4-yloxy)phenyl)-3-(2-phenylacetyl)thiourea



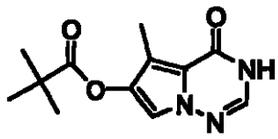
A) **6-(1-Hydroxy-1-methyl-ethyl)-5-methyl-3*H*-pyrrolo[2,1-*f*]1,2,4]triazin-4-one**

A mixture of 1.9 kg of 5-methyl-4-oxo-3,4-dihydro-pyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylic acid ethyl ester, prepared generally according to the procedures described in, United States Patent Application Serial No. 09/573829, and 17.9 kg of THF was prepared under an inert atmosphere and cooled to -10 °C. To this mixture was added 14.2 kg methylmagnesium chloride as a 3 M solution in THF at a rate to maintain the reaction temperature < 35 °C. The reaction mixture was held at 25-45 °C until complete, then cooled to 0 °C. A solution of 9.9 kg ammonium chloride in 36.7 kg water was prepared and cooled to 5 °C. The organic reaction mixture was added to the ammonium chloride solution at a rate to maintain the internal temperature < 15 °C. The phases were allowed to settle and the lower aqueous phase drained off and re-extracted with 9.5 kg additional THF. To the combined organic phases was added 8.6 kg EtOAc and the mixture washed with 7.6 kg of saturated aqueous sodium chloride solution. The reaction mixture was filtered, then solvent was removed *in vacuo* (temperature < 40 °C) to about 1/3 the original volume. Additional EtOAc was added with continuing distillation until the THF level was < 7%. The resulting slurry was cooled to 0-5 °C, then the solid collected by filtration. The wet cake was washed with cold (-10 °C) EtOAc, then dried in vacuo at 40 °C to produce 1.5 kg 6-(1-hydroxy-1-methyl-ethyl)-5-methyl-*3H*-pyrrolo[2,1-*f*]1,2,4]triazin-4-one with a purity of 96-99%.



B) **6-Hydroxy-5-methyl-3*H*-pyrrolo[2,1-*f*][1,2,4]triazin-4-one**

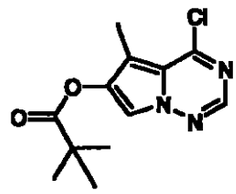
A one liter, 3-neck, round bottom flask as equipped with mechanical stirrer and a cooling bath of ice/acetone. To this was charged 20 g of 6-(1-hydroxy-1-methyl-ethyl)-5-methyl-*3H*-pyrrolo[2,1-*f*][1,2,4]triazin-4-one, 235 mL of THF and 47 mL 50% aqueous hydrogen peroxide. An exotherm from -7 °C to 7.3 °C was observed and the mixture became a solution. To this was added a pre-cooled solution of 28.5 mL water and 63 mL methanesulfonic acid over 40 min, keeping the temperature between -5 °C and -0.7 °C. The solution was stirred at -2 °C for 95 min until HPLC indicated reaction was complete; reaction mixture was quenched, while keeping it at -2 °C, by adding it portion wise to a cooled solution of 28.5 mL water, 89 g $NaHSO_3$ and 128 mL 28% aqueous ammonium hydroxide over 40 min, at 15 °C to 25 °C. The mixture was stirred at room temperature for 20 min; pH was 6.80 and a peroxide test was negative. The layers were separated and the aqueous layer was extracted with 100 mL THF. The two organic layers were combined and concentrated, removing 280 mL solvent. To the thick slurry was added 250 mL water and the concentration continued until 88 mL of solvent was removed. The slurry was filtered and the cake was washed with 25 mL water twice and then 25 mL acetonitrile. It was dried by suction on the filter to constant weight to yield 12.51 g of 6-hydroxy-5-methyl-3*H*- pyrrolo[2,1-*f*][1,2,4]triazin-4-one, 75.9% yield, 96.5% purity.



C) **2,2- Dimethyl-propionic acid 5-methyl-4-oxo-3,4-dihydro-pyrrolo[2,1-*f*][1,2,4]triazin-6-yl ester**

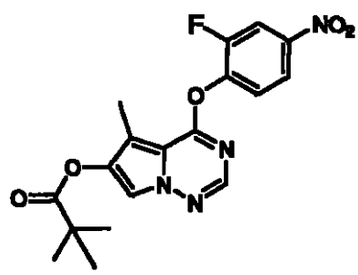
A mixture of 2.9 kg 6-hydroxy-5-methyl-3*H*-pyrrolo[2,1-*f*][1,2,4]triazin-4-one, 4.6 kg of diisopropylethylamine and 17.0 kg of THF was cooled to 0-10 °C, then treated with 2.6 kg pivaloyl chloride at a rate to maintain the temperature < 20 °C. The mixture was stirred until the reaction was complete by HPLC, then 17.8 kg of toluene was added, followed by 20.6 kg of 15% aqueous potassium dihydrogen phosphate solution. The phases were separated and the organic was washed with 10.2

kg water. The organic phase was filtered, then distilled under vacuum with a maximum temperature of 65 °C. Additional toluene can be added and distillation continued until the concentration of THF was < 8%, and the total reactor volume was reduced to 31 L. The resulting slurry was cooled to 20-25 °C and treated with 20.3 kg heptane over 1.5 h. The slurry was cooled to 0-5 °C and held for 1 h, then the solid was collected by filtration and dried to yield 4.0 kg of 2,2-dimethyl-propionic acid 5-methyl-4-oxo-3,4-dihydro-pyrrolo[2,1-*f*][1,2,4]triazin-6-yl ester with a purity of 95-99%.



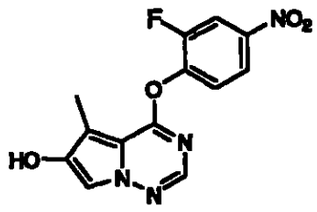
D) **4-Chloro-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yl pivalate**

To a mixture of 5-methyl-4-oxo-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-6-yl pivalate (300 mg, 1.20 mmol), phosphorus oxychloride (2.0 mL, 21.4 mmol) and DIEA (0.5 mL, 2.80 mmol) was added toluene (10 mL). The reaction was heated at 110 °C for 4 hours and then cooled to room temperature. The mixture was diluted with ethyl acetate (10 mL) and water (5 mL). The organic layer was separated and dried with sodium sulfate, concentrated *in vacuo* and purified by silica gel flash chromatography (eluted with 1 – 25% EtOAc/CH_2Cl_2) to give the title compound (250 mg, 78%) as a white solid.



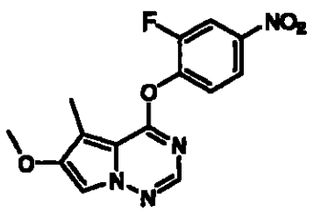
E) **4-(2-Fluoro-4-nitrophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yl pivalate**

To a mixture 4-chloro-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yl pivalate (250 mg, 0.94 mmol), 2-fluoro-4-nitrophenol (176 mg, 1.12 mmol, Aldrich) and K_2CO_3 (154 mg, 1.12 mmol) was added DMF (5 mL). The reaction was stirred at room temperature for 24 h. The reaction was quenched with water (5 mL) and CH_2Cl_2 (10 mL). The organic layer was separated, dried with sodium sulfate, concentrated *in vacuo*, and purified by silica gel flash chromatography (eluted with 1 – 25% EtOAc/CH_2Cl_2) to give the title compound (160 mg, 44%) as a white solid.



F) **4-(2-Fluoro-4-nitrophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-ol**

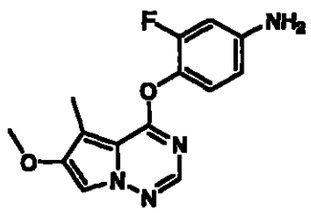
To a solution of 4-(2-fluoro-4-nitrophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yl pivalate (80 mg, 0.2 mmol) in THF (1 mL) was added a solution of NaOH in MeOH / H_2O (0.2 mL, 1 M). The solution turned red instantly. After 5 minutes, the reaction was quenched with EtOAc (5 mL) and H_2O (5 mL). The organic layer was separated, dried with sodium sulfate and concentrated *in vacuo* to give the title compound (52 mg, 85%) as a yellow solid.



G) **4-(2-Fluoro-4-nitrophenoxy)-6-methoxy-5-methylpyrrolo[2,1-*f*][1,2,4]triazine**

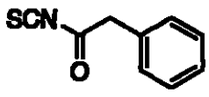
To a solution of 4-(2-fluoro-4-nitrophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-ol (52 mg, 0.17 mmol) in DMF (2 mL) was added Cs_2CO_3 (65 mg, 0.2 mmol) and the mixture was stirred at RT for 10 minutes. A solution of methyl iodide in DMF (0.2 mL, 0.2 mmol, 1 M) was added and the reaction solution was stirred at RT for 2 h. The reaction was quenched with EtOAc (5 mL) and H_2O (5

mL). The organic layer was separated, dried with sodium sulfate and concentrated *in vacuo* to give the title compound (35 mg, 65%) as a yellow solid.



H) **3-Fluoro-4-(6-methoxy-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine**

To a solution of 4-(2-fluoro-4-nitrophenoxy)-6-methoxy-5-methylpyrrolo[2,1-*f*][1,2,4]triazine (35 mg, 0.11 mmol) in THF (1.0 mL) was added MeOH (1.0 mL) followed by Zn (100 mg, 1.5 mmol) and NH_4Cl (43 mg, 0.80 mmol). The reaction was heated at 60 °C for 3 h. The solution was filtered through Celite® and concentrated *in vacuo*. The product mixture was purified by a SCX cartridge (eluted with ammonia in methanol (2 M) to give the title compound (15 mg, 50%) as a white solid.



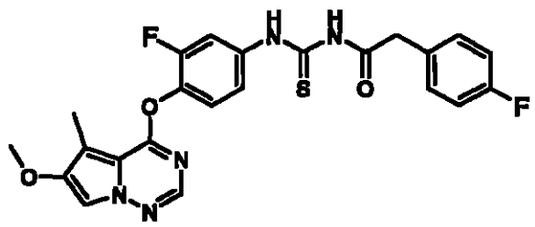
I) **2-Phenyl-1-thiocyanatoethanone**

To a solution of NaSCN (49 mg, 0.60 mmol) in EtOAc (2 mL) was added phenylacetyl chloride (0.066 mL; 0.50 mmol, Aldrich) to provide a 0.25 M solution of 2-phenyl-1-thiocyanatoethanone. After 10 min, completion of the reaction was determined by reacting an aliquot of the reaction mixture with 4-(phenyloxy)aniline to form the corresponding thiocyanate which was detected by LCMS(ESI$^+$) *m/z* 363 $(M + H)^+$. The 2-phenyl-1-thiocyanatoethanone was used directly without isolation or further purification.

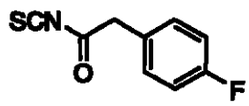
J) **1-(3-Fluoro-4-(6-methoxy-5-methylpyrrolo[2,1-*f*][1,2,4] triazin-4-yloxy)phenyl)-3-(2-phenylacetyl)thiourea**

To a solution of 3-fluoro-4-(6-methoxy-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine (7.5 mg, 0.026 mmol) in CH_2Cl_2 (1 mL) was added a solution of 2-phenyl-1-thiocyanatoethanone (0.133 mL, 0.033 mmol, 0.25 M in ethyl acetate). The reaction was stirred at room temperature for 20 minutes, concentrated *in vacuo* and purified by silica gel flash chromatography (eluted with 1 - 25% EtOAc/CH_2Cl_2) to give the title compound (6.1 mg, 50%) as a pale yellow solid. ^{1}H NMR ($CDCl_3$) δ 8.51 (s, 1H), 7.87 (m, 1H), 7.83 (s, 1H), 7.47 (m, 5H), 7.31 (m, 4H), 3.89 (s, 3H) 3.74 (d, 2H, J = 10.5 Hz), 2.44 (s, 3H); MS(ESI$^+$) *m/z* 466 $(M + H)^+$.

EXAMPLE 2



1-(3-Fluoro-4-(6-methoxy-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea



A) 2-(4-Fluorophenyl)-1-thiocyanatoethanone

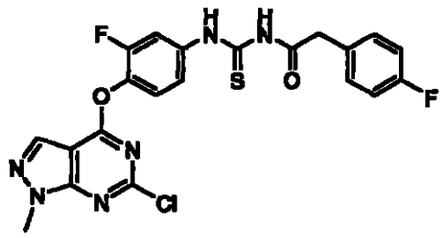
To a solution of NaSCN (49 mg, 0.60 mmol) in EtOAc (2 mL) was added 4-fluorophenylacetyl chloride (0.066 mL, 0.50 mmol, Aldrich). The reaction was stirred at room temperature for 1 h to give a 0.25 M solution of 2-(4-fluorophenyl)-1-thiocyanatoethanone in EtOAc, which was used directly without further purification.

B) 1-(3-Fluoro-4-(6-methoxy-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea

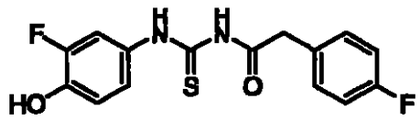
The title compound was prepared from 3-fluoro-4-(6-methoxy-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine and 2-(4-fluorophenyl)-1-thiocyanatoethanone in a similar manner as described for Compounds H and J of

Example 1. ^{1}H NMR ($CDCl_3$) δ 8.49 (s, 1H), 7.88 (m, 1H), 7.83 (s, 1H), 7.45 (s, 1H), 7.28 (m, 5H), 7.12 (m, 2H), 3.89 (s, 3H), 3.71 (s, 2H) 2.44 (s, 3H); MS(ESI$^+$) *m/z* 484 $(M + H)^+$.

EXAMPLE 3



1-(4-(6-Chloro-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea



A) 1-(3-Fluoro-4-hydroxyphenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea

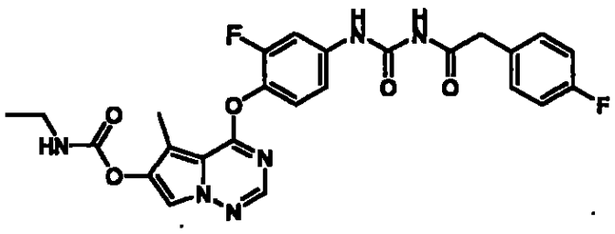
To a solution of 4-amino-2-fluorophenol (50 mg, 0.3 mmol, Indofine Chemical Co.) in CH_2Cl_2 (5 mL) was added a 0.25 M solution of 2-(4-fluorophenyl)-1-thiocyanatoethanone (prepared using a similar procedure for the synthesis of Compound A of Example 2) in EtOAc (1.6 mL, 0.4 mmol). The reaction was stirred at room temperature for 20 minutes, concentrated *in vacuo* and purified by silica gel flash chromatography (eluted with 1 - 25% EtOAc/CH_2Cl_2) to give the title compound (100 mg, 95%) as a white solid.

B) 1-(4-(6-Chloro-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea

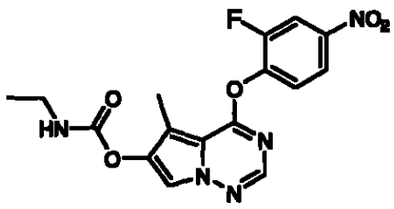
To a mixture of 1-(3-fluoro-4-hydroxyphenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea (24 mg, 0.075 mmol), 4,6-dichloro-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (15.3 mg, 0.075 mmol, preparation: *J. Org. Chem.* **1958**, *23*, 852, the disclosure of which is herein incorporated by reference) and K_2CO_3 (10 mg, 0.075 mmol) was added DMF (2 mL). The reaction was stirred at RT for 24 h.

The reaction was quenched with water (2 mL) and CH_2Cl_2 (5mL). The organic layer was separated, dried with sodium sulfate, concentrated *in vacuo* and purified by reverse phase preparative HPLC to give the title compound (22.9 mg, 60%) as a white solid. MS(ESI$^+$) *m/z* 457 $(M + H)^+$.

EXAMPLE 4

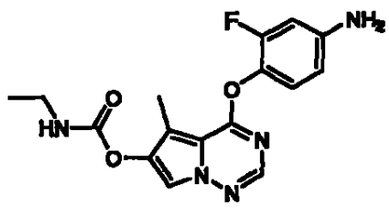


4-(2-Fluoro-4-(3-(2-(4-fluorophenyl)acetyl)ureido)phenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yl ethylcarbamate



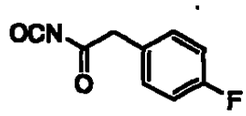
A) 4-(2-Fluoro-4-nitrophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yl ethylcarbamate

To a mixture of 4-(2-fluoro-4-nitrophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-ol (25 mg, 0.082 mmol, Compound F of Example 1), DIEA (0.017 mL, 0.1 mmol) in CH_2Cl_2 (5 mL) was added ethyl isocyanate (0.078 mL, 0.1 mL) and stirred at room temperature for 2 h. The reaction was quenched with water (5 mL). The organic layer was separated, dried and concentrated *in vacuo*. The mixture was purified by flash chromatography (1-5% Methanol/CH_2Cl_2) to give the title compound (12.5 mg, 32%) as a white solid.



B) **4-(4-Amino-2-fluorophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yl ethylcarbamate**

To a solution of 4-(2-fluoro-4-nitrophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yl ethylcarbamate (12.5 mg, 0.033 mmol) in ethanol (2 mL) was added Zn (20 mg, 0.3 mmol) and NH_4Cl (20 mg, 0.37 mmol). The reaction was stirred at room temperature for 1 h, filtered through Celite® and concentrated *in vacuo* to give the title compound (8 mg, 70%) as a white solid.



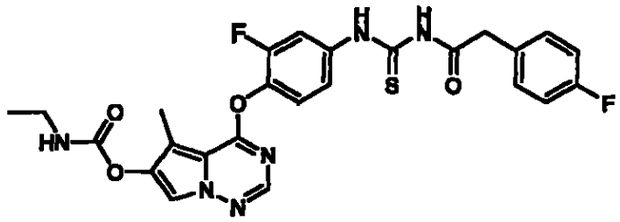
C) **2-(4-Fluorophenyl)acetyl isocyanate**

To a solution/suspension of 4-fluorophenylacetamide (77 mg, 0.50 mmol, see generally, *J. Med. Chem.* 2003, *46*, 4333-4341, the disclosure of which is herein incorporated by reference) in dichloroethane (2 mL) was added oxalyl chloride (0.175 mL, 2.00 mmol). The reaction was heated at 80 °C for 24 h and then 70 °C for two days. By this time, most of the solids had dissolved and the reaction was yellow. LC/MS analysis found a peak with a molecular weight of 211 corresponding to methyl 2-(4-fluorophenyl)acetylcarbamate, resulting from quenching of the isocyanate with methanol. The reaction was concentrated *in vacuo* to give a yellow slurry. The slurry was redissolved in dichloroethane (2 mL) and again concentrated *in vacuo*. The resulting residue was redissolved again in dichloroethane (2 mL) to give a 0.25 M solution of 2-(4-fluorophenyl)acetyl isocyanate in dichloroethane, which was used directly in subsequent reactions.

D) **4-(2-Fluoro-4-(3-(2-(4-fluorophenyl)acetyl)ureido)phenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yl ethylcarbamate**

To a solution of 4-(4-amino-2-fluorophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yl ethylcarbamate (10 mg, 0.029 mmol) in CH_2Cl_2 (1 mL) was added a solution of 2-(4-fluorophenyl)acetyl isocyanate (2 mL, 0.25 M in dichloroethane). The reaction was stirred at room temperature for 1 h, LC/MS analysis indicated consumption of starting carbamate. The mixture was concentrated *in vacuo* and the residue was suspended in methanol and filtered to give the title compound. The filtrate was purified by flash chromatography to provide more of the title compound as a pale yellow solid (combined yield 5.9 mg, 40%). ^{1}H NMR ($CDCl_3$) δ 10.63 (s, 1H), 8.42 (s, 1H), 7.88 (s, 1H), 7.82 (s, 1H), 7.67 (dd, 1H, J = 12.1, 2.2 Hz), 7.28 (m, 4H), 7.10 (m, 2H), 3.73 (s, 3H), 3.36 (m, 2H), 2.48 (s, 3H), 1.26 (m, 3H); MS(ESI$^+$) *m/z* 525 $(M + H)^+$.

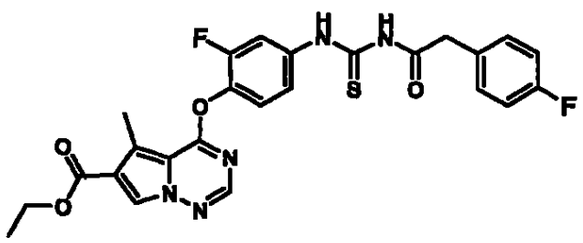
EXAMPLE 5



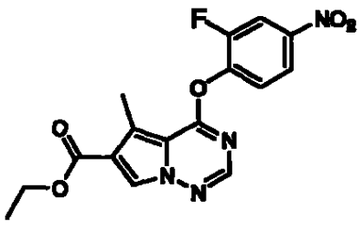
4-(2-Fluoro-4-(3-(2-(4-fluorophenyl)acetyl)thioureido)phenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yl ethylcarbamate

To a solution of 4-(4-amino-2-fluorophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yl ethylcarbamate (8 mg, 0.023 mmol, preparation Compound B of Example 4) in CH_2Cl_2 (1 mL) was added a solution of 2-(4-fluorophenyl)-1-thiocyanatoethanone (0.120 mL, 0.025 mmol, 0.25 M in ethyl acetate, Compound A of Example 2). The reaction was stirred at room temperature for 1 h, concentrated *in vacuo* and purified by silica gel flash chromatography (eluted with 1 - 25% EtOAc/CH_2Cl_2) to give the title compound (5.4 mg, 43%) as a pale yellow solid. ^{1}H NMR ($CDCl_3$) δ 12.41 (s, 1H), 8.58 (s, 1H), 7.88 (m, 3H), 7.28 (m, 5H), 7.12 (m, 2H), 3.72 (s, 2H), 3.37 (m, 2H), 2.46 (m, 3H), 1.26 (m, 3H); MS(ESI$^+$) *m/z* 541 $(M + H)^+$.

EXAMPLE 6

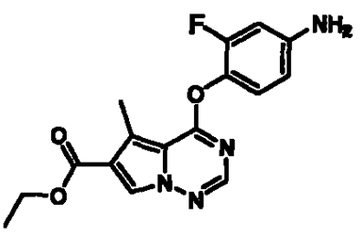


Ethyl 4-(2-fluoro-4-(3-(2-(4-fluorophenyl)acetyl)thioureido)phenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate



A) Ethyl 4-(2-fluoro-4-nitrophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate

To a mixture of ethyl 4-chloro-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate (24 mg, 0.10 mmol, preparation: See, US Pat. No. 6,670,357, especially example 61, the disclosure of which is hererin incorporated by reference), 2-fluoro-4-nitrophenol (20 mg, 0.125 mmol) and K_2CO_3 (28 mg, 0.20 mmol) was added DMF (0.5 mL). The reaction was heated at 70 °C for 20 minutes, cooled to room temperature and 2 mL of water was added. The mixture was filtered, the solid was washed with water, and dried to give the title compound (36 mg, 100%) as a light yellow solid.



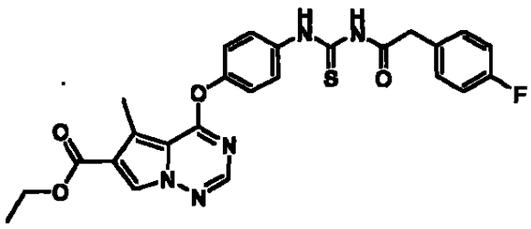
B) Ethyl 4-(4-amino-2-fluorophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate

To a solution of ethyl 4-(2-fluoro-4-nitrophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate (36 mg, 0.1 mmol) in THF (1.0 mL) was added MeOH (0.7 mL) followed by Zn (130 mg, 2.0 mmol) and NH_4Cl (53 mg, 1.0 mmol). The reaction was heated at 70 °C overnight. LC/MS analysis indicated mostly starting material. The solution was shaken vigorously and then heated to 75 °C. LC/MS analysis after 4 h showed the desired product and many other peaks. The reaction was filtered through a coarse filter, and the filtrate was concentrated to a give 55 mg of a brown residue. The residue was suspended in THF and passed through an HPLC filter resulting in a clear filtrate. The filtrate was concentrated *in vacuo* to give 54 mg of the title compound as a crude mixture which was used in the next step without further purification.

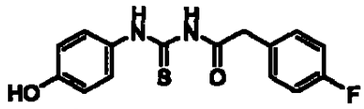
C) Ethyl 4-(2-fluoro-4-(3-(2-(4-fluorophenyl)acetyl)thioureido)phenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate

To a suspension of ethyl 4-(4-amino-2-fluorophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate (54 mg) in CH_2Cl_2 (0.6 mL) was added a solution of 2-(4-fluorophenyl)-1-thiocyanatoethanone (0.5 mL, 0.12 mmol, 0.25 M in ethyl acetate Compound A of Example 2). The reaction was stirred at room temperature for 15 minutes, LC/MS analysis indicated mostly starting material. The reaction was warmed to 45 °C, after 30 min most of the suspension had dissolved to give a cloudy solution. LC/MS analysis indicated mostly desired product. The reaction was shaken at room temperature for an additional 2 h, evaporated to dryness, and purified by column chromatography eluting with 1-7% ethyl acetate/dichloromethane to the title compound (9 mg, 17% overall yield for 3 steps) as a white solid. ^{1}H NMR ($CDCl_3$) δ 12.45 (s, 1H), 8.66 (s, 1H), 8.18 (s, 1H), 7.92 (dd, 1H, J = 11.4, 2.4 Hz), 7.90 (s, 1H), 7.41 (m, 1H), 7.29 (m, 3H), 7.12 (m, 2H), 4.38 (q, 2H, J = 7.1 Hz), 3.73 (s, 2H), 2.82 (s, 3H), 1.40 (t, 3H, J = 7.1 Hz); MS(ESI$^+$) m/z 526 $(M + H)^+$.

EXAMPLE 7



Ethyl 4-(4-(3-(2-(4-fluorophenyl)acetyl)thioureido)phenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate



A) **1-(2-(4-Fluorophenyl)acetyl)-3-(4-hydroxyphenyl)thiourea**

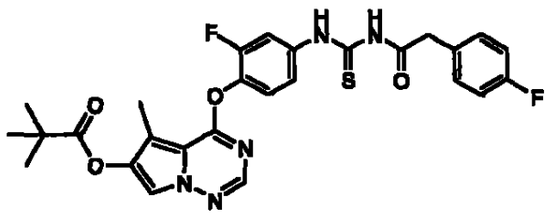
To a solution of 4-amino-phenol (11 mg, 0.1 mmol, Aldrich) in CH_2Cl_2 (0.55 mL) was added a solution of 2-(4-fluorophenyl)-1-thiocyanatoethanone (0.5 mL, 0.125 mmol, 0.25 M in ethyl acetate, Compound A of Example 2). The reaction was stirred at room temperature for 10 minutes, *LC/MS* analysis indicated formation of the title compound. The crude reaction mixture was used directly in the next reaction.

B) **Ethyl 4-(4-(3-(2-(4-fluorophenyl)acetyl)thioureido)phenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate**

To a room temperature solution of ethyl 4-chloro-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate (7.2 mg, 0.03 mmol) (for preparation see U.S. Pat. 6,670,357, the disclosure of which is herein incorporated by reference) and DABCO (7 mg, 0.06 mmol) in acetonitrile (0.5 mL) was added 1-(2-(4-fluorophenyl)acetyl)-3-(4-hydroxyphenyl)thiourea (0.5 mL, 0.05 mmol). The reaction was shaken at room temperature. After 30 min, *LC/MS* analysis indicated mostly product. The reaction was stirred at room temperature overnight. The mixture was evaporated to dryness. Purification by silica gel chromatography (eluting with 1% methanol/dichloromethane) provided the desired product contaminated with impurities. A second purification by silica gel chromatography (1-6% Ethyl acetate/dichloromethane) again did not remove all of the impurities. The resulting solid mixture was washed with methanol and dried to provide the title compound (6

mg, 39%) as a yellow solid. ^{1}H NMR ($CDCl_3$) δ 12.32 (s, 1H), 8.62 (s, 1H), 8.16 (s, 1H), 7.91 (s, 1H), 7.76 (m, 2H), 7.29 (m, 4H), 7.12 (m, 2H), 4.38 (q, 2H, J = 7.1 Hz), 3.72 (s, 2H), 2.82 (s, 3H), 1.40 (t, 3H, J = 7.1 Hz); MS(ESI$^+$) m/z 508 $(M + H)^+$.

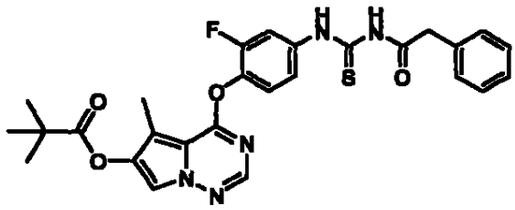
EXAMPLE 8



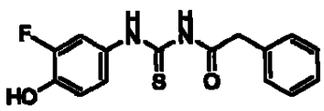
4-(2-Fluoro-4-(3-(2-(4-fluorophenyl)acetyl)thioureido)phenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yl pivalate

To a mixture of 1-(3-fluoro-4-hydroxyphenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea (60 mg, 0.19 mmol, Compound A of Example 3), 4-chloro-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yl pivalate (50 mg, 0.19 mmol, Compound D of Example 1) and 1,4-diazabicyclo[2.2.2]octane (DABCO, 21.3 mg, 0.19 mmol) was added MeCN (5 mL). The reaction was stirred at RT for 1 h and concentrated *in vacuo*. The residue was purified by flash chromatography (eluted with 1 – 15% MeOH / CH_2Cl_2) to give the title compound (91 mg, 86 %) as a white solid. ^{1}H NMR ($CDCl_3$) δ 12.40 (s, 1H), 8.54 (s, 1H), 7.87 (m, 3H), 7.29 (m, 4H), 7.12 (m, 2H), 3.71 (s, 2H), 2.43 (s, 3H), 1.39 (s, 9H); MS(ESI$^+$) m/z 554 $(M + H)^+$.

EXAMPLE 9



4-(2-Fluoro-4-(3-(2-phenylacetyl)thioureido)phenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yl pivalate



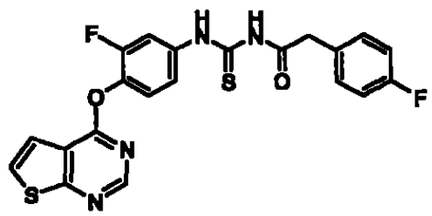
A) 1-(3-Fluoro-4-hydroxyphenyl)-3-(2-phenylacetyl)thiourea

To a solution of 4-amino-3-fluorophenol (50 mg, 0.3 mmol) in CH_2Cl_2 (2 mL) was added a solution of 2-phenyl-1-thiocyanatoethanone (2 mL, 0.4 mmol, 0.2 M in ethyl acetate, Compound I of Example 1). The reaction was stirred at room temperature for 20 minutes, LC/MS analysis indicated formation of the title compound. The mixture was concentrated to give a residue that was used without further purification.

B) 4-(2-Fluoro-4-(3-(2-phenylacetyl)thioureido)phenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yl pivalate

A vial was charged with 4-chloro-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yl pivalate (13.3 mg, 0.19 mmol, Compound D of Example 1), 1-(3-fluoro-4-hydroxyphenyl)-3-(2-phenylacetyl)thiourea (16 mg, 0.05 mmol), cesium carbonate (spatula tip) and DMF (2 mL) and warmed to 100 °C for 26 h. The mixture was concentrated *in vacuo*. The residue was purified by flash chromatography to give the title compound (6.2 mg, 25 %) as a white solid. ^{1}H NMR ($CDCl_3$) δ 12.46 (s, 1H), 8.50 (s, 1H), 7.88 (m, 3H), 7.40 (m, 4H), 7.31 (m, 2H), 3.75 (s, 3H), 2.44 (s, 3H), 1.40 (s, 9H); MS(ESI$^+$) *m/z* 536 $(M + H)^+$.

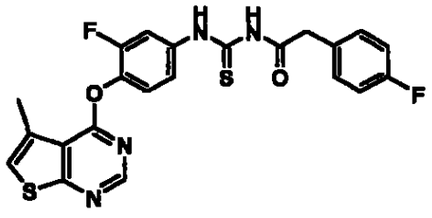
EXAMPLE 10



1-(4-(4a,7a-Dihydrothieno[2,3-*d*]pyrimidin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea

To a mixture of 1-(3-fluoro-4-hydroxyphenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea (24 mg, 0.075 mmol, Compound A of Example 3), 4-chloro-5-thieno[2,3-*d*]pyrimidine (12.8 mg, 0.075 mmol, commercially available) and 1,4-diazabicyclo[2.2.2]octane (DABCO, 8.4 mg, 0.075 mmol) was added MeCN (2 mL). The reaction was stirred at RT for 4 h and concentrated *in vacuo*. The residue was purified by reverse phase preparative HPLC to give the title compound (13.8 mg, 40%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 12.41 (s, 1H), 8.62 (s, 1H), 8.53 (s, 1H), 7.93 (dd, 1H, J = 13.8, 2.2 Hz), 7.56 (m, 2H) 7.46 (m, 1H), 7.29 (m, 3H), 7.12 (m, 2H), 3.73 (s, 2H); MS(ESI$^+$) *m/z* 457 $(M + H)^+$.

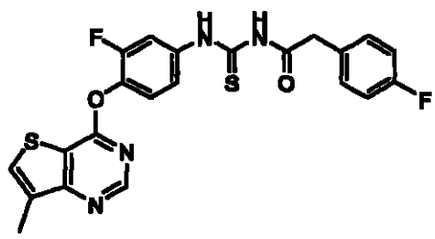
EXAMPLE 11



1-(3-Fluoro-4-(5-methyl-4a,7a-dihydrothieno[2,3-*d*]pyrimidin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea

In a similar manner as described for the preparation of Example 10, the title compound was prepared from commercially available 4-chloro-5-methylthieno[2,3-*d*]pyrimidine and 1-(3-fluoro-4-hydroxyphenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea (24 mg, 0.075 mmol, Compound A of Example 3). ^{1}H NMR ($CDCl_3$) δ 12.42 (s, 1H), 8.67 (s, 1H), 8.53 (s, 1H), 7.88 (dd, 1H, J = 13.8, 2.2 Hz), 7.43 (s, 1H), 7.32 (m, 3H), 7.09 (m, 3H), 3.72 (S, 2H), 2.67 (s, 3H); MS(ESI$^+$) *m/z* 471 $(M + H)^+$.

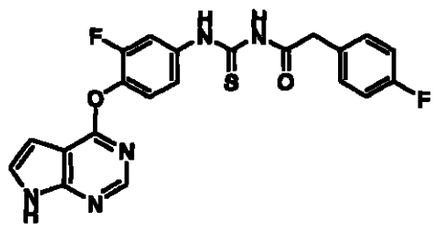
EXAMPLE 12



1-(3-Fluoro-4-(7-methyl-4a,7a-dihydrothieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea

To a mixture of 1-(3-fluoro-4-hydroxyphenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea (24 mg, 0.075 mmol, Compound A of Example 3), 4-chloro-7-methylthieno[3,2-*d*]pyrimidine (13.8 mg, 0.075 mmol, commercially available) and 1,4-diazabicyclo[2.2.2]octane (DABCO, 8.4 mg, 0.075 mmol) was added MeCN (2 mL). The reaction was stirred at RT for 4 h and concentrated *in vacuo*. The residue was purified by reverse phase preparative HPLC to give the title compound (11.2 mg, 31%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 12.45 (s, 1H), 8.79 (s, 1H), 8.61 (s, 1H), 7.93 (dd, 1H, J = 13.8, 2.2 Hz), 7.46 (s, 1H), 7.43 (m, 1H), 7.28 (m, 3H), 7.12 (m, 2H), 3.72 (s, 2H), 2.51 (s, 3H); MS(ESI$^+$) m/z 471 $(M+H)^+$.

EXAMPLE 13

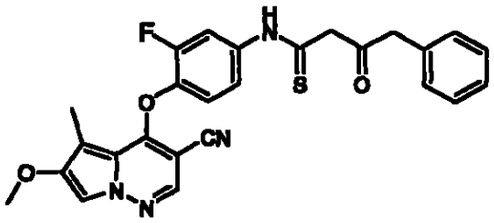


1-(4-(7,7a-Dihydro-4a*H*-pyrrolo[2,3-*d*]pyrimidin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea

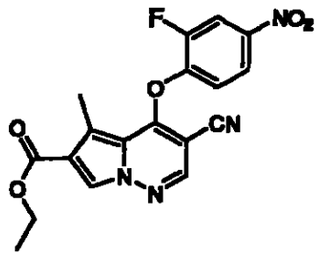
To a mixture 1-(3-fluoro-4-hydroxyphenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea (24 mg, 0.075 mmol, Compound A of Example 3), 4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine (11 mg, 0.075 mmol, commercially available) and 1,4-diazabicyclo[2.2.2]octane (DABCO, 8.4 mg, 0.075 mmol) was added MeCN (2 mL). The reaction was stirred at RT for 4 h and concentrated *in vacuo*. The residue was purified reverse phase preparative HPLC to give the title compound (5.3

mg, 16%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 12.46 (s, 1H), 8.48 (s, 1H), 8.44 (s, 1H), 7.95 (dd, 1H, J = 11.6, 2.8 Hz), 7.43 (m, 1H), 7.34 (m, 1H), 7.29 (m, 4H), 7.13 (app. T, 2H, J = 8.6 Hz), 6.80 (s, 1H), 3.72 (s, 2H); MS(ESI$^+$) m/z 440 $(M + H)^+$.

EXAMPLE 14

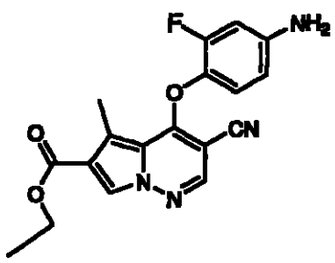


***N*-(4-(3-Cyano-6-methoxy-5-methyl*H*-pyrrolo[1,2-*b*]pyridazin-4-yloxy)-3-fluorophenyl)-3-oxo-4-phenylbutanethioamide**



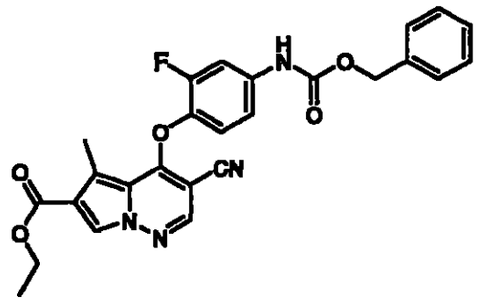
A) Ethyl 3-cyano-4-(2-fluoro-4-nitrophenoxy)-5-methyl*H*-pyrrolo[1,2-*b*]pyridazine-6-carboxylate

To a mixture of ethyl 4-chloro-3-cyano-5-methyl*H*-pyrrolo[1,2-*b*]pyridazine-6-carboxylate (500 mg, 1.90 mmol, see U.S. Pat. Application No. 2004/063712, especially example 1, the disclosure of which is herein incorporated by reference in its entirety), 2-fluoro-4-nitrophenol (361 mg, 2.3 mmol) and K_2CO_3 (315 mg, 2.3 mmol) was added DMF (5 mL). The reaction stirred at RT for 2 h. The reaction was quenched with water (5 mL). The mixture was filtered and the solid was washed with water, dried to give the title compound (630 mg, 86%) as a light yellow solid.



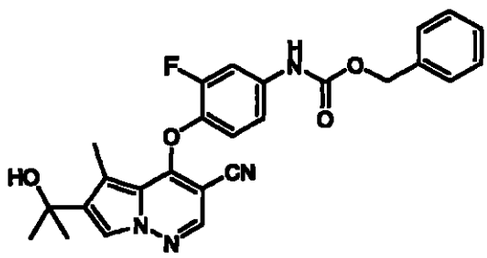
B) **Ethyl 4-(4-amino-2-fluorophenoxy)-3-cyano-5-methyl*H*-pyrrolo[1,2-*b*]pyridazine-6-carboxylate**

To a solution of ethyl 3-cyano-4-(2-fluoro-4-nitrophenoxy)-5-methyl*H*-pyrrolo[1,2-*b*]pyridazine-6-carboxylate (630 mg, 1.64 mmol) in THF (5 mL) was added MeOH (5 mL) followed by Zn (200 mg, 3.0 mmol) and NH_4Cl (200 mg, 3.7 mmol). The reaction was heated at 60 °C for 2 h, filtered and concentrated *in vacuo*. The filtrate was purified by a SCX cartridge (eluted with 2M ammonia in MeOH) to give the title compound (420 mg, 72%) as a white solid.



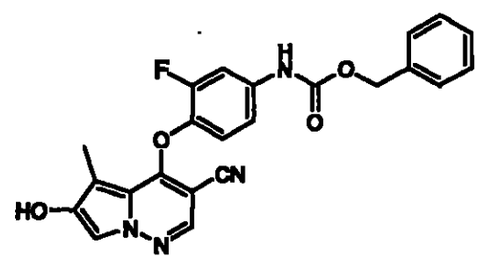
C) **Ethyl 4-(4-(benzyloxycarbonyl)-2-fluorophenoxy)-3-cyano-5-methyl*H*-pyrrolo[1,2-*b*]pyridazine-6-carboxylate**

To a solution of ethyl 4-(4-amino-2-fluorophenoxy)-3-cyano-5-methyl*H*-pyrrolo[1,2-*b*]pyridazine-6-carboxylate (420 mg, 1.19 mmol) in CH_2Cl_2 (10 mL) was added potassium carbonate (200 mg, 1.43 mmol) and benzyl chloroformate (0.261 mL, 1.43 mmol). The solution was stirred at RT for 24 h. The solution was filtered, concentrated *in vacuo* and recrystallized from EtOAc/CH_2Cl_2 to give the title compound (490 mg, 84%) as a white solid.



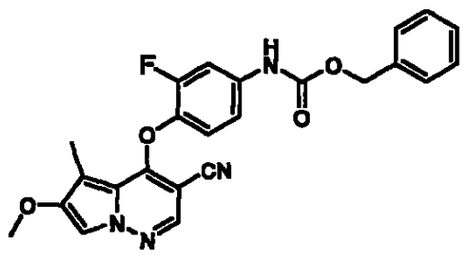
D) **Benzyl 4-(3-cyano-6-(2-hydroxypropan-2-yl)-5-methyl*H*-pyrrolo[1,2-*b*]pyridazin-4-yloxy)-3-fluorophenylcarbamate**

A solution of ethyl 4-(4-(benzyloxycarbonyl)-2-fluorophenoxy)-3-cyano-5-methyl*H*-pyrrolo[1,2-*b*]pyridazine-6-carboxylate (123 mg, 0.25 mmol) in THF (5 mL) was cooled to 0°C. A solution of methylmagnesium bromide (0.336 mL, 1.00 mmol, 3 M in THF) was added and the solution stirred at RT for 30 minutes. More methylmagnesium bromide (0.336 mL, 1.00 mmol, 3 M in THF) was added, and the solution was heated to 60 °C for 30 minutes. Ethyl acetate (10 mL) and water (5 mL) was added and the organic layer was washed, separated, dried and concentrated *in vacuo*. The mixture was purified by flash chromatography (20 - 50% EtOAc in CH_2Cl_2) to give the title compound (97 mg, 81%) as a white solid.



E) **Benzyl 4-(3-cyano-6-hydroxy-5-methyl*H*-pyrrolo[1,2-*b*]pyridazin-4-yloxy)-3-fluorophenylcarbamate**

To a solution of benzyl 4-(3-cyano-6-(2-hydroxypropan-2-yl)-5-methyl*H*-pyrrolo[1,2-*b*]pyridazin-4-yloxy)-3-fluorophenylcarbamate (97 mg, 0.2 mmol) in CH_2Cl_2 (2 mL) was added to a premixed solution of hydrogen peroxide (0.033 mL) in water and boron trifluoride diethetate (0.570 mL) at -5 °C. After 10 minutes, the reaction was quenched with sodium sulfite solution, dried, concentrated *in vacuo* and the residue recrystallized with EtOAc and hexane to give the title compound (70 mg, 80%) as a white solid.



F) **Benzyl 4-(3-cyano-6-methoxy-5-methyl*H*-pyrrolo[1,2-*b*]pyridazin-4-yloxy)-3-fluorophenylcarbamate**

To a solution of benzyl 4-(3-cyano-6-hydroxy-5-methyl*H*-pyrrolo[1,2-*b*]pyridazin-4-yloxy)-3-fluorophenylcarbamate (25 mg, 0.06 mmol) in DMF (1 mL) was added cesium carbonate (39 mg. 0.12 mmol) and methyl iodide (0.05 mL, 0.072 mmol). The solution was stirred at RT for 2 h. Water (1 mL) was added and the product was extracted with ethyl acetate (2 x 5 mL), dried and concentrated to give the title compound (20 mg, 74%) as a white solid.



G) **4-(4-Amino-2-fluorophenoxy)-6-methoxy-5-methyl*H*-pyrrolo[1,2-*b*]pyridazine-3-carbonitrile**

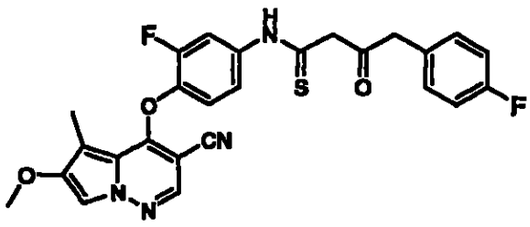
To a solution of benzyl 4-(3-cyano-6-methoxy-5-methyl*H*-pyrrolo[1,2-*b*]pyridazin-4-yloxy)-3-fluorophenylcarbamate (20 mg, 0.045 mmol) in ethanol (3 mL) was added 10% palladium on carbon (20 mg) and the mixture was stirred under balloon of hydrogen for 2 h. The solution was filtered through a pad of Celite® and concentrated *in vacuo* to give the title compound (12 mg, 85%).

H) ***N*-(4-(3-Cyano-6-methoxy-5-methyl*H*-pyrrolo[1,2-*b*]pyridazin-4-yloxy)-3-fluorophenyl)-3-oxo-4-phenylbutanethioamide**

To a solution of 4-(4-amino-2-fluorophenoxy)-6-methoxy-5-methyl*H*-pyrrolo[1,2-*b*]pyridazine-3-carbonitrile (6 mg, 0.02 mmol) in CH_2Cl_2 (1 mL) was

added a solution of 2-phenyl-1-thiocyanatoethanone (0.1 mL, 0.025 mmol, 0.25 M in ethyl acetate, Compound F of Example 1). The reaction was stirred at room temperature for 20 minutes, concentrated *in vacuo* and purified by silica gel flash chromatography (eluted with 1 - 25% EtOAc/CH_2Cl_2) to afford the title compound (3.90 mg, 40%) as a pale yellow solid. ^{1}H NMR (CD_3OD) δ 8.01 (d, 1H, J = 12.7 Hz), 7.86 (s, 1H), 7.72 (s, 1H), 7.19 (m, 5H), 6.75 (m, 2H), 3.79 (s, 3H), 3.20 (m, 2H), 2.18 (s, 3H); MS(ESI$^+$) *m/z* 490 $(M + H)^+$.

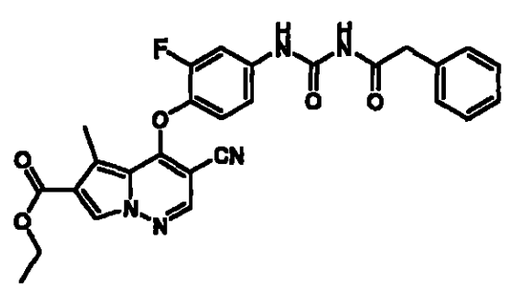
EXAMPLE 15



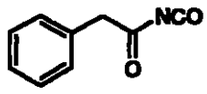
***N*-(4-(3-Cyano-6-methoxy-5-methyl*H*-pyrrolo[1,2-*b*]pyridazin-4-yloxy)-3-fluorophenyl)-4-(4-fluorophenyl)-3-oxobutanethioamide**

The title compound was prepared from 4-(4-amino-2-fluorophenoxy)-6-methoxy-5-methyl*H*-pyrrolo[1,2-*b*]pyridazine-3-carbonitrile (Compound G of Example 14) and 2-(4-fluorophenyl)-1-thiocyanatoethanone (Compound A of Example 2) by the procedure described for Compound H of Example 14. ^{1}H NMR (CD_3OD) δ 8.08 (dd, 1H, J = 12.7, 1.7 Hz), 7.95 (s, 1H), 7.80 (s, 1H), 7.34 (m, 3H), 7.19 (m, 1H), 7.04 (s, 2H), 6.87 (m, 2H), 3.89 (s, 3H), 3.30 (m, 2H), 2.27 (s, 3H); MS(ESI$^+$) *m/z* 508 $(M + H)^+$.

EXAMPLE 16



Ethyl 3-cyano-4-(2-fluoro-4-(3-(2-phenylacetyl)ureido)phenoxy)-5-methyl*H*-pyrrolo[1,2-*b*]pyridazine-6-carboxylate



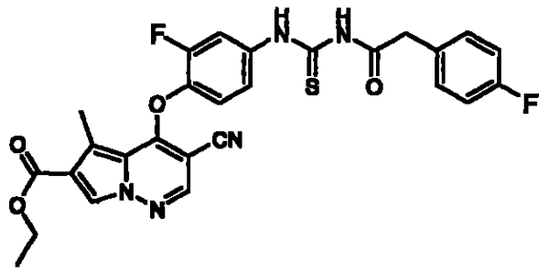
A) 2-Phenylacetyl isocyanate

To a suspension of 2-phenylacetamide (68 mg, 0.5 mmol) in dichloroethane (2 mL) was added oxalyl chloride (0.175 mL, 2.0 mmol). The suspension dissolved quickly and a new suspension formed. *LC/MS* analysis of the reaction mixture after 5 min indicated none of the desired product had formed. The mixture was warmed to 80 °C, *LC/MS* after 30 min indicated a small amount of product. The reaction was heated at 70 °C for 2 days and became mostly clear. *LC/MS* analysis indicated mostly product. The mixture was shaken and heated at 80 °C for another 4 h. Almost all of the yellow solid on the walls of the reaction vessel had dissolved. The mixture was concentrated *in vacuo*. The residue dissolved in dichloroethane (1.5 mL), concentrated, and redissolved in dichloroethane (2 mL). The resulting 0.25 M solution was used without further purification.

B) Ethyl 3-cyano-4-(2-fluoro-4-(3-(2-phenylacetyl)ureido)phenoxy)-5-methyl*H*-pyrrolo[1,2-*b*]pyridazine-6-carboxylate

To a solution of ethyl 4-(4-amino-2-fluorophenoxy)-3-cyano-5-methyl*H*-pyrrolo[1,2-*b*]pyridazine-6-carboxylate (7 mg, 0.02 mmol, Compound B of Example 14) in dichloromethane (0.3 mL) was added a solution of 2-phenylacetyl isocyanate (0.04 mmol, 0.25 M in dichloroethane,). The reaction was shaken at room temperature and monitored by LC/MS. After 2 h, all of the starting material had been consumed. The mixture was concentrated and the residue was purified by silica gel chromatography (1-10% ethyl acetate/dichloromethane) to give the title compound (8 mg, 78%) as a yellow solid. ^{1}H NMR ($CDCl_3$) δ 10.77 (s, 1H), 8.51 (s, 1H), 8.21 (s, 1H), 7.86 (s, 1H), 7.73 (dd, 1H, J = 12.2, 2.2 Hz), 7.43 – 7.21 (m, 7H), 4.37 (q, 2H, J = 7.1 Hz), 3.76 (s, 2H), 2.80 (s, 3H), 1.40 (t, 3H, J = 7.1 Hz); MS(ESI$^+$) *m/z* 516 (M + H)$^+$.

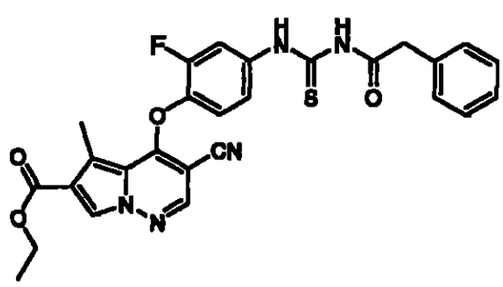
EXAMPLE 17



Ethyl 3-cyano-4-(2-fluoro-4-(3-(2-(4-fluorophenyl)acetyl)thioureido)phenoxy)-5-methyl*H*-pyrrolo[1,2-*b*]pyridazine-6-carboxylate

To a solution of ethyl 4-(4-amino-2-fluorophenoxy)-3-cyano-5-methyl*H*-pyrrolo[1,2-*b*]pyridazine-6-carboxylate (10.6 mg, 0.03 mmol, Compound B of Example 14) in dichloromethane (0.5 mL) was added a solution of 2-(4-fluorophenyl)-1-thiocyanatoethanone (0.04 mmol, 0.25 M in ethyl acetate, Compound A of Example 2). The reaction instantly became cloudy. The reaction was shaken at room temperature for 2 h and then at 40 °C for 1 h. *LC/MS* analysis indicated that the reaction was complete. The reaction was concentrated and the residue was purified by silica gel chromatography (1-6% ethyl acetate/dichloromethane) to give the title compound (16 mg, 97%) as a yellow film/solid. ^{1}H NMR ($CDCl_3$) δ 12.52 (s, 1H), 8.63 (s, 1H), 8.24 (s, 1H), 8.01 (dd, 1H, J = 11.9, 2.4 Hz), 7.88 (s, 1H), 7.41 (m, 1H), 7.29 (m, 3H), 7.11 (m, 2H), 4.37 (q, 2H, J = 7.1 Hz), 3.71 (s, 2H), 2.78 (s, 3H), 1.40 (t, 3H, J = 7.1 Hz); MS(ESI$^+$) *m/z* 550 $(M + H)^+$.

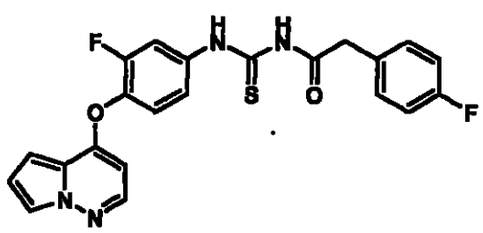
EXAMPLE 18



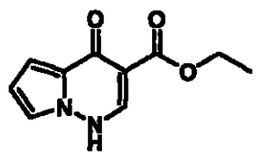
Ethyl 3-cyano-4-(2-fluoro-4-(3-(2-phenylacetyl)thioureido)phenoxy)-5-methyl*H*-pyrrolo[1,2-*b*]pyridazine-6-carboxylate

The title compound was prepared from ethyl 4-(4-amino-2-fluorophenoxy)-3-cyano-5-methyl*H*-pyrrolo[1,2-*b*]pyridazine-6-carboxylate (Compound B of Example 14) and 2-phenyl-1-thiocyanatoethanone (0.1 mL, 0.025 mmol, 0.25 M in ethyl acetate, Compound I of Example 1) by the method described in Example 17. ^{1}H NMR ($CDCl_3$) δ 12.55 (s, 1H), 8.58 (s, 1H), 8.23 (s, 1H), 8.01 (dd, 1H, J = 11.9, 2.4 Hz), 7.88 (s, 1H), 7.42 (m, 4H), 7.30 (m, 3H), 4.37 (q, 2H, J = 7.1 Hz), 3.74 (s, 2H), 2.78 (s, 3H), 1.40 (t, 3H, J = 7.1 Hz); MS(ESI$^+$) m/z 532 $(M + H)^+$.

EXAMPLE 19

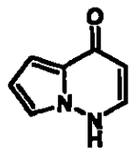


1-(4-(*H*-Pyrrolo[1,2-*b*]pyridazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea



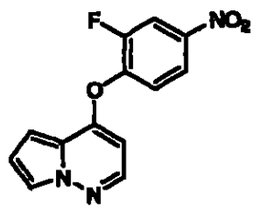
A) **Ethyl 4-oxo-1,4-dihydropyrrolo[1,2-*b*]pyridazine-3-carboxylate**

A mixture of *N*-aminopyrrole (575 mg, 7.0 mmol, commercially available) and diethyl ethoxymethylenemalonate (1.82 g, 8.4 mmol) was heated at 125 °C for 2 hours to give crude diethyl 2-((1*H*-pyrrol-1-ylamino)methylene)malonate. To this intermediate was added diphenyl ether (2 mL). The reaction was put under nitrogen and heated at 220 °C for 2 hours, while allowing the ethanol formed in the reaction to be distilled off. The reaction was cooled to room temperature and purified by silica gel flash chromatography (eluted with 100% CH_2Cl_2) to give the title compound (1.03 g, 71%) as a yellow solid.



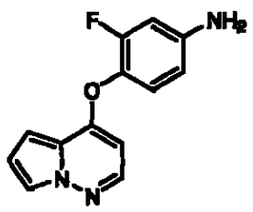
B) **Pyrrolo[1,2-*b*]pyridazin-4(1*H*)-one**

A mixture of ethyl 4-oxo-1,4-dihydropyrrolo[1,2-*b*]pyridazine-3-carboxylate (206 mg, 1.0 mmol), NaCl (64 mg, 1.1 mmol), water (0.054 mL, 3.0 mmol) and DMSO (2 mL) was heated at 150 °C for 3 hours. At the end of the reaction DMSO was distilled off and the residue was purified by silica gel flash chromatography (eluted with 1 - 10% EtOAc/CH_2Cl_2) to give the title compound (90 mg, 67%) as a light yellow solid.



C) **4-(2-Fluoro-4-nitrophenoxy)*H*-pyrrolo[1,2-*b*]pyridazine**

To a mixture of pyrrolo[1,2-*b*]pyridazin-4(1*H*)-one (13.4 mg, 0.10 mmol), 3,4-difluoronitrobenzene (24 mg, 0.15 mmol) and 1,4-diazabicyclo[2.2.2]octane (DABCO, 22 mg, 0.20 mmol) was added MeCN (0.7 mL). The reaction was heated at 70 °C for 72 h and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (eluted with 100% CH_2Cl_2) to give the title compound (20 mg, 73%) as a yellow solid.



D) **4-(*H*-Pyrrolo[1,2-*b*]pyridazin-4-yloxy)-3-fluorobenzenamine**

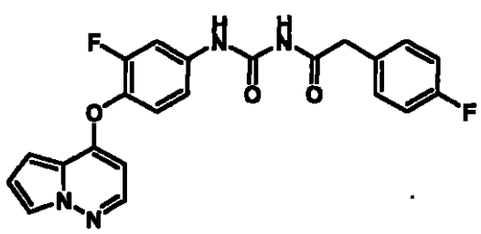
To a solution of 4-(2-fluoro-4-nitrophenoxy)*H*-pyrrolo[1,2-*b*]pyridazine (17 mg, 0.062 mmol) in THF (1.2 mL) was added MeOH (0.8 mL) followed by Zn (100

mg, 1.5 mmol) and NH_4Cl (43 mg, 0.80 mmol). The reaction was heated at 70 °C for 90 minutes and concentrated *in vacuo*. To the residue was added CH_2Cl_2 (2 mL) and a few drops of Et_3N. The solid was partially dissolved and the mixture was filtered. The filtrate was concentrated *in vacuo* and purified by silica gel flash chromatography (eluted with 1 - 6% EtOAc/CH_2Cl_2) to give the title compound (15 mg, 99%) as a white solid.

E) 1-(4-(*H*-Pyrrolo[1,2-*b*]pyridazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea

To a solution of 4-(*H*-pyrrolo[1,2-*b*]pyridazin-4-yloxy)-3-fluorobenzenamine (7 mg, 0.03 mmol) in CH_2Cl_2 (0.3 mL) was added a 0.25 M solution of isocyante (0.16 mL, 0.04 mmol, 0.25 M in ethyl acetate, Compound A of Example 2) in EtOAc. The reaction was stirred at room temperature for 20 minutes, concentrated *in vacuo* and purified by silica gel flash chromatography (eluted with 1 - 5% EtOAc/CH_2Cl_2) to give the title compound (12 mg, 95%) as a pale yellow solid. ^{1}H NMR ($CDCl_3$) δ 12.46 (s, 1H), 8.67 (s, 1H), 7.92 (dd, 1H, J = 11.5, 2.4 Hz), 7.85 (d, 1H, J = 5.3 Hz), 7.77 (dd, 1H, J = 2.6, 1.5 Hz), 7.39 (m, 1H), 7.28 (m, 3H), 7.13 (m, 2H), 6.83 (dd, 1H, J = 4.3, 2.6 Hz), 6.74 (dd, 1H, J = 4.3, 1.5 Hz), 5.70 (d, 1H, J = 5.3 Hz), 3.73 (s, 2H); MS(ESI$^+$) *m/z* 439 $(M + H)^+$.

EXAMPLE 20

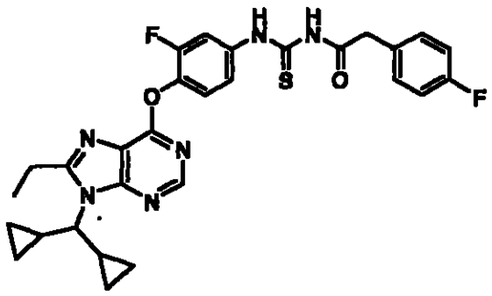


1-(4-(*H*-Pyrrolo[1,2-*b*]pyridazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea

To a solution of the 4-(*H*-pyrrolo[1,2-*b*]pyridazin-4-yloxy)-3-fluorobenzenamine (5 mg, 0.02 mmol, Compound D of Example 19) in CH_2Cl_2 (0.3 mL) was added a solution of 2-(4-fluorophenyl)acetyl isocyanate (0.16 mL, 0.04 mmol, 0.25 M in dichloromethane, Compound C of Example 4). The reaction was

stirred at room temperature for 2 h, concentrated *in vacuo* and purified by silica gel flash chromatography (eluted with 1 - 15% EtOAc/CH_2Cl_2) to give the title compound (5.5 mg, 63%) as a pale yellow solid. ^{1}H NMR ($CDCl_3$) δ 10.68 (s, 1H), 8.69 (s, 1H), 7.83 (d, 1H, J = 5.3 Hz), 7.77 (dd, 1H, J = 2.6, 1.5 Hz), 7.68 (dd, 1H, J = 11.5, 2.4 Hz), 7.33 – 7.17 (m, 4H), 7.09 (m, 2H), 6.82 (dd, 1H, J = 4.3, 2.6 Hz), 6.74 (dd, 1H, J = 4.3, 1.5 Hz), 5.69 (d, 1H, J = 5.3 Hz), 3.76 (s, 2H); MS(ESI$^+$) *m/z* 423 $(M + H)^+$.

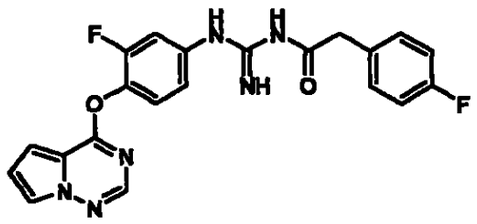
EXAMPLE 21



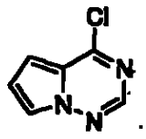
1-(4-(9-(Dicyclopropylmethyl)-8-ethyl-9*H*-purin-6-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea

To a mixture 1-(3-fluoro-4-hydroxyphenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea (24 mg, 0.075 mmol, Compound A of Example 3), 6-chloro-9-(dicyclopropylmethyl)-8-ethyl-9*H*-purine (20.7 mg, 0.075 mmol, PCT Appl. WO 99/01454, U.S. Pat. 6,143,743, example 831, the disclosure of which is herein incorporated by reference) and 1,4-diazabicyclo[2.2.2]octane (DABCO, 8.4 mg, 0.075 mmol) was added MeCN (2 mL). The reaction was stirred at RT for 4 h and concentrated *in vacuo*. The residue was purified by reverse phased preparative HPLC to give the title compound (15.3 mg, 36%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 12.43 (m, 1H), 8.48 (m, 1H), 8.40 (m, 1H), 7.92 (m, 1H), 7.28 (m, 4H), 7.13 (m, 2H), 3.72 (s, 2H), 3.34 (m, 3H), 1.53 (m, 3H), 0.81 (m, 2H), 0.46 (m, 4H), 0.23 (m, 2H); MS(ESI$^+$) *m/z* 489 $(M + H)^+$.

EXAMPLE 22

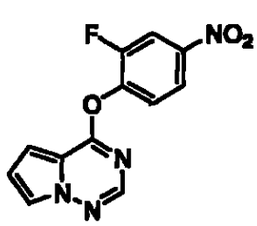


1-(3-Fluoro-4-(pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)guanidine



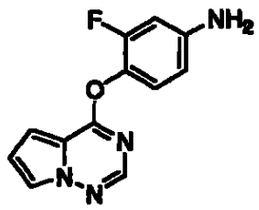
A) 4-Chloropyrrolo[2,1-*f*][1,2,4]triazine

To a solution of pyrrolo[2,1-*f*][1,2,4]triazin-4-ol (3.70 g, 27.4 mmol, see generally, PCT Appl. WO 2000/071129 the disclosure of which is herein incorporated by reference in its entirety) in 40 mL of toluene at room temperature was added 4.77 mL (27.4 mmol) of diisopropylethylamine followed by 7.70 mL (82.6 mmol) of phosphorus oxychloride. The reaction mixture was heated at 100 °C for 18 h. After cooling to room temperature, the reaction was slowly added to a solution of 5% aq $NaHCO_3$ solution (100 mL) at 0 °C. Upon completion of the addition, the biphasic mixture was allowed to stir at room temperature for 30 min. The aqueous layer was extracted with EtOAc (3 x 100 mL) and the pooled organic extracts were washed with brine (100 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to give the crude product (4.10 g, 97%) as a yellow solid. ^1H NMR ($CDCl_3$) δ 8.14 (*s*, 1H), 7.80 (dd, 1H, *J* = 2.4, 1.5 Hz), 6.91 (m, 2H).



B) 4-(2-Fluoro-4-nitrophenoxy)pyrrolo[2,1-*f*][1,2,4]triazine

4-Chloropyrrolo[2,1-*f*][1,2,4]triazine (4.1g, 27 mmol), 2-fluoro-4-nitrophenol (5.0 g, 32 mmol), and potassium carbonate (7.4 g, 53 mmol) in 100 mL of dimethylformamide was stirred at 60 °C for 15 h. After cooling to room temperature, the reaction mixture was filtered through a plug of silica gel with EtOAc. The filtrate was concentrated *in vacuo* and the resulting crude product was purified by flash chromatography on silica gel (SiO_2, EtOAc/Hexane 1:4) to give the title compound (4.25 g, 58%) as a white solid. ^1H NMR ($CDCl_3$) δ 8.09 (m, 2H), 7.88 (s, 1H), 7.77 (dd, 1H, J = 2.6, 1.2 Hz), 7.46 (t, 1H, J = 7.6 Hz), 6.98 (dd, 1H, J = 4.6, 1.4 Hz), 6.84 (dd, 1H, J = 4.5, 2.6 Hz); ^{13}C NMR ($CDCl_3$) δ 160.6, 154.3 (J = 254 Hz), 146.5, 145.8, 144.8 (J = 12.9 Hz), 125.0, 121.7, 120.7, 114.5, 113.9, 113.6 (J = 23.2 Hz), 103.6.



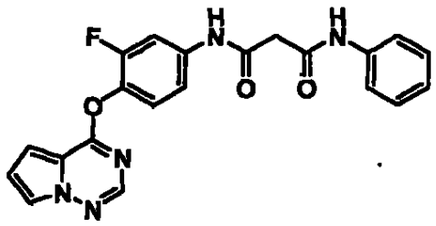
C) **3-Fluoro-4-(pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine (4)**

To a solution of 4-(2-fluoro-4-nitrophenoxy)pyrrolo[2,1-*f*][1,2,4]triazine (4.25 g, 15.5 mmol) in 40 mL of tetrahydrofuran and 60 mL of methanol at 0 °C was added zinc dust (3.04 g, 46.5 mmol, <10 micron) followed by ammonium chloride (2.49 g, 46.5 mmol). The mixture was stirred at room temperature overnight. Additional zinc dust (6.08 g, 93 mmol) and ammonium chloride (5.0 g, 93 mmol) were added and the reaction was allowed to stir at room temperature for 4 h. The heterogeneous mixture was filtered through a thin pad of Celite® with methanol and the filtrate was concentrated *in vacuo*. Purification by flash chromatography on silica gel (SiO_2, EtOAc/Hexane 1:1) gave the title compound (3.5 g, 92%) as a yellow foam. ^1H NMR ($CDCl_3$) δ 7.92 (s, 1H), 7.70 (dd, 1H, J = 2.5, 1.6 Hz), 6.98 (t, 1H, J = 8.5 Hz), 6.92 (dd, 1H, J = 4.4, 1.4 Hz), 6.77 (m, 1H), 6.42 (m, 2H), 3.71 (br s, 2H); MS(ESI$^+$) *m/z* 245.2 $(M + H)^+$.

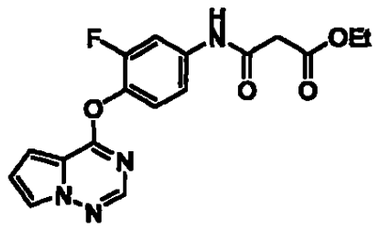
D) 1-(3-Fluoro-4-(pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)guanidine

To a test tube containing 3-fluoro-4-(pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine (20 mg, 0.082 mmol) and 1-(2-(4-fluorophenyl)acetyl)-2-methylisothiourea (20 mg, 0.086 mmol) was added 0.3 mL of toluene followed by diisopropylethylamine (15 µL, 0.086 mmol). The reaction was stirred at 110 °C for 6 h. Additional portions of 1-(2-(4-fluorophenyl)-acetyl)-2-methylisothiourea (20 mg, 0.086 mmol) and diisopropylethylamine (15 µL, 0.086 mmol) were added. After stirring at 110 °C overnight, the reaction was cooled to room temperature and purified directly by flash chromatography on silica gel (SiO_2, EtOAc/Hexane 1:1) to give the title compound as a white solid. The solid was treated with 4 N HCl in dioxane at 0°C for 30 min. The solution was concentrated *in vacuo* to give the HCl salt of the title compound (15 mg, 40%) as a white powder. ^{1}H NMR ($CDCl_3$) δ 13.8 (br s, 1H), 11.5 (br s, 1H), 9.48 (br s, 1H), 7.85 (s, 1H), 7.78 (dd, 1H, J = 2.5, 1.4 Hz), 7.30 (m, 5H), 7.01 (m, 3H), 6.85 (m, 1H); MS(ESI$^+$) *m/z* 423.1 $(M+H)^+$.

EXAMPLE 23

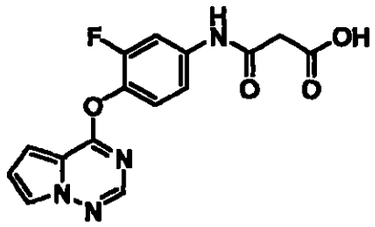


N^1-(3-Fluoro-4-(pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-N^3-phenylmalonamide



A) Ethyl 3-(3-fluoro-4-(pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenylamino)-3-oxopropanoate

To a solution of 3-fluoro-4-(pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine (112 mg, 0.459 mmol, Compound C of Example 22) in methylene chloride (4 mL) at 0 °C was added 96 µL (0.55 mmol) of diisopropylethylamine followed by 61 µL (0.48 mmol) of ethyl 3-chloro-3-oxopropanoate. The reaction was stirred at 0 °C for 1 h and was then quenched with 10 mL of saturate $NaHCO_3$ solution. The aqueous layer was extracted with chloroform (3 x 15 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give the crude product as a yellow oil that solidified on standing (180 mg). ^1H NMR ($CDCl_3$) δ 9.45 (br s, 1H), 7.89 (s, 1H), 7.71 (dd, 1H, J = 2.5, 1.5 Hz), 7.68 (dd, 1H, J = 11.8, 2.2 Hz), 7.18 (m, 2H), 6.93 (dd, 1H, J = 4.4, 1.4 Hz), 6.78 (dd, 1H, J = 4.4, 2.6 Hz), 4.19 (q, 2H, J = 7.2 Hz), 3.41 (s, 2H), 1.25 (t, 3H, J = 7.2 Hz); MS(ESI$^+$) *m/z* 359.1 $(M + H)^+$.



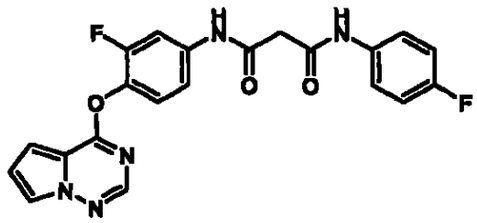
B) 3-(3-Fluoro-4-(pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenylamino)-3-oxopropanoic acid

To a solution of the above crude ethyl 3-(3-fluoro-4-(pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenylamino)-3-oxopropanoate (180 mg) in ethanol (10 mL) at 0 °C was added 1 N aq NaOH solution (10 mL). After stirring at 0 °C for 3 h, the reaction was washed with 20 mL of EtOAc. The EtOAc layer was back-extracted with 20 mL of 1 N aq NaOH solution. The combined aqueous solution was acidified to pH 5 with 1 N aq HCl solution. The aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give the crude acid which was used without further purification (150 mg). MS(ESI$^+$) *m/z* 331.1 $(M^+ + H)^+$.

C) N^1-(3-Fluoro-4-(pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-N^3-phenylmalonamide

A solution of 3-(3-fluoro-4-(pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenylamino)-3-oxopropanoic acid (17 mg, 0.052 mmol), BOP reagent (34 mg, 0.077 mmol), 4-methylmorpholine (28 μL, 0.26 mmol), and aniline (4.7 μL, 0.052 mmol) in dimethylformamide (0.5 mL) was stirred at room temperature for 16 h. The reaction was diluted with EtOAc (4 mL) and washed with water, 10% aq LiCl solution, and brine (1 x 3 mL each). The organic solution was dried over anhydrous Na_2SO_4 and then concentrated *in vacuo*. Purification by flash chromatography on silica gel (SiO_2, EtOAc/Hexane 7:3) gave the desired compound as a white solid. The product was lyophilized with acetonitrile / water to give the title compound (12 mg, 57%) as a white powder. ^{1}H NMR ($CDCl_3$) δ 9.23 (br s, 1H), 8.22 (br s, 1H), 7.90 (s, 1H), 7.72 (m, 1H), 7.46 (d, 1H, J = 8.2 Hz), 7.20 (m, 7H), 6.95 (m, 1H), 6.78 (m, 1H), 3.47 (s, 2H); MS(ESI$^+$) *m/z* 406.1 $(M+H)^+$.

EXAMPLE 24

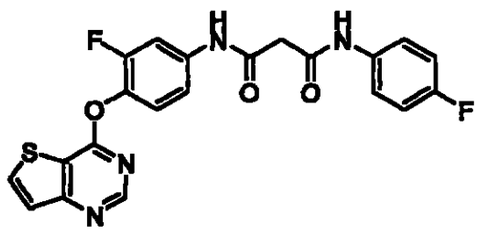


***N*^{1}-(3-Fluoro-4-(pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-*N*^{3}-(4-fluorophenyl)malonamide**

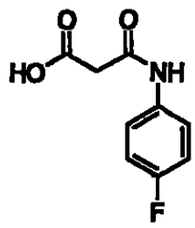
A solution of 3-(3-fluoro-4-(pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenylamino)-3-oxopropanoic acid (18 mg, 0.55 mmol, Compound B of Example 23), BOP reagent (36 mg, 0.082 mmol), 4-methylmorpholine (30 μL, 0.27 mmol), and 4-fluoroaniline (5.2 μL, 0.055 mmol) in dimethylformamide (0.5 mL) was stirred at room temperature for 16 h. The reaction was diluted with EtOAc (4 mL) and washed with water, 10% aq LiCl solution, and brine (1 x 3 mL each). The organic solution was dried over anhydrous Na_2SO_4 and then concentrated *in vacuo*. Purification by flash chromatography on silica gel (SiO_2, EtOAc/Hexane 7:3) gave the desired compound as a white solid. The product was lyophilized with acetonitrile / water to give the title compound (14 mg, 61%) as a white powder. ^{1}H NMR ($CDCl_3$) δ 9.28 (br s, 1H), 8.64 (br s, 1H), 7.89 (s, 1H), 7.73 (dd, 1H, J = 2.5, 1.5 Hz), 7.69 (dd,

1H, J = 11.6, 1.9 Hz), 7.42 (m, 3H), 7.21 (m, 1H), 6.97 (m, 3H), 6.80 (dd, 1H, J = 4.5, 2.6 Hz), 3.49 (s, 2H); MS(ESI$^+$) m/z 424.1 $(M+H)^+$.

EXAMPLE 25



N^1-(3-Fluoro-4-(thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)-N^3-(4-fluorophenyl)malonamide

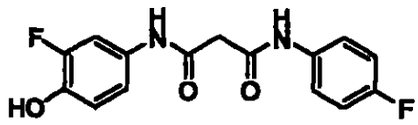


A) **3-(4-Fluorophenylamino)-3-oxopropanoic acid**

To a solution of ethyl 3-chloro-3-oxopropanoate (5.0 mL, 40 mmol, Aldrich) in methylene chloride (100 mL) at 0 °C was added diisopropylethylamine (8.4 mL, 48 mmol) followed by 4-fluoroaniline (3.6 mL, 38 mmol, Aldrich). The reaction was stirred at room temperature overnight and was then quenched with 100 mL of saturated $NaHCO_3$ solution. The aqueous layer was extracted with chloroform (3 x 100 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give the crude product as a yellow oil that solidified on standing (10 g). ^{1}H NMR ($CDCl_3$) δ 9.30 (br s, 1H), 7.55 (m, 2H), 7.05 (t, 2H, J = 8.8 Hz), 4.28 (q, 2H, J = 7.2 Hz), 3.49 (s, 2H), 1.35 (t, 3H, J = 7.1 Hz); MS(ESI$^+$) m/z 226.1 $(M+H)^+$.

The above ester was dissolved in 100 mL of ethanol and cooled to 0 °C. 1 N aq NaOH solution (100 mL) was added and the reaction was stirred at 0 °C for 1 h. The reaction was concentrated to remove ethanol. The aqueous solution was extracted with EtOAc (50 mL) and was then made acidic with 1 N aq HCl solution. The

aqueous solution was extracted with EtOAc (5 x 100 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give the crude product (6.31 g, 84%) as a yellow solid which was used without further purification. ^{1}H NMR (DMSO-d_6) δ 12.9 (br s, 1H), 10.3 (br s, 1H), 7.59 (m, 2H), 7.16 (t, 2H, J = 8.9 Hz), 3.34 (s, 2H); MS(ESI$^+$) m/z 198.4 $(M+H)^+$.



B) **N^1-(3-Fluoro-4-hydroxyphenyl)-N^3-(4-fluorophenyl)malonamide**

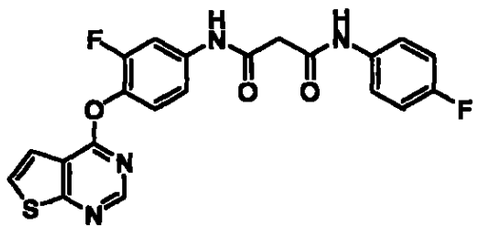
To a solution of 2-fluoro-4-nitrophenol (1.00 g, 6.37 mmol) in 4 mL of tetrahydrofuran and 6 mL of methanol at 0 °C was added zinc dust (2.08 g, 31.8 mmol, <10 micron) followed by ammonium chloride (1.70 g, 31.8 mmol). The mixture was stirred at room temperature overnight. The heterogeneous mixture was filtered through a thin pad of Celite® with methanol and the filtrate was concentrated *in vacuo* to give a brown solid which was used without further purification (656 mg, 81%).

3-(4-Fluorophenylamino)-3-oxopropanoic acid (197 mg, 1.00 mmol) was dissolved in 4 mL of dimethylformamide. Triethylamine (140 µL, 1.00 mmol) was added and the solution was cooled to 0 °C. 4-Amino-2-fluorophenol (127 mg, 1.00 mmol, Aldrich) was added followed BOP reagent (442 mg, 1.00 mmol). The reaction was allowed to warm to room temperature and was then stirred at room temperature for 3 h. The reaction mixture was concentrated to remove methylene chloride and water was added to precipitate the product. Filtration and trituration with water gave the title compound (211 mg, 69%) as a white solid. ^{1}H NMR (CD_3OD) δ 7.61 (m, 2H), 7.51 (dd, 1H, J = 13, 2.5 Hz), 7.08 (m, 3H), 6.88 (t, 1H, J = 9.4 Hz), 3.51 (s, 2H); MS(ESI$^+$) m/z 307.4 $(M+H)^+$.

C) **N^1-(3-Fluoro-4-(thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl)-N^3-(4-fluorophenyl)malonamide**

N^1-(3-Fluoro-4-hydroxyphenyl)-N^3-(4-fluorophenyl)malonamide (46 mg, 0.15 mmol), 4-chlorothieno[3,2-*d*]pyrimidine (17 mg, 0.10 mmol), cesium carbonate (49 mg, 0.15 mmol), and copper(I) chloride (10 mg, 0.10 mmol) were placed in a test tube. The tube was sealed, flushed with nitrogen, charged with 1-methyl-2-pyrrolidinone (0.3 mL) followed by 2,2,6,6-tetramethyl-3,5-heptanedione (4.0 µL, 0.02 mmol). The reaction was stirred at 120 °C for 2 h. The reaction mixture was purified by preparative HPLC. The appropriate fraction was concentrated to remove methanol and the resulting aqueous solution was made basic with saturated $NaHCO_3$ solution (5 mL). The aqueous solution was extracted with EtOAc (3 x 10mL) and the combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give the desired product as a colorless oil. Lyophilization with methanol / water gave the title compound (23 mg, 52%) as a white solid. ^{1}H NMR (CD_3OD) δ 8.54 (s, 1H), 8.21 (d, 1H, J = 5.5 Hz), 7.69 (dd, 1H, J = 12.4, 2.0 Hz), 7.49 (m, 3H), 7.27 (m, 2H), 6.96 (t, 2H, J = 8.9 Hz), 3.47 (s, 2H); MS(ESI$^+$) *m/z* 441.1 $(M+H)^+$.

EXAMPLE 26

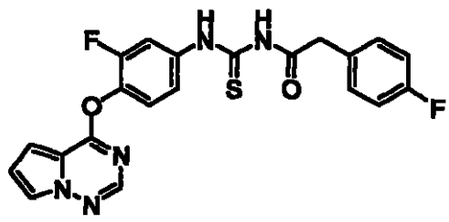


N^1-(3-Fluoro-4-(thieno[2,3-*d*]pyrimidin-4-yloxy)phenyl)-N^3-(4-fluorophenyl)malonamide

N^1-(3-Fluoro-4-hydroxyphenyl)-N^3-(4-fluorophenyl)malonamide (46 mg, 0.15 mmol, Compound B of Example 25), 4-chlorothieno[2,3-*d*]pyrimidine (17 mg, 0.10 mmol), cesium carbonate (49 mg, 0.15 mmol), and copper(I) chloride (10 mg, 0.10 mmol) were placed in a test tube. The tube was sealed, flushed with nitrogen, charged with 1-methyl-2-pyrrolidinone (0.3 mL) followed by 2,2,6,6-tetramethyl-3,5-heptanedione (4.0 µL, 0.02 mmol). The reaction was stirred at 120 °C for 1 h. The reaction mixture was purified by preparative HPLC. The appropriate fraction was concentrated to remove methanol and the resulting aqueous solution was made basic with saturated $NaHCO_3$ solution (5 mL). The aqueous solution was extracted with

EtOAc (3 x 10 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give the desired product as a colorless oil. Lyophilization with methanol / water gave the title compound (27 mg, 61%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 10.7 (s, 1H), 10.4 (s, 1H), 8.77 (s, 1H), 8.15 (d, 1H, J = 5.9 Hz), 7.95 (dd, 1H, J = 12.8, 2.0 Hz), 7.85 (d, 1H, J = 5.9 Hz), 7.77 (m, 2H), 7.54 (m, 2H), 7.30 (t, 2H, J = 8.8 Hz), 3.48 (s, 2H); MS(ESI$^+$) *m/z* 441.1 (M + H)$^+$.

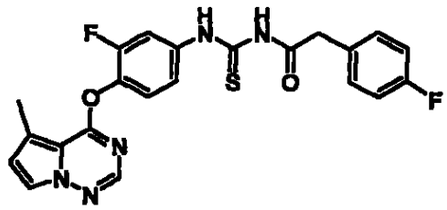
EXAMPLE 27



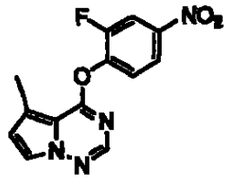
1-(3-Fluoro-4-(pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)-acetyl)thiourea

To a homogeneous solution of sodium thiocyanate (21 mg, 0.26 mmol) in ethyl acetate (1 mL), at room temperature under a nitrogen atmosphere, was added 4-fluorophenyl-acetyl chloride (28 μL, 0.20 mmol). The mixture was stirred for 30 minutes before being added directly to a homogeneous solution of 3-fluoro-4-(pyrrolo[2,1-*f*][1,2,4]-triazin-4-yloxy)benzenamine (37 mg, 0.15 mmol, Compound C of Example 22) in anhydrous dichloromethane (3 mL), under a nitrogen atmosphere. The mixture was stirred at ambient temperature for 4 h before being concentrated *in vacuo*. Purification by silica gel (Merck KGaA, 230-400 mesh particle size) flash chromatography, eluting with chloroform, afforded the title compound (55 mg, 83%). ^{1}H NMR ($CDCl_3$) δ 12.41 (s, 1H), 8.50 (s, 1H), 7.97 (s, 1H), 7.92 (m, 1H), 7.81 (m, 1H), 7.42 (m, 1H), 7.35-7.25 (m, 3H), 7.17-7.10 (m, 2H), 7.05-7.02 (m, 1H), 6.85-6.90 (m, 1H), 3.72 (s, 2H); HRMS(ESI), 440.0993 (M + H)$^+$ calc, 440.0988 (M + H)$^+$ found.

EXAMPLE 28

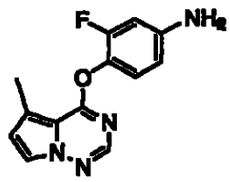


1-(3-Fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea



A) **4-(2-Fluoro-4-nitrophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazine**

To a mixture of 4-chloro-5-methylpyrrolo[2,1-*f*][1,2,4]triazine (3.37 g, 20.11 mmol, PCT Appl.WO 2000/071129, U.S. pat. application 2003/0186982, the disclosure of which is herein incorporated by reference) and 2-fluoro-4-nitrophenol (3.48 g, 22.12 mmol) in anhydrous DMF (100 mL), stirred for 5 minutes under a nitrogen atmosphere, was added anhydrous potassium carbonate (6.11 g, 44.24 mmol). The mixture was heated at 60 °C for 15 h before 2-fluoro-4-nitrophenol (1.00 g, 6.37 mmol) was added and stirring continued at 60 °C for 4.5 h. The mixture was cooled to room temperature, diluted with dichloromethane, washed sequentially with water and 10% aqueous lithium chloride, dried over anhydrous magnesium sulfate and concentrated *in vacuo* to yield a tan solid. Purification by silica gel (Merck KGaA, 230-400 mesh particle size) flash chromatography, eluting with chloroform, afforded the title compound (4.19 g, 72%) as a pale yellow solid. ^{1}H NMR ($CDCl_3$) δ 8.20-8.13 (m, 2H), 7.83 (s, 1H), 7.73 (d, 1H, J = 2.6 Hz); 7.58-7.53 (m, 1H), 6.69 (d, 1H, J = 2.4 Hz), 2.62 (s, 3H); HRMS(ESI), 289.0737 $(M + H)^+$ calc, 289.0733 $(M + H)^+$ found.



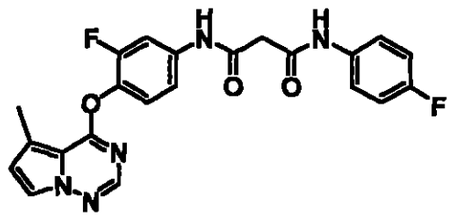
B) **3-Fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine**

To a heterogeneous mixture of 4-(2-fluoro-4-nitrophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazine (3.04 g, 10.55 mmol) in anhydrous methanol (60 mL) and anhydrous tetrahydrofuran (40 mL), at ambient temperature under nitrogen atmosphere, was added zinc dust (6.90 g, 105 mmol) and ammonium chloride (5.64g, 105 mmol). The mixture was stirred for 7 h before the catalyst was filtered off and the filtrate was concentrated *in vacuo* to a pale yellow solid which was partitioned between chloroform and water. The aqueous layer was then extracted twice with chloroform. The combined chloroform layers were washed with water, dried over anhydrous magnesium sulfate and concentrated *in vacuo* to yield the title compound (2.51 g, 92%) as a solid. ^{1}H NMR ($CDCl_3$) δ 7.86 (s, 1H), 7.64 (d, 1H, J = 2.6 Hz); 7.08-7.03 (m, 1H), 6.61 (d, 1H, J = 2.4 Hz), 6.55-6.45 (m, 2H), 3.78 (s, 2H), 2.60 (s, 3H); HRMS(ESI), 259.0995 $(M + H)^+$ calc, 259.0997 $(M + H)^+$ found.

C) **1-(3-Fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea**

3-Fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine (39 mg, 0.15 mmol) was converted to the title compound (42 mg, 62%) in a manner similar to the preparation of Example 27. ^{1}H NMR ($CDCl_3$) δ 12.41 (s, 1H), 8.48 (s, 1H), 7.92-7.82 (m, 2H), 7.68 (d, 1H, J = 2.5 Hz), 7.39-7.27 (m, 4H), 7.15-7.10 (m, 2H), 6.64 (d, 1H, J = 2.3 Hz), 3.72 (s, 2H), 2.60 (s, 3H); HRMS(ESI), 454.1149 $(M + H)^+$ calc, 454.1154 $(M + H)^+$ found.

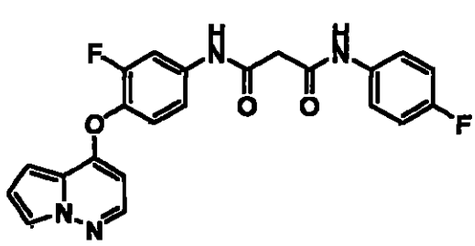
EXAMPLE 29



N^1-(3-Fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-N^3-(4-fluoro-phenyl)malonamide

To a homogeneous solution of 3-fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine (52 mg, 0.20 mmol, Compound B of Example 28) and 3-(4-fluorophenylamino)-3-oxopropanoic acid (39 mg, 0.20 mmol, Compound A of Example 25) in anhydrous DMF (2 mL), at room temperature under nitrogen atmosphere, was added diisopropylethylamine (52 µL, 0.30 mmol). The mixture was stirred for 5 minutes before o-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (96 mg, 0.30 mmol) was added in one portion. The mixture was stirred for 17.5 h before the reaction was concentrated *in vacuo* to remove volatiles. The resultant residue was diluted with ethyl acetate and washed twice with 10% aqueous lithium chloride before being concentrated *in vacuo*. Purification by silica gel (Merck KGaA, 230-400 mesh particle size) flash chromatography, eluting with 1% methanol in chloroform, afforded an off-white solid that was triturated and sonicated in the presence of anhydrous ethyl ether (3 mL). The title compound (66 mg, 75%) was isolated by filtration as a white solid. ^{1}H NMR ($CDCl_3$) δ 9.28 (s, 1H), 8.67 (s, 1H), 7.83 (s, 1H), 7.80-7.73 (m, 1H), 7.67 (d, 1H, J = 2.5 Hz), 7.54-7.49 (m, 2H), 7.28-7.26 (m, 2H), 7.10-7.02 (m, 2H), 6.64 (d, 1H, J = 2.3 Hz), 3.56 (s, 2H), 2.60 (s, 3H); HRMS(ESI), 436.1221 $(M + H)^+$ calc, 436.1230 $(M + H)^+$ found.

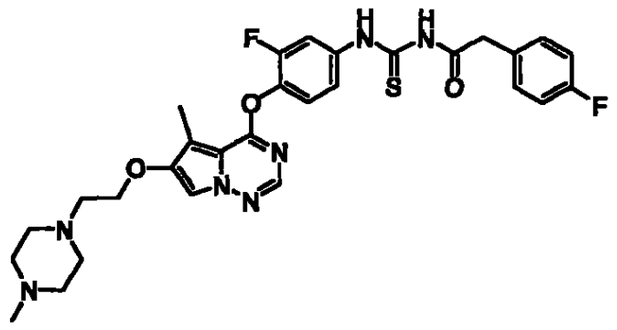
EXAMPLE 30



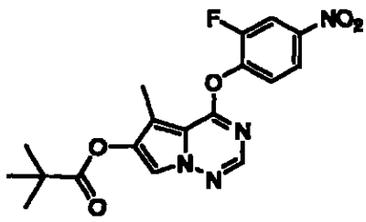
N^1-(4-(*H*-Pyrrolo[1,2-*b*]pyridazin-4-yloxy)-3-fluorophenyl)-N^3-(4-fluorophenyl)malonamide

A solution of 4-(*H*-pyrrolo[1,2-*b*]pyridazin-4-yloxy)-3-fluorobenzenamine (51 mg, 0.21 mmol, Compound D of Example 19) in DMF (1 mL) was treated with 3-(4-fluorophenylamino)-3-oxopropanoic acid (41 mg, 0.21 mmol, Compound A of Example 25), DIPEA (42 µL, 0.25 mmol) and TBTU (81 mg, 0.25 mmol) and the mixture stirred at RT for 16 h. The mixture was concentrated *in vacuo* to remove the DMF and the residue was partitioned between EtOAc (2 mL) and saturated sodium bicarbonate solution (2 mL). The EtOAc phase was washed with 10% aqueous LiCl (2 mL), brine (2 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was triturated twice with EtOAc and two times with MeOH to give the title compound (17 mg, 19%) as an off-white solid. ^{1}H NMR (DMSO-d_6) δ 10.56 (s, 1H), 10.28 (s, 1H), 8.01, (d, 1H, J = 5.4 Hz), 7.92-7.91 (m, 1H), 7.65-7.62 (m, 2H), 7.48-7.44 (m, 2H), 7.22-7.15 (m, 3H), 6.86 (dd, 1H, J = 4.2, 2.7 Hz), 6.72 (dd, 1H, J = 4.4, 1.4 Hz), 5.81 (d, 1H, J = 5.4 Hz), 3.51 (s, 2H); MS(ESI$^+$) m/z 423.3 $(M+H)^+$.

EXAMPLE 31

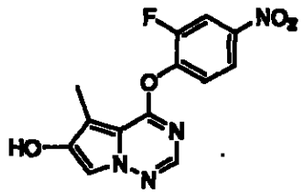


1-(3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*]-[1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea, bis-hydrochloride salt



A) **4-(2-Fluoro-4-nitrophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]-triazin-6-yl pivalate**

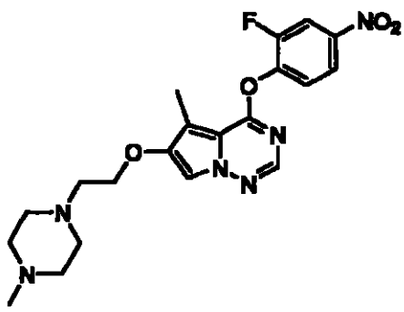
To a homogeneous solution of 4-chloro-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yl pivalate (1.00 g, 3.74 mmol, Compound D of Example 1) and 2-fluoro-4-nitrophenol (588 mg, 3.74 mmol) in anhydrous acetonitrile (25 mL), at room temperature under a nitrogen atmosphere, was added DABCO (462 mg, 4.12 mmol). The mixture was then heated at 50 °C for 3 h. The mixture was cooled to room temperature then partitioned between chloroform and saturated aqueous ammonium chloride. The aqueous layer was extracted twice with chloroform. The combined organic layers were washed once each with saturated aqueous ammonium chloride and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and concentrated *in vacuo* to yield a pale yellow solid that was used in the next step without further purification. MS(ESI$^+$) *m/z* 389.1 $(M + H)^+$.



B) **4-(2-Fluoro-4-nitrophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]-triazin-6-ol**

To a heterogeneous mixture of 4-(2-fluoro-4-nitrophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]-triazin-6-yl pivalate (1.45 g, 3.74 mmol) in absolute ethanol (19 mL), at room temperature under a nitrogen atmosphere, was added 1 N aqueous sodium hydroxide. The reaction mixture was stirred at ambient temperature for 1.5 h before being neutralized to pH 7 with 1 N aqueous hydrochloride. The reaction mixture was concentrated to remove ethanol, before being partitioned between ethyl acetate and water. The aqueous layer was extracted twice with ethyl acetate. The combined organic extracts were washed twice with water, once with

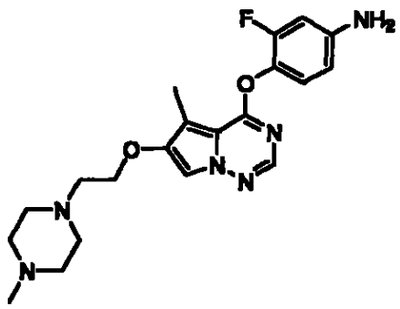
saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification by silica gel (Merck KGaA, 230-400 mesh particle size) flash chromatography, eluting with 2:1 hexane/ethyl acetate, afforded the title compound (602 mg, 53% for Steps A-B) as a yellow solid. ^{1}H NMR ($CDCl_3$) δ 8.20-8.12 (m, 2H), 7.84 (s, 1H), 7.58-7.53 (m, 1H), 7.53 (s, 1H), 4.76 (s, 1H), 2.48 (s, 3H); MS(ESI$^+$) *m/z* 305.2 $(M + H)^+$.



C) **4-(2-Fluoro-4-nitrophenoxy)-5-methyl-6-(2-(4-methylpiperazin-1-yl)-ethoxy)pyrrolo[2,1-*f*][1,2,4]triazine**

To a homogeneous mixture of 4-(2-fluoro-4-nitrophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]-triazin-6-ol (100 mg, 0.33 mmol) and triphenylphosphine (129 mg, 0.49 mmol) in 4 mL of 1:1 anhydrous dichloromethane/anhydrous tetrahydrofuran, cooled to 0 °C under a nitrogen atmosphere, was added dropwise a mixture of 2-(4-methylpiperazin-1-yl)ethanol (71 mg, 0.49 mmol) and diisopropylazodicarboxylate (0.10 μL, 0.49 mmol) in 2mL of 1:1 anhydrous dichloromethane/anhydrous tetrahydrofuran. The mixture was stirred and allowed to warm to room temperature. The reaction was stirred for twelve hours before being concentrated *in vacuo*. The residue was purified by preparative HPLC (YMC S10 ODS, 30 x 500 mm, 30 minute gradient from 50% to 90% aqueous methanol with 0.1% TFA). The appropriate fractions were combined, neutralized with saturated aqueous sodium bicarbonate, and then concentrated *in vacuo* to remove methanol. The mixture was extracted with chloroform (3 x 10 mL). The combined organic layers were washed once each with water and brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to yield the title compound (34 mg, 24%) as a yellow solid. ^{1}H NMR ($CDCl_3$) δ 8.20-8.10 (m, 2H), 7.82 (s, 1H), 7.58-7.52 (m, 1H),

7.49 (s, 1H), 4.16 (t, 2H, J = 5.7 Hz), 2.87 (t, 2H, J = 5.7 Hz), 2.80-2.40 (m, 8H), 2.45 (s, 3H), 2.31 (s, 3H); MS(ESI$^+$) m/z 431.3 $(M + H)^+$.



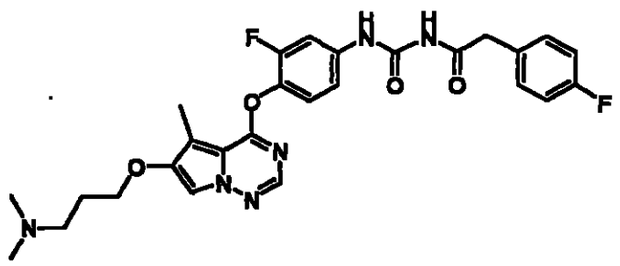
D) **3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*]-[1,2,4]triazin-4-yloxy)benzenamine**

4-(2-Fluoro-4-nitrophenoxy)-5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazine (20 mg, 0.05 mmol) was converted to the title compound (16 mg, 87%) in a manner similar to the preparation of Compound B of Example 28. ^{1}H NMR ($CDCl_3$) δ 7.86-7.83 (m, 1H), 7.50-7.38 (m, 2H), 7.09-7.00 (m, 1H), 6.56-6.45 (m, 1H), 4.14 (t, 2H, J = 5.5 Hz), 2.99-2.38 (m, 18H); MS(ESI$^+$) m/z 401.4 $(M + H)^+$.

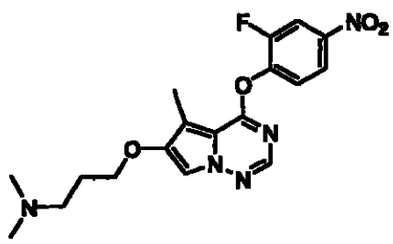
E) **1-(3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4] triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea, bis-hydrochloride salt**

3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]-triazin-4-yloxy)benzenamine (18 mg, 0.05 mmol) was converted to the title compound (7 mg, 26%) in a manner similar to the preparation of Example 27. Treatment with 1 N aqueous hydrochloric acid (0.05 mL, 0.05 mmol), followed by lyophilization, resulted in the title compound as a pale yellow solid (5 mg, 64%). ^{1}H NMR (CD_3OD) δ 8.06-7.99 (m, 2H), 7.83 (s, 1H), 7.79 (s, 1H), 7.48-7.30 (m, 4H), 7.13-7.02 (m, 2H), 4.56-4.45 (m, 2H), 3.87-3.59 (m, 4H), 3.09-2.44 (m, 15H); HRMS(ESI), 596.2255 $(M+H)^+$ calc, 596.2261 $(M + H)^+$ found.

EXAMPLE 32

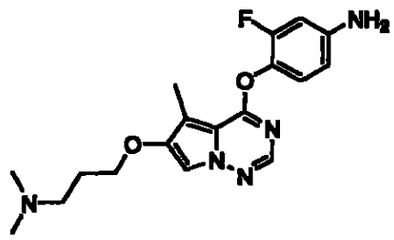


1-(4-(6-(3-(Dimethylamino)propoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, hydrochloride salt



A) 3-(4-(2-Fluoro-4-nitrophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yloxy)-*N*,*N*-dimethylpropan-1-amine

To a mixture of polymer bound triphenylphosphine (3 mmol triphenylphosphine per 1 g of resin, 583 mg, 1.75 mmol) in anhydrous tetrahydrofuran (5 mL), at 0 °C under a nitrogen atmosphere, was added diethylazodicarboxylate (138 µL, 0.87 mmol) dropwise via syringe. The mixture was stirred for 15 minutes before 3-dimethyl-aminopropanol (103 µL, 0.87 mmol) was added. After 30 minutes at 0 °C, 4-(2-fluoro-4-nitrophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]-triazin-6-ol (133 mg, 0.44 mmol, Compound B of Example 31) was added, and the mixture was allowed to slowly warm to room temperature. After 14.5 h, the resin was removed by filtration and rinsed with 1:1 methanol/tetrahydrofuran. The combined filtrate was concentrated *in vacuo* to a yellow residue that was used in the next step without further purification. MS(ESI$^+$) *m/z* 390.2 $(M + H)^+$.



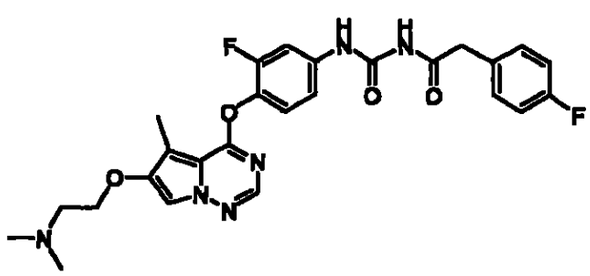
B) **4-(6-(3-(Dimethylamino)propoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorobenzenamine**

3-(4-(2-fluoro-4-nitrophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yloxy)-*N,N*-dimethylpropan-1-amine (170 mg, 0.44 mmol) was converted to the title compound in a manner similar to the preparation of Compound B of Example 28. The resultant yellow solid was used in the next step without further purification. MS(ESI$^+$) *m/z* 360.3 $(M + H)^+$.

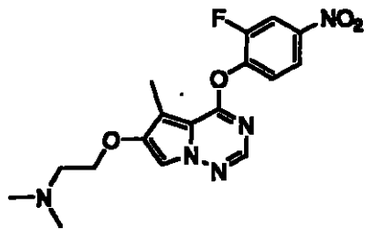
C) **1-(4-(6-(3-(Dimethylamino)propoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, hydrochloride salt**

4-(6-(3-(Dimethylamino)propoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorobenzenamine (12 mg, 0.03 mmol) was converted to the title compound (2.5 mg, 13%) in a manner similar to the preparation of Compound E of Example 31, except that 2-(4-fluorophenyl)-acetyl isocyanate (0.10 mL, 0.04 mmol, Compound C of Example 4) was used instead of benzenesulfonyl isocyanate. ^{1}H NMR (CD_3OD) δ 10.77 (s, 1H), 7.80 (s, 1H), 7.69 (s, 1H), 7.40-7.23 (m, 5H), 7.11-7.02 (m, 3H), 4.15-4.12 (m, 2H), 3.71 (s, 2H), 3.41-3.36 (m, 2H), 2.97 (s, 6H), 2.44 (s, 3H), 2.31-2.22 (m, 2H); HRMS(ESI), 539.2218 $(M + H)^+$ calc, 539.2218 $(M + H)^+$ found.

EXAMPLE 33

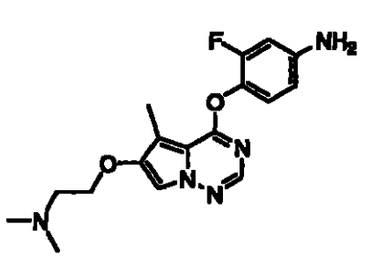


1-(4-(6-(2-(Dimethylamino)ethoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, hydrochloride salt



A) **2-(4-(2-Fluoro-4-nitrophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yloxy)-*N,N*-dimethylethanamine**

4-(2-Fluoro-4-nitrophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]-triazin-6-ol (91 mg, 0.30 mmol, Compound B of Example 31) was converted to the title compound in a manner similar to the preparation of Compound A of Example 32, except that *N,N*-dimethylethanolamine (75 µL, 0.75 mmol) was used instead of 3-dimethylaminopropanol and diisopropylazodicarboxylate (148 µL, 0.75 mmol) was used instead of diethylazodicarboxylate. The residue was purified by preparative HPLC (YMC S10 ODS, 30 x 500 mm, 30 minute gradient from 70% to 90% aqueous methanol with 0.1% TFA). The appropriate fractions were combined, neutralized with saturated aqueous sodium bicarbonate, and then concentrated *in vacuo* to remove methanol. The mixture was extracted with chloroform (3 x 10mL). The combined organic layers were washed once each with water and brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to yield the title compound (22 mg, 19%) as a solid. MS(ESI$^+$) *m/z* 376.2 $(M+H)^+$.



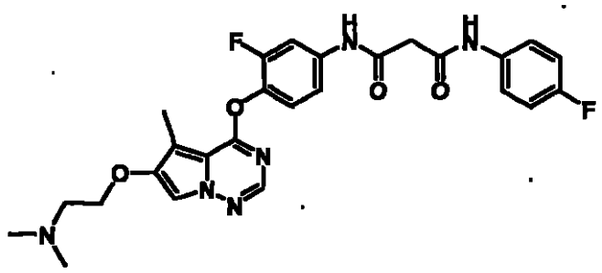
B) **4-(6-(2-(Dimethylamino)ethoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorobenzenamine**

2-(4-(2-Fluoro-4-nitrophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yloxy)-*N*,*N*-dimethylethanamine (22 mg, 0.06 mmol) was converted to the title compound (20 mg, 100%) in a manner similar to the preparation of Compound B of Example 28. The resultant yellow glass was used in the next step without further purification. MS(ESI$^+$) *m/z* 346.3 $(M + H)^+$.

C) 1-(4-(6-(2-(Dimethylamino)ethoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, hydrochloride salt

4-(6-(2-(Dimethylamino)ethoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorobenzenamine (20 mg, 0.06 mmol) was converted to the title compound (6.5 mg, 19%) in a manner similar to the preparation of Compound C of Example 32. ^{1}H NMR (CD_3OD) δ 10.79 (s, 1H), 7.84 (s, 1H), 7.77 (s, 1H), 7.40-7.21 (m, 5H), 7.10-6.97 (m, 3H), 4.43-4.39 (m, 2H), 3.71 (s, 2H), 3.68-3.62 (m, 2H), 3.03 (s, 6H), 2.48 (s, 3H); HRMS(ESI), 525.2062 $(M + H)^+$ calc, 525.2079 $(M + H)^+$ found.

EXAMPLE 34

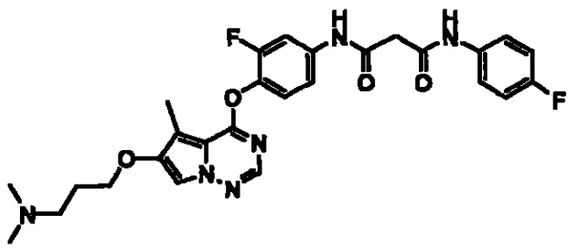


N^1-(4-(6-(2-(Dimethylamino)ethoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-N^3-(4-fluorophenyl)malonamide, hydrochloride salt

4-(6-(2-(Dimethylamino)ethoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorobenzenamine (35 mg, 0.10 mmol, Compound B of Example 33) was converted to the title compound (4.2 mg, 8%) in a manner similar to the preparation of Example 29, except that PyBroP (52 mg, 0.11 mmol) was used instead of o-benzotriazol-1-yl-*N*,*N*,*N*',*N*'-tetramethyl-uronium tetrafluoroborate. Treatment with 1 N aqueous hydrochloric acid (1 mL, 1 mmol), followed by lyophilization, resulted in

the title compound (1.7 mg, 38%) as a pale yellow solid. ^{1}H NMR (CD_3OD) δ 7.83 (s, 1H), 7.77 (s, 1H), 7.62-7.58 (m, 2H), 7.40-7.27 (m, 5H), 7.09-7.04 (m, 2H), 4.43-4.41 (m, 2H), 3.70-3.54 (m, 4H), 3.04 (s, 6H), 2.50 (s, 3H); HRMS(ESI), 525.2062 $(M + H)^+$ calc, 525.2059 $(M + H)^+$ found.

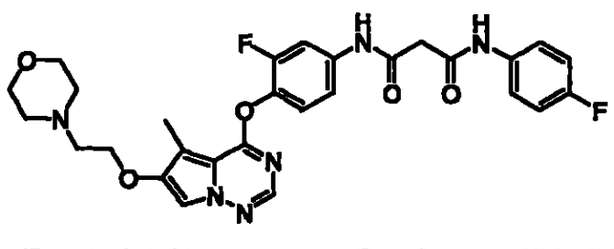
EXAMPLE 35



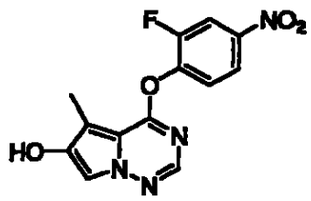
N^1-(4-(6-(3-(Dimethylamino)propoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-N^3-(4-fluorophenyl)malonamide, hydrochloride salt

4-(6-(3-(Dimethylamino)propoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorobenzenamine (54 mg, 0.15 mmol, Compound B of Example 32) was converted to the title compound (13 mg, 15%) in a manner similar to the preparation of Example 34. ^{1}H NMR (CD_3OD) δ 7.83-7.75 (m, 2H), 7.67 (s, 1H), 7.63-7.57 (m, 2H), 7.39-7.27 (m, 2H), 7.09-7.02 (m, 2H), 4.18-4.13 (m, 2H), 3.58 (s, 2H), 3.42-3.36 (m, 2H), 2.96 (s, 6H), 2.48-2.42 (m, 4H), 2.32-2.25 (m, 2H); HRMS(ESI), 537.2062 $(M-H)^-$ calc, 537.2073 $(M-H)^-$ found.

EXAMPLE 36

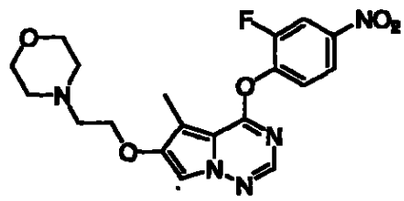


N^1-(3-Fluoro-4-(5-methyl-6-(2-morpholinoethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-N^3-(4-fluorophenyl)malonamide, hydrochloride salt



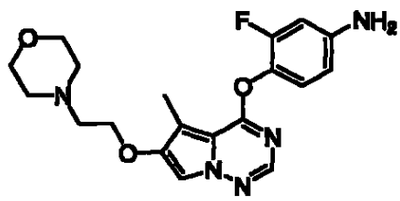
A) **4-(2-Fluoro-4-nitrophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-ol**

To a solution of 4-(2-fluoro-4-nitrophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yl pivalate (2.40 g, 6.19 mmol, Compound E of Example 1) in a mixture of 20 mL of THF and 30 mL of EtOH was added 1 N NaOH (12 mL, 12 mmol) dropwise at room temperature. The resulting solution was allowed to stir for 45 min, by that time HPLC analysis indicated the completion of the reaction. The reaction was thus quenched with 13 mL of 1 N HCl. After the organic solvent was removed under reduced pressure, the product precipitated out and was collected through filtration. The product obtained is 4-(2-fluoro-4-nitrophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-ol (1.65 g, 88%). MS(ESI$^+$) *m/z* 305.1 $(M + H)^+$.



B) **4-(2-Fluoro-4-nitrophenoxy)-5-methyl-6-(2-morpholinoethoxy)pyrrolo[2,1-*f*][1,2,4]triazine**

To a solution of 4-(2-fluoro-4-nitrophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-ol (55 mg, 0.18 mmol), 2-morpholinoethanol (47 mg, 0.36 mmol), and polymer-bound PPh_3 (3.0 mmol/g, 167 mg, 0.50 mmol) in 1 mL of THF at room temperature was added DIAD (72 mg, 0.36 mmol). The mixture was stirred for 1 h and HPLC analysis indicated most of the starting material disappeared. The polymer was filtered off through Celite® and the filtrate was concentrated and purified by preparative HPLC to afford the title compound (50 mg, 67%). MS(ESI$^+$) *m/z* 418.2 $(M + H)^+$.



C) **3-Fluoro-4-(5-methyl-6-(2-morpholinoethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine**

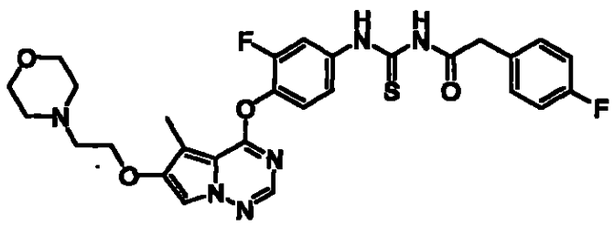
To a solution of 4-(2-fluoro-4-nitrophenoxy)-5-methyl-6-(2-morpholinoethoxy)pyrrolo[2,1-*f*][1,2,4]triazine (54 mg, 0.13 mmol) in a mixture of 0.8 mL of THF and 1.2 mL of MeOH were added NH_4Cl (70 mg, 1.3 mmol) and Zn powder (85 mg, 1.3 mmol). The suspension was allowed to stir at room temperature for 2 h. Both HPLC analysis and LC-MS analysis indicated the completion of the reaction and the solid was thus filtered off. After concentration of the filtrate, the residue was taken into 10% MeOH in CH_2Cl_2. The solution was then filtered again and the filtrate was concentrated *in vaco* to provide the title compound (50 mg, 92%). MS(ESI$^+$) *m/z* 388.4 $(M + H)^+$.

D) **N^1-(3-Fluoro-4-(5-methyl-6-(2-morpholinoethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-N^3-(4-fluorophenyl)malonamide, hydrochloride salt**

To a solution of 3-fluoro-4-(5-methyl-6-(2-morpholinoethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine (16 mg, 0.041 mmol), 3-(4-fluorophenylamino)-3-oxopropanoic acid (12 mg, 0.06 mmol, Compound A of Example 25) in 1 mL of THF were added DIEA (0.04 mL) and PyBrOP (32 mg, 0.06 mmol) at room temperature. The reaction was allowed to stir over the weekend and LC-MS analysis indicated the formation of the product, although there was still some staring material left. The solution was directly subject to preparative HPLC purification and the HPLC fraction containing the desired product was passed through a Waters Oasis® MCX 20cc 500mg LP Extraction cartridge and washed with MeOH to remove TFA. After that, the cartridge was eluted with 7 N NH_3 in MeOH and the ammonia solution was concentrated under reduced pressure to dryness. The residue was then suspended in a mixture of MeOH and H_2O and a few drops of 1 N HCl was added. The suspension

became a clear solution and it was frozen in dry ice-acetone bath. The frozen solution was then lyophilized to afford the title compound (20 mg, 80%). ^{1}H NMR (CD_3OD) δ 7.71 (m, 2H), 7.60 (s, 1H), 7.53 (m, 2H), 7.28 (m, 2H), 7.00 (m, 2H), 4.13 (s, 2H), 3.67 (s, 4H), 2.80 (s, 2H), 2.58 (s, 4H), 2.37 (s, 3H); MS(ESI$^+$) *m/z* 567.2 $(M + H)^+$.

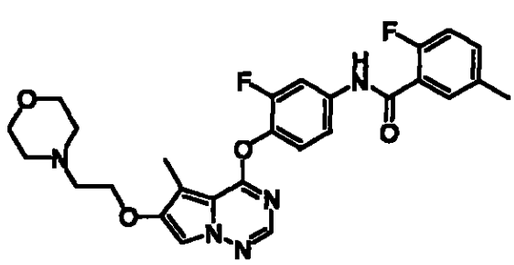
EXAMPLE 37



1-(3-Fluoro-4-(5-methyl-6-(2-morpholinoethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea, hydrochloride salt

To a solution of 3-fluoro-4-(5-methyl-6-(2-morpholinoethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine (30 mg, 0.072 mmol, Compound C of Example 36) in 1 mL of THF was added 2-(4-fluorophenyl)ethanoyl isothiocyanate (19 mg, 0.1 mmol, Compound A of Example 2). The solution was allowed to stir at room temperature for 2 h and HPLC analysis indicated the completion of the reaction. The reaction was then quenched with NH_3 in propanol and the resulting solution was loaded on a preparative HPLC to be purified. Following a work-up procedure similar to that for Compound D of Example 36, the title compound (13 mg, 30%) was obtained as a HCl salt. ^{1}H NMR (DMSO-d_6) δ 12.45 (s, 1H), 11.85 (s, 1H), 11.50 (br s, 1H), 8.15 (s, 1H), 8.10 (s, 1H), 7.90 (d, 1H), 7.50 (m, 2H), 7.40 (m, 2H), 7.20 (m, 2H), 4.50 (br s, 2H), 4.00 (m, 2H), 3.85 (s, 2H), 3.25-3.70 (m, 8H), 2.40 (s, 3H); *MS(ESI$^+$) m/z 583.2 $(M + H)^+$*.

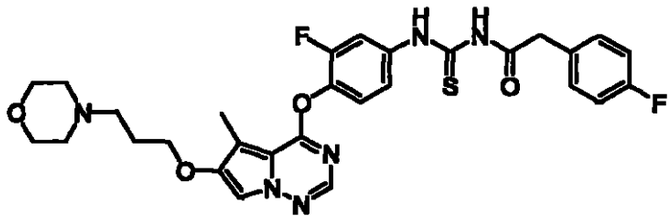
EXAMPLE 38



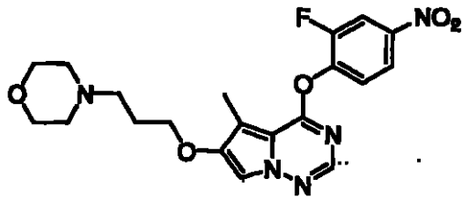
2-Fluoro-*N*-(3-fluoro-4-(5-methyl-6-(2-morpholinoethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-5-methylbenzamide, hydrochloride salt

Following a procedure similar to that for the synthesis of Compound D of Example 36, 3-fluoro-4-(5-methyl-6-(2-morpholinoethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine (16 mg, 0.042 mmol, Compound C of Example 36) was converted to the title compound (5.6 mg, 23%) as a HCl salt. ^{1}H NMR (CD_3OD) δ 7.85 (d, 1H), 7.80 (s, 1H), 7.69 (s, 1H), 7.55 (m, 1H), 7.50 (m, 1H), 7.35 (m, 2H), 7.13 (m, 1H), 4.22 (m, 2H), 3.73 (m, 4H), 2.88 (m, 2H), 2.66 (m, 4H), 2.44 (s, 3H), 2.38 (s, 3H); MS(ESI$^+$) *m/z* 262.3 $(M + H)^+$.

EXAMPLE 39

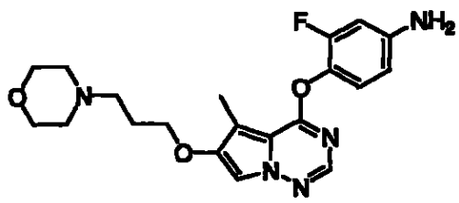


1-(3-Fluoro-4-(5-methyl-6-(3-morpholinopropoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea, hydrochloride salt



A) **4-(2-Fluoro-4-nitrophenoxy)-5-methyl-6-(3-morpholinopropoxy)pyrrolo[2,1-*f*][1,2,4]triazine**

Following a procedure similar to that for the synthesis of Compound B of Example 36 , 4-(2-fluoro-4-nitrophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-ol (50 mg, 0.16 mmol, Compound A of Example 36) was converted to the title compound (32 mg, 46%). MS(ESI$^+$) *m/z* 432.2 $(M + H)^+$.



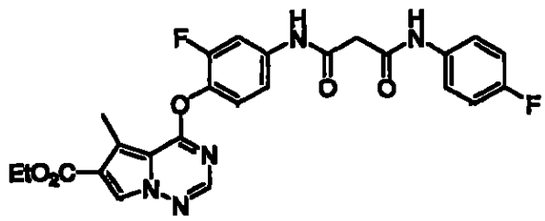
B) **3-Fluoro-4-(5-methyl-6-(3-morpholinopropoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine**

Following a procedure similar to that for the synthesis of Compound C of Example 36, 4-(2-fluoro-4-nitrophenoxy)-5-methyl-6-(3-morpholinopropoxy)pyrrolo[2,1-*f*][1,2,4]triazine (31 mg, 0.072 mmol) was converted to the title compound (28 mg, 95%). MS(ESI$^+$) *m/z* 402.3 $(M + H)^+$.

C) **1-(3-Fluoro-4-(5-methyl-6-(3-morpholinopropoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea, hydrochloride salt**

Following a procedure similar to Compound D of Example 36, 3-fluoro-4-(5-methyl-6-(3-morpholinopropoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine (28 mg, 0.07 mmol) was converted to the title compound (30 mg, 68%) as a HCl salt. ^{1}H NMR (DMSO-d_6) 12.45 (s, 1H), 11.80 (s, 1H), 11.65 (br s, 1H), 8.00 (s, 2H), 7.90 (d, 1H), 7.50 (m, 2H), 7.40 (m, 2H), 7.25 (m, 2H), 3.10-4.10 (m, 16H), 2.40 (s, 3H); MS(ESI$^+$) *m/z* 597.2 $(M + H)^+$.

EXAMPLE 40

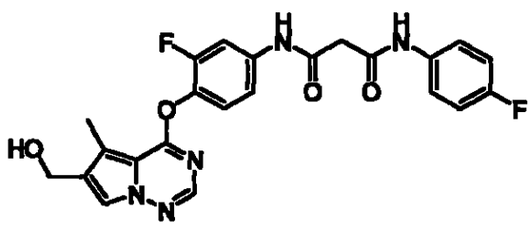


Ethyl 4-(2-fluoro-4-(3-(4-fluorophenylamino)-3-oxopropanamido)phenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate

Following a procedure similar to that for the synthesis of Compound D of Example 36, ethyl 4-(4-amino-2-fluorophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate (70 mg, 0.21 mmol, Compound B of Example 6) was

converted to the title compound (50 mg, 47%). ^{1}H NMR (DMSO-d_6) δ 10.50 (s, 1H), 10.30 (s, 1H), 8.45 (s, 1H), 8.16 (s, 1H), 7.90 (d, 1H), 7.67 (m, 2H), 7.51 (t, 1H), 7.40 (t, 1H), 7.20 (m, 2H), 4.33 (q, 2H), 3.52 (s, 2H), 2.77 (s, 3H), 1.35 (t, 3H); MS(ESI$^+$) *m/z* 510.1 $(M+H)^+$.

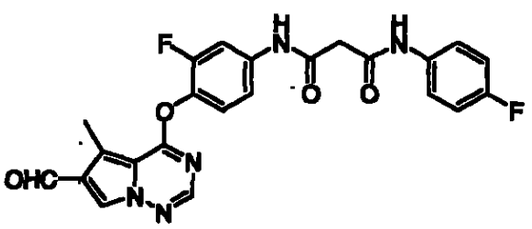
EXAMPLE 41



N^1-(3-Fluoro-4-(6-(hydroxymethyl)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-N^3-(4-fluorophenyl)malonamide

To a solution of ethyl 4-(2-fluoro-4-(3-(4-fluorophenylamino)-3-oxopropanamido)phenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate (66 mg, 0.13 mmol, Example 40) in 20 mL of THF at -78 °C was added DIBAL-H (1 M, 1.65 mL). The reaction mixture was allowed to stir at -78 °C for 1 h and then at room temperature for 2 h. At that time, HPLC analysis indicated the completion of the reaction. The reaction was quenched with 4 mL of MeOH, followed by addition of 4 mL of H_2O. The mixture was allowed to stir for 0.5 h and then Na_2SO_4 was added. The stirring was continued for 1 h. Filtration and concentration gave rise to the title compound (50 mg, 82%). ^{1}H NMR (CD_3OD) δ 7.70 (m, 3H), 7.50 (m, 2H), 7.25 (m, 2H), 7.00 (m, 2H), 4.60 (s, 2H), 3.45 (s, 2H), 2.50 (s, 3H); MS(ESI$^+$) *m/z* 468.2 $(M+H)^+$.

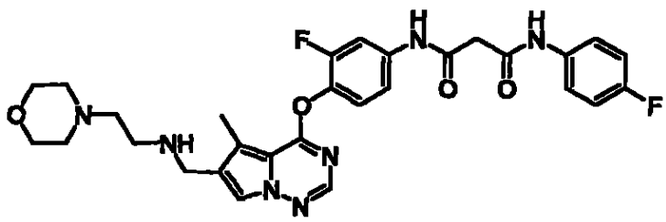
EXAMPLE 42



N^1-(3-Fluoro-4-(6-formyl-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl) N^3-(4-fluorophenyl)malonamide

To a solution of N^1-(3-fluoro-4-(6-(hydroxymethyl)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-N^3-(4-fluorophenyl)malonamide (12 mg, 0.026 mmol, Example 41) in 1 mL of THF was added Dess-Martin periodinane (48 mg, 0.11 mmol, Aldrich) at room temperature. The mixture was allowed to stir for 2 h and HPLC analysis indicated total consumption of the starting material. The mixture was filtered through a plug of SiO_2, washed with EtOAc. The organic solvent was then removed under reduced pressure and the residue was purified on preparative HPLC to afford the title compound (10 mg, 83%). MS(ESI$^+$) *m/z* 466.2 $(M + H)^+$.

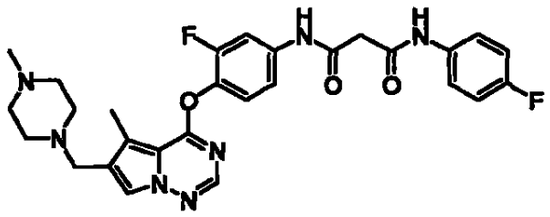
EXAMPLE 43



N^1-(3-Fluoro-4-(5-methyl-6-((2-morpholinoethylamino)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-N^3-(4-fluorophenyl)malonamide, bis-trifluoroacetic acid salt

To a solution of N^1-(3-fluoro-4-(6-formyl-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-N^3-(4-fluorophenyl)malonamide (15 mg, 0.032 mmol, Example 42) in 1 mL of DMF were added 2-morpholinoethanamine (21 mg, 0.16 mmol), DIEA (0.04 mL) and $NaBH(OAc)_3$ (52 mg, 0.2 mmol). The mixture was allowed to stir at room temperature for 4 days. HPLC analysis and LC-MS analysis indicated formation of the product. The solution was then dissolved in MeOH and purified by preparative HPLC to give the title compound (4 mg, 21%) as a 2•TFA salt. ^{1}H NMR (CD_3OD) δ 7.92 (s, 1H), 7.82 (s, 1H), 7.70 (d, 1H), 7.50 (m, 2H), 7.28 (m, 2H), 6.98 (m, 2H), 4.31 (s, 2H), 3.68 (s, 4H), 3.20 (m, 4H), 2.82 (m, 2H), 2.65 (s, 4H), 2.56 (s, 3H); MS(ESI$^+$) *m/z* 580.2 $(M + H)^+$.

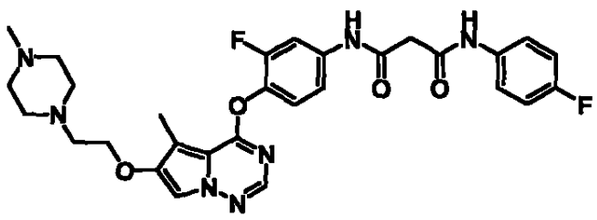
EXAMPLE 44



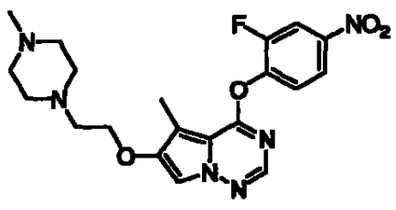
N^1-(3-Fluoro-4-(5-methyl-6-((4-methylpiperazin-1-yl)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-N^3-(4-fluorophenyl)malonamide, bis-trifluoroacetic acid salt

Following a procedure similar to that for the synthesis of Example 43, N^1-(3-fluoro-4-(6-formyl-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-N^3-(4-fluorophenyl)malonamide (15 mg, 0.032 mmol, Example 42) was converted to the title compound (4 mg, 23%) as a 2•TFA salt. MS(ESI$^+$) *m/z* 550.2 $(M + H)^+$.

EXAMPLE 45



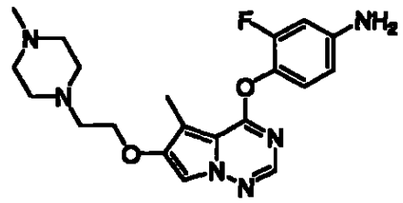
N^1-(3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-N^3-(4-fluorophenyl)malonamide, bis hydrochloride salt



A) **4-(2-Fluoro-4-nitrophenoxy)-5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazine**

Following a procedure similar to that for the synthesis of Compound B of Example 36, 4-(2-fluoro-4-nitrophenoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-ol (55 mg, 0.18 mmol, Compound A of Example 36), 2-morpholinoethanol (304 mg, 1.0

mmol) was converted to the title compound (352 mg, 82%). MS(ESI$^+$) *m/z* 431.2 (M + H)$^+$.



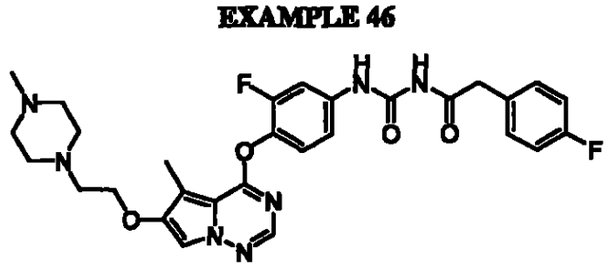
B) **3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine**

Following a procedure similar to that for the synthesis of Compound C of Example 36, 4-(2-fluoro-4-nitrophenoxy)-5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazine (2.90 g, 6.74 mmol) was converted to the title compound (1.38 g, 51%). MS(ESI$^+$) *m/z* 401.3 (M + H)$^+$.

C) **N^1-(3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-N^9-(4-fluorophenyl)malonamide, bis-hydrochloride salt**

Following a procedure similar to that for the synthesis of Compound D of Example 36, 3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine (60 mg, 0.15 mmol) was converted the title compound (30 mg, 46%) as a 2•HCl salt. ^{1}H NMR (DMSO-d_6) δ 10.63 (s, 1H), 10.37 (s, 1H), 8.04 (s, 1H), 7.99 (s, 1H), 7.80 (d, 1H), 7.61 (m, 2H), 7.40 (m, 2H), 7.16 (m, 2H), 4.42 (br s, 2H), 3.38-3.60 (m, 10H), 2.81 (s, 3H), 2.40 (s, 3H);). MS(ESI$^+$) *m/z* 580.3 (M + H)$^+$:

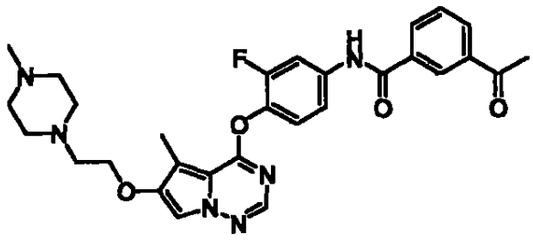
EXAMPLE 46



1-(3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea, bis-hydrochloride salt

To a solution of 3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine (20 mg, 0.05 mmol, Compound B of Example 45) in 1 mL of THF at room temperature was added a solution of 2-(4-fluorophenyl)acetyl isocyanate in toluene (0.36 M, 0.18 mL, Compound C of Example 4) and the solution was allowed to stir overnight. HPLC analysis and LC-MS analysis indicated the completion of the reaction and the organic solvent was thus removed under reduced pressure. The residue was purified on preparative HPLC. The title compound (15 mg, 46%) was finally obtained as a 2•HCl salt after a work-up similar to that described for Compound D of Example 36. ^{1}H NMR (DMSO-d_6) δ 11.02 (s, 1H), 10.58 (s, 1H), 8.04 (s, 1H), 7.99 (s, 1H), 7.70 (d, 1H), 7.35 (m, 4H), 7.16 (m, 2H), 4.44 (br.s, 2H), 3.40-3.70 (m, 12H), 2.81 (s, 3H), 2.39 (s, 3H); MS(ESI$^+$) *m/z* 580.1 $(M + H)^+$.

EXAMPLE 47

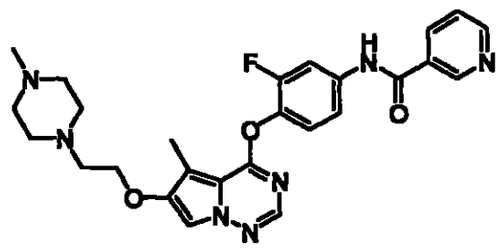


3-Acetyl-*N*-(3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)benzamide, bis-hydrochloride salt

Following a procedure similar to that for the synthesis of Compound D of example 36, 3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine (20 mg, 0.05 mmol, Compound B of Example 45) was converted to the title compound (11 mg, 35%) as a 2•HCl salt. ^{1}H NMR (CD_3OD) δ 8.20 (m, 1H), 7.90 (m, 2H), 7.84 (s, 1H), 7.80 (s, 1H), 7.70 (m, 1H), 7.50

(m, 2H), 7.32 (m, 1H), 4.54 (m, 2H), 3.60-4.10 (m, 10H), 3.08 (s, 3H), 2.50 (s, 3H); MS(ESI$^+$) *m/z* 547.2 $(M + H)^+$.

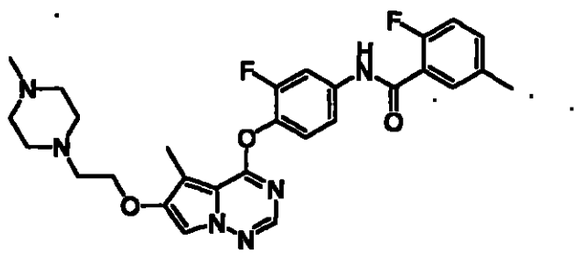
EXAMPLE 48



***N*-(3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)nicotinamide, tris hydrochloride salt**

Following a procedure similar to that for the synthesis of Compound D of Example 36, 3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine (20 mg, 0.05 mmol, Compound B of Example 45) was converted the tile compound (10 mg, 32%) as a 3•HCl salt. ^{1}H NMR (CD_3OD) δ 9.46 (s, 1H), 9.20 (d, 1H), 9.08 (d, 1H), 8.29 (m, 1H), 7.92 (d, 1H), 7.81 (s, 1H), 7.82 (s, 1H), 7.61 (m, 1H), 7.42 (m, 1H), 4.54 (m, 2H), 3.82-4.05 (m, 10H), 3.05 (s, 3H), 2.51 (s, 3H); MS(ESI$^+$) *m/z* 506.2 $(M + H)^+$.

EXAMPLE 49

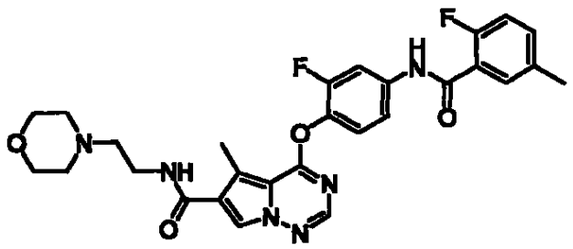


2-Fluoro-*N*-(3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-5-methylbenzamide, bis-hydrochloride salt

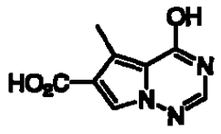
Following a procedure similar to that for the synthesis of Compound D of Example 36, 3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine (20 mg, 0.05 mmol, Compound B of Example

45) was converted to the title compound (8 mg, 26% yield) as a 2•HCl salt. ^{1}H NMR (CD_3OD) δ 7.85 (d, 1H), 7.85 (s, 1H), 7.80 (s, 1H), 7.55 (m, 1H), 7.50 (m, 1H), 7.33 (m, 2H), 7.13 (t, 1H), 4.54 (m, 2H), 3.70-4.10 (m, 10H), 3.04 (s, 3H), 2.50 (s, 3H), 2.37 (s, 3H); MS(ESI$^+$) *m/z* 537.2 $(M + H)^+$.

EXAMPLE 50

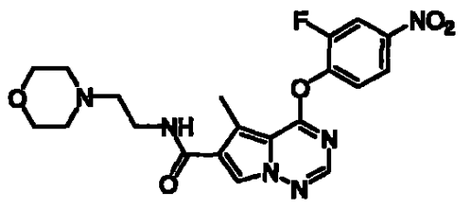


4-(2-Fluoro-4-(2-fluoro-5-methylbenzamido)phenoxy)-5-methyl-*N*-(2-morpholinoethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carboxamide, hydrochloride salt



A) 4-Hydroxy-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylic acid

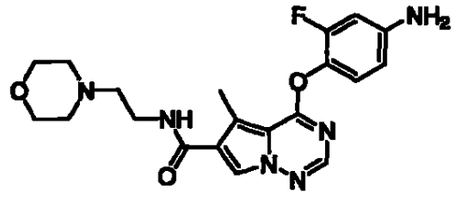
To a solution of ethyl 4-hydroxy-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate (442 mg, 2.0 mmol) (see example 6 of US Pat. App. 2003/0186982, the disclosure of which is herein incorporated by reference) in 10 mL of THF was added a solution of NaOH (1 N, 6.0 mL). The mixture was heated at 60 °C overnight and HPLC analysis indicated the completion of the reaction. After cooling down, the solution was neutralized with 6.0 mL of 1 N HCl. The organic solvent was then removed and the solid was collected after filtration to the title compound (350 mg, 91%). MS(ESI$^+$) *m/z* 194.2 $(M + H)^+$.



B) 4-(2-Fluoro-4-nitrophenoxy)-5-methyl-*N*-(2-morpholinoethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carboxamide

A suspension of 4-hydroxy-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylic acid (100 mg, 0.52 mmol) in 2 mL of $POCl_3$ was heated at 110 °C for 4 h. The suspension became a clear solution and the excess of $POCl_3$ was removed with toluene. The residue was then dissolved in 5 mL of acetonitrile at 0 °C. To this solution were added Et_3N (0.72 mL, 5.2 mmol) and 2-morpholinoethanamine (0.13 mL, 1.04 mmol). The mixture was stirred for 0.5 h and HPLC analysis indicated the formation of the product. The solution was then diluted with EtOAc and washed with H_2O and brine. The organic layer was dried over $MgSO_4$. After filtration and concentration, the crude material was carried to the next reaction.

The crude material was dissolved in 2 mL of acetonitrile and to it were added 2-fluoro-4-nitrophenol (94 mg, 0.60 mmol) and DABCO (78 mg, 0.70 mmol). The reaction was allowed to stir for 1 h and HPLC analysis indicated the completion of the reaction. After concentration, the residue was purified on preparative HPLC to give the title compound (75 mg, 33%). MS(ESI$^+$) *m/z* 445.2 $(M + H)^+$.



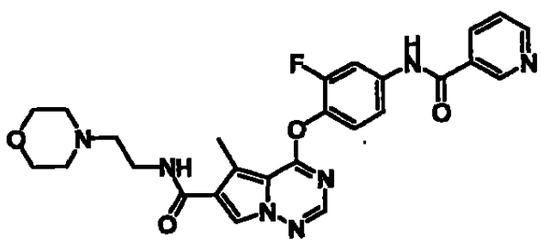
C) 4-(4-Amino-2-fluorophenoxy)-5-methyl-*N*-(2-morpholinoethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carboxamide

Following a procedure similar to that for the synthesis of Compound C of Example 36, 4-(2-fluoro-4-nitrophenoxy)-5-methyl-*N*-(2-morpholinoethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carboxamide (75 mg, 0.17 mmol) was converted to the title compound (65 mg, 92%). LCMS(ESI$^+$) *m/z* 415.3 $(M + H)^+$.

D) 4-(2-Fluoro-4-(2-fluoro-5-methylbenzamido)phenoxy)-5-methyl-*N*-(2-morpholinoethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carboxamide, hydrochloride salt

To a solution of 4-(4-amino-2-fluorophenoxy)-5-methyl-*N*-(2-morpholinoethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carboxamide (25 mg, 0.06 mmol) in 1 mL of THF were added Et_3N (0.2 mL) and a solution of 2-fluoro-5-methylbenzoyl chloride (20 mg, 0.11 mmol) in 1 mL of THF at room temperature. The mixture was allowed to stir for 1 h and HPLC analysis indicated the consumption of the starting material. The reaction was quenched with MeOH. The solution was then concentrated *in vacuo* and the residue was purified by preparative HPLC to give the title compound (8.0 mg, 23%) as a HCl salt. ^{1}H NMR (CD_3OD) δ 8.48 (d, 1H), 7.83 (m, 3H), 7.28 (m, 3H), 7.00 (m, 1H), 2.90-4.00 (m, 12H), 2.76 (s, 3H), 2.33 (s, 3H); MS(ESI$^+$) *m/z* 551.2 $(M+H)^+$.

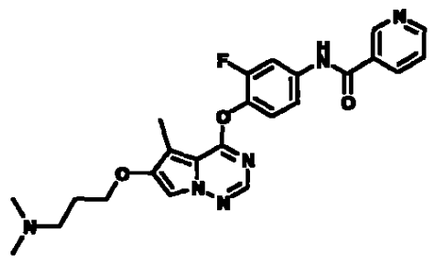
EXAMPLE 51



4-(2-Fluoro-4-(nicotinamido)phenoxy)-5-methyl-*N*-(2-morpholinoethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carboxamide, bis-hydrochloride salt

Following a procedure similar to that for the synthesis of Compound D of Example 50, 4-(4-amino-2-fluorophenoxy)-5-methyl-*N*-(2-morpholinoethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carboxamide (30 mg, 0.07 mmol, Compound C of Example 50) was converted the title compound (16 mg, 39%) as a 2•HCl salt. ^{1}H NMR (CD_3OD) δ 9.08 (s, 1H), 8.70 (s, 1H), 8.44 (s, 1H), 8.17 (s, 1H), 7.87 (m, 2H), 7.38 (m, 2H), 7.22 (m, 2H), 3.82 (s, 4H), 3.61 (m, 2H), 2.75 (m, 9H); MS(ESI$^+$) *m/z* 520.2 $(M+H)^+$.

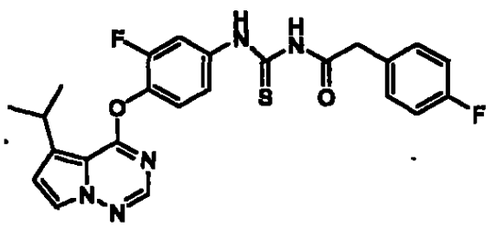
EXAMPLE 52



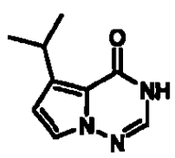
***N*-(4-(6-(3-(Dimethylamino)propoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)nicotinamide, dihydrochloride salt**

4-(6-(3-(Dimethylamino)propoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorobenzenamine (54 mg, 0.15 mmol, Compound B of Example 32) as converted to the title compound (8.7 mg, 11%) in a manner similar to the preparation of Compound D of Example 36. ^{1}H NMR (CD_3OD) δ 9.47 (s, 1H), 9.20-9.19 (m, 1H), 9.08-9.07 (m, 1H), 8.30-8.27 (m, 1H), 7.97-7.93 (m, 1H), 7.82 (s, 1H), 7.72 (s, 1H), 7.64-7.61 (m, 1H), 7.43-7.39 (m, 1H), 4.26-4.11 (m, 2H), 3.43-3.39 (m, 2H), 2.98 (s, 6H), 2.46 (s, 3H), 2.34-2.30 (m, 2H); HRMS(ESI), 463.1894 $(M-H)^-$ calc, 463.1905 $(M-H)^-$ found.

EXAMPLE 53



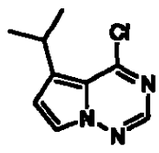
1-(3-Fluoro-4-(5-isopropyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea



A) **5-Isopropylpyrrolo[2,1-*f*][1,2,4]triazin-4(3H)-one**

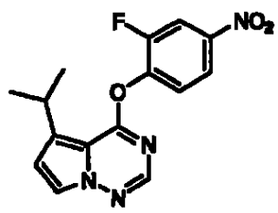
5-Isopropyl-4-oxo-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylic acid (0.025 g, 1.13 mmol, 1.0 equiv, prepared in a manner similar to that described in

patent application : US 2004/063708, herein incorporated by reference in its entiretyz) was added to polyphosphoric acid (5.0 g) and the reaction mixture was heated to 160 °C for 1 h. The reaction was cooled to room temperature and quenched with water (50 ml). The solution was extracted with ethyl acetate (3 x 50 ml), the combined organic fractions washed with sat $NaHCO_3$ (1 x 100 ml), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by silica gel (Merck KGaA, 230-400 mesh particle size) flash chromatography, eluting with 3/1 ethyl acetate / hexane, afforded the title compound (0.060 g, 30%). MS(ESI) *m/z* 176 $(M-H)^-$; HRMS(ESI), 176.0824 $(M-H)^-$ calc, 176.0818$(M-H)^-$ found.



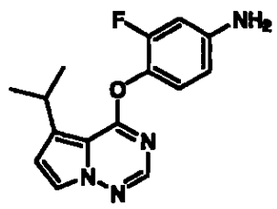
B) 4-Chloro-5-isopropylpyrrolo[2,1-*f*][1,2,4]triazine

5-Isopropylpyrrolo[2,1-*f*][1,2,4]triazin-4(3*H*)-one (0.035 g, 0.198 mmol, 1.0 equiv) was added to phosphorous oxychloride (2.0 ml, 21.5 mmol, 109 equiv) under a nitrogen atmosphere. The reaction mixture was heated to reflux for 1.5 h. The mixture was cooled to room temperature then concentrated *in vacuo*. The residue was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The aqueous layer was extracted twice with ethyl acetate. The combined organic washes were dried over anhydrous magnesium sulfate and concentrated *in vacuo* to yield a tan solid that was used in the next step without further purification. MS(ESI$^+$) *m/z* 196 $(M+H)^+$.



C) 4-(2-Fluoro-4-nitrophenoxy)-5-isopropyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazine

To a mixture of 4-chloro-5-isopropylpyrrolo[2,1-*f*][1,2,4]triazine (0.038g, 0.194 mmol, 1.0 equiv) and 2-fluoro-4-nitrophenol (0.062 g, 0.388 mmol, 2.0 equiv) in anhydrous CH_3CN (2mL), stirred for five minutes under a nitrogen atmosphere then was added DABCO (0.044 g, 0.388 mmol, 2.0 equiv) and the reaction mixture was heated at 50 °C for 2 h. The mixture was cooled to room temperature and quenched with 1 N HCl. The solution was extracted with CH_2Cl_2 (3 x 30 ml), the combined organic extracts dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by silica gel (Merck KGaA, 230-400 mesh particle size) flash chromatography, eluting with 2/1 hexane / ethyl acetate, afforded the title compound (0.048g, 79%). ^1H NMR ($CDCl_3$) δ 8.07-8.13 (m, 2H), 7.77 (s, 1H), 7.68-7.69 (m, 1H), 7.46-7.50 (m, 1H), 6.71-6.72 (m, 1H), 3.53-3.56 (m, 1H), 1.29-1.31 (m, 6H); HRMS(ESI), calc, 317.1050 $(M + H)^+$ found, 317.1039.



D) 3-Fluoro-4-(5-isopropyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine

To a heterogeneous mixture of 4-(2-fluoro-4-nitrophenoxy)-5-isopropyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazine (0.044 g, 1.39 mmol, 10 equiv) in 1/1 anhydrous methanol / tetrahydrofuran (2 mL), at ambient temperature under nitrogen atmosphere, was added zinc dust (0.090 g, 0.139 mmol, 1.0 equiv) and ammonium chloride (0.075 g, 1.39 mmol, 10 equiv). The mixture was stirred for 4 h before the catalyst was filtered off and the filtrate was concentrated *in vacuo* to yield the title compound (0.040g, 100%) as a solid, that was used without further purification. HRMS(ESI), 287.1308 $(M + H)^+$ calc, 287.1300 $(M + H)^+$ found.

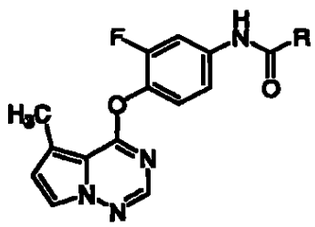
E) 1-(3-Fluoro-4-(5-isopropyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea

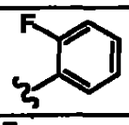
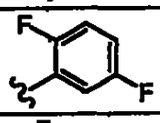
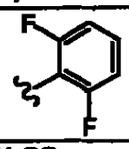
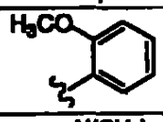
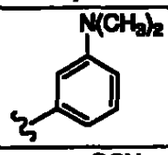
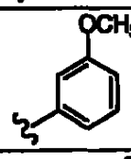
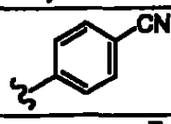
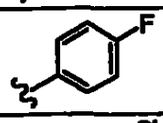
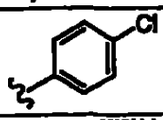
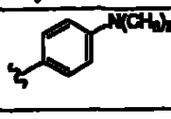
To a homogeneous solution of sodium thiocyanate (0.037 g, 0.46 mmol, 3.3 equiv) in ethyl acetate (1 mL), at room temperature under a nitrogen atmosphere, was added 4-fluorophenyl-acetyl chloride (0.048 ml, 0.35mmol, 2.5 equiv). The mixture was stirred for 2 h before being added directly to a homogeneous solution of 3-fluoro-4-(5-isopropyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine (0.040g, 0.139 mmol, 1.0 equiv) in anhydrous 1/1 THF/dichloromethane (3 mL), under a nitrogen atmosphere. The reaction mixture was stirred at ambient temperature for 16 h before being quenched with 1 N HCl. The solution was extracted with CH_2Cl_2 (3 x 50 ml), the combined organic fractions washed with 1 N NaOH (50 ml), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by silica gel (Merck KGaA, 230-400 mesh particle size) flash chromatography, eluting with 4/1 hexane/ ethyl acetate, afforded the title compound (0.050 g, 75%). ^{1}H NMR ($CDCl_3$) δ 12.34 (s, 1H), 8.47 (m, 1H), 7.65-7.78 (m, 2H), 7.63-7.64 (m, 1H), 7.19-7.32 (m, 4H), 7.03-7.08 (m, 2H), 6.66-6.67 (m, 1H), 3.65 (s, 2H), 3.40-3.50 (m, 1H), 1.28-1.30 (m, 6H); HRMS(BSI) 482.1462, calc, $(M+H)^+$ 482.1461 found. Elemental Analysis: $C_{24}H_{21}N_5O_2SF_2$. 0.23 H_2O. calc: C; 59.35, H; 4.45, N; 14.42, found: C; 59.36, H; 4.44, N; 14.03.

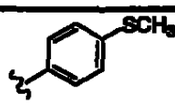
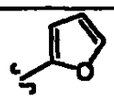
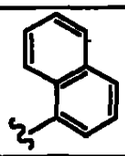
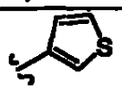
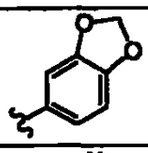
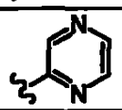
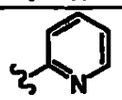
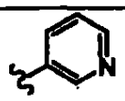
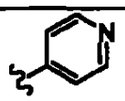
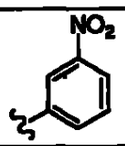
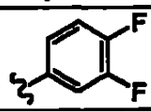
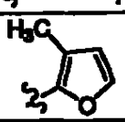
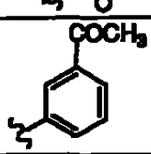
EXAMPLES 54 TO 85

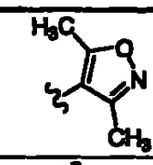
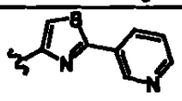
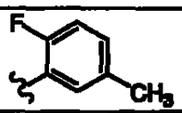
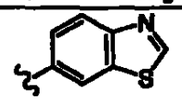
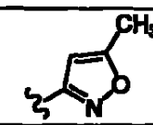
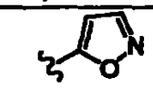
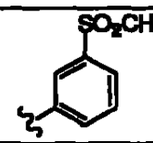
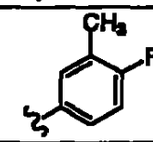
Examples 54 to 85 illustrated in Table 1 below were synthesized from 3-fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine (Compound B of Example 28) using one equivalent of the corresponding carboxylic acid, (1 eq) PyBrOP (1 eq), DIEA (1 eq) in DMF. The reaction mixture was heated to 70 °C and the crude products were purified by preparative HPLC (H_2O/MeOH/0.1% TFA, gradient 35–90% MeOH over 10 min, 20 ×100 mm 5 μm YMC ODS-A column) utilizing mass-directed fractionation. The purified sample was reconstituted in 1:1/MeOH:DCE, transferred to a tared 2.5 mL plastic microtube, dried via centrifugal evaporation, weighed and analyzed by LCMS (H_2O/MeOH/0.1% TFA).

TABLE 1



Example #	R	Compound Name	LC/MS $(M+H)^+$
54	Ph	*N*-(3-Fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)benzamide	363.4
55		2-Fluoro-*N*-(3-fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)benzamide	381.4
56		2,5-Difluoro-*N*-(3-fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)benzamide	399.3
57		2,6-Difluoro-*N*-(3-fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)benzamide	399.3
58		*N*-(3-Fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-2-methoxybenzamide	393.4
59		3-(Dimethylamino)-*N*-(3-fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)benzamide	406.4
60		*N*-(3-Fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-methoxybenzamide	393.4
61		4-Cyano-*N*-(3-fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)benzamide	388.4
62		4-Fluoro-*N*-(3-fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)benzamide	381.4
63		4-Chloro-*N*-(3-fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)benzamide	397.8
64		4-(Dimethylamino)-*N*-(3-fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)benzamide	406.4

Example #	R	Compound Name	LC/MS $(M+H)^+$
65		*N*-(3-Fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-4-(methylthio)benzamide	409.5
66		*N*-(3-Fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)furan-2-carboxamide	353.3
67		*N*-(3-Fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-1-naphthamide	413.4
68		*N*-(3-Fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)thiophene-3-carboxamide	369.4
69		*N*-(3-Fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)benzo[*d*][1,3]dioxole-5-carboxamide	407.4
70		*N*-(3-Fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)pyrazine-2-carboxamide	365.3
71		*N*-(3-Fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)picolinamide	364.4
72		*N*-(3-Fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)nicotinamide	364.4
73		*N*-(3-Fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)isonicotinamide	364.4
74		*N*-(3-Fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-nitrobenzamide	408.4
75		3,4-Difluoro-*N*-(3-fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)benzamide	399.3
76		*N*-(3-Fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-methylfuran-2-carboxamide	367.4
77		3-Acetyl-*N*-(3-fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)benzamide	405.4

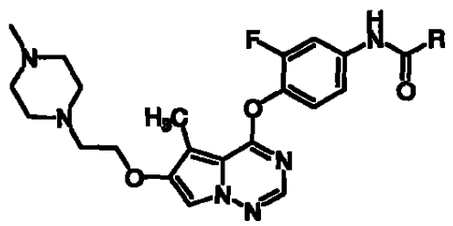
Example #	R	Compound Name	LC/MS $(M+H)^+$
78		*N*-(3-Fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3,5-dimethylisoxazole-4-carboxamide	382.4
79		*N*-(3-Fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-2-(pyridin-3-yl)thiazole-4-carboxamide	447.5
80		2-Fluoro-*N*-(3-fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-5-methylbenzamide	395.4
81		*N*-(3-Fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)benzo[*d*]thiazole-6-carboxamide	420.4
82		*N*-(3-Fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-5-methylisoxazole-3-carboxamide	368.3
83		*N*-(3-Fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)isoxazole-5-carboxamide	354.3
84		*N*-(3-Fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(methylsulfonyl)benzamide	441.5
85		4-Fluoro-*N*-(3-fluoro-4-(5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-methylbenzamide	395.4

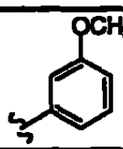
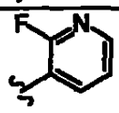
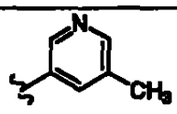
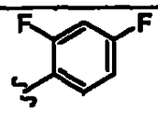
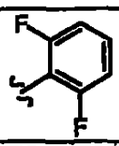
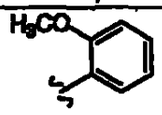
EXAMPLES 86 TO 130

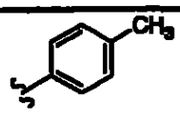
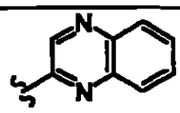
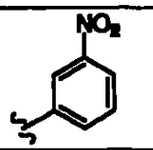
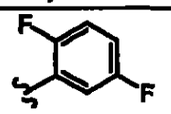
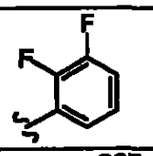
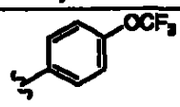
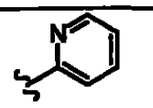
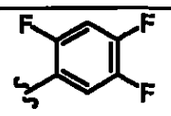
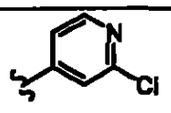
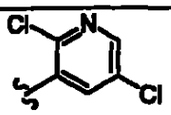
Examples 86 to 130 illustrated in Table 2 below were synthesized from 3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine (Compound B of Example 45). To an individual well of a 48-position MiniBlock® XT reactor was added 375 µL of a 0.2 M solution of the acid chloride in 1,2-dichloroethane (DCE) (0.075 mmol, 2.5 eq); 50 µL of pyridine (0.62 mmol, 20 eq); and 150 µL of a 0.2 M solution of the amine in DCE (0.03 mmol, 1 eq). The reactor was agitated via orbital shaker for 14 h. The crude product in DCE was diluted to a volume of 1 mL with methanol, then purified by standard preparative

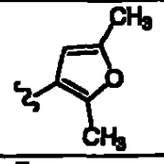
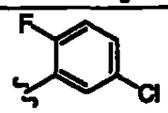
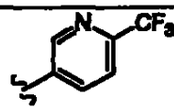
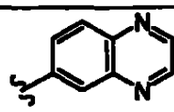
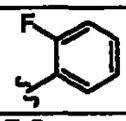
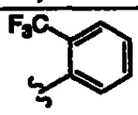
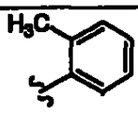
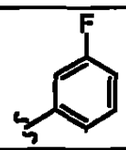
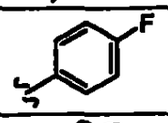
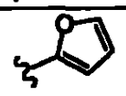
HPLC (H_2O/MeOH/0.1% TFA, gradient 35–90% MeOH over 10 min, 20×100 mm 5μm YMC ODS-A column) utilizing mass-directed fractionation. The purified sample was reconstituted in 1:1/MeOH:DCE, transferred to a tared 2.5 mL plastic microtube, dried via centrifugal evaporation, weighed and analyzed by *LCMS* (H_2O/MeOH/0.1% TFA).

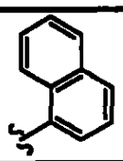
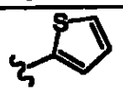
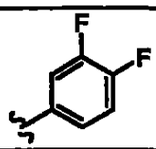
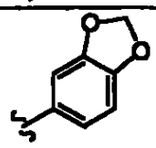
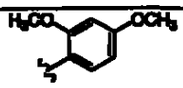
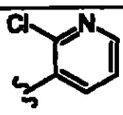
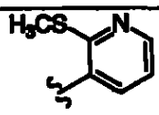
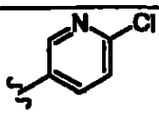
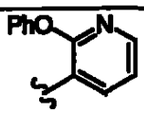
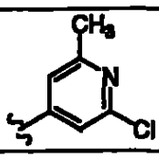
TABLE 2

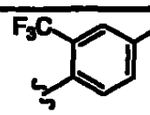
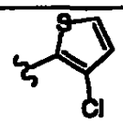
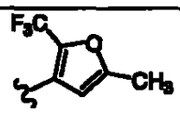
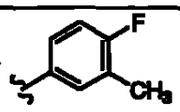
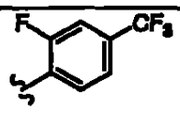
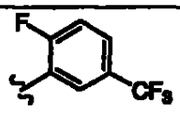
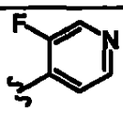
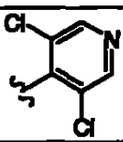


Example #	R	Compound Name	LC/MS $(M+H)^+$
86		*N*-(3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-methoxybenzamide	535.6
87		2-Fluoro-*N*-(3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)nicotinamide	524.6
88		*N*-(3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-5-methylnicotinamide	520.6
89		2,4-Difluoro-*N*-(3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)benzamide	541.6
90		2,6-Difluoro-*N*-(3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)benzamide	541.6
91		*N*-(3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-2-methoxybenzamide	535.6

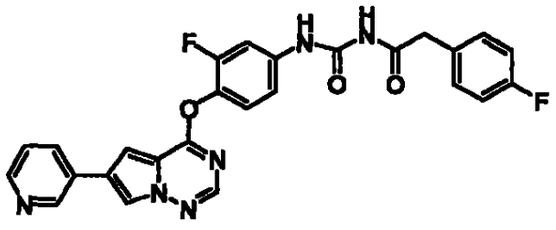
Example #	R	Compound Name	LC/MS $(M+H)^+$
92		*N*-(3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-4-methylbenzamide	519.6
93		*N*-(3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)quinoxaline-2-carboxamide	557.6
94		*N*-(3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-nitrobenzamide	550.6
95		2,5-Difluoro-*N*-(3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)benzamide	541.6
96		2,3-Difluoro-*N*-(3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)benzamide	541.6
97		*N*-(3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-4-(trifluoromethoxy)benzamide	589.6
98		*N*-(3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)picolinamide	506.6
99		2,4,5-Trifluoro-*N*-(3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)benzamide	559.5
100		2-Chloro-*N*-(3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)isonicotinamide	541.0
101		2,5-Dichloro-*N*-(3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)nicotinamide	575.4

Example #	R	Compound Name	LC/MS $(M+H)^+$
102		*N*-(3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-2,5-dimethylfuran-3-carboxamide	523.6
103		5-Chloro-2-fluoro-*N*-(3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)benzamide	558.0
104		*N*-(3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-6-(trifluoromethyl)nicotinamide	574.6
105		*N*-(3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)furan-3-carboxamide	495.5
106		*N*-(3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)quinoxaline-6-carboxamide	557.6
107		2-Fluoro-*N*-(3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)benzamide	523.6
108		*N*-(3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-2-(trifluoromethyl)benzamide	573.6
109		*N*-(3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-2-methylbenzamide	519.6
110		3-Fluoro-*N*-(3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)benzamide	523.6
111		4-Fluoro-*N*-(3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)benzamide	523.6
112		*N*-(3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)furan-2-carboxamide	495.5

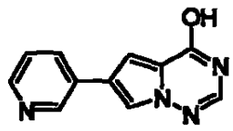
Example #	R	Compound Name	LC/MS $(M+H)^+$
113		*N*-(3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-1-naphthamide	555.6
114		*N*-(3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)thiophene-2-carboxamide	511.6
115		3,4-Difluoro-*N*-(3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)benzamide	541.6
116		*N*-(3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)benzo[d][1,3]dioxole-5-carboxamide	549.6
117		*N*-(3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-2,4-dimethoxybenzamide	565.6
118		2-Chloro-*N*-(3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)nicotinamide	541.0
119		*N*-(3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-2-(methylthio)nicotinamide	552.7
120		6-Chloro-*N*-(3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)nicotinamide	541.0
121		*N*-(3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-2-phenoxynicotinamide	598.7
122		2-Chloro-*N*-(3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-6-methylisonicotinamide	555.0

Example #	R	Compound Name	LC/MS $(M+H)^+$
123		4-Fluoro-*N*-(3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-2-(trifluoromethyl)benzamide	591.6
124		3-Chloro-*N*-(3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)thiophene-2-carboxamide	546.0
125		*N*-(3-Fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-5-methyl-2-(trifluoromethyl)furan-3-carboxamide	577.6
126		4-Fluoro-*N*-(3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-methylbenzamide	537.6
127		2-Fluoro-*N*-(3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-4-(trifluoromethyl)benzamide	591.6
128		2-Fluoro-*N*-(3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-5-(trifluoromethyl)benzamide	591.6
129		3-Fluoro-*N*-(3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)isonicotinamide	524.6
130		3,5-Dichloro-*N*-(3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)isonicotinamide	575.5

EXAMPLE 131

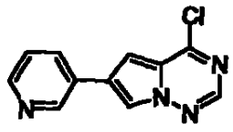


1-(3-Fluoro-4-(6-(pyridin-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2(4-fluorophenyl)acetyl)urea, trifluoroacetic acid salt



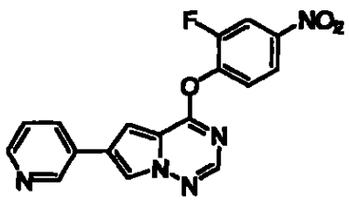
A) **6-(Pyridin-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol**

A solution of 6-bromopyrrolo[2,1-*f*][1,2,4]triazin-4-ol (100 mg, 0.47 mmol, prepared from methyl 4-bromo-1*H*-pyrrole-2-carboxylate: see, generally, Kitamura, C. and Yamashita, Y. *J. Chem. Soc. Perkin Trans.* 1, 1997, 1443, the disclosure of which is herein incorporated by reference, using a similar procedure outlined in the PCT Appl. WO 00/71129) and pyridin-3-ylboronic acid (172 mg, 1.40 mmol) in 2 mL of DMF and 2 mL of saturated aqueous K_2CO_3 was degassed and then $Pd(PPh_3)_4$ (57 mg, 0.05 mmol) was added. The mixture was then heated to 120 °C for 3 h. LC-MS analysis indicated the disappearance of starting material. The mixture was cooled down and the solution was filtered. The filtrate was purified on preparative HPLC to afford the title compound (100 mg, 65%) as a TFA salt. MS(ESI$^+$) *m/z* 213.2 $(M + H)^+$.



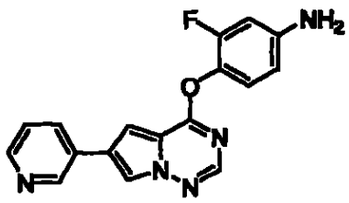
B) **4-Chloro-6-(pyridin-3-yl)pyrrolo[2,1-*f*][1,2,4]triazine**

To a suspension of 6-(pyridin-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol (100 mg, 0.30 mmol) in 10 mL of toluene were added $POCl_3$ (0.18 mL, 1.88 mmol) and DIEA (0.09 mL, 0.5 mmol). The suspension was heated at 100 °C for 7 h. After cooling down, the excess $POCl_3$ was removed under reduced pressure. The residue was suspended in EtOAc, and then neutralized with sat. $NaHCO_3$. The organic layer was then washed with brine and dried over $MgSO_4$. After filtration and concentration, the residue was purified by flash column chromatography to afford the title compound (23 mg, 33%). MS(ESI$^+$) *m/z* 231.2/233.2 $(M + H)^+$.



C) **4-(2-Fluoro-4-nitrophenoxy)-6-(pyridin-3-yl)pyrrolo[2,1-*f*][1,2,4]triazine**

Following a procedure similar to the that for the synthesis of Compound B of Example 2, 4-chloro-6-(pyridin-3-yl)pyrrolo[2,1-*f*][1,2,4]triazine (23 mg, 0.1 mmol) was converted to the title compound (35 mg, 95%). MS(ESI$^+$) *m/z* 352.3 $(M + H)^+$.



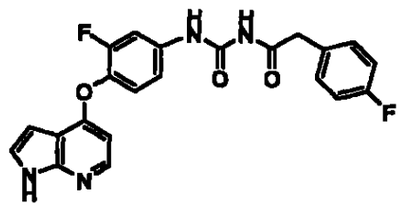
D) **3-Fluoro-4-(6-(pyridin-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine**

Following a procedure similar to that for the synthesis of Compound C of Example 36, 4-(2-fluoro-4-nitrophenoxy)-6-(pyridin-3-yl)pyrrolo[2,1-*f*][1,2,4]triazine (35 mg, 0.10 mmol) was converted to the title compound (15 mg, 46%). MS(ESI$^+$) *m/z* 322.3 $(M + H)^+$.

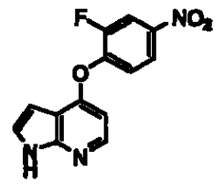
E) **1-(3-Fluoro-4-(6-(pyridin-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3(2-(4-fluorophenyl)acetyl)urea, trifluoroacetic acid salt**

The title compound was prepared using following a procedure similar to that for the synthesis of Example 46, 3-fluoro-4-(6-(pyridin-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine (15 mg, 0.046 mmol) was converted to the title compound (5.0 mg, 18%) as a TFA salt. ^{1}H NMR (DMSO-d_6) δ 10.99 (s, 1H), 10.53 (s, 1H), 9.12 (s, 1H), 8.75 (s, 1H), 8.50 (m, 1H), 8.30 (m, 1H), 8.12 (s, 1H), 7.67 (m, 2H), 7.30-7.50 (m, 5H), 7.12 (m, 2H), 3.69 (s, 2H); MS(ESI$^+$) *m/z* 501.2 $(M + H)^+$.

EXAMPLE 132

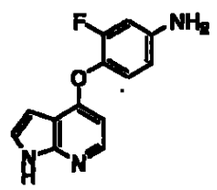


1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl) acetyl)urea, hydrochloride salt



A) **4-(2-Fluoro-4-nitrophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridine**

A mixture of 4-chloro-1*H*-pyrrolo[2,3-*b*]pyridine (457 mg, 3.0 mmol, prepared according to Thibault, C. et al. *Org. Lett.* 2003, *5*, 5023) and 2-fluoro-4-nitrophenol (706 mg, 4.5 mmol), and *N,N*-diisopropylethylamine (580 mg, 4.5 mmol) in 1-methyl-2-prolidinone (NMP) (3 mL) was heated at 200 °C under microwave irradiation for 1.0 h. The mixture was diluted with ethyl acetate (150 mL), washed with sat. aq. KH_2PO_4 solution, and Na_2CO_3 (aq. 1 M), dried over Na_2SO_4. The product was purified by flash column chromatography (silica gel, eluting with CH_2Cl_2 to 30% EtOAc/CH_2Cl_2) to afford a brown solid (350 mg, 43%). MS(ESI$^+$) *m/z* 274 $(M + H)^+$.



B) **4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorobenzenamine**

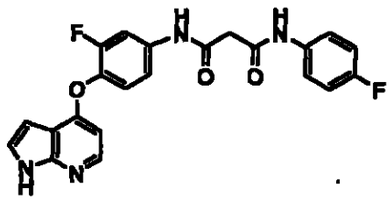
To a suspension of 4-(2-fluoro-4-nitrophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridine (300 mg, 1.1 mmol) in tetrahydrofuran (5 mL) and methanol (10 mL), were added zinc powder (350 mg, 5.5 mmol) and ammonium chloride (294 mg, 5.5 mmol). The mixture was stirred at rt overnight. The mixture was filtered through a pad of Celite®,

rinsed with methanol. The filtrate was concentrated. The product was purified by flash column chromatography (silica gel, 1-5% MeOH in CH_2Cl_2) to afford the desired product (205 mg, 77%) as an off-white solid. MS(ESI$^+$) *m/z* 244 $(M + H)^+$.

C) **1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, hydrochloride salt**

A mixture of 4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorobenzenamine (30 mg, 0.12 mmol) and 2-(4-fluorophenyl)acetyl isocyanate, (Compound C, Example 4) (0.25 M in toluene, 0.18 mmol) in THF (0.5 mL) was stirred at rt for 1 h. The mixture was concentrated *in vacuo*, purified by preparative HPLC. The desired fractions were lyophilized to give a white TFA salt, which was dissolved in small amount of MeOH/H_2O with 1 N HCl (0.2 mL). This solution was then lyophilized to afford the title compound (15 mg, 27%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 11.74 (s, 1H), 8.12 (d, 1H, J = 6.4 Hz), 7.73 (dd, 1H, J = 2.4, 13.0 Hz), 7.39 (d, 1H, J = 3.6 Hz), 6.90-7.3 (m, 6H), 6.65 (d, 1H, J = 6.4 Hz), 6.50 (d, 1H, J = 3.2 Hz), 3.68 (s, 2H); MS(ESI$^+$) *m/z* 423 $(M + H)^+$.

EXAMPLE 133

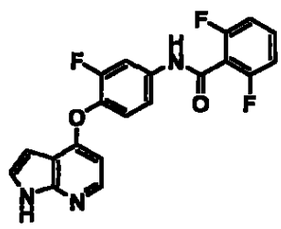


N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(4-fluorophenyl) malonamide, trifluoroacetic acid salt

To a solution of 4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorobenzenamine (Compound B, Example 132; 25 mg, 0.10 mmol) and 3-(4-fluorophenylamino)-3-oxopropanoic acid, Compound A, Example 25 (25 mg, 1.27 mmol) in DMF (0.5 mL), was added TBTU (48 mg, 0.15 mmol), followed by DIPEA (0.1 mL). The resulting mixture was stirred at rt for 2 h. The product was purified by preparative HPLC to afford the title compound (TFA salt, 26 mg, 62%) as a white solid. ^{1}H NMR ($CDCl_3$)

δ 7.94 (d, 1H, J = 6.4 Hz), 7.66 (dd, 1H, J = 2.4, 13.0 Hz), 7.54 (m, 2H), 6.90-7.25 (m, 5H), 6.31 (d, 2H, J = 2.8 Hz), 3.37 (s, 2H); MS(ESI$^+$) m/z 423 $(M + H)^+$.

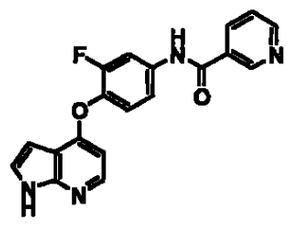
EXAMPLE 134



***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-2,6-difluorobenzamide**

To a solution of 4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorobenzenamine (Compound B, Example 132; 20 mg, 0. 08 mmol) in DMF (0.5 mL), was added 2,6-difluorobenzoyl chloride (20 mg, 0.11 mmol), followed by DIPEA (0.1 mL). The mixture was stirred at rt for 2 h and the product was purified by preparative HPLC. The desired fractions were lyophilized to give a white TFA salt, which was neutralized with sat. aq. sodium bicarbonate solution. The mixture was extracted with EtOAc (3 x 5 mL). The organic layers were dried and concentrated *in vacuo* to afford the title compound (14 mg, 37%) as a white solid. ^{1}H NMR (CD_3OD) δ 8.15 (d, 1H, J = 6.4 Hz), 7.87 (d, 1H, J = 2.4, 12.8 Hz), 7.40 (m, 4H), 7.04 (m, 2H), 6.69 (d, 2H, J = 7.6 Hz), 6.52 (m, 1H); MS(ESI$^+$) m/z 384 $(M + H)^+$.

EXAMPLE 135

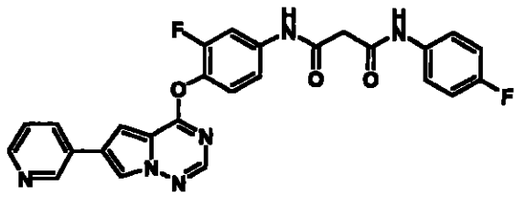


***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)nicotinamide**

In a similar manner as described for the preparation of Example 134, the title compound was isolated as a TFA salt and was prepared using commercially available nicotinyl chloride and 4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorobenzenamine (Compound B, Example 132). Yield: 55%. ^{1}H NMR (CD_3OD) δ 9.09 (s, 1H), 8.73 (d,

1H, J = 4.4 Hz), 8.44 (d, 1H, J = 8.0 Hz), 8.22 (d, 1H, J = 6.8 Hz), 8.22 (dd, 1H, J = 2.4, 12.4 Hz), 7.40-7.80 (m, 4H), 6.79 (d, 1H, J = 6.8 Hz), 6.59 (d, 1H, J = 3.6 Hz); MS(ESI$^+$) m/z 349 $(M + H)^+$.

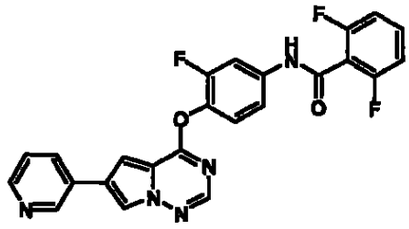
EXAMPLE 136



N^1-(3-Fluoro-4-(6-(pyridin-3-yl)pyrrolo[2,1-f][1,2,4]triazin-4-yloxy)phenyl)-N^3-(4-fluorophenyl)malonamide, trifluoroacetic acid salt

To a homogeneous solution of 3-fluoro-4-(6-(pyridin-3-yl)pyrrolo[2,1-f][1,2,4]triazin-4-yloxy)benzenamine (32 mg, 0.10 mmol, Compound D of Example 131) and 3-(4-fluorophenylamino)-3-oxopropanoic acid (20 mg, 0.10 mmol, Compound A of Example 25) in anhydrous DMF (3 mL), at room temperature under nitrogen atmosphere, was added diisopropylethylamine (26 µL, 0.15 mmol). The mixture was stirred for five minutes before o-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate (48 mg, 0.15 mmol) was added in one portion. The mixture was stirred for sixty-three hours before being partitioned between chloroform and brine. The aqueous layer was extracted three times with chloroform, and the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to remove volatiles. The resultant residue was purified by preparative HPLC (YMC S10 ODS, 30 x 500mm, 30 minute gradient from 58% to 90% aqueous methanol with 0.1% TFA). The appropriate fractions were combined and lyophilized to afford the title compound (18 mg, 30%) as an off-white solid. ^{1}H NMR ($CDCl_3$) δ 10.35 (br s, 1H), 9.49 (s, 1H), 9.18 (s, 1H), 8.80-8.65 (m, 2H), 8.36-8.29 (m, 1H), 8.17 (s, 1H), 8.04 (s, 1H), 7.83-7.68 (m, 2H), 7.55-7.49 (m, 2H), 7.35-7.23 (m, 2H), 7.10-7.00 (m, 2H), 3.58 (s, 2H); HRMS(ESI), 501.1487 $(M + H)^+$ calc, 501.1491 $(M + H)^+$ found.

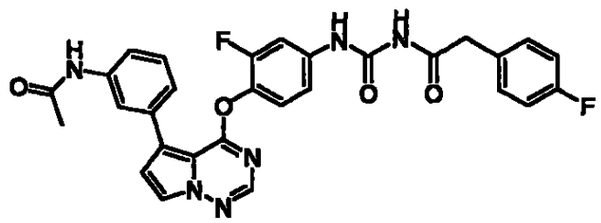
EXAMPLE 137



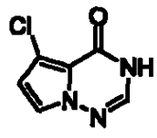
2,6-Difluoro-*N*-(3-fluoro-4-(6-(pyridin-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)benzamide, trifluoroacetic acid salt

To a homogeneous solution of 3-fluoro-4-(6-(pyridin-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine (64 mg, 0.20 mmol, Compound D of Example 131) in anhydrous chloroform (5 mL), at room temperature under nitrogen atmosphere, was added diisopropylethylamine (49 µL, 0.28 mmol). The mixture was stirred for five minutes before 2,6-difluorobenzoyl chloride (33 µL, 0.26 mmol, Aldrich) was added. The mixture was stirred for eighty-seven hours before being partitioned between chloroform and saturated aqueous sodium bicarbonate. The organic layer was washed once with saturated aqueous sodium bicarbonate and once with brine, before the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to remove volatiles. The resultant residue was purified by preparative HPLC (YMC S10 ODS, 30 x 500mm, 30 minute gradient from 58% to 90% aqueous methanol with 0.1% TFA). The appropriate fractions were combined and lyophilized to afford the title compound (24 mg, 21%) as a white solid. ^{1}H NMR (CD_3OD) δ 9.20 (s, 1H), 8.85-8.78 (m, 1H), 8.65-8.60 (m, 1H), 8.51 (d, 1H, J = 1.6 Hz), 8.00 (s, 1H), 7.98-7.90 (m, 1H), 7.81-7.74 (m, 1H), 7.58 (d, 1H, J = 1.8 Hz), 7.51-7.27 (m, 3H), 7.00-7.10 (m, 2H); HRMS(ESI), 462.1178 $(M + H)^+$ calc, 462.1168 $(M + H)^+$ found.

EXAMPLE 138

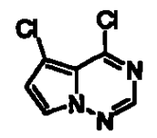


1-(4-(5-(3-Acetamidophenyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea



A) 5-Chloropyrrolo[2,1-*f*][1,2,4]triazin-4(3*H*)-one

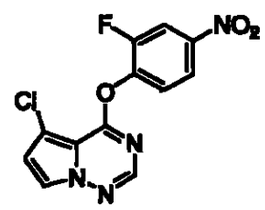
A solution of methyl 1-amino-3-chloro-1*H*-pyrrole-2-carboxylate (10.0 g, 57.3 mmol, WO 03/099286: Compound A of Example 9) in formamide (40 mL) was heated at 170 °C for 1 h and then at 190 °C for 1 h. Upon cooling to room temperature, the mixture solidified. The product was purified by recrystallization from ethyl acetate to give the title compound (6.53 g, 67%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 10.24 (br s, 1H), 7.48 (d, 1H, J = 3.6 Hz), 7.29 (d, 1H, J = 2.8 Hz), 6.47 (d, 1H, J = 2.8 Hz); MS(ESI$^+$) *m/z* 170.1 $(M + H)^+$.



B) 4,5-Dichloropyrrolo[2,1-*f*][1,2,4]triazine

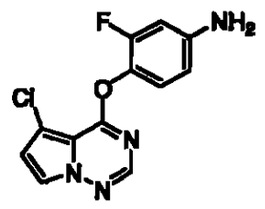
To a solution of 5-chloropyrrolo[2,1-*f*][1,2,4]triazin-4(3*H*)-one (5.00 g, 29.5 mmol) in toluene (100 mL) at rt under nitrogen was added diisopropylethylamine (5.14 mL, 29.5 mmol) followed by phosphorus(III) oxychloride (8.25 mL, 88.5 mmol). The mixture was heated at 100 °C for 20 h and was then cooled to rt. The reaction was slowly added to saturated aqueous sodium bicarbonate solution (500 mL) at 0 °C. After the addition was complete, the mixture was stirred at rt for 30 min. The aqueous phase was extracted with ethyl acetate (3 x 500 mL), dried over anhydrous

$MgSO_4$, and concentrated *in vacuo* to give the crude product (3.73 g, 67%) as a yellow solid which was used without further purification. ^1H NMR ($CDCl_3$) δ 8.03 (s, 1H), 7.70 (d, 1H, J = 2.8 Hz), 6.84 (d, 1H, J = 2.8 Hz); MS(ESI$^+$) *m/z* 188.1 $(M + H)^+$.



C) **5-Chloro-4-(2-fluoro-4-nitrophenoxy)pyrrolo[2,1-*f*][1,2,4]triazine**

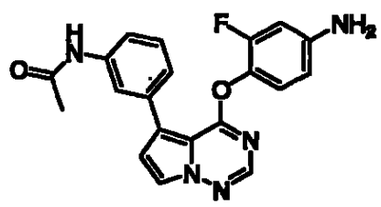
A mixture of 4,5-dichloropyrrolo[2,1-*f*][1,2,4]triazine (3.73 g, 19.8 mmol), 2-fluoro-4-nitrophenol (3.43 g, 21.8 mmol) and potassium carbonate (5.47 g, 39.6 mmol) in DMF (100 mL) was stirred at 60 °C for 1 h. After cooling to rt, the reaction was filtered through a short plug of silica gel with ethyl acetate and then concentrated *in vacuo*. The crude product was purified by recrystallization from ethyl acetate / hexanes (1:1) to give the title compound (4.37 g, 71%) as a white solid. ^1H NMR ($CDCl_3$) δ 8.22-8.17 (m, 2H), 7.92 (s, 1H), 7.77 (d, 1H, J = 2.8 Hz), 7.58 (t, 1H, J = 7.2 Hz), 6.87 (d, 1H, J = 3.2 Hz); MS(ESI$^+$) *m/z* 309.3 $(M + H)^+$.



D) **4-(5-Chloropyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorobenzenamine**

To a solution of 5-chloro-4-(2-fluoro-4-nitrophenoxy)pyrrolo[2,1-*f*][1,2,4]triazine (2.00 g, 6.48 mmol) in THF (50 mL) / MeOH (80 mL) was added zinc dust (2.12 g, 32.4 mmol) followed by ammonium chloride (1.73 g, 32.4 mmol). After stirring at rt for 8 h, the reaction mixture was filtered through Celite® with MeOH and then concentrated *in vacuo*. The residue was taken up in ethyl acetate (200 mL) and washed with water (2 x 100 mL) then brine (1 x 100 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (50 % EtOAc / hexanes) to give the

title compound (1.51 g, 84%) as a pale yellow solid. ^{1}H NMR ($CDCl_3$) δ 7.95 (s, 1H), 7.69 (d, 1H, J = 2.8 Hz), 7.09 (t, 1H, J = 8.4 Hz), 6.79 (d, 1H, J = 2.8 Hz), 6.58 (dd, 1H, J = 11.6, 2.6 Hz), 6.51 (d, 1H, J = 8.7 Hz), 3.92 (br s, 2H); MS(ESI$^+$) *m/z* 279.2 $(M + H)^+$.



E) ***N*-(3-(4-(4-Amino-2-fluorophenoxy)pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)phenyl)acetamide**

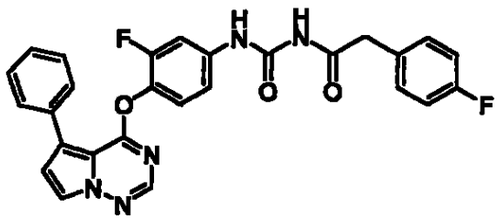
A flask was charged with palladium acetate (4.5 mg, 0.02 mmol), X-Phos ligand (24 mg, 0.05 mmol, Strem), 4-(5-chloropyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorobenzenamine (56 mg, 0.20 mmol), 3-acetamidobenzene boronic acid (72 mg, 0.40 mmol, Lancaster), and potassium phosphate (127 mg, 0.60 mmol) in that order. The flask was flushed with nitrogen and then *t*-BuOH was added (0.40 mL). The mixture was heated at 80 °C for 8 h. Additional shots of palladium acetate (4.5 mg, 0.02 mmol), X-Phos ligand (24 mg, 0.05 mmol), and 3-acetamidobenzene boronic acid (72 mg, 0.40 mmol) were added and the reaction was stirred an additional 9 h at 80 °C. After cooling to rt, the reaction was filtered using MeOH to remove the potassium phosphate and then concentrated *in vacuo*. The crude product was purified by reverse phase prep HPLC and the appropriate fractions were concentrated *in vacuo* to remove MeOH. The resulting aqueous layer was made basic with saturated sodium bicarbonate solution and extracted with ethyl acetate. The combined organic extracts were dried over anhydrous sodium sulfate and concentrated *in vacuo* to give the title compound (20 mg, 26%) as a white solid. ^{1}H NMR (CD_3OD) δ 7.84-7.94 (m, 2H), 7.44-7.41 (m, 1H), 7.34-7.19 (m, 3H), 6.92 (t, 1H, J = 8.8 Hz), 6.87 (d, 1H, J = 2.8 Hz), 6.50 (dd, 1H, J = 12.4, 2.4 Hz), 6.46-6.43 (m, 1H), 2.04 (s, 3H); MS(ESI$^+$) *m/z* 378.3 $(M + H)^+$.

F) 1-(4-(5-(3-Acetamidophenyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea

To a solution of *N*-(3-(4-(4-amino-2-fluorophenoxy)pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)phenyl)acetamide (20 mg, 0.053 mmol) in dichloromethane (0.5 mL) at rt under nitrogen was added 2-(4-fluorophenyl)acetyl isocyanate (250 µL, 0.064 mmol, 0.25 M in toluene, Compound C of Example 4). The reaction was stirred at rt for 1 h and was then concentrated *in vacuo*. The residue was suspended in methanol and filtered to collect 14 mg (47%) of the title compound as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.09 (s, 1H), 10.63 (s, 1H), 10.04 (s, 1H), 8.25-8.21 (m, 2H), 8.05 (s, 1H), 7.78 (d, 1H, J = 13.2 Hz), 7.51-7.38 (m, 7H), 7.23 (t, 2H, J = 8.4 Hz), 7.13 (s, 1H), 3.81 (s, 2H), 2.10 (s, 3H); MS(ESI$^+$) *m/z* 557.4 $(M + H)^+$.

Examples 139-144 were prepared in a manner similar to Example 138.

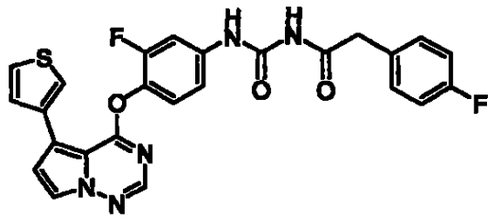
EXAMPLE 139



1-(3-Fluoro-4-(5-phenylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea

^{1}H NMR (DMSO-d_6) δ 10.56 (s, 1H), 8.55 (s, 1H), 7.89 (s, 1H), 7.77 (d, 1H, J = 2.8 Hz), 7.62-7.57 (m, 3H), 7.33 (t, 2H, J = 7.7 Hz), 7.26-7.19 (m, 4H), 7.10 (m, 1H), 7.02 (t, 2H, J = 8.6 Hz), 6.88 (d, 1H, J = 2.7 Hz), 3.65 (s, 2H); MS(ESI$^+$) *m/z* 500.3 $(M + H)^+$.

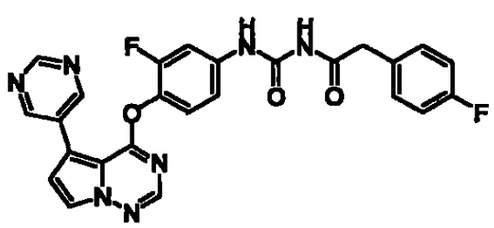
EXAMPLE 140



1-(3-Fluoro-4-(5-(thiophen-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea

^{1}H NMR (DMSO-d_6) δ 11.05 (s, 1H), 10.59 (s, 1H), 8.16 (d, 1H, J = 2.8 Hz), 8.12 (s, 1H), 7.81 (d, 1H, J = 1.6 Hz), 7.75 (dd, 1H, J = 12.4, 2 Hz), 7.62-7.49 (m, 3H), 7.39-7.36 (m, 3H), 7.21-7.16 (m, 3H), 3.76 (s, 2H); MS(ESI$^+$) *m/z* 506.3 (M + H)$^+$.

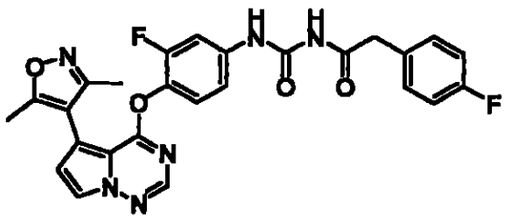
EXAMPLE 141



1-(3-Fluoro-4-(5-(pyrimidin-5-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea

^{1}H NMR (DMSO-d_6) δ 11.10 (s, 1H), 10.65 (s, 1H), 9.21 (s, 2H), 9.18 (s, 1H), 8.37 (d, 1H, J = 2.4 Hz), 8.31 (s, 1H), 7.80 (dd, 1H, J = 12.4, 2 Hz), 7.58 (t, 1H, J = 8.8 Hz), 7.44-7.40 (m, 4H), 7.23 (t, 2H, J = 8.4 Hz), 3.80 (s, 2H); MS(ESI$^+$) *m/z* 502.3 (M + H)$^+$.

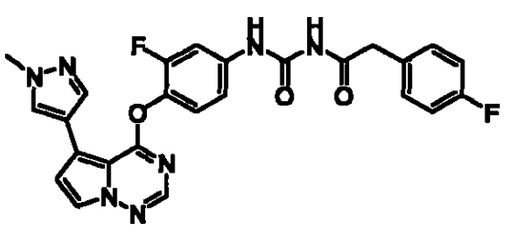
EXAMPLE 142



1-(4-(5-(3,5-Dimethylisoxazol-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea

^{1}H NMR (DMSO-d_6) δ 11.04 (s, 1H), 10.58 (s, 1H), 8.24 (d, 1H, J = 2.4 Hz), 8.17 (s, 1H), 7.42 (dd, 1H, J = 13.2, 2 Hz), 7.38-7.35 (m, 4H), 7.18 (t, 2H, J = 7.6 Hz), 7.06 (d, 1H, J = 2.8 Hz), 3.75 (s, 2H), 2.37 (s, 3H), 2.20 (s, 3H); MS(ESI$^+$) *m/z* 519.3 $(M + H)^+$.

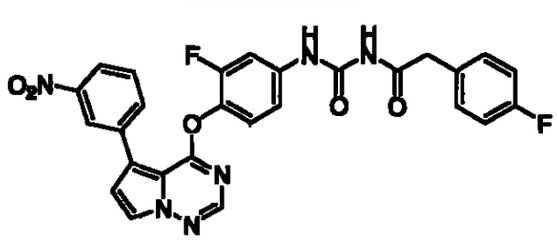
EXAMPLE 143



1-(3-Fluoro-4-(5-(1-methyl-1*H*-pyrazol-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea

^{1}H NMR (DMSO-d_6) δ 11.04 (s, 1H), 10.59 (s, 1H), 8.11 (d, 1H, J = 2.8 Hz), 8.05 (d, 2H, J = 2.4 Hz), 7.85 (s, 1H), 7.76 (dd, 1H, J = 12.4, 2 Hz), 7.52 (t, 1H, J = 8.4 Hz), 7.39-7.36 (m, 3H), 7.18 (t, 2H, J = 8.8 Hz), 7.12 (d, 1H, J = 2.8 Hz), 3.86 (s, 3H), 3.76 (s, 2H); MS(ESI$^+$) *m/z* 504.3 $(M + H)^+$.

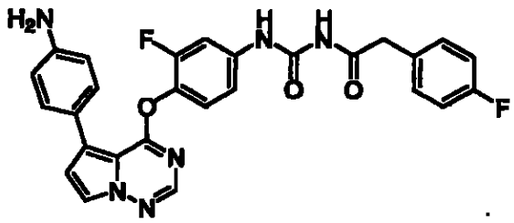
EXAMPLE 144



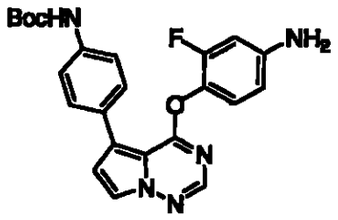
1-(3-Fluoro-4-(5-(3-nitrophenyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea

^{1}H NMR (DMSO-d_6) δ 11.03 (s, 1H), 10.57 (s, 1H), 8.62 (s, 1H), 8.27 (d, 1H, J = 2.4 Hz), 8.23 (s, 1H), 8.20-8.16 (m, 2H), 7.76-7.72 (m, 2H), 7.49 (t, 1H, J = 8.8 Hz), 7.39-7.34 (m, 4H), 7.18 (t, 2H, J = 9.2 Hz), 3.75 (s, 2H); MS(ESI$^+$) m/z 545.2 (M + H)$^+$.

EXAMPLE 145



1-(4-(5-(4-Aminophenyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea



A) ***tert*-Butyl 4-(4-(4-amino-2-fluorophenoxy)pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)phenylcarbamate**

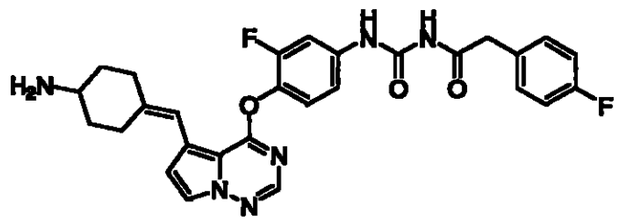
Prepared in a similar manner as Step B of Example 138 to give the title compound (46%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.88 (s, 1H), 7.73 (d, 1H, J = 4 Hz), 7.54 (d, 2H, J = 8 Hz), 7.33-7.30 (m, 2H), 6.93 (t, 1H, J = 7.6 Hz), 6.82 (d, 1H, J = 4 Hz), 6.60-6.47 (m, 2H), 1.44 (s, 9H); MS(ESI$^+$) m/z 436.4 (M + H)$^+$.

B) **1-(4-(5-(4-Aminophenyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea**

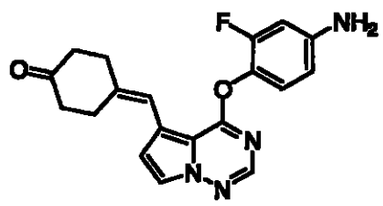
Prepared in a similar manner as Step F of Example 138 to give the Boc protected material (51%). The Boc protected material was suspended in ether (2 mL), cooled to 0 °C, and charged with TFA (0.5 mL). After stirring at rt for 1 h, the reaction was concentrated *in vacuo*. The residue was suspended in ethyl acetate (10 mL),

washed with saturated aqueous sodium bicarbonate solution (5 mL), dried over anhydrous sodium sulfate, and concentrated. The crude product was purified by flash chromatography on silica gel (60 % EtOAc / hexanes). Lyophilization from acetonitrile (1 mL) / water (3 mL) gave the title compound (38%) as a light brown solid. ^{1}H NMR (DMSO-d_6) δ 10.95 (s, 1H), 10.50 (s, 1H), 8.02 (d, 1H, J = 2.8 Hz), 7.98 (s, 1H), 7.67 (dd, 1H, J = 12.4, 2 Hz), 7.36 (t, 1H, J = 8.8 Hz), 7.31-7.28 (m, 5H), 7.10 (t, 2H, J = 8.8 Hz), 6.89 (d, 1H, J = 2.8 Hz), 6.51 (d, 2H, J = 8.8 Hz), 5.08 (s, 2H), 3.68 (s, 2H); MS(ESI$^+$) m/z 515.3 $(M + H)^+$.

EXAMPLE 146

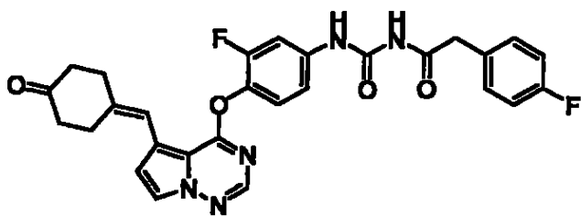


1-(4-(5-((4-Aminocyclohexylidene)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea



A) **4-((4-(4-Amino-2-fluorophenoxy)pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)methylene)cyclohexanone**

Prepared in a similar manner as Step E of Example 138 using 4-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methylene)cyclohexanone (prepared according to the procedure of Morrill, C. and Grubbs, R. H. *J. Org. Chem.* 2003, *68*, 6031-6034). to give the title compound (11%) as a yellow oil. ^{1}H NMR (CD_3OD) δ 7.76 (s, 1H), 7.73 (d, 1H, J = 2.8 Hz), 7.54-7.51 (m, 1H), 7.33 (d, 1H, J = 2.8 Hz), 6.92 (t, 1H, J = 7.6 Hz), 6.84 (d, 1H, J = 2.8 Hz), 6.46-6.41 (m, 1H), 2.83 (t, 2H, J = 6.8 Hz), 2.65 (t, 2H, J = 6.8 Hz), 2.45-2.38 (m, 4H); MS(ESI$^+$) m/z 353.2 $(M + H)^+$.



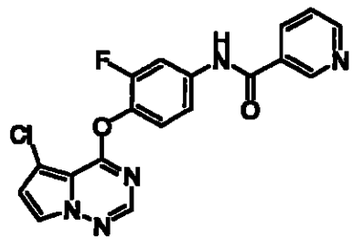
B) **1-(4-(5-(4-Aminophenyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea**

Prepared in a similar manner as Step F of Example 138 to give the title compound (38%) as a yellow solid. ^{1}H NMR (acetone-d_6) δ 10.62 (s, 1H), 9.87 (s, 1H), 7.80 (s, 1H), 7.79 (d, 1H, J = 2.8 Hz), 7.70 (dd, 1H, J = 12.8, 2.4 Hz), 7.33-7.19 (m, 4H), 6.96-6.93 (m, 3H), 6.16 (m, 1H), 3.75 (s, 2H), 2.82 (t, 2H, J = 6.8 Hz), 2.62 (t, 2H, J = 6.8 Hz), 2.37 (t, 2H, J = 6.8 Hz), 2.30 (t, 2H, J = 6.8 Hz); MS(ESI$^+$) *m/z* 532.2 $(M+H)^+$.

C) **1-(4-(5-((4-Aminocyclohexylidene)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea**

A solution of 1-(4-(5-(4-aminophenyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea (21 mg, 0.040 mmol) in methanol (0.5 mL) and THF (0.5 mL) at 0 °C was charged with ammonium acetate (30 mg, 0.40 mmol) followed by sodium cyanoborohydride (2.5 mg, 0.040 mmol). After stirring at 0 °C for 1 h, the reaction was concentrated *in vacuo*. The crude product was purified by reverse phase prep HPLC and the appropriate fractions were concentrated *in vacuo*. Toluene was added (2 x 5 mL) and concentrated to remove excess TFA. Lyophilization from acetonitrile (1 mL) / water (3 mL) gave the TFA salt of the title compound (19%) as a white solid. ^{1}H NMR (CD_3OD) δ 7.77 (s, 1H), 7.76 (d, 1H, J = 2.8 Hz), 7.63 (dd, 1H, J = 12.8, 2.4 Hz), 7.29-7.14 (m, 4H), 7.03-6.93 (m, 2H), 6.91 (d, 1H, J = 2.8 Hz), 6.67 (s, 1H), 3.62 (s, 2H), 3.15-3.08 (m, 1H), 2.50-2.30 (m, 2H), 2.21-2.05 (m, 2H), 1.46-1.30 (m, 4H); MS(ESI$^+$) *m/z* 533.2 $(M+H)^+$.

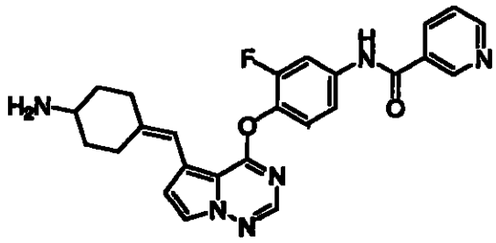
EXAMPLE 147



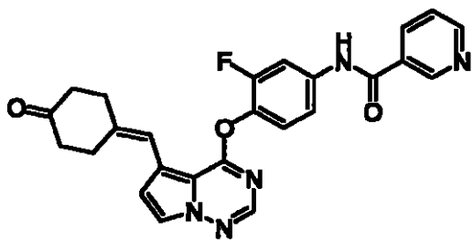
N-(4-(5-Chloropyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)nicotinamide

To 4-(5-chloropyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorobenzenamine (100 mg, 0.359 mmol, Compound D of Example 138) in DMF (2 mL) was added nicotinic acid (53 mg, 0.431 mmol, Aldrich), DIPEA (300 µL, 1.80 mmol), followed by TBTU (173 mg, 0.539 mmol, Fluka). After stirring at rt overnight, the reaction was diluted with 20 mL of EtOAc, washed with 10% aqueous lithium chloride solution (2 x 10 mL) followed by brine (1 x 10 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (10% MeOH / EtOAc) to give the title compound (125 mg, 91%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 10.75 (s, 1H), 9.14 (d, 1H, J = 2 Hz), 8.80 (dd, 1H, J = 4.8, 1.2 Hz), 8.34-8.31 (m, 1H), 8.18 (d, 1H, J = 2.8 Hz), 8.17 (s, 1H), 7.96 (dd, 1H, J = 12.8, 2 Hz), 7.66-7.60 (m, 2H), 7.54 (t, 1H, J = 8.8 Hz), 7.10 (d, 1H, J = 2.8 Hz); MS(ESI$^+$) *m/z* 383.9 $(M + H)^+$.

EXAMPLE 148



N-(4-(5-((4-Aminocyclohexylidene)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)nicotinamide



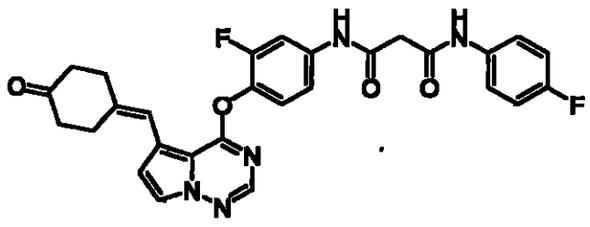
A) ***N*-(3-Fluoro-4-(5-((4-oxocyclohexylidene)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)nicotinamide**

Prepared in a similar manner as Step E of Example 138 to give the title compound (66%) as a yellow solid. ^{1}H NMR (DMSO-d_6) δ 10.75 (s, 1H), 9.14 (d, 1H, J = 2 Hz), 8.82 (dd, 1H, J = 4.8, 1.2 Hz), 8.36-8.33 (m, 1H), 8.13 (d, 1H, J = 2.8 Hz), 8.10 (s, 1H), 7.99-7.93 (m, 1H), 7.68-7.63 (m, 1H), 7.54 (t, 1H, J = 8.8 Hz), 7.07 (d, 1H, J = 2.8 Hz), 6.92 (s, 1H), 2.90 (t, 2H, J = 6.8 Hz), 2.74 (t, 2H, J = 6.8 Hz), 2.51 (t, 2H, J = 6.8 Hz), 2.42 (t, 2H, J = 6.8 Hz); MS(ESI$^+$) *m/z* 458.2 $(M + H)^+$.

B) ***N*-(4-(5-((4-Aminocyclohexylidene)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)nicotinamide**

Prepared in a similar manner as Step C of Example 146 to give the TFA salt of the title compound (6%) as a pale yellow solid. ^{1}H NMR (CD_3OD) δ 9.15 (s, 1H), 8.80 (s, 1H), 8.59 (d, 1H, J = 8 Hz), 7.84-7.76 (m, 4H), 7.48 (d, 1H, J = 8 Hz), 7.29 (t, 1H, J = 8 Hz), 6.80 (d, 1H, J = 4 Hz), 6.67 (s, 1H), 3.62 (s, 2H), 3.10-3.08 (m, 1H), 2.48-2.05 (m, 4H), 1.47-1.20 (m, 4H); MS(ESI$^+$) *m/z* 459.2 $(M + H)^+$.

EXAMPLE 149

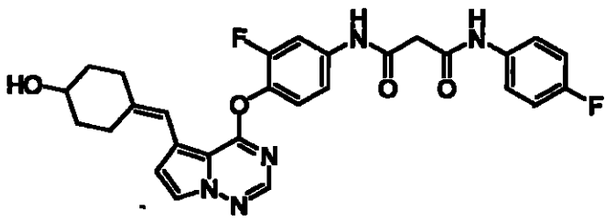


N^1-(3-Fluoro-4-(5-((4-oxocyclohexylidene)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-N^3-(4-fluorophenyl)malonamide

Suzuki coupling in a similar manner as Step E of Example 138 followed by malonamide formation as in Step A of Example 133 gave the title compound (39%) as

a yellow solid. ^{1}H NMR (DMSO-d_6) δ 10.55 (s, 1H), 10.31 (s, 1H), 8.15 (d, 1H, J = 2.4 Hz), 8.11 (s, 1H), 7.86 (dd, 1H, J = 12.4, 2.8 Hz), 7.52 (t, 1H, J = 8.8 Hz), 7.44-7.42 (m, 1H), 7.25-7.19 (m, 2H), 7.09 (d, 1H, J = 2.8 Hz), 6.93 (s, 1H), 3.54 (s, 2H), 2.91 (t, 2H, J = 6.8 Hz), 2.73 (t, 2H, J = 6.4 Hz), 2.53 (t, 2H, J = 6.8 Hz), 2.45 (t, 2H, J = 6.8 Hz); MS(ESI$^+$) m/z 532.3 $(M + H)^+$.

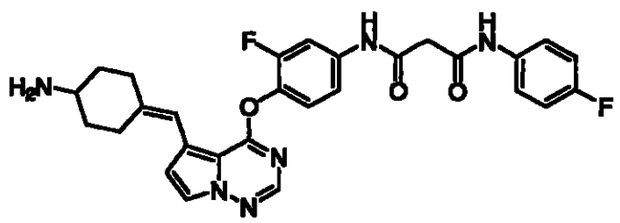
EXAMPLE 150



N^1-(3-Fluoro-4-(5-((4-hydroxycyclohexylidene)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-N^3-(4-fluorophenyl)malonamide

To N^1-(3-fluoro-4-(5-((4-oxocyclohexylidene)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-N^3-(4-fluorophenyl)malonamide (80 mg, 0.15 mmol, Example 149) in methanol (2 mL) at 0 °C was added a spatula tip of sodium borohydride. The reaction was stirred at 0 °C for 30 min and was then quenched with saturated aqueous ammonium chloride solution (10 mL) and stirred at 0 °C for 5 min. The mixture was extracted with ethyl acetate (3 x 10 mL) and the combined organic extracts were dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (10% MeOH / EtOAc) to give the title compound (30 mg, 37%) as an off-white solid. ^{1}H NMR (DMSO-d_6) δ 10.57 (s, 1H), 10.34 (s, 1H), 8.11 (d, 1H, J = 2.8 Hz), 8.10 (s, 1H), 7.86 (dd, 1H, J = 12.8, 2.4 Hz), 7.71-7.68 (m, 2H), 7.53 (t, 1H, J = 8.4 Hz), 7.46-7.43 (m, 1H), 7.25-7.21 (m, 2H), 6.99 (d, 1H, J = 2.8 Hz), 6.64 (s, 1H), 4.65 (br s, 1H), 3.76-3.75 (m, 1H), 3.56 (s, 2H), 2.90-2.85 (m, 1H), 2.51-2.45 (m, 1H), 2.27-2.24 (m, 2H), 1.92-1.85 (m, 2H), 1.46-1.41 (m, 2H); MS(ESI$^+$) m/z 534.3 $(M + H)^+$.

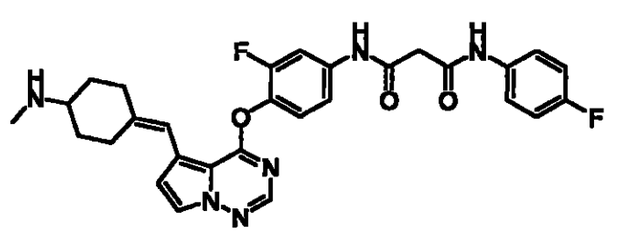
EXAMPLE 151



N^1-(4-(5-((4-Aminocyclohexylidene)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-N^3-(4-fluorophenyl)malonamide

Prepared in a similar manner as Step C of Example 146 to give the TFA salt of the title compound (12%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 10.51 (s, 1H), 10.26 (s, 1H), 8.02 (d, 1H, J = 2.4 Hz), 7.99 (s, 1H), 7.74 (dd, 1H, J = 12.8, 2 Hz), 7.59-7.55 (m, 2H), 7.38 (t, 1H, J = 8.4 Hz), 7.32-7.35 (m, 1H), 7.13-7.08 (m, 2H), 6.90 (d, 1H, J = 2.8 Hz), 6.59 (s, 1H), 3.44 (s, 2H), 2.95-3.00 (m, 1H), 2.20-2.41 (m, 2H), 1.96-2.11 (m, 2H), 1.32-1.39 (m, 2H), 1.17-1.13 (m, 2H); MS(ESI$^+$) *m/z* 533.3 $(M + H)^+$.

EXAMPLE 152

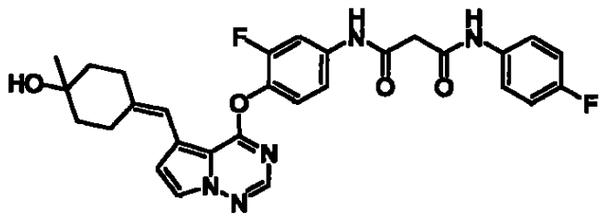


N^1-(3-Fluoro-4-(5-((4-(methylamino)cyclohexylidene)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-N^3-(4-fluorophenyl)malonamide, trifluoroacetic acid salt

To N^1-(3-fluoro-4-(5-((4-oxocyclohexylidene)methyl)pyrrolo[2,1-*f*][,2,4]triazin-4-yloxy)phenyl)-N^3-(4-fluorophenyl)malonamide (20 mg, 0.038 mmol, Example 149) in dichloroethane (1 mL) was added methylamine (23 μL, 0.045 mmol, 2 M THF), acetic acid (2.6 μL, 0.045 mmol), followed by sodium triacetoxyborohydride (13 mg, 0.056 mmol). After stirring at rt for 2 h, the reaction was quenched with 5% aqueous sodium bicarbonate solution (1 mL). The layers were separated and the organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The crude product was purified by reverse phase

prep HPLC and the appropriate fractions were concentrated *in vacuo*. Toluene was added (2 x 4 mL) and concentrated to remove excess TFA. Lyophilization from acetonitrile (1 mL) / water (3 mL) gave the TFA salt of the title compound (11 mg, 44%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 10.51 (s, 1H), 10.26 (s, 1H), 8.02 (d, 1H, J = 2.8 Hz), 8.00 (s, 1H), 7.74 (dd, 1H, J = 12.8, 2 Hz), 7.59-7.55 (m, 2H), 7.40 (t, 1H, J = 8.4 Hz), 7.35-7.32 (m, 1H), 7.13-7.06 (m, 2H), 6.90 (d, 1H, J = 2.8 Hz), 6.60 (s, 1H), 3.44 (s, 2H), 3.10-3.13 (m, 1H), 3.02-2.98 (m, 1H), 2.52-2.39 (m, 4H), 2.23-2.21 (m, 1H), 2.08-2.02 (m, 3H), 1.36-1.31 (m, 2H); MS(ESI$^+$) *m/z* 547.1 (M + H)$^+$.

EXAMPLE 153

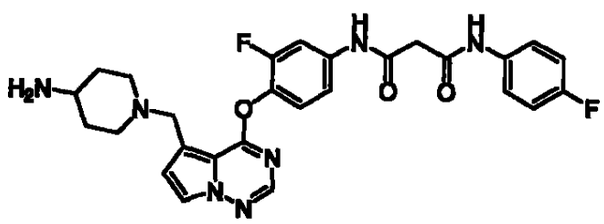


***N*^{1}-(3-Fluoro-4-(5-((4-hydroxy-4-methylcyclohexylidene)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-*N*^{3}-(4-fluorophenyl)malonamide, trifluoroacetic acid salt**

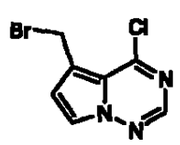
To *N*^{1}-(3-fluoro-4-(5-((4-oxocyclohexylidene)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-*N*^{3}-(4-fluorophenyl)malonamide (10 mg, 0.019 mmol, Example 149) in THF (1 mL) at 0 °C was added methyllithium (76 µL, 0.076 mmol, 1 M THF). After stirring at rt overnight, the reaction was quenched with brine (1 mL). The layers were separated and the organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was purified by reverse phase prep HPLC and the appropriate fractions were concentrated *in vacuo*. Toluene was added (2 x 2 mL) and concentrated to remove excess TFA. Lyophilization from acetonitrile (1 mL) / water (3 mL) gave the TFA salt of the title compound (3 mg, 21%) as a pale yellow solid. ^{1}H NMR (DMSO-d_6) δ 10.45 (s, 1H), 10.21 (s, 1H), 7.98 (d, 1H, J = 2.8 Hz), 7.96 (s, 1H), 7.74 (dd, 1H, J = 12.8, 2 Hz), 7.58-7.55 (m, 2H), 7.40 (t, 1H, J = 8 Hz), 7.33-7.31 (m, 1H), 7.13-7.08 (m, 2H), 6.87 (d, 1H, J = 2.8 Hz),

6.51 (s, 1H), 4.20 (br s, 1H), 3.43 (s, 2H), 2.60-2.45 (m, 3H), 2.09-2.06 (m, 1H), 1.56-1.52 (m, 2H), 1.41-1.36 (m, 2H), 1.07 (s, 3H); MS(ESI$^+$) *m/z* 548.3 $(M+H)^+$.

EXAMPLE 154

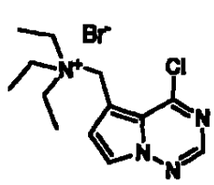


N^1-(4-(5-((4-Aminopiperidin-1-yl)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-N^3-(4-fluorophenyl)malonamide, trifluoroacetic acid salt



A) **5-Bromomethyl-4-chloro-pyrrolo[2,1-*f*][1,2,4]triazine**

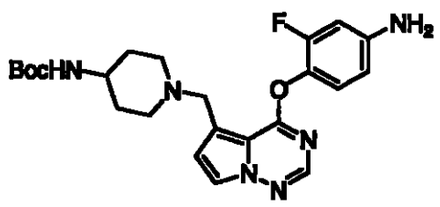
A mixture of 4-chloro-5-methyl-pyrrolo[2,1-*f*][1,2,4]triazine (2.0 g, 11.93 mmol, WO 03/042172) and AIBN (195 mg, 1.19 mmol) in CCl_4 (80 mL) under N_2 was heated to 100 °C for 5 min, NBS (2.55 g, 14.3 mmol) was added. The reaction mixture was stirred for 10 min, then cooled to rt, filtered. The CCl_4 layer was washed with dilute $NaHCO_3$ aqueous solution, dried ($MgSO_4$), filtered and concentrated to give the desired product (2.70 g, 92%).



B) **(4-Chloro-pyrrolo[2,1-*f*][1,2,4]triazin-5-ylmethyl)-triethylammonium bromide**

A mixture of 5-bromomethyl-4-chloro-pyrrolo[2,1-*f*][1,2,4]triazine (2.7 g, 11 mmol), Et_3N (5 mL, 36 mmol) in THF (20 mL) was stirred at rt for 12 h. The solid was filtered and rinsed with THF and Et_2O, dried to give the desired product (3.38 g,

89%). Analytical HPLC retention time = 0.776 min. (Chromolith SpeedROD 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm); MS(ESI$^+$) *m/z* 267 $(M + H)^+$.



C) ***tert*-Butyl 1-((4-(4-amino-2-fluorophenoxy)pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)methyl)piperidin-4-ylcarbamate**

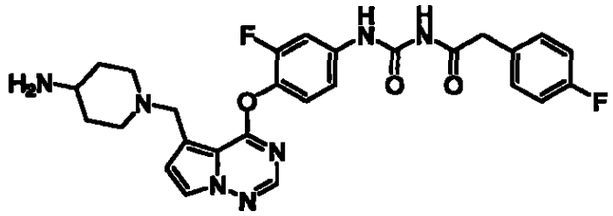
To 4-amino-2-fluorophenol (82 mg, 0.646 mmol) in THF (5 mL) at -78 °C under nitrogen was added NaHMDS (650 µL, 0.650 mmol, 1 M hexanes). After stirring at -78 °C for 20 min, the flask was transferred to a bath at 0 °C and solid *N*-((4-chloropyrrolo[2,1-*f*][1,2,4]triazin-5-yl)methyl)-triethylammonium bromide (200 mg, 0.807 mmol) was immediately added. The reaction was allowed to warm to rt and stirred for 2 h. DIPEA (280 µL, 1.6 mmol), *tert*-butyl piperidin-4-ylcarbamate (129 mg, 0.646 mmol, Aldrich), and DMF (2 mL) was added. The reaction was heated to 120 °C for 4 h. After cooling to rt, the reaction was concentrated *in vacuo* and the crude product was purified by reverse phase prep HPLC. The appropriate fractions were concentrated *in vacuo*. Toluene was added (2 x 2 mL) and concentrated to give the TFA salt of the title compound (100 mg, 27%) as a yellow solid. ^{1}H NMR (CD_3OD) δ 8.09 (s, 1H), 8.03 (d, 1H, J = 2.4 Hz), 7.23-7.13 (m, 2H), 6.83-6.61 (m, 2H), 4.73 (s, 2H), 3.67-3.64 (m, 1H), 3.30-3.19 (m, 2H), 2.31-2.24 (m, 2H), 1.76-1.63 (m, 2H), 1.49-1.45 (m, 2H), 1.45 (s, 9H); MS(ESI$^+$) *m/z* 457.5 $(M + H)^+$.

D) **N^4-(4-(5-((4-Aminopiperidin-1-yl)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-N^5-(4-fluorophenyl)malonamide, trifluoroacetic acid salt**

Prepared in similar manner as Step A of Example 133. The resulting Boc protected material was dissolved in ether (1 mL) at 0 °C and charged with 4 N HCl in dioxane (3 mL). After stirring at 0 °C for 3 h, the reaction was concentrated *in vacuo*.

The crude product was purified by reverse phase prep HPLC and the appropriate fractions were concentrated *in vacuo*. Toluene was added (2 x 2 mL) and concentrated to give the TFA salt of the title compound (4 mg, 12%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 10.49 (s, 1H), 10.22 (s, 1H), 8.18 (s, 1H), 7.90 (d, 1H, J = 2.8 Hz), 7.76 (dd, 1H, J = 12.8, 2.4 Hz), 7.57-7.56 (m, 2H), 7.43-7.36 (m, 2H), 7.13-7.09 (m, 3H), 4.57 (s, 2H), 3.51-3.48 (m, 1H), 3.44 (s, 2H), 3.09-3.06 (m, 2H), 2.53-2.50 (m, 2H), 2.00-1.97 (m, 2H), 1.72-1.67 (m, 2H); MS(ESI$^+$) *m/z* 536.5 $(M + H)^+$.

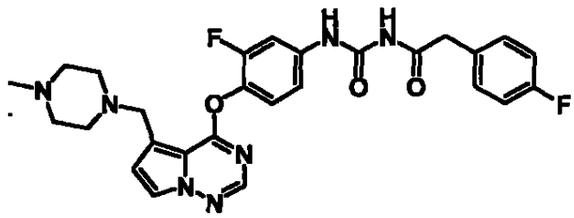
EXAMPLE 155



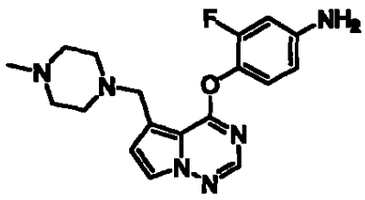
1-(4-(5-((4-Aminopiperidin-1-yl)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, trifluoroacetic acid salt

To *tert*-butyl 1-((4-(4-amino-2-fluorophenoxy)pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)methyl)piperidin-4-ylcarbamate (50 mg, 0.088 mmol, Compound C of Example 154) in dichloromethane (1 mL) at 0 °C was added 2-(4-fluorophenyl)acetyl isocyanate (290 uL, 0.088 mmol, 0.3 M in toluene, Compound C of Example 4). The reaction was stirred at 0 °C for 0.5 h and was purified directly by by flash chromatography on silica gel (10% MeOH / EtOAc) to give the Boc protected material (33 mg, 59%) as a colorless oil. The Boc protected material was suspended in ether (2 mL) at 0 °C and charged with 4 N HCl in dioxane (5 mL). After stirring at 0 °C for 1.5 h, the reaction was concentrated *in vacuo*. The crude product was purified by reverse phase prep HPLC and the appropriate fractions were concentrated *in vacuo*. Toluene was added (2 x 2 mL) and concentrated to give the TFA salt of the title compound (3 mg, 8%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.01 (s, 1H), 10.57 (s, 1H), 8.21-8.18 (m, 2H), 7.73 (dd, 1H, J = 12.8, 2.4 Hz), 7.48-7.33 (m, 4H), 7.18-7.11 (m, 3H), 4.57 (m, 1H), 3.69 (s, 2H), 3.44 (s, 2H), 3.59-3.48 (m, 2H), 3.13-3.06 (m, 2H), 2.05-1.98 (m, 2H), 1.71-1.55 (m, 2H); MS(ESI$^+$) *m/z* 535.3 $(M + H)^+$.

EXAMPLE 156



1-(3-Fluoro-4-(5-((4-methylpiperazin-1-yl)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea



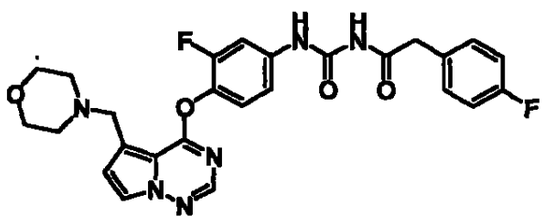
A) 1-(3-Fluoro-4-(5-((4-methylpiperazin-1-yl)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea

Prepared in a similar manner as Step C of Example 154 to give the TFA salt of the title compound (9%) as a brown solid. ^{1}H NMR (CD_3OD) δ 7.90 (s, 1H), 7.85 (d, 1H, J = 2.8 Hz), 7.17 (t, 1H, J = 8.8 Hz), 6.94 (d, 1H, J = 2.8 Hz), 6.75 (dd, 1H, J = 11.6, 2.4 Hz), 6.72-6.69 (m, 1H), 4.39 (s, 2H), 3.40-3.31 (m, 8H), 2.79 (s, 3H); MS(ESI$^+$) *m/z* 357.3 $(M + H)^+$.

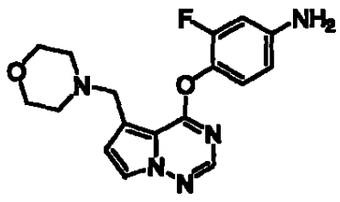
B) 1-(3-Fluoro-4-(5-((4-methylpiperazin-1-yl)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea

Prepared in similar manner as Example 155 to give the title compound (83%) as a white solid. ^{1}H NMR (CD_3OD) δ 7.80 (s, 1H), 7.77 (d, 1H, J = 2 Hz), 7.62 (dd, 1H, J = 12.4, 2.4 Hz), 7.27-7.17 (m, 4H), 6.99-6.95 (m, 2H), 6.84 (d, 1H, J = 2.4 Hz), 3.94 (s, 2H), 3.62 (s, 2H), 2.70-2.45 (m, 8H), 2.26 (s, 3H); MS(ESI$^+$) *m/z* 536.2 $(M + H)^+$.

EXAMPLE 157



1-(3-Fluoro-4-(5-(morpholinomethyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea



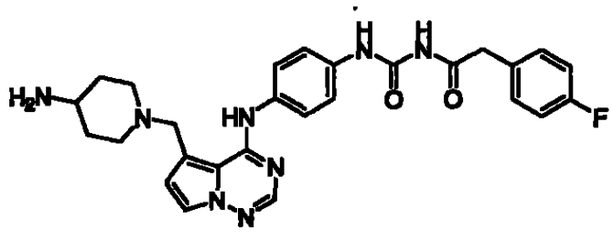
A) 3-Fluoro-4-(5-(morpholinomethyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine

Prepared in a similar manner as Step C of Example 154 to give the TFA salt of the title compound (10%) as a light brown solid. ^{1}H NMR (CD_3OD) δ 7.98 (s, 1H), 7.91 (d, 1H, J = 2.8 Hz), 7.11 (t, 1H, J = 8.4 Hz), 7.02 (d, 1H, J = 2.8 Hz), 6.62 (dd, 1H, J = 12.4, 2.8 Hz), 6.60-6.57 (m, 1H), 4.67 (s, 2H), 4.00-3.94 (m, 2H), 3.68-3.61 (m, 2H), 3.43-3.40 (m, 2H), 3.22-3.20 (m, 2H); MS(ESI$^+$) *m/z* 344.3 $(M + H)^+$.

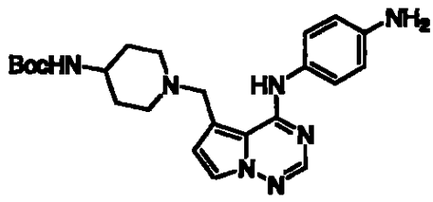
B) 1-(3-Fluoro-4-(5-(morpholinomethyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea

Prepared in similar manner as Example 155 to give the title compound (83%) as a white solid. ^{1}H NMR (CD_3OD) δ 7.89 (s, 1H), 7.85 (d, 1H, J = 2.8 Hz), 7.67 (dd, 1H, J = 12.4, 2.4 Hz), 7.30-7.19 (m, 4H), 7.01-6.94 (m, 3H), 4.28 (s, 2H), 3.70-3.76 (m, 4H), 3.62 (s, 2H), 2.88-2.80 (m, 2H); MS(ESI$^+$) *m/z* 523.2 $(M + H)^+$.

EXAMPLE 158



1-(4-(5-((4-Aminopiperidin-1-yl)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ylamino)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea



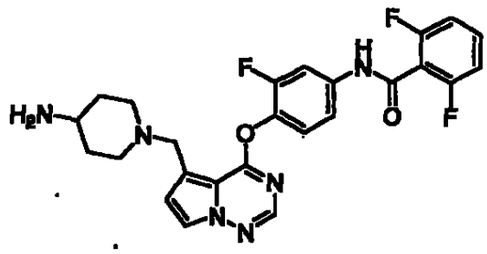
A) ***tert*-Butyl 1-((4-(4-aminophenylamino)pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)methyl)piperidin-4-ylcarbamate**

Prepared in a similar manner as Step C of Example 154 to give the TFA salt of the title compound (38%) as a yellow oil. ^{1}H NMR (CD_3OD) δ 7.57 (s, 1H), 7.33 (d, 1H, J = 2.4 Hz), 7.24-7.21 (m, 2H), 6.71-6.68 (m, 2H), 6.45 (d, 1H, J = 2.8 Hz), 3.67 (s, 2H), 3.34-3.28 (m, 1H), 2.95-2.90 (m, 2H), 1.80-1.77 (m, 2H), 1.41-1.33 (m, 2H), 1.32 (s, 9H); MS(ESI$^+$) *m/z* 438.3 $(M + H)^+$.

B) **1-(4-(5-((4-Aminopiperidin-1-yl)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ylamino)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea**

Prepared in similar manner as Example 155 to give the title compound (47%) as an off-white solid. ^{1}H NMR (DMSO-d_6) δ 11.01 (s, 1H), 10.53 (s, 1H), 8.00-7.89 (m, 2H), 7.61-7.59 (m, 3H), 7.45-7.41 (m, 2H), 7.26-7.22 (m, 4H), 3.77 (s, 2H), 3.63 (s, 2H), 3.35-3.32 (m, 1H), 3.20-3.14 (m, 2H), 2.19-1.90 (m, 6H); MS(ESI$^+$) *m/z* 517.3 $(M + H)^+$.

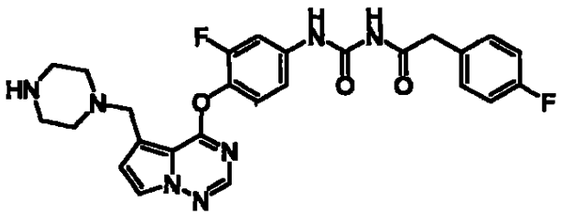
EXAMPLE 159



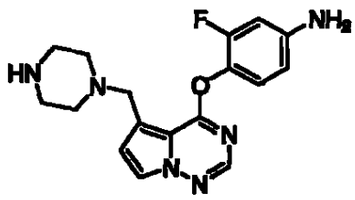
N-(4-(5-((4-Aminopiperidin-1-yl)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-2,6-difluorobenzamide

Prepared in a similar manner as Example 147 to give the TFA salt of the title compound (5%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.10 (s, 1H), 8.19-8.17 (m, 2H), 7.82 (dd, 1H, J = 12.8, 2.4 Hz), 7.49 (t, 1H, J = 8.8 Hz), 7.49-7.47 (m, 2H), 7.25-7.21 (m, 2H), 7.14-7.09 (m, 1H), 4.59 (s, 2H), 3.54-3.48 (m, 3H), 3.15-3.08 (m, 2H), 2.08-2.00 (m, 2H), 1.74-1.66 (m, 2H); MS(ESI$^+$) *m/z* 497.2 $(M + H)^+$.

EXAMPLE 160



1-(3-Fluoro-4-(5-(piperazin-1-ylmethyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea



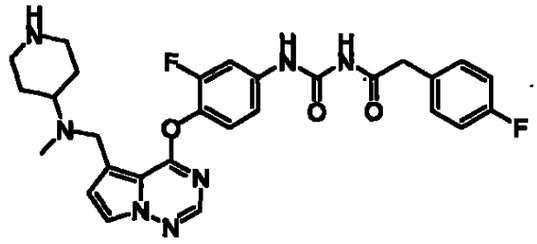
A) **3-Fluoro-4-(5-(piperazin-1-ylmethyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine**

Prepared in a similar manner as Step C of Example 154 to give the title compound as a yellow oil. MS(ESI$^+$) *m/z* 443.3 $(M + H)^+$.

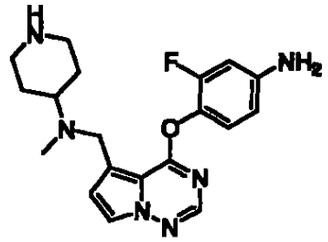
B) **1-(3-Fluoro-4-(5-(piperazin-1-ylmethyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea**

Prepared in similar manner as Example 155 to give the title compound (6%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.00 (s, 1H), 10.55 (s, 1H), 8.12 (s, 1H), 8.11 (d, 1H, J = 2.8 Hz), 7.71 (dd, 1H, J = 12.8, 2.4 Hz), 7.42 (t, 1H, J = 8.8 Hz), 7.35-7.28 (m, 3H), 7.11 (t, 2H, J = 9.2 Hz), 7.03 (m, 1H), 4.58 (s, 2H), 3.69 (s, 2H), 3.66-3.59 (m, 4H), 3.32-3.05 (m, 4H); MS(ESI$^+$) m/z 522.3 $(M + H)^+$.

EXAMPLE 161



1-(3-Fluoro-4-(5-((methyl(piperidin-4-yl)amino)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea



A) ***N*-((4-(4-Amino-2-fluorophenoxy)pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)methyl)-*N*-methylpiperidin-4-amine**

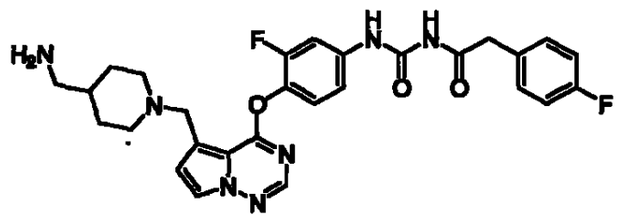
Prepared in a similar manner as Step C of Example 154 to give the title compound (38%) as a yellow oil. MS(ESI$^+$) m/z 471.3 $(M + H)^+$.

B) **1-(3-Fluoro-4-(5-((methyl(piperidin-4-yl)amino)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea**

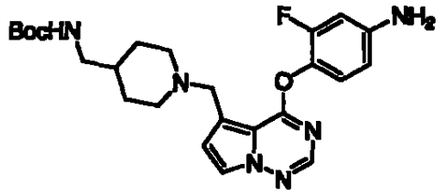
Prepared in similar manner as Example 155 to give the title compound (32%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.00 (s, 1H), 10.55 (s, 1H), 8.19 (s, 1H), 8.16 (d, 1H, J = 2.4 Hz), 7.71 (dd, 1H, J = 12.4, 2 Hz), 7.42-7.34 (m, 2H), 7.32-7.28

(m, 2H), 7.16-7.06 (m, 3H), 4.44 (s, 2H), 3.69 (s, 2H), 3.64-3.59 (m, 4H), 2.87-2.84 (m, 1H), 2.72 (s, 3H), 2.19-2.15 (m, 2H), 1.87-1.82 (m, 2H); MS(ESI$^+$) *m/z* 550.3 (M + H)$^+$.

EXAMPLE 162



1-(4-(5-((4-(Aminomethyl)piperidin-1-yl)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea



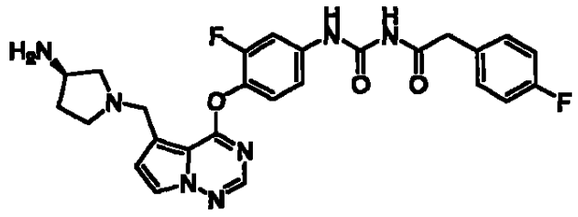
A) ***tert*-Butyl (1-((4-(4-amino-2-fluorophenoxy)pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)methyl)piperidin-4-yl)methylcarbamate**

Prepared in a similar manner as Step C of Example 154 to give the title compound (29%) as a yellow oil. MS(ESI$^+$) *m/z* 471.3 (M + H)$^+$.

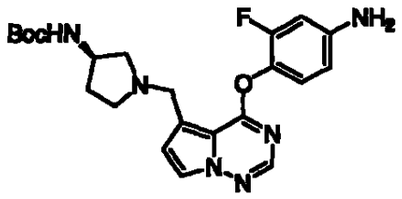
B) **1-(4-(5-((4-(Aminomethyl)piperidin-1-yl)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea**

Prepared in similar manner as Example 155 to give the title compound (26%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.01 (s, 1H), 10.53 (s, 1H), 7.99 (s, 1H), 7.97 (d, 1H, J = 2.4 Hz), 7.66 (dd, 1H, J = 13.2, 2.4 Hz), 7.36-7.28 (m, 4H), 7.09 (t, 2H, J = 8.8 Hz), 6.82 (d, 1H, J = 2.4 Hz), 3.77 (s, 2H), 3.68 (s, 2H), 3.84-3.82 (m, 2H), 2.38-2.36 (m, 1H), 1.88 (t, 2H, J = 10 Hz), 1.58-1.55 (m, 2H), 1.20-1.01 (m, 4H); MS(ESI$^+$) *m/z* 550.2 (M + H)$^+$.

EXAMPLE 163



(*R*)-1-(4-(5-((3-Aminopyrrolidin-1-yl)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea



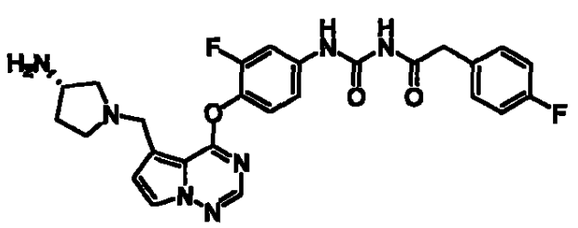
A) **(*R*)-*tert*-Butyl 1-((4-(4-amino-2-fluorophenoxy)pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)methyl)pyrrolidin-3-ylcarbamate**

Prepared in a similar manner as Step C of Example 154 to give the title compound (30%) as a yellow oil. MS(ESI$^+$) *m/z* 443.3 $(M + H)^+$.

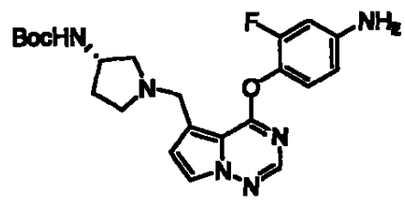
B) **(*R*)-1-(4-(5-((3-Aminopyrrolidin-1-yl)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea**

Prepared in similar manner as Example 155 to give the title compound (11%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 10.54 (s, 1H), 10.21 (s, 1H), 7.99 (s, 1H), 7.98 (d, 1H, J = 2.4 Hz), 7.67 (dd, 1H, J = 12.4, 2 Hz), 7.40-7.26 (m, 3H), 7.13-7.07 (m, 3H), 6.84 (d, 1H, J = 2.8 Hz), 3.90 (s, 2H), 3.68 (s, 2H), 2.67-2.41 (m, 3H), 2.20-2.16 (m, 2H), 1.96-1.91 (m, 1H), 1.32-1.29 (m, 1H); MS(ESI$^+$) *m/z* 522.2 $(M + H)^+$.

EXAMPLE 164



(*S*)-1-(4-(5-((3-Aminopyrrolidin-1-yl)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea



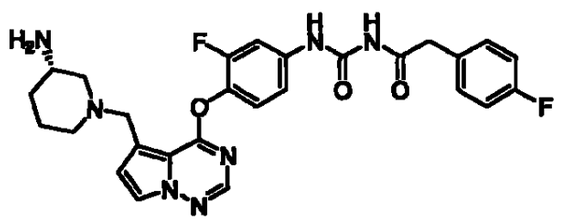
A) **(*S*)-*tert*-Butyl 1-((4-(4-amino-2-fluorophenoxy)pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)methyl)pyrrolidin-3-ylcarbamate**

Prepared in a similar manner as Step C of Example 154 to give the title compound (30%) as a yellow oil. MS(ESI$^+$) *m/z* 443.3 $(M + H)^+$.

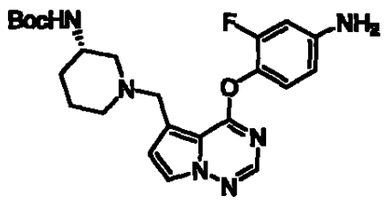
B) **(*S*)-1-(4-(5-((3-Aminopyrrolidin-1-yl)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea**

Prepared in similar manner as Example 155 to give the title compound (7%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 10.54 (s, 1H), 10.21 (s, 1H), 7.99 (s, 1H), 7.98 (d, 1H, J = 2.4 Hz), 7.67 (dd, 1H, J = 12.4, 2 Hz), 7.40-7.26 (m, 3H), 7.13-7.07 (m, 3H), 6.84 (d, 1H, J = 2.8 Hz), 3.90 (s, 2H), 3.68 (s, 2H), 2.67-2.41 (m, 3H), 2.20-2.16 (m, 2H), 1.96-1.91 (m, 1H), 1.32-1.29 (m, 1H); MS(ESI$^+$) *m/z* 522.2 $(M + H)^+$.

EXAMPLE 165



(*S*)-1-(4-(5-((3-Aminopiperidin-1-yl)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea



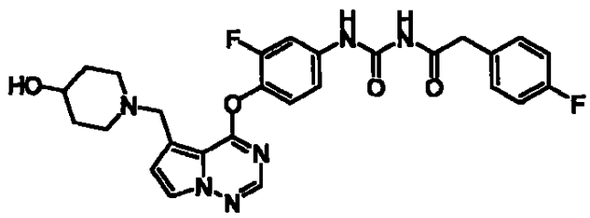
A) **(*S*)-*tert*-Butyl 1-((4-(4-amino-2-fluorophenoxy)pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)methyl)piperidin-3-ylcarbamate**

Prepared in a similar manner as Step C of Example 154 to give the title compound (40%) as a yellow oil. MS(ESI$^+$) *m/z* 457.3 $(M + H)^+$.

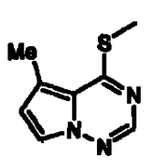
B) **(*S*)-1-(4-(5-((3-Aminopiperidin-1-yl)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea**

Prepared in similar manner as Example 155 to give the TFA salt of the title compound (29%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.00 (s, 1H), 10.55 (s, 1H), 8.15 (m, 2H), 7.71 (dd, 1H, J = 12.4, 2 Hz), 7.41 (t, 1H, J = 8.4 Hz), 7.35-7.28 (m, 3H), 7.11 (t, 2H, J = 8.8 Hz), 7.05 (d, 1H, J = 2.8 Hz), 4.58 (s, 2H), 3.69 (s, 2H), 3.66-3.30 (m, 5H), 1.95-1.83 (m, 2H), 1.67-1.53 (m, 1H), 1.40-1.32 (m, 1H); MS(ESI$^+$) *m/z* 536.2 $(M + H)^+$.

EXAMPLE 166

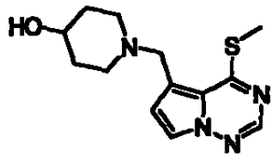


1-(3-Fluoro-4-(5-((4-hydroxypiperidin-1-yl)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea, trifluoroacetic acid salt



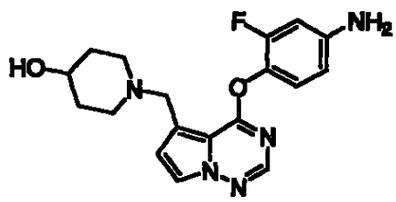
A) 5-Methyl-4-methylsulfanyl-pyrrolo[2,1-*f*][1,2,4]triazine

To a solution of 4-chloro-5-methyl-pyrrolo[2,1-*f*][1,2,4]triazine (4.02 g, 24.0 mmol, WO 03/042172) in dry THF (200 mL) sparged with N_2 at 0°C was added NaSMe (1.85 g, 26.3 mmol). The sparging was continued for 5 min. The reaction mixture was then stirred at rt overnight, concentrated *in vacuo* to about 50 mL volume, diluted with H_2O (280 mL) and stirred at 0 °C. The solid was filtered, washed with cold water, dried to give the desired product (3.91 g, 91%). Analytical HPLC retention time = 3.38 min. (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 ml/min, monitoring at 220 nm); MS(ESI$^+$) *m/z* 180 $(M + H)^+$.



B) 1-((4-(Methylthio)pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)methyl)piperidin-4-ol

A solution of 5-methyl-4-methylsulfanyl-pyrrolo[2,1-*f*] [1,2,4]triazine (200 mg, 1.12 mmol), NBS (218 mg, 1.23 mmol), and AIBN (spatula tip) in carbon tetrachloride (4 mL) was heated at 80 °C for 1 h. After cooling to rt, the solution was filtered to remove succinimide. To the filtrate was added 4-hydroxypiperidine (126 mg, 1.34 mmol, Aldrich) and DIPEA (214 µL, 1.23 mmol). The reaction was stirred at rt overnight and was then concentrated *in vacuo*. The residue was suspended in methanol and filtered. The filtrate was concentrated and the crude product was purified by flash chromatography on silica gel (20% MeOH / EtOAc) to give the title compound (229 mg, 74%) as a colorless solid. ^{1}H NMR (DMSO-d_6) δ 8.25 (s, 1H), 7.88 (d, 1H, J = 2 Hz), 6.81 (d, 1H, J = 2 Hz), 4.54 (br s, 1H), 3.76 (s, 2H), 3.48-3.44 (m, 1H), 2.75-2.71 (m, 2H), 2.62 (s, 3H), 2.10-2.08 (m, 2H), 1.70-1.68 (m, 2H), 1.38-1.36 (m, 2H); MS(ESI$^+$) *m/z* 279.3 $(M + H)^+$.



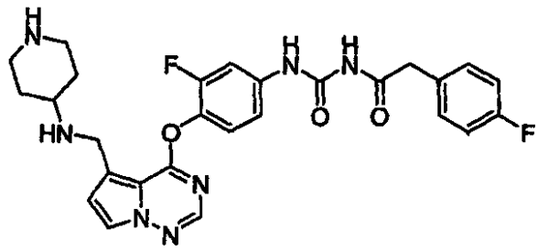
C) 1-((4-(4-Amino-2-fluorophenoxy)pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)methyl)piperidin-4-ol

To 1-((4-(methylthio)pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)methyl)piperidin-4-ol (188 mg, 0.675 mmol) in dichloromethane (7 mL) at 0 °C was added TFA (78 µL, 1.01 mmol) followed by *m*-CPBA (166 mg, 0.675 mmol, ~70% pure). After stirring at 0 °C for 1 h, the mixture was concentrated *in vacuo*. Ether (20 mL) was added and then decanted off to remove the benzoic acid. The resulting crude sulfoxide was dried under high vacuum. 4-Amino-2-fluorophenol (343 mg, 2.7 mmol) was dissolved in THF (10 mL), cooled to -78 °C, and charged with NaHMDS (2.7 mL, 2.7 mmol, 1 M in THF). After stirring at 0 °C for 5 min, the crude sulfoxide in THF (3 mL) was added. The reaction was stirred at 0 °C for 30 min and was then concentrated *in vacuo*. The residue was suspended in EtOAc (20 mL), washed with water (10 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The crude product was purified by reverse phase prep HPLC and the appropriate fractions were concentrated *in vacuo* to remove methanol. The resulting aqueous solution was made basic with 5% aqueous sodium bicarbonate solution and extracted with EtOAc (3 x 10 mL). The combined extracts were dried over anhydrous sodium sulfate and concentrated *in vacuo* to give 36 mg (15%) of the title compound as a white solid. ^{1}H NMR (DMSO-d_6) δ 8.04 (s, 1H), 8.00 (d, 1H, J = 2.8 Hz), 7.02 (t, 1H, J = 8.8 Hz), 6.88 (d, 1H, J = 2.8 Hz), 6.51 (dd, 1H, J = 12.8, 2.8 Hz), 6.46-6.42 (m, 1H), 5.45 (br s, 2H), 3.83 (s, 2H), 3.18 (m, 1H), 2.76-2.71 (m, 2H), 2.12-2.06 (m, 2H), 1.72-1.67 (m, 2H), 1.41-1.38 (m, 2H); MS(ESI$^+$) *m/z* 358.4 $(M + H)^+$.

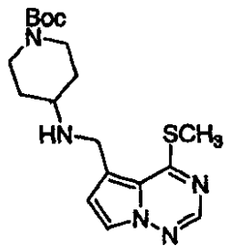
D) 1-(3-Fluoro-4-(5-((4-hydroxypiperidin-1-yl)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea, trifluoroacetic acid salt

Prepared in similar manner as Example 155 to give the TFA salt of the title compound (12%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.00 (s, 1H), 10.55 (s, 1H), 8.18 (s, 1H), 8.16-8.14 (m, 1H), 7.71 (d, 1H, J = 12.4 Hz), 7.41-7.28 (m, 4H), 7.11-7.08 (m, 3H), 4.59-4.54 (m, 2H), 3.68 (s, 2H), 3.60-3.00 (m, 5H), 1.92-1.87 (m, 1H), 1.81-1.68 (m, 2H), 1.53-1.48 (m, 1H); MS(ESI$^+$) m/z 537.2 $(M + H)^+$.

EXAMPLE 167

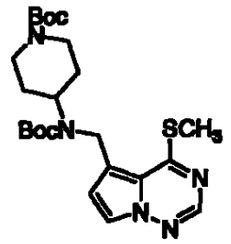


1-(3-Fluoro-4-(5-((piperidin-4-ylamino)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea



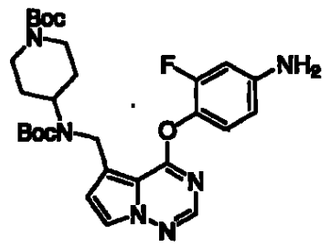
A) *tert*-Butyl 4-((4-(methylthio)pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)methylamino)piperidine-1-carboxylate

Prepared in a similar manner as Step A of Example 166 to give the title compound (50%) as a colorless oil. ^{1}H NMR (CD_3OD) δ 8.14 (s, 1H), 7.73 (d, 1H, J = 2.8 Hz), 6.91 (d, 1H, J = 2.8 Hz), 4.21 (s, 2H), 4.10-4.07 (m, 2H), 2.83-2.77 (m, 3H), 2.71 (s, 3H), 1.99-1.97 (m, 2H), 1.48 (s, 9H), 1.34-1.31 (m, 2H); MS(ESI$^+$) m/z 378.3 $(M + H)^+$.



B) **4-[*tert*-Butoxycarbonyl-(4-methylsulfanyl-pyrrolo[2,1-*f*][1,2,4]triazin-5-ylmethyl)-amino]-piperidine-1-carboxylic acid *tert*-butyl ester**

tert-Butyl 4-((4-(methylthio)pyrrolo[1,2-*f*][1,2,4]triazin-5-yl)methylamino)piperidine-1-carboxylate (210 mg, 0.556 mmol) was dissolved in dichloromethane (5 mL) and triethylamine (120 µL, 0.834 mmol) followed by di-*tert*-butyl dicarbonate (134 mg, 0.612 mmol) was added. After stirring at rt for 8 h, the reaction was diluted with methylene chloride (20 mL), washed with saturated aqueous ammonium chloride solution (10 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (20% EtOAc / hexanes) to give the title compound (207 mg, 78%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 8.01 (s, 1H), 7.51 (d, 1H, J = 2.8 Hz), 6.57 (d, 1H, J = 2.8 Hz), 4.71 (s, 2H), 4.06-4.04 (m, 3H), 2.68-2.61 (m, 2H), 2.61 (s, 3H), 1.60-1.57 (m, 2H), 1.46-1.36 (m, 2H), 1.35 (s, 18H); MS(ESI$^+$) *m/z* 478.2 $(M + H)^+$.



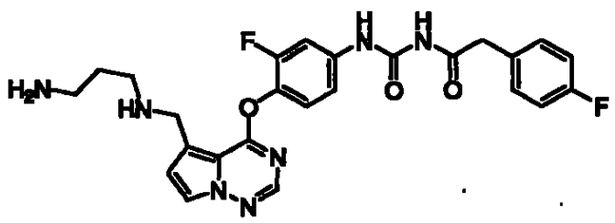
C) **4-[[4-(4-Amino-2-fluoro-phenoxy)-pyrrolo[2,1-*f*][1,2,4]triazin-5-ylmethyl]-*tert*-butoxycarbonyl-amino}-piperidine-1-carboxylic acid *tert*-butyl ester**

Prepared in a similar manner as Step C of Example 166 to give the title compound (43%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.84 (s, 1H), 7.62 (d, 1H, J = 2.8 Hz), 6.98 (t, 1H, J = 8.8 Hz), 6.70 (d, 1H, J = 2.8 Hz), 6.47-6.41 (m, 2H), 4.72 (s, 2H), 4.10-4.04 (m, 2H), 3.77-3.75 (m, 1H), 2.62-2.60 (m, 2H), 1.71-1.38 (m, 4H), 1.35 (s, 18H); MS(ESI$^+$) *m/z* 557.2 $(M + H)^+$.

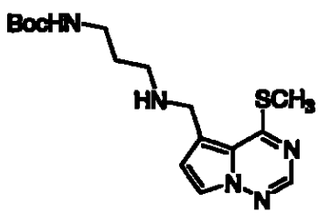
D) **1-(3-Fluoro-4-(5-((piperidin-4-ylamino)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea**

Prepared in a similar manner as Example 155 to give the title compound (34%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.01 (s, 1H), 10.55 (s, 1H), 8.16 (s, 1H), 8.12 (d, 1H, J = 2.4 Hz), 7.71 (dd, 1H, J = 12.4, 2 Hz), 7.42-7.28 (m, 4H), 7.18-7.08 (m, 3H), 4.51 (s, 2H), 3.69 (s, 2H), 3.50-3.29 (m, 3H), 2.88-2.85 (m, 2H), 2.23-2.18 (m, 2H), 1.72-1.64 (m, 2H); MS(ESI$^+$) *m/z* 536.2 $(M + H)^+$.

EXAMPLE 168

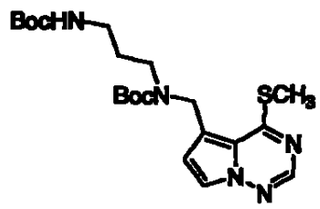


1-(4-(5-((3-Aminopropylamino)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea



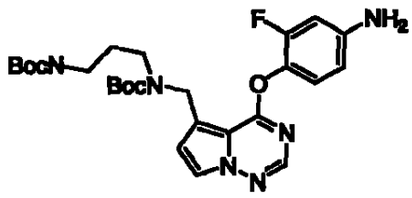
A) ***tert*-Butyl 3-((4-(methylthio)pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)methylamino)propylcarbamate**

Prepared in a similar manner as Step B of Example 166 to give the title compound (51%) as a yellow solid. ^{1}H NMR (CD_3OD) δ 8.16 (s, 1H), 7.75 (d, 1H, J = 2.4 Hz), 6.94 (d, 1H, J = 2.8 Hz), 4.30 (s, 2H), 3.14 (t, 2H, J = 6.4 Hz), 2.83 (t, 2H, J = 7.2 Hz), 2.72 (s, 3H), 1.82-1.75 (m, 2H), 1.40 (s, 9H); MS(ESI$^+$) *m/z* 352.3 $(M + H)^+$.



B) **{3-[*tert*-Butoxycarbonyl-(4-methylsulfanyl-pyrrolo[2,1-*f*][1,2,4]triazin-5-ylmethyl)-amino]-propyl}-carbamic acid *tert*-butyl ester**

Prepared in a similar manner to Step B of Example 167 to give the title compound (77%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 8.14 (s, 1H), 7.73 (d, 1H, J = 2.4 Hz), 6.75 (d, 1H, J = 2 Hz), 4.88 (s, 2H), 3.29-3.25 (m, 2H), 3.04-3.02 (m, 2H), 2.71 (s, 3H), 1.72-1.68 (m, 2H), 1.54 (s, 9H), 1.42 (s, 9H); MS(ESI$^+$) *m/z* 452.2 (M + H)$^+$.



C) **(3-{[4-(4-Amino-2-fluoro-phenoxy)-pyrrolo[2,1-*f*][1,2,4]triazin-5-ylmethyl]-*tert*-butoxycarbonyl-amino}-propyl)-carbamic acid *tert*-butyl ester**

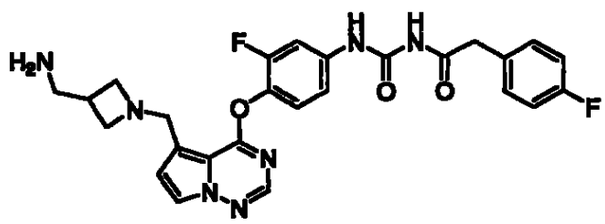
Prepared in a similar manner as Step C of Example 166 to give the title compound (29%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.85 (s, 1H), 7.64 (d, 1H, J = 2.8 Hz), 7.00 (t, 1H, J = 8.8 Hz), 6.82-6.78 (m, 1H), 6.62 (dd, 1H, J = 12.8, 2.4 Hz), 6.54-6.51 (m, 1H), 4.72 (m, 2H), 3.28-3.23 (m, 2H), 3.02-3.00 (m, 2H), 1.58-1.55 (m, 2H), 1.43 (s, 9H), 1.35 (s, 9H); MS(ESI$^+$) *m/z* 531.2 (M + H)$^+$.

D) **1-(4-(5-((3-Aminopropylamino)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea**

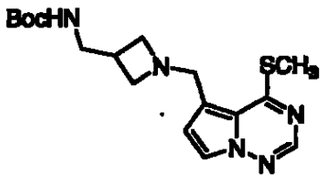
Prepared in a similar manner as Example 155 to give the title compound (17%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.01 (s, 1H), 10.52 (s, 1H), 8.00 (s, 1H), 7.98 (d, 1H, J = 2.8 Hz), 7.68 (dd, 1H, J = 12.8, 2.4 Hz), 7.34-7.28 (m, 4H), 7.13

(t, 2H, J = 9.2 Hz), 6.84 (d, 1H, J = 2.4 Hz), 3.68 (s, 2H), 3.52 (s, 2H), 2.90-2.85 (m, 2H), 2.28-2.20 (m, 2H), 1.35-1.30 (m, 2H); MS(ESI$^+$) m/z 510.2 $(M + H)^+$.

EXAMPLE 169

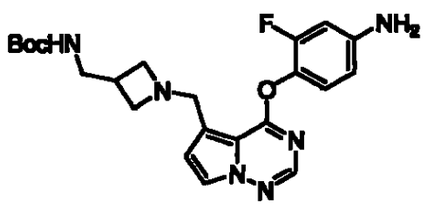


1-(4-(5-((3-(Aminomethyl)azetidin-1-yl)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea



A) ***tert*-Butyl (1-((4-(methylthio)pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)methyl)azetidin-3-yl)methylcarbamate**

Prepared in a similar manner as Step B of Example 166 to give the title compound (31%) as a white solid. ^{1}H NMR (CD_3OD) δ 8.12 (s, 1H), 7.72 (d, 1H, J = 2.4 Hz), 6.81 (d, 1H, J = 2.8 Hz), 4.07 (s, 2H), 3.46 (t, 2H, J = 8 Hz), 3.34-3.33 (m, 1H), 3.20-3.18 (m, 2H), 3.08 (t, 2H, J = 7.6 Hz), 2.65 (s, 3H), 1.44 (s, 9H); MS(ESI$^+$) m/z 364.3 $(M + H)^+$.



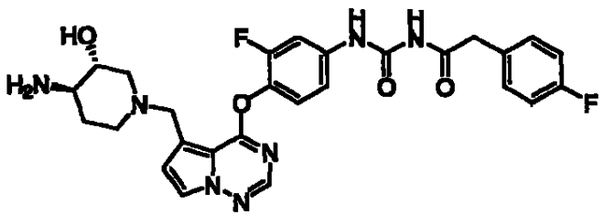
B) ***tert*-Butyl (1-((4-(4-amino-2-fluorophenoxy)pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)methyl)azetidin-3-yl)methylcarbamate**

Prepared in a similar manner as Step C of Example 166 to give the title compound (33%) as a brown solid. MS(ESI$^+$) m/z 443.2 $(M + H)^+$.

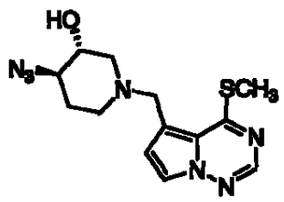
C) **1-(4-(5-((3-(Aminomethyl)azetidin-1-yl)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea**

Prepared in a similar manner as Example 155 to give the title compound (4%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.02 (s, 1H), 10.56 (s, 1H), 8.18-8.15 (m, 2H), 7.68 (dd, 1H, J = 12.8, 2.4 Hz), 7.45-7.28 (m, 4H), 7.18-7.08 (m, 3H), 4.67 (s, 2H), 4.44-4.41 (m, 2H), 4.05-3.98 (m, 2H), 3.69 (s, 2H), 3.10-2.97 (m, 3H); MS(ESI$^+$) m/z 522.3 $(M + H)^+$.

EXAMPLE 170

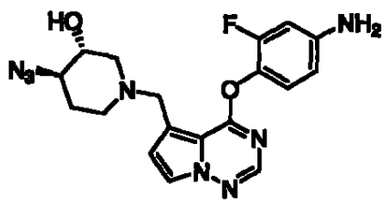


1-(4-(5-(((3*R*,4*R*)-4-Amino-3-hydroxypiperidin-1-yl)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea



A) **(3*R*,4*R*)-4-Azido-1-((4-(methylthio)pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)methyl)piperidin-3-ol**

Prepared in a similar manner as Step B of Example 166 to give the title compound (65%) as a yellow foam. ^{1}H NMR (CD_3OD) δ 8.36 (s, 1H), 7.99 (d, 1H, J = 2.4 Hz), 6.93 (d, 1H, J = 2.8 Hz), 3.92-3.88 (m, 2H), 3.35-3.30 (m, 1H), 3.08-2.90 (m, 2H), 2.72 (s, 3H), 2.14-2.10 (m, 2H), 2.00-1.91 (m, 2H), 1.47-1.44 (m, 1H); MS(ESI$^+$) m/z 320.2 $(M + H)^+$.



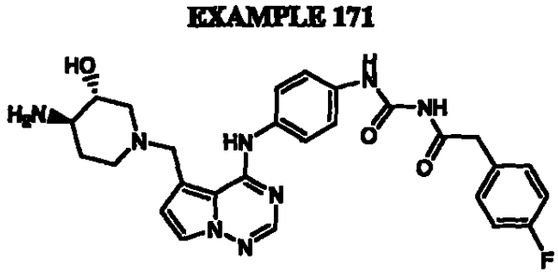
B) **(3*R*,4*R*)-1-((4-(4-Amino-2-fluorophenoxy)pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)methyl)-4-azidopiperidin-3-ol**

Prepared in a similar manner as Step C of Example 166 to give the title compound (24%) as a brown solid. MS(ESI$^+$) *m/z* 399.2 $(M + H)^+$.

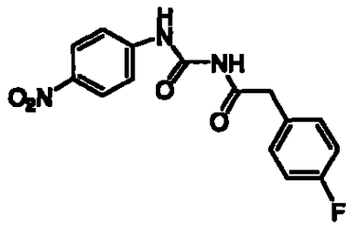
C) **1-(4-(5-(((3*R*,4*R*)-4-Amino-3-hydroxypiperidin-1-yl)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea**

The acylurea was prepared in a similar manner as Example 155 to give the corresponding azide (48%). MS(ESI$^+$) *m/z* 578.16 $(M + H)^+$. The azide (35 mg, 0.06 mmol) was then dissolved in ethyl acetate (1 mL) at 0 °C and charged with trimethylphosphine (0.11 mL, 0.11 mmol) followed by water (1 drop). After stirring at rt for 3 h, the reaction was concentrated *in vacuo* and purified by reverse phase prep HPLC. The appropriate fractions were concentrated *in vacuo* and toluene was added (2 x 2 mL) and concentrated to give the TFA salt of the title compound (8 mg, 17%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.00 (s, 1H), 10.55 (s, 1H), 8.18-8.16 (m, 2H), 7.72 (dd, 1H, J = 12.8, 2.4 Hz), 7.36-7.28 (m, 4H), 7.14-7.09 (m, 3H), 4.62 (s, 2H), 3.69 (s, 2H), 3.22-2.85 (m, 6H), 2.03-1.98 (m, 1H), 1.68-1.65 (m, 1H); MS(ESI$^+$) *m/z* 510.2 $(M + H)^+$.

EXAMPLE 171

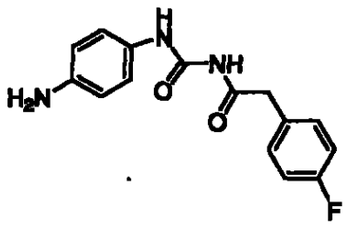


1-(4-(5-(((3*R*,4*R*)-4-Amino-3-hydroxypiperidin-1-yl)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ylamino)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea



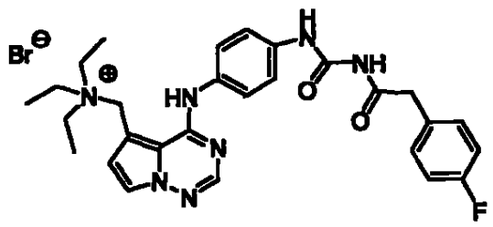
A) 1-(2-(4-Fluorophenyl)acetyl)-3-(4-nitrophenyl)urea

To a stirred solution of *p*-nitroaniline (200 mg, 1.45 mmol) in tetrahydrofuran (1 mL) at room temperature was added 2-(4-fluorophenyl)acetyl isocyanate (2 mL, 0.32 M in toluene, Compound C of Example 4). After 18 h, the mixture was concentrated *in vacuo* and the residue was dissolved in ethyl acetate (5 mL). The solution was slowly concentrated on rotary evaporator without heating. When a precipitate started to form, the flask was removed from the rotory evaporator and allowed to sit for 2 h. The solid formed was filtered and washed with small amount of ethyl acetate and dried in vacuo to afford light yellow crystalline compound (200 mg, 44%). MS(ESI$^+$) *m/z* 318.3 $(M+H)^+$.



B) 1-(4-Aminophenyl)-3-(2-(4-fluorophenyl)acetyl)urea

To a solution of 1-(2-(4-fluorophenyl)acetyl)-3-(4-nitrophenyl)urea (200 mg, 0.63 mmol) in ethyl acetate (10 mL) was added 10% palladium on carbon (15 mg) and the flask was filled with hydrogen using a balloon. The mixture was stirred for 18 h, filtered and the catalyst was washed with ethyl acetate. The filtrate was concentrated *in vacuo* to give a solid which was was triturated with small amount of ether and dried in vacuo to obtain the desired compound (180 mg) as pale yellow solid. MS(ESI$^+$) *m/z* 287.4 $(M+H)^+$.



C) ***N,N*-diethyl-*N*-((4-(4-(3-(2-(4-fluorophenyl)acetyl)ureido)phenylamino)pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)methyl)ethanaminium bromide**

To a solution of (4-chloro-pyrrolo[2,1-*f*][1,2,4]triazin-5-ylmethyl)-triethylammonium bromide (75 mg, 0.22 mmol, Compound B of Example 154) in chloroform (1.5 mL) was added 1-(4-aminophenyl)-3-(2-(4-fluorophenyl)acetyl)urea (50 mg, 0.17 mmol) and the mixture was heated at reflux for 6 h. The mixture was cooled to room temperature, concentrated in vacuo and the residue was triturated with acetonitrile. The resulting solid was used in the next step without purification.

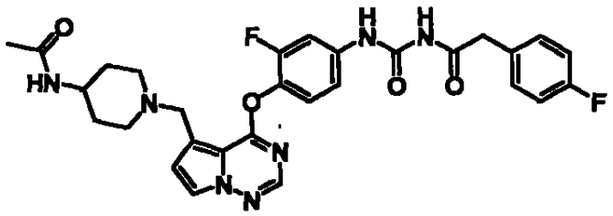
D) **1-(4-(5-(((3*R*,4*R*)-4-Azido-3-hydroxypiperidin-1-yl)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ylamino)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea**

To a solution of crude *N,N*-diethyl-*N*-((4-(4-(3-(2-(4-fluorophenyl)acetyl)ureido)phenylamino)pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)methyl)ethanaminium bromide in chloroform (3 mL), were added (3*R*,4*R*)-4-azidopiperidin-3-ol (0.28 mg, 0.2 mmol, WO 04/058144) and triethylamine (0.2 mL). The reaction mixture was stirred at 60 °C for 2 h, cooled to room temperature and was then washed with water. The aqueous layer was extracted with chloroform (3 x 8 mL). The combined organic extracts were concentrated *in vacuo* to give the crude product as a yellow solid.

The above crude solid was dissolved in tetrahydrofuran (3 mL), triphenylphosphine (80 mg) and water (0.02 mL) were added and the resulting reaction mixture was heated to reflux for 2 h. The reaction mixture was cooled to room temperature, concentrated *in vacuo* and the crude product was purified by preparative reverse phase HPLC. The appropriate fractions were collected, concentrated and treated with 1 N HCl (2 mL). The solution was concentrated *in vacuo*, dissolved in water and lyophilized to obtain the title compound (48 mg, 47%

over three steps) as a white solid. ^{1}H NMR (CD_3OD) δ 7.87 (s, 1H), 7.77 (s, 1H), 7.65 (d, 2H, J = 8.4 Hz), 7.46 (d, 2H, J = 8.3 Hz), 7.28 (dd, 2H , J = 5.4, 8.4 Hz), 7.06 (s, 1H), 6.98 (t, 2 H, J = 8.7 Hz), 4.7 (br s, 2H), 3.9 (br s, 2H), 3.63 (s, 2H), 3.56 (br s, 2H), 3.20-3.10 (br s, 2H), 2.99-2.87 (br s, 1H), 2.96 (br d, 1H, J = 10.8 Hz), 1.91 (br t, J = 10.8 Hz); MS(ESI$^+$) *m/z* 533.4 $(M+H)^+$.

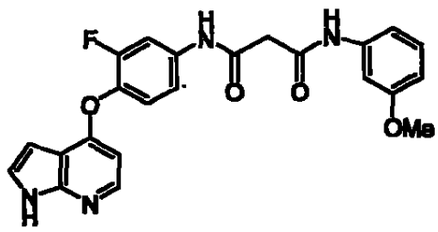
EXAMPLE 172



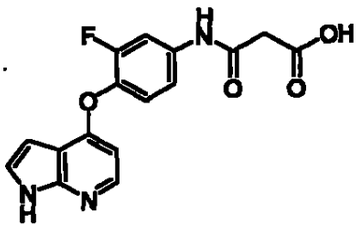
1-(4-(5-((4-Acetamidopiperidin-1-yl)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea

To 1-(4-(5-((4-aminopiperidin-1-yl)methyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea (30 mg, 0.056 mmol, Example 155) in methylene chloride (1 mL) was added pyridine (6 µL, 0.067 mmol) followed by acetyl chloride (5 µL, 0.067 mmol). DMF (0.5 mL) was added to solubilize the reaction. After stirring at rt for 2 h, a second shot of pyridine (6 uL) and acetyl chloride (5 µL) was added. After stirring at rt for 1 h, the reaction was diluted with ethyl acetate (10 mL), washed with 10% aqueous lithium chloride solution followed by brine (1 x 5 mL each), dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The crude product was purified by reverse phase prep hplc. The appropriate fractions were concentrated *in vacuo* and toluene was added (2 x 2 mL) and concentrated to give the TFA salt of the title compound (15 mg, 39%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.00 (s, 1H), 10.55 (s, 1H), 8.19 (s, 1H), 8.14 (d, 1H, J = 2.8 Hz), 7.89 (d, 1H, J = 7.2 Hz), 7.71 (dd, 1H, J = 12.4, 2.4 Hz), 7.43-7.28 (m, 4H), 7.14-7.07 (m, 3H), 4.54 (s, 2H), 3.68 (s, 2H), 3.45-2.42 (m, 3H), 3.12-3.10 (m, 2H), 1.88-1.85 (m, 2H), 1.73 (s, 3H), 1.52-1.50 (m, 2H); MS(ESI$^+$) *m/z* 578.2 $(M+H)^+$.

EXAMPLE 173



N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(3-methoxyphenyl)malonamide, trifluoroacetic acid salt



A) 3-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenylamino)-3-oxopropanoic acid

To a solution of 4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorobenzenamine (900 mg, 3.7 mmol, Compound B of Example 132) in CH_2Cl_2 (30 mL) at –40 °C, was added ethyl 3-chloro-3-oxopropanoate (555 mg, 3.7 mmol, Aldrich), followed by pyridine (1 mL). The resulting mixture was stirred at –40 °C for 1 h. The mixture was diluted with CH_2Cl_2, washed with sat. KH_2PO_4, and dried over $MgSO_4$. The mixture was filtered through a short pad of silica gel, eluting with 2% MeOH/EtOAc to give a brown oil (1.1 g). The ester was saponified in EtOH (15 mL) and NaOH (1 N in H_2O, 15 mL) at 0 °C for 1 h, neutralized with 1 N HCl to pH 4. EtOH was removed from the reaction mixture under reduced pressure and the solid was collected by filtration. The solid was then rinsed with H_2O and dried ($MgSO_4$) to afford the title compound (670 mg, 55%) as a beige solid. LC/MS(ESI$^+$) *m/z* 330 $(M + H)^+$.

B) N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(3-methoxyphenyl)malonamide, trifluoroacetic acid salt

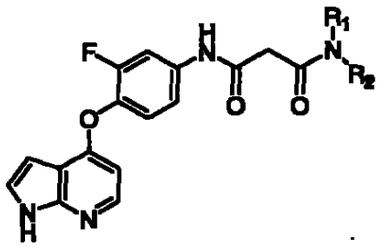
To a stirred solution of 3-(4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenylamino)-3-oxopropanoic acid (16.5 mg, 0.05 mmol) in DMF (0.4 mL), was added HATU (38 mg, 0.1 mmol), followed by 3-methoxybenzenamine (18 mg,

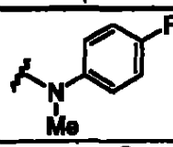
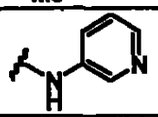
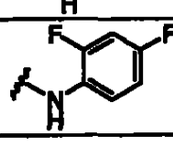
0.15 mmol) and DMAP (3 mg). The mixture was heated at 45 °C for 4 h. The desired product was purified by prep-HPLC to give the title compound (17 mg, 62%) as a white solid. ^{1}H NMR (CD_3OD) δ 8.15 (d, 1H, J = 6.6 Hz), 7.80 (dd, 1H, J = 11.8, 2.2 Hz), 7.41 (d, 1H, J = 3.9 Hz), 7.29-7.38 (m, 2H), 7.23 (m, 1H), 7.12 (t, 1H, J = 8.3 Hz), 7.00 (dd, 1H, J = 8.3, 1.1 Hz), 6.69 (d, 1H, J = 6.6 Hz), 6.60 (dd, 1H, J = 8.3, 2.2 Hz), 6.51 (d, 1H, J = 3.3 Hz), 3.90 (s, 3H); LCMS(ESI$^+$) m/z 435 $(M + H)^+$.

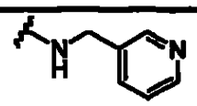
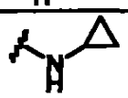
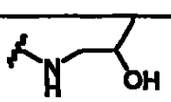
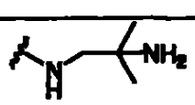
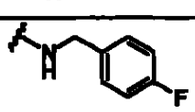
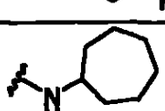
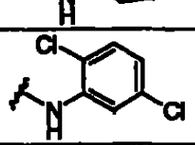
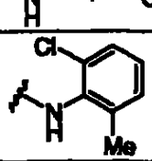
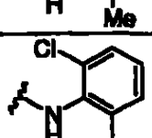
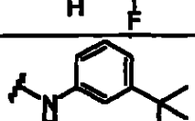
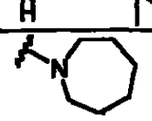
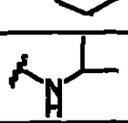
EXAMPLES 174–236

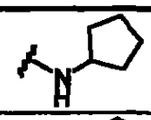
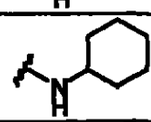
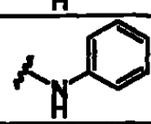
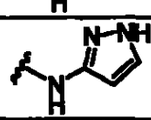
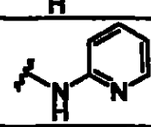
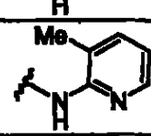
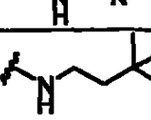
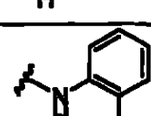
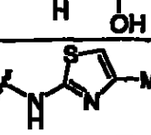
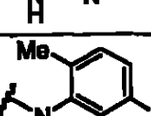
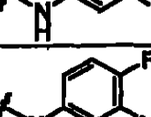
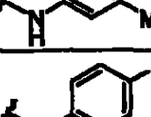
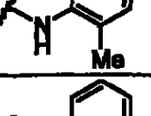
The examples 174–236 illustrated in Table 3 were prepared from 3-(4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenylamino)-3-oxopropanoic acid (Compound A of Example 173) and the corresponding amines, in the presence of HATU, DIPEA, and DMAP in DMF. The crude products were purified by prep-HPLC (H_2O/MeOH/0.1% TFA, gradient 35–90% MeOH over 10 min, 20 ×100 mm 5 µm YMC ODS-A column)! The desired fraction(s) was/were centrifugally evaporated, weighed and analyzed by LCMS (H_2O/MeOH/0.1% TFA).

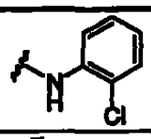
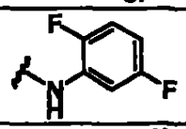
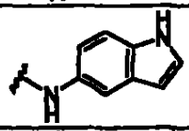
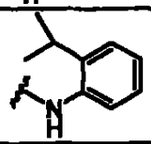
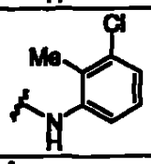
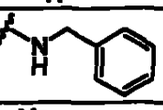
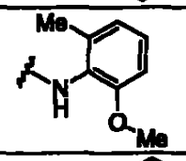
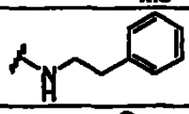
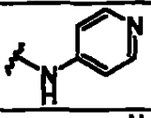
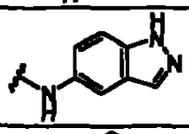
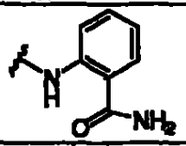
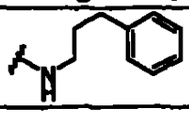
TABLE 3

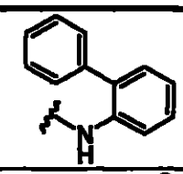
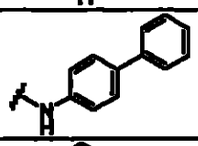
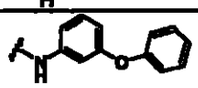
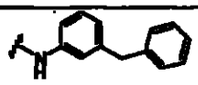
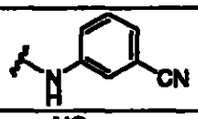
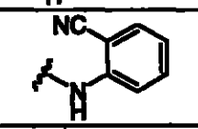
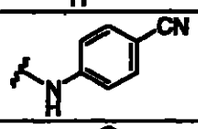
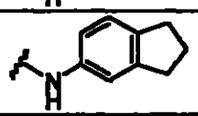
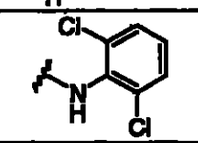
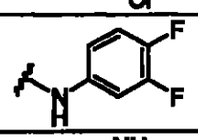
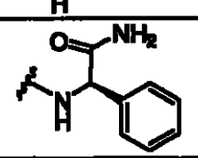
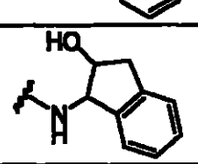


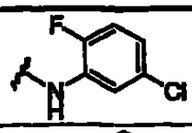
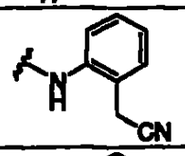
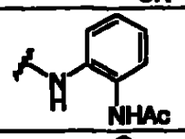
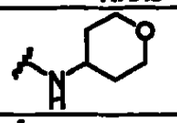
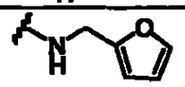
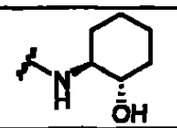
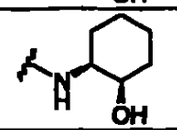
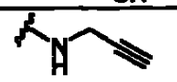
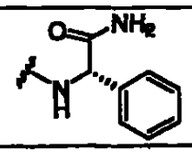
EXAMPLE #	NR_1R_2	Compound Name	*LC/MS* $(M+H)^+$
174		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(4-fluorophenyl)-N^3-methylmalonamide	437
175		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(pyridin-3-yl)malonamide	406
176		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(2,4-difluorophenyl)malonamide	441

EXAMPLE #	NR_1R_2	Compound Name	LC/MS $(M+H)^+$
177		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(pyridin-3-ylmethyl)malonamide	420
178		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-allylmalonamide	369
179		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-cyclopropylmalonamide	369
180		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(2-hydroxypropyl)malonamide	387
181		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(2-amino-2-methylpropyl)malonamide	400
182		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(4-fluorobenzyl)malonamide	437
183		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-cycloheptylmalonamide	425
184		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(2,5-dichlorophenyl)malonamide	474
185		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(2-chloro-6-methylphenyl)malonamide	453
186		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(2-chloro-6-fluorophenyl)malonamide	457
187		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(3-*tert*-butylphenyl)malonamide	461
188		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-3-(azepan-1-yl)-3-oxopropanamide	411
189		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-isopropylmalonamide	371
190		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-*tert*-butylmalonamide	385

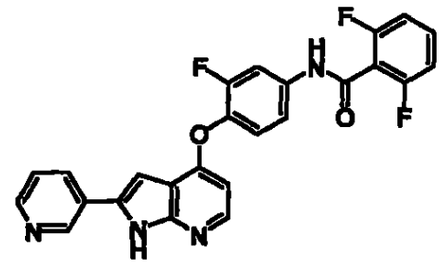
EXAMPLE #	NR_1R_2	Compound Name	LC/MS $(M+H)^+$
191		*N*^{1}-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-*N*^{3}-cyclopentylmalonamide	397
192		*N*^{1}-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-*N*^{3}-cyclohexylmalonamide	411
193		*N*^{1}-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-*N*^{3}-phenylmalonamide	405
194		*N*^{1}-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-*N*^{3}-(1*H*-pyrazol-3-yl)malonamide	395
195		*N*^{1}-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-*N*^{3}-(pyridin-2-yl)malonamide	406
196		*N*^{1}-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-*N*^{3}-(3-methylpyridin-2-yl)malonamide	420
197		*N*^{1}-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-*N*^{3}-(3,3-dimethylbutyl)malonamide	413
198		*N*^{1}-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-*N*^{3}-(2-hydroxyphenyl)malonamide	421
199		*N*^{1}-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-*N*^{3}-(4-methylthiazol-2-yl)malonamide	426
200		*N*^{1}-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-*N*^{3}-(5-fluoro-2-methylphenyl)malonamide	437
201		*N*^{1}-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-*N*^{3}-(4-fluoro-3-methylphenyl)malonamide	437
202		*N*^{1}-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-*N*^{3}-(4-fluoro-2-methylphenyl)malonamide	437
203		*N*^{1}-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-*N*^{3}-(3-fluoro-2-methylphenyl)malonamide	437

EXAMPLE #	NR_1R_2	Compound Name	LC/MS $(M+H)^+$
204		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(2-chlorophenyl)malonamide	439
205		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(2,5-difluorophenyl)malonamide	441
206		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(1*H*-indol-5-yl)malonamide	444
207		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(2-isopropylphenyl)malonamide	447
208		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(3-chloro-2-methylphenyl)malonamide	453
209		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-benzylmalonamide	419
210		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(2-methoxy-6-methylphenyl)malonamide	449
211		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-phenethylmalonamide	433
212		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(pyridin-4-yl)malonamide	406
213		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(1*H*-indazol-5-yl)malonamide	445
214		2-(3-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenylamino)-3-oxopropanamido)benzamide	448
215		N^1-(4-(1*H*-Pyrrolo[2,3-b]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(3-phenylpropyl)malonamide	447

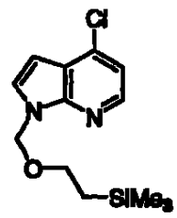
EXAMPLE #	NR_1R_2	Compound Name	LC/MS $(M+H)^+$
216		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(2-biphenyl)malonamide	481
217		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(4-biphenyl)malonamide	481
218		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(3-phenoxyphenyl)malonamide	497
219		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(3-benzylphenyl)malonamide	495
220		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(3-cyanophenyl)malonamide	430
221		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(2-cyanophenyl)malonamide	430
222		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(4-cyanophenyl)malonamide	430
223		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(2,3-dihydro-1*H*-inden-5-yl)malonamide	445
224		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(2,6-dichlorophenyl)malonamide	474
225		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(3,4-difluorophenyl)malonamide	441
226		(*R*)- N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(2-amino-2-oxo-1-phenylethyl)malonamide	462
227		N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-N^3-(2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)malonamide	461

EXAMPLE #	NR_1R_2	Compound Name	LC/MS $(M+H)^+$
228		*N*¹-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-*N*³-(5-chloro-2-fluorophenyl)malonamide	457
229		*N*¹-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-*N*³-(2-(cyanomethyl)phenyl)malonamide	444
230		*N*¹-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-*N*³-(2-acetamidophenyl)malonamide	462
231		*N*¹-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-*N*³-(tetrahydro-2*H*-pyran-4-yl)malonamide	413
232		*N*¹-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-*N*³-(furan-2-ylmethyl)malonamide	409
233		*N*¹-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-*N*³-(*trans*-2-hydroxycyclohexyl)malonamide	427
234		*N*¹-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-*N*³-(*cis*-2-hydroxycyclohexyl)malonamide	427
235		*N*¹-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-*N*³-(prop-2-yuyl)malonamide	367
236		(*S*)-*N*¹-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-*N*³-(2-amino-2-oxo-1-phenylethyl)malonamide	462

EXAMPLE 237

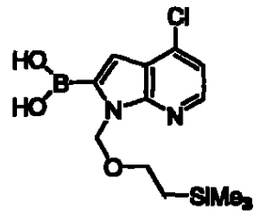


2,6-Difluoro-*N*-(3-fluoro-4-(2-(pyridin-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)benzamide, hydrochloride salt



A) **4-Chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridine**

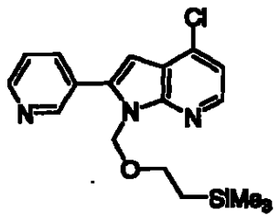
To a solution of 4-chloro-1*H*-pyrrolo[2,3-*b*]pyridine (3.05 g, 20 mmol, prepared according to Thibault, C. et al. *Org. Lett.* **2003**, *5*, 5023) in DMF (50 mL) at –40 °C under N_2, was added NaH (60% in mineral oil, 880 mg, 22 mmol). The mixture was stirred at rt for 15 min, then cooled to –40 °C. To this solution was added (2-(chloromethoxy)ethyl)trimethylsilane (3.67 g, 22 mmol). The resulting mixture was stirred at rt overnight. The mixture was diluted with EtOAc, washed twice with 10% LiCl, and dried over $MgSO_4$. The title compound was purified by flash column chromatography (silica gel, eluding with hexane, followed by Et_2O) to give the desired product (5.6 g, quantitiatve yield) as an oil. LC/*MS*(ESI$^+$) *m/z* 283 $(M+H)^+$.



B) **4-Chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-ylboronic acid**

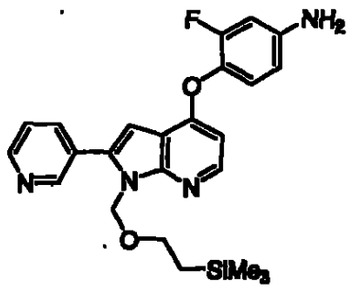
To a solution of 4-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridine (565 mg, 2 mmol) in THF (5 mL) at –40 °C under N_2, was added *n*-BuLi (2.0 M in cyclohexane, Aldrich, 2.4 mmol). The reaction mixture was stirred at –40 °C for 1 h and then treated with triisopropylborate (489 mg, 2.6 mmol). The mixture was slowly warmed to rt and stirred overnight. To this solution was added 1 N HCl in

H_2O (20 mL), and the mixture was stirred for 20 min., neutralized with saturated aq. K_2HPO_4 solution and extracted with ether. The organic layer was dried over Na_2SO_4. After filtration and concentration under reduced pressure, the title compound was obtained as a light beige solid (640 mg, quantitative yield). LC/MS(ESI$^+$) *m/z* 327 $(M+H)^+$.



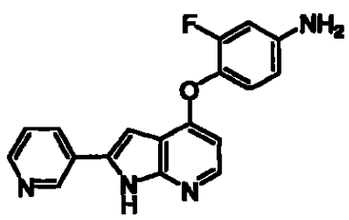
C) **4-Chloro-2-(pyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridine**

Argon was bubbled through a mixture of 4-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-ylboronic acid (5.55 g, 17 mmol), 3-iodopyridine (6.97 g, 34 mmol), $Pd(OAc)_2$, 2-dicyclohexylphosphino-2',4',6'-tri-i-propyl-1,1'-biphenyl (405 mg, 0.85 mmol), and K_3PO_4 (2 M in H_2O, 34 mmol) in DME (50 mL) for 10 min and then heated at reflux overnight. The reaction mixture was diluted with EtOAc and washed with saturated aq. K_2HPO_4 solution. The title compound was purified by flash column chromatography (silica gel, 20% EtOAc/CH_2Cl_2) to afford the desired product (3.2 g, 52% yield) as an oil. LC/MS(ESI$^+$) *m/z* 361 $(M+H)^+$.



D) **3-Fluoro-4-(2-(pyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)benzenamine**

A mixture of 4-chloro-2-(pyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridine (3.2 g, 8.9 mmol), 2-fluoro-4-nitrophenol (2.79 g, 17.8 mmol), and DIPEA (3.5 mL, 20 mmol) in NMP (15 mL) was heated in a sealed tube at 185 °C for 3 days. The mixture was diluted with EtOAc and filtered through a short pad of Celite® (EtOAc). The filtrate was washed with 5% aq. Na_2CO_3 solution and dried over $MgSO_4$. The title compound was purified by flash column chromatography (silica gel, 100% CH_2Cl_2 to 50% EtOAc/CH_2Cl_2) to afford the desired product (295 mg, 7.4%) as a light brown solid. LC/MS(ESI$^+$) *m/z* 451 $(M + H)^+$.



E) **3-Fluoro-4-(2-(pyridin-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)benzenamine**

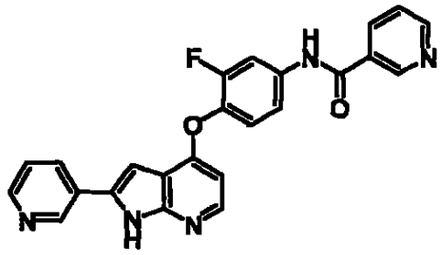
A mixture of 3-fluoro-4-(2-(pyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)benzenamine (275 mg, 0.61 mmol), tetrabutylammonium fluoride (1 M in THF, 4 mL), and 1,2-diaminoethane (0.2 mL) in THF (4 mL) was heated at 65 °C for 24 h. The solvent was removed *in vacuo*. The residue was purified by flash column chromatography (silica gel, 5% MeOH/EtOAc) to afford the desired product (180 mg, 92%) as a yellow solid. LC/MS(ESI$^+$) *m/z* 321 $(M + H)^+$.

F) **2,6-Difluoro-*N*-(3-fluoro-4-(2-(pyridin-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)benzamide, hydrochloride salt**

To a solution of 3-fluoro-4-(2-(pyridin-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)benzenamine (15 mg, 0.047 mmol) and pyridine (0.1 mmol) in THF at 0 °C was added 2,6-difluorobenzoyl chloride (10 mg, 0.056 mmol). The reaction mixture was stirred at 0 °C for 1 h, concentrated *in vacuo*, and the resulting residue was purified by preparative HPLC. The desired fractions were lyophilized to give a white TFA salt, which was dissolved in small amount of MeOH/H_2O with 1 N HCl (0.2 mL). This

solution was then lyophilized to afford the title compound (HCl salt, 12 mg, 48%) as a yellow solid. ^{1}H NMR (CD_3OD) δ 9.29 (s, 1H), 8.85 (d, 1H, J = 9.6 Hz), 8.74 (d, 1H, J = 5.2 Hz), 8.26 (d, 1H, J = 6.8 Hz), 8.01 (dd, 1H, J = 8.4, 5.6 Hz), 7.88 (dd, 1H, J = 12.4, 2.4 Hz), 7.50-7.35 (m, 4H), 7.10-7.00 (m, 2H), 6.73 (d, 1H, J = 6.4 Hz); LC/MS(ESI$^+$) m/z 461 $(M + H)^+$.

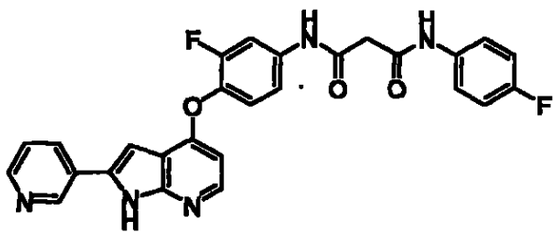
EXAMPLE 238



***N*-(3-Fluoro-4-(2-(pyridin-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)nicotinamide**

Prepared in a similar manner as Example 237. ^{1}H NMR (CD_3OD) δ 9.36 (s, 1H), 9.33 (s, 1H), 9.00-8.90 (m, 3H), 8.79 (d, 1H, J = 5.2 Hz), 8.31 (d, 1H, J = 6.8 Hz), 8.12-8.05 (m, 2H), 7.99 (dd, 1H, J = 12.8, 2.4 Hz), 7.63 (d, 1H, J = 8.8 Hz), 7.52 (s, 1H), 7.48-7.40 (m, 2H), 6.78 (d, 1H, J = 6.4 Hz); LC/MS(ESI$^+$) m/z 461 $(M + H)^+$.

EXAMPLE 239

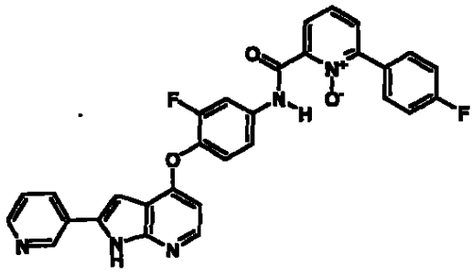


***N*^{1}-(3-Fluoro-4-(2-(pyridin-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)-*N*^{3}-(4-fluorophenyl)malonamide, hydrochloride salt**

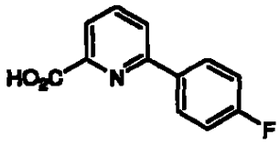
To a stirred solution of 3-fluoro-4-(2-(pyridin-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)benzenamine (16 mg, 0.05 mmol, Compound E of Example 237), 3-(4-fluorophenylamino)-3-oxopropanoic acid (19.7 mg, 0.1 mmol, Compound A of Example 25), and HATU (38 mg, 0.1 mmol) in DMF (0.5 mL) was added DIPEA (0.1

mL). The mixture was stirred at rt for 2 h, concentrated *in vacuo*, and the residue was purified by preparative HPLC. The desired fractions were lyophilized to give a white TFA salt, which was dissolved in small amount of MeOH/H_2O with 1 N HCl (0.2 mL) and lyophilized to afford the title compound (HCl salt, 12 mg, 42%) as a yellow solid. ^1H NMR (CD_3OD) δ 9.25 (s, 1H), 8.81 (d, 1H, J = 8.7 Hz), 8.72 (d, 1H, J = 5.4 Hz), 8.25 (d, 1H, J = 6.7 Hz), 8.00 (dd, 1H, J = 8.1, 6.1 Hz), 7.82 (dd, 1H, J = 12.1, 1.3 Hz), 7.53-7.48 (m, 2H), 7.40-7.32 (m, 3H), 7.00-6.95 (m, 2H), 6.71 (d, 1H, J = 6.72 Hz), 3.48 (s, 2H); *LC/MS*(ESI$^+$) *m/z* 500 $(M+H)^+$.

EXAMPLE 240



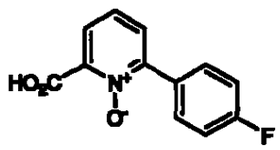
6-(4-Fluoro-phenyl)-1-oxy-pyridine-2-carboxylic acid [3-fluoro-4-(2-pyridin-3-yl-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-phenyl]-amide, trifluoroacetic acid salt



A) **6-(4-Fluorophenyl)picolinic acid**

A solution of 2-bromo-picolinic acid (2.02 g, 10 mmol, Aldrich) in DME containing 4 mL of 10% aq. Na_2CO_3 was purged with Ar gas, treated with $Pd(PPh_3)_4$ followed by 2-(4-fluorophenyl)-5,5-dimethyl-1,3,2-dioxaborinane (2.40 g, 11.5 mmol, Aldrich) and EtOH (20 mL). This mixture was then also purged with Ar gas. The reaction mixture was heated at 100 °C for 2.5 h in a sealed tube. Additional 2-bromo-picolinic acid (900 mg) and $Pd(PPh_3)_4$ was added, and after purging with Ar gas it was heated at 100 °C for 4.5 h. Trifluoroacetic acid (20 mL) was added to the reaction and the mixture was concentrated *in vacuo*. MeOH (150 mL) was added to the residue and the insoluble material was filtered. The filtrate was concentrated *in*

vacuo, and the resulting residue was purified by flash column chromatography on silica gel eluting with EtOAc/MeOH (9:1) followed by EtOAc/MeOH/HOAc (14:30:1) to afford the desired product (1.0 g, 40% based on borinane starting material) as a white solid. ^{1}H NMR (CD_3OD) δ 8.01 (d, 1H, J = 7.7 Hz), 7.94-7.87 (m, 3H), 7.73 (d, 1H, J = 7.7 Hz), 7.13 (t, 2H, J = 8.8 Hz); MS(ESI$^+$) m/z 234 (M + H)$^+$.



B) **6-(4-Fluorophenyl)picolinic acid-*N*-oxide**

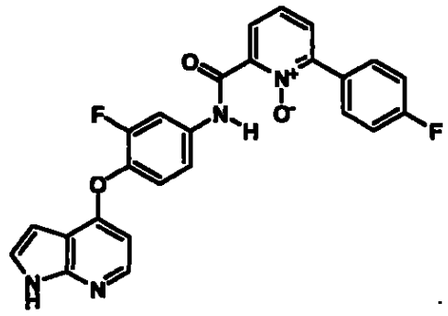
A mixture of the picolinic acid derivative above (1.0 g, 4.6 mmol), Na_2HPO_4 (1.2 g) and *m*-CPBA (1.1 g, ~70 % from Aldrich) in CH_2ClCH_2Cl (30 mL) was stirred at rt for 2 h. Additional Na_2HPO_4 (0.8 g) and *m*-CPBA (1.0 g) were added to the reaction mixture and it was stirred for 3 h at rt. Na_2HPO_4 (0.5 g) and *m*-CPBA (0.5 g) were again added to the reaction mixture and it was stirred at rt overnight. $CHCl_3$ (160 mL) and 2 N aq. HCl solution (50 mL) were added to the mixture and the organic layer was separated, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel eluting with EtOAc/MeOH/HOAc (70:24:6) to obtain the desired product which was contaminated with *m*-CPBA. This impure material was purified by preparative HPLC to obtain the desired product (175 mg, 16%) as a white solid. ^{1}H NMR (DMF-d_7) 8.45 (dd, 1H, J = 8.3, 2.2 Hz), 8.15 (d, 1H, J = 2.2 Hz), 8.13-8.00 (m, 4H), 7.45 (t, 2H, J = 8.7 Hz).

C) **6-(4-Fluoro-phenyl)-1-oxy-pyridine-2-carboxylic acid [3-fluoro-4-(2-pyridin-3-yl-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-phenyl]-amide, trifluoroacetic acid salt**

To a solution of 6-(4-fluorophenyl)picolinic acid *N*-oxide (30 mg, 0.13 mmol), HOBT (16 mg), and EDCI.HCl (50 mg, 0.26 mmol) in DMF (4 mL) at room temperature was added 3-fluoro-4-(2-(pyridin-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)benzenamine (40 mg, 0.12 mmol, Compound E of Example 237). The reaction

mixture was stirred at room temperature overnight and concentrated under reduced pressure. The residue was purified by preparative HPLC to afford the desired product (20 mg, 24%) as a beige solid. ^{1}H NMR (DMF-d_7) δ 14.07 (br s, 1H), 12.64 (br s, 1H), 9.35 (s, 1H), 8.65 (d, 1H, J = 4.4 Hz), 8.53 (d, 1H, J = 7.7 Hz), 8.49 (dd, 1H, J = 8.2, 2.2 Hz), 8.23 (d, 1H, J = 5.5 Hz), 8.19 (dd, 1H, J = 13.2, 2.8 Hz), 8.02-7.62 (m, 6H), 7.55 (t, 1H, J = 8.8 Hz), 7.43 (t, 2H, J = 8.8 Hz), 7.22 (s, 1H), 6.55 (d, 1H, J = 5.5 Hz); MS(ESI$^+$) m/z 459.1 $(M+H)^+$.

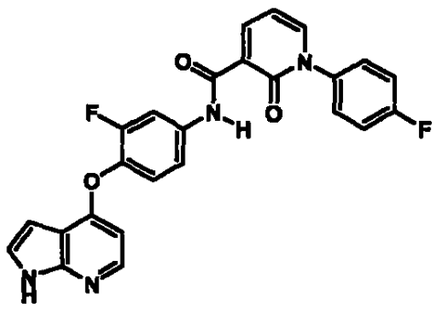
EXAMPLE 241



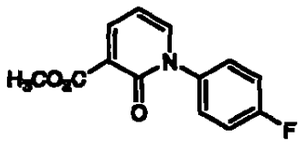
6-(4-Fluoro-phenyl)-1-oxy-pyridine-2-carboxylic acid [3-fluoro-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-phenyl]-amide, trifluoroacetic acid salt

To a solution of 6-(4-fluorophenyl)picolinic acid *N*-oxide (47 mg, 0.20 mmol, Compound B of Example 240), HOBT (20 mg), and EDCI.HCl (60 mg, 0.31 mmol) in DMF (4 mL) at room temperature was added 4-(1*H*-pyrrolo[2,3-b]pyridin-4-yloxy)-3-fluorobenzenamine (50 mg, 0.20 mmol, Compound B of Example 132). The mixture was stirred at room temperature overnight and concentrated under reduced pressure. The resulting residue was purified by preparative HPLC to afford the desired product (68 mg, 12%) as a white solid. ^{1}H NMR (DMF-d_7) δ 14.07 (br s, 1H), 12.14 (br s, 1H), 8.49 (dd, 1H, J = 7.7, 1.7 Hz), 8.26 (d, 1H, J = 6.1 Hz), 8.18 (dd, 1H, J = 12.7, 1.7 Hz), 8.02-7.96 (m, 3H), 7.84 (t, 1H, J = 8.3 Hz), 7.67 (d, 1H, J = 8.8 Hz), 7.57-7.52 (m, 2H), 7.43 (d, 2H, J = 8.8 Hz), 6.62 (d, 1H, J = 6.0 Hz), 6.46 (d, 1H, J = 2.8 Hz); MS(ESI$^+$) m/z 536.1 $(M+H)^+$.

EXAMPLE 242

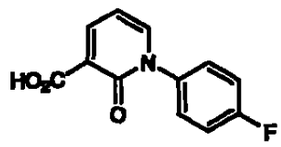


***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, trifluoroacetic acid salt**



A) **Methyl 1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate**

To a solution of methyl 2-oxo-2*H*-pyran-3-carboxylate (2.31 g, 15 mmol, Aldrich) in THF (40 mL) and DMF (10 mL) at rt was added 4-fluoroaniline (1.67 g, 15 mmol), and the reaction mixture was stirred for 2.5 h. To the 4-fluoroaniline intermediate formed *via* a Michael addition was added EDCI.HCl (3.85 g, 20 mmol) and DMAP (120 mg) at rt. The reaction mixture was stirred at rt overnight. To the reaction mixture were added 1 N aq. HCl (50 mL) and EtOAc (150 mL). The EtOAc layer was separated, and the aqueous layer was washed with EtOAc (150 mL). The combined EtOAc layers were dried over $MgSO_4$ and concentrated *in vacuo* to obtain a semi-solid material (~4.4 g). The crude product was dissolved in ether (100 mL) and methanol (15 mL), and the solid which formed after stirring was filtered off. The filtrate was concentrated *in vacuo* to afford the desired product (2.95 g, 80%) as a semi-solid, which was sufficiently pure to use in the next step without further purification. ^{1}H NMR (DMSO-d_6) δ 8.23 (dd, 1H, J = 7.2, 2.2 Hz), 7.57 (dd, 1H, J = 6.6, 1.7 Hz), 7.32-7.34 (m, 2H), 7.17 (t, 2H, J = 8.8 Hz), 6.32 (t, 1H, J = 7.1 Hz), 3.89 (s, 3H); MS(ESI$^+$) *m/z* 248.2 $(M + H)^+$.



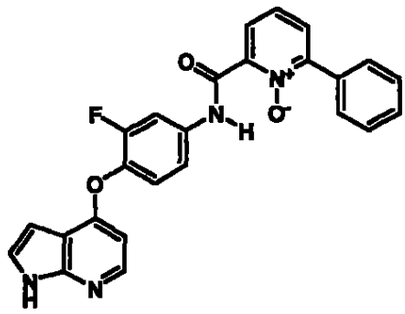
B) **1-(4-Fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid**

A mixture of methyl 1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (crude 2.45 g, 12 mmol) and 6 N aq. NaOH (2.5 mL) in methanol (60 mL) was stirred at rt for 4 h. To the reaction mixture was added conc. HCl (1 mL) slowly with stirring at rt. The precipitate which formed was filtered, washed with a small amount water and dried to obtain the desired acid product (2.1 g) as a yellow solid. The filtrate was concentrated *in vacuo*. The residue was mixed with water (50 mL) and washed with EtOAc (2 × 130 mL). The EtOAc layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with a small amount of ether to obtain a 2nd crop of product (195 mg, total 2.30 g, 82%). ^{1}H NMR (DMSO-d_6) δ 8.47 (dd, 1H, J = 7.2, 2.2 Hz), 8.19 (dd, 1H, J = 6.6, 1.7 Hz), 7.62-7.60 (m, 2H), 7.42 (t, 2H, J = 8.8 Hz), 6.78 (t, 1H, J = 7.1 Hz); MS(ESI$^+$) *m/z* 234.2 $(M + H)^+$.

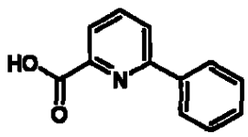
C) ***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, trifluoroacetic acid salt**

To a solution of 1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (70 mg, 0.30 mmol), HOBT (30 mg), and EDCLHCl (200 mg, 1.04 mmol) in DMF (8 mL) at room temperature was added 4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorobenzenamine (70 mg, 0.29 mmol, Compound B of Example 132). The mixture was stirred at room temperature overnight and concentrated *in vacuo*. The resulting residue was purified by preparative HPLC to afford the desired product (71 mg, 43%) as a beige solid. ^{1}H NMR (DMSO-d_6) δ 12.04 (br s, 1H), 11.96 (br s, 1H), 8.52 (dd, 1H, J = 7.2, 2.2 Hz), 8.08 (t, 2H, J = 5.5 Hz), 7.96 (dd, 1H, J = 12.7, 2.2 Hz), 7.55-7.53 (m, 2H), 7.84 (t, 1H, J = 8.3 Hz), 7.43 (dd, 1H, J = 8.8, 1.7 Hz), 7.38-7.32 (m, 3H), 6.67 (t, 1H, J = 7.2 Hz), 6.43 (d, 1H, J = 6.1 Hz), 6.46 (dd, 1H, J = 3.3, 1.4 Hz); MS(ESI$^+$) *m/z* 459.1 $(M + H)^+$.

EXAMPLE 243

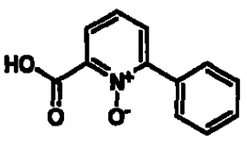


1-Oxy-6-phenyl-pyridine-2-carboxylic acid [3-fluoro-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-phenyl]-amide, trifluoroacetic acid salt



A) 6-Phenylpicolinic acid

A mixture of 6-bromopicolinic acid (2.02 g, 10 mmol), phenyboronic acid (1.22 g, 10 mmol), cesium carbonate (5.00 g) and $PdCl_2$ [(*t*-Bu)$_2$P(OH)]$_2$ (70 mg, CombiPhos Catalysts, Inc. Princeton, NJ) in DMF (20 mL) and water (3 mL) was purged with Ar-gas and heated at 110 °C for 24 h. The reaction was incomplete and did not progress further. To the reaction mixture were added EtOAc (200 mL) and 1 N aq. HCl (40 mL). The EtOAc layer was separated, and the aqueous layer was washed with EtOAc (150 mL). The combined EtOAc layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by preparative HPLC to afford the desired product (350 mg, 18%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 10.45 (s, 1H), 8.18-7.96 (m, 5H), 7.51-7.53 (m, 3H).



B) 6-Phenylpicolinic acid *N*-oxide

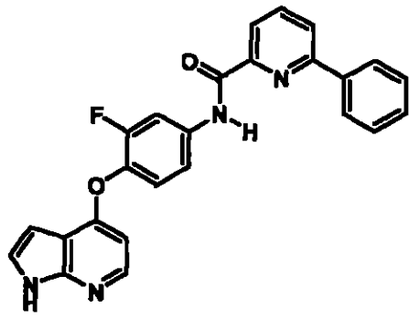
A mixture of 6-phenylpicolinic acid (150 mg, 0.75 mmol), K_2HPO_4 (600 mg) *m*-CPBA (300 mg, max 70 % from Aldrich) in dichloroethane (8.0 mL) was heated at

60 °C for 1.5 h. Additional *m*-CPBA (2 x 300 mg) was added and the mixture was heated at 60 °C for 40 min. The reaction mixture was purified by preparative HPLC to afford the desired product (110 mg, 68 %) as a white solid. ^{1}H NMR (DMF-d_7) δ 8.57 (s, 1H), 8.43 (d, 1H, J = 2.2 Hz), 8.10-7.88 (m, 5H), 7.59-7.57 (m, 3H).

C) **1-Oxy-6-phenyl-pyridine-2-carboxylic acid [3-fluoro-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-phenyl]-amide, trifluoroacetic acid salt**

To a solution of 6-phenylpicolinic acid *N*-oxide (25 mg, 0.12 mmol), HOBT (20 mg), and EDCI.HCl (120 mg, 1.14 mmol) in DMF (3.5 mL) at room temperature was added 4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorobenzenamine (40 mg, 0.16 mmol, Compound B of Example 132). The reaction mixture was stirred at room temperature overnight and concentrated *in vacuo*. The resulting residue was purified by preparative HPLC to afford the desired product (36 mg, 54%) as a white solid. ^{1}H NMR (DMF-d_7) δ 14.12 (br s, 1H), 12.10 (br s, 1H), 8.48 (dd, 1H, J = 7.9, 1.6 Hz), 8.24 (d, 1H, J = 5.5 Hz), 8.18 (dd, 1H, J = 14.8, 2.2 Hz), 7.95-7.89 (m, 3H), 7.83 (t, 1H, J = 7.7 Hz), 7.67 (dd, 1H, J = 8.6, 1.2 Hz), 7.61-7.51 (m, 5H), 6.60 (d, 1H, J = 5.5 Hz), 6.44 (d, 1H, J = 3.3 Hz); MS(ESI$^+$) *m/z* 441.1 $(M+H)^+$.

EXAMPLE 244

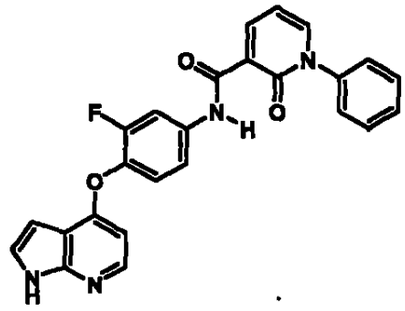


***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-6-phenylpicolinamide, trifluoroacetic acid salt**

To a solution of 6-phenylpicolinic acid (48 mg, 0.24 mmol, Compound A of Example 243), HOBT (25 mg), and EDCI.HCl (155 mg, 0.81 mmol) in DMF (3.5 mL) at room temperature was added 4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorobenzenamine (65 mg, 0.26 mmol, Compound B of Example 132). The mixture

was stirred at room temperature overnight and concentrated *in vacuo*. The residue was purified by preparative HPLC to afford the desired product (25 mg, 19%) as a light brown solid. ^{1}H NMR (DMF-d_7) δ 11.93 (br s, 1H), 11.01 (br s, 1H), 8.36 (dd, 2H, J = 7.2, 1.6 Hz), 8.31-8.17 (m, 5H), 7.59-7.50 (m, 6H), 6.53 (d, 1H, J = 5.5 Hz), 6.41 (d, 1H, J = 2.8 Hz); MS(ESI$^+$) m/z 425.1 $(M+H)^+$.

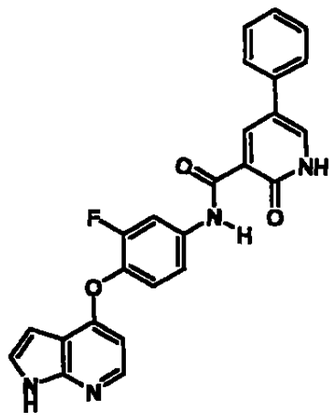
EXAMPLE 245



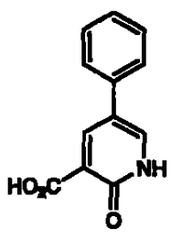
***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide, trifluoroacetic acid salt**

To a solution of 2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxylic acid (30 mg, 0.14 mmol, prepared in a similar manner as Steps A and B of Example 242), HOBT (20 mg), and EDCI.HCl (80 mg, 0.42 mmol) in DMF (3.5 mL) at room temperature was added 4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorobenzenamine (31 mg, 0.13 mmol, Compound B of Example 132). The reaction mixture was stirred at room temperature overnight and concentrated *in vacuo*. The residue was purified by preparative HPLC to afford the desired product (10 mg, 14 %) as a beige solid. ^{1}H NMR (acetone-d_6) δ 13.40 (br s, 1H), 12.32 (br s, 1H), 8.66 (dd, 1H, J = 7.1, 1.6 Hz), 8.43 (d, 1H, J = 6.6 Hz), 8.18 (dd, 1H, J = 13.2, 2.2 Hz), 8.03 (dd, 1H, J = 6.6, 2.2 Hz), 7.67-7.49 (m, 8H), 6.89 (d, 1H, J = 6.6 Hz), 6.75 (t, 1H, J = 6.3 Hz), 6.58 (d, 1H, J = 3.3 Hz); MS(ESI$^+$) m/z 441.1 $(M+H)^+$.

EXAMPLE 246



***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-2-oxo-5-phenyl-1,2-dihydropyridine-3-carboxamide, trifluoroacetic acid salt**



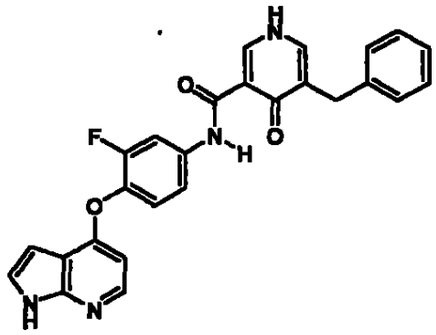
A) **2-Oxo-5-phenyl-1,2-dihydropyridine-3-carboxylic acid**

A mixture of 5-bromo-2-hydroxynicotinic acid (436 mg, 2.00 mmol, *Syn. Comm.*, 19 (3&4), 553-559 (1989)), phenylboronic acid (248 mg, 2.03 mmol), Cs_2CO_3 (1.20 g) and $PdCl_2$ [(*t*-Bu)$_2$P(OH)]$_2$ (170 mg, CombiPhos Catalysts, Inc. Princeton, NJ) in DMF (10 mL) and water (1.0 mL) was purged with Ar gas and heated at 110 °C for 6 h. Additional phenylboronic acid (75 mg) was added and the mixture was heated at 110 °C for 5 h. To the reaction was added TFA (3 mL), and the mixture was concentrated *in vacuo* to a volume of ~12 mL. The mixture was purified by preparative HPLC to afford the desired product (78 mg, 18 %). ^{1}H NMR (DMF-d_7) δ 14.8 (br s, 1H), 13.8 (br s, 1H), 8.73 (s, 1H), 8.46 (s, 1H), 7.74 (d, 1H, J = 7.2 Hz), 7.53-7.42 (m, 3H), 5.81 (s, 1H).

B) ***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-2-oxo-5-phenyl-1,2-dihydropyridine-3-carboxamide**

To a solution of 2-oxo-5-phenyl-1,2-dihydropyridine-3-carboxylic acid (35mg, 0.16 mmol), HOBT (25 mg), and EDCI.HCl (80 mg, 0.42 mmol) in DMF (3.0 mL) at room temperature was added 4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorobenzenamine (30 mg, 0.12 mmol, Compound B of Example 132). The mixture was stirred at room temperature overnight and concentrated *in vacuo*. The residue was purified by preparative HPLC to afford the desired product (12 mg, 13%) as a light brown solid. ^{1}H NMR (CD_3OD) δ 8.81 (d, 1H, J = 2.8 Hz), 8.17 (d, 1H, J = 6.6 Hz), 8.00 (dd, 1H, J = 12.6, 2.2 Hz), 7.94 (d, 1H, J = 3.3 Hz), 7.52-7.27 (m, 7H), 6.80 (d, 1H, J = 9.3 Hz), 6.72 (d, 1H, J = 6.6 Hz), 6.54 (d, 1H, J = 3.8 Hz); MS(ESI$^+$) *m/z* 441.1 $(M+H)^+$.

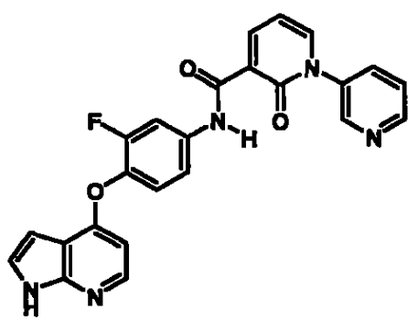
EXAMPLE 247



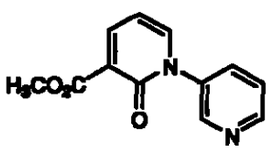
***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-5-benzyl-4-oxo-1,4-dihydropyridine-3-carboxamide, trifluoroacetic acid salt**

To a solution of 5-benzyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (35 mg, 0.15 mmol) and HOBt (30 mg) in DMF (2.5 mL) at rt was added EDCI.HCl (80 mg, 0.42 mmol) followed by 4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorobenzenamine (35 mg, 0.16 mmol, Compound B of Example 132). The reaction mixture was stirred at rt for 40 h and concentrated *in vacuo*. The resulting residue was purified by preparative HPLC to afford the desired product (38 mg, 45%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 13.21 (br s, 1H), 12.38 (s, 1H), 12.08 (br s, 1H), 8.59 (d, 1H, J = 4.4 Hz), 8.17 (d, 1H, J = 5.5 Hz), 8.03 (dd, 1H, J = 13.2, 2.2 Hz), 7.80 (d, 1H, J = 3.9 Hz), 7.48-7.19 (m, 8H), 6.52 (d, 1H, J = 5.5 Hz), 6.34 (d, 1H, J = 1.6 Hz), 3.81 (s, 2H); MS(ESI$^+$) *m/z* 455.1 $(M+H)^+$.

EXAMPLE 248

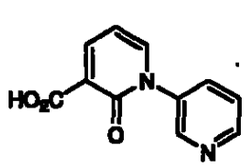


***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-2-oxo-1-(pyridin-3-yl)-1,2-dihydropyridine-3-carboxamide, trifluoroacetic acid salt**



A) Methyl 2-oxo-1-(pyridin-3-yl)-1,2-dihydropyridine-3-carboxylate

To a solution of methyl 2-oxo-2*H*-pyran-3-carboxylate (462 mg, 3 mmol, Aldrich) in DMF (6 mL) at rt was added 3-aminopyridine (282 mg, 3 mmol). The reaction mixture was stirred overnight at rt, treated with EDCI.HCl (650 mg, 3.4 mmol) and DMAP (200 mg), stirred for an additional 24 h, and concentrated *in vacuo*. The residue was purified by preparative HPLC to afford the desired product (980 mg, 95%) as a beige solid. ^{1}H NMR ($CDCl_3$) δ 13.00 (br s, 1H), 8.83 (br s, 1H), 8.74 (br s, 1H), 8.29 (dd, 1H, J = 7.2, 1.7 Hz), 8.18 (d, 1H, J = 8.3 Hz), 7.73 (dd, 1H, J = 7.7, 5.0 Hz), 7.66 (dd, 1H, J = 6.6, 1.6 Hz), 6.42 (t, 1H, J = 7.1 Hz), 3.87 (s, 3H).



B) 2-Oxo-1-(pyridin-3-yl)-1,2-dihydropyridine-3-carboxylic acid

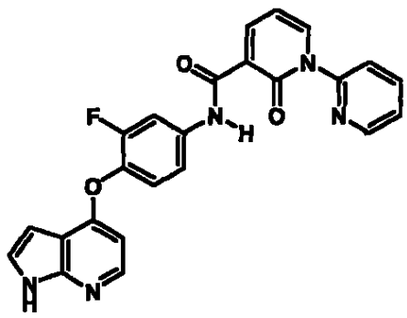
A mixture of methyl 2-oxo-1-(pyridin-3-yl)-1,2-dihydropyridine-3-carboxylate (980 mg, 2.85 mmol) and 6 N NaOH (1 mL) and methanol (20 mL) was stirred at rt overnight. To the reaction mixture was added 1 N aq. HCl (6 mL) and the mixture

was concentrated *in vacuo* to obtain the acid (1.0 g, 100 %) as a light yellow solid containing a small amount of NaCl. This material was used directly in the next step without further purification. ^{1}H NMR (CD_3OD) δ 8.85 (d, 1H, J = 1.7 Hz), 8.77 (d, 1H, J = 4.9 Hz), 8.59 (dd, 1H, J = 7.1, 1.7 Hz), 8.21 (d, 1H, J = 8.2 Hz), 8.10 (dd, 1H, J = 6.6, 2.2 Hz), 7.79 (dd, 1H, J = 8.2, 5.0 Hz), 6.80 (t, 1H, J = 6.6 Hz); MS(ESI$^+$) *m/z* 217.2 $(M + H)^+$.

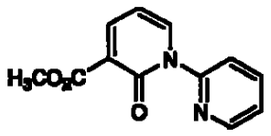
C) ***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-2-oxo-1-(pyridin-3-yl)-1,2-dihydropyridine-3-carboxamide, trifluoroacetic acid salt**

To a solution of 2-oxo-1-(pyridin-3-yl)-1,2-dihydropyridine-3-carboxylic acid (22 mg, 0.10 mmol) and HOBt (5 mg) in DMF (3 mL) at rt was added EDCI.HCl (24.5 mg, 0.13 mmol) followed by 4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorobenzenamine (24 mg, 0.10 mmol, Compound B of Example 132). The reaction mixture was stirred at rt overnight and concentrated *in vacuo*. The resulting residue was purified by preparative HPLC to afford the desired product (25 mg, 45%) as a beige solid. ^{1}H NMR (DMF-d_7) δ 12.26 (br s, 1H), 12.18 (s, 1H), 8.90 (d, 1H, J = 2.2 Hz), 8.78 (d, 1H, J = 3.9 Hz), 8.71 (dd, 1H, J = 7.1, 2.2 Hz), 8.28-8.15 (m, 4H), 7.72-7.48 (m, 4H), 6.87 (t, 1H, J = 7.2 Hz), 6.64 (d, 1H, J = 5.5 Hz), 6.47 (br s, 1H); MS(ESI$^+$) *m/z* 442.2 $(M + H)^+$.

EXAMPLE 249

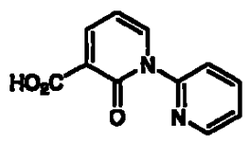


***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-2-oxo-1-(pyridin-2-yl)-1,2-dihydropyridine-3-carboxamide, trifluoroacetic acid salt**



A) **Methyl 2-oxo-1-(pyridin-2-yl)-1,2-dihydropyridine-3-carboxylate**

To a solution of methyl 2-oxo-2*H*-pyran-3-carboxylate (462 mg, 3 mmol, Aldrich) in DMF (6 mL) at rt was added 3-aminopyridine (282 mg, 3 mmol). The reaction mixture was stirred at rt for 12 h and treated with EDCLHCl (650 mg, 3.4 mmol) and DMAP (200 mg). The reaction mixture was stirred for 2.5 days at rt, and most of the DMF was removed *in vacuo*. The residue was purified by preparative HPLC to afford the desired product (500 mg, 72%) as a glassy material. ^{1}H NMR ($CDCl_3$) δ 8.53 (d, 1H, J = 5.0 Hz), 8.20 (dd, 1H, J = 9.2, 2.2 Hz), 8.06 (dd, 1H, J = 6.0, 1.1 Hz), 7.89-7.82 (m, 2H), 7.32 (dd, 1H, J = 6.6, 5.0 Hz), 6.36 (t, 1H, J = 6.6 Hz), 3.86 (s, 3H); MS(ESI$^+$) *m/z* 231.2 $(M + H)^+$.



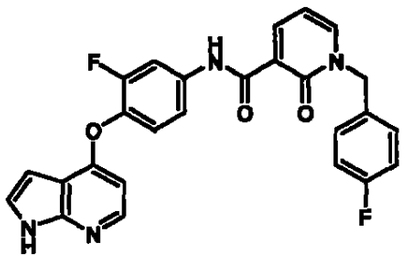
B) **2-Oxo-1-(pyridin-2-yl)-1,2-dihydropyridine-3-carboxylic acid**

A mixture of methyl 2-oxo-1-(pyridin-2-yl)-1,2-dihydropyridine-3-carboxylate (500 mg, 2.17 mmol) and 3 N NaOH (1 mL) and methanol (10 mL) was stirred at rt overnight. To the reaction was added TFA (0.5 mL) and the mixture was concentrated *in vacuo*. The residue was dissolved in water (3 mL) and *i*-PrOH (10 mL). The solid which formed was filtered, washed with a small amount of water and *i*-PrOH, and dried to obtain the acid (260 mg, 55 %) as a white solid. ^{1}H NMR (DMF-d_7) δ 14.14 (br s, 1H), 8.72 (d, 1H, J = 4.9 Hz), 8.62 (dd, 1H, J = 7.7, 2.2 Hz), 8.47 (dd, 1H, J = 6.6, 2.2 Hz), 8.18-7.98 (m, 2H), 7.67 (dd, 1H, J = 7.2, 5.3 Hz), 6.97 (t, 1H, J = 6.6 Hz); MS(ESI$^+$) *m/z* 217.2 $(M + H)^+$.

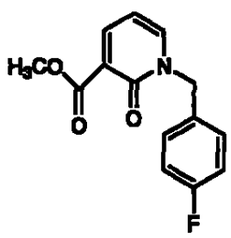
C) ***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-2-oxo-1-(pyridin-2-yl)-1,2-dihydropyridine-3-carboxamide, trifluoroacetic acid salt**

To a solution of 2-oxo-1-(pyridin-2-yl)-1,2-dihydropyridine-3-carboxylic acid (200 mg, 0.93 mmol) and HOBt (100 mg) in DMF (5 mL) at rt was added EDCI.HCl (250 mg, 1.30 mmol) followed by 4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorobenzenamine (226 mg, 0.93 mmol, Compound B of Example 132) in DMF (4 mL). The reaction mixture was stirred at rt overnight and concentrated *in vacuo*. The residue was purified by preparative HPLC to afford the desired product (290 mg, 56%) as a white solid. ^{1}H NMR (DMF-d_7) δ 12.16 (br s, 1H), 12.15 (br s, 1H), 11.99 (br s, 1H), 8.77-8.55 (m, 2H), 8.39-8.35 (m, 1H), 8.22-8.15 (m, 4H), 7.72-7.47 (m, 3H), 6.87 (t, 1H, J = 7.2 Hz), 6.55 (t, 1H, J = 5.5 Hz), 6.42 (d, 1H, J = 2.3 Hz); MS(ESI$^+$) *m/z* 442.1 $(M + H)^+$.

EXAMPLE 250



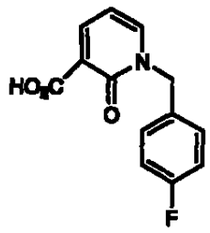
***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorobenzyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, hydrochloride salt**



A) Methyl 1-(4-fluorobenzyl)-2-oxo-1,2-dihydropyridine-3-carboxylate

A heterogeneous mixture of methyl 2-oxo-2*H*-pyran-3-carboxylate (2.0 g, 13 mmol, 1.0 eq, Aldrich) and 4-fluorobenzylamine (1.5 mL, 13 mmol, 1.0 eq) in DMF (10 mL) was stirred at room temperature for 3 h. The reaction mixture was treated with EDCI (3.4 g, 18 mmol, 1.4 eq) and DMAP (0.11 g, 9.91 mmol, 0.07 eq) at room temperature and the resulting solution was stirred for 12 h. The reaction mixture was

quenched with 1 N aqueous HCl and the solution was extracted with ethyl acetate (4 x 50 mL). The combined organic extracts were washed with 10% aqueous LiCl (3 x 70 mL), dried (Na_2SO_4), filtered and the filtrate concentrated *in vacuo* to afford the product (2.5 g, 73%) as a solid, which was used without further purification. ^{1}H NMR (DMSO-d_6) δ 8.17-8.20 (m, 1H), 8.03-8.05 (m, 1H), 7.38-7.46 (m, 2H),7.16-7.22 (m, 2H), 6.37 (dd, 1H, J = 6.94 Hz), 5.13 (s, 2H), 3.73 (s, 3H); HRMS(ESI): calcd.: 262.0879, found: 262.0885.



B) **1-(4-Fluorobenzyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid**

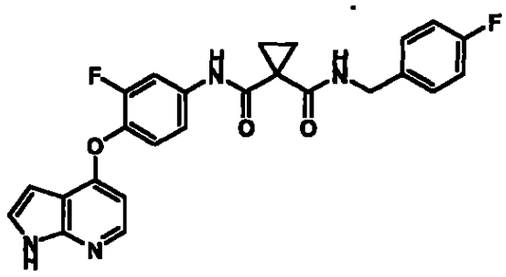
A solution of methyl 1-(4-fluorobenzyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (2.4 g, 9.2 mmol, 1.0 eq) in MeOH (25 ml) was treated with 5 N aqueous sodium hydroxide (4.6 mL, 24 mmol, 2.6 eq) at room temperature and the reaction mixture was stirred for 15 h. The reaction mixture was concentrated *in vacuo*, diluted with water and the solution was extracted with ethyl acetate (discarding the organic fraction). The aqueous fraction was cooled to 0 °C and acidified with concentrated HCl. The resulting solid was filtered, washed with water and the solid dried *in vacuo* to afford the product (1.6 g, 70%) which was sufficiently pure to use in the subsequent step without further purification.. ^{1}H NMR (DMSO-d_6) δ 8.44-8.39 (m, 2H), 7.46-7.42 (m, 2H), 7.24-7.18 (m, 2H), 6.78 (d, 1H, J = 6.98 Hz), 5.31 (s, 2H); HRMS(ESI), calcd.: 248.0723, found: 248.0718.

C) ***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorobenzyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, hydrochloride salt**

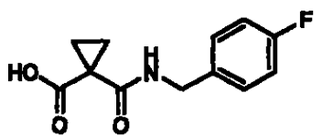
A homogeneous solution of 1-(4-fluorobenzyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (0.051 g, 0.21 mmol, 1.0 eq), 4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorobenzenamine (0.50 g, 0.21 mmol, 1.0 eq, Compound B of Example 132) and

TBTU (0.086 g, 0.23 mmol, 1.1 eq) in DMF (1 mL) was treated with DIPEA (0.11 mL, 0.62 mmol, 3.0 eq) at room temperature. The reaction mixture was stirred for 12 h and quenched with 10% aqueous LiCl (15 mL). The resulting solution was extracted with ethyl acetate (4 x 40 mL). The combined organic extracts were washed with 10% aqueous LiCl (4 x 50 mL), dried (Na_2SO_4), filtered and the filtrate concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, eluting 0-2.5% MeOH in $CHCl_3$) and the appropriate fractions were isolated and concentrated *in vacuo*. The free base was dissolved in THF, cooled to 0 °C and the homogeneous solution treated with anhydrous 4 N HCl in dioxane. The reaction mixture was warmed to room temperature, concentrated *in vacuo* and the residue triturated with diethyl ether. The solid was dried *in vacuo* to afford the title compound (0.062 g, 59%) as a HCl salt. ^{1}H NMR (DMSO-d_6) δ 12.43 (s, 1H), 12.27 (s, 1H), 8.50-8.52 (m, 1H), 8.35-8.37 (m, 1H), 8.25-8.27 (m, 1H), 8.05-8.08 (m, 1H), 7.43-7.55 (m, 5H), 7.20-7.24 (m, 2H), 6.71 (t, 1H, J = 6.89 Hz), 6.65 (d, 1H, J = 6.03 Hz), 6.43 (s, 1H), 5.32 (s, 2H); HRMS(ESI$^+$): calcd: 473.1425, found: 473.1427.

EXAMPLE 251



***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-*N*-(4-fluorobenzyl)cyclopropane-1,1-dicarboxamide, trifluoroacetic acid salt**



A) **1-((4-Fluorobenzyl)carbamoyl)cyclopropanecarboxylic acid**

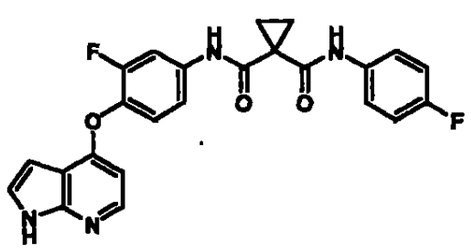
To a solution of 1,1-cyclopropanecarboxylic acid (390 mg, 3.0 mmol, Aldrich) in THF (5 mL) at 0 °C was added triethylamine (0.418 mL, 3.0 mmol). The reaction

mixture was stirred at 0 °C for 30 min and treated with thionyl chloride (0.219 mL, 3.0 mmol, Aldrich). The reaction mixture was then stirred at 0 °C for another 30 min and a solution of 4-fluorobenzylamine (375 mg, 3.0 mmol, Aldrich) in 2 mL of THF was added. The reaction mixture was stirred at 0 °C for 2 h, diluted with 100 mL of ethyl acetate and extracted with 1 N NaOH (10 mL). The aqueous phase was acidified with 1 N HCl to pH 1-2. The solid that formed was collected by filtration (343 mg, 48%). MS(ESI$^+$) *m/z* 238.2 $(M+H)^+$.

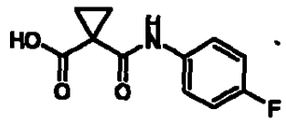
B) ***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-*N*-(4-fluorobenzyl)cyclopropane-1,1-dicarboxamide, trifluoroacetic acid salt**

To a solution of 4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorobenzenamine (45 mg, 0.1 mmol, Compound B of Example 132) and 1-((4-fluorobenzyl)carbamoyl)cyclopropanecarboxylic acid (24 mg, 0.1 mmol) in DMF (0.5 mL) at room temperature was added HATU (57 mg., 0.15 mmol, Perseptive Biosystem) and DIEA (0.05 mL, 0.3 mmol, Aldrich). The reaction mixture was stirred at rt for 2 h, and then quenched by the addition of 2 mL of methanol. The reaction mixture was purified by preparative HPLC. The desired fractions were combined, concentrated under reduced pressure, and lyophilized to dryness to afford the desired product (39 mg, 67%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.99 (br s, 1H), 10.81 (s, 1H), 8.46 (t, 1H, J = 5.8 Hz), 8.13 (d, 1H, J = 6.1 Hz), 7.86 (dd, 1H, J = 13.2, 2.2 Hz), 7.41-7.46 (m, 2H), 7.37 (t, 1H, J = 9.1 Hz), 7.28-7.32 (m, 2H), 7.13 (t, 3H, J = 9.1 Hz), 6.44 (d, 1H, J = 6.1 Hz), 6.30 (s, 1H), 4.30 (d, 2H, J = 5.5 Hz), 1.39 (d, 4H, J = 2.2 Hz); MS(ESI$^+$) *m/z* 463.1 $(M+H)^+$.

EXAMPLE 252



***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-*N*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide**



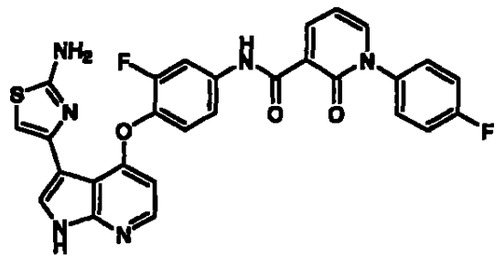
A) . . 1-((4-Fluorophenyl)carbamoyl)cyclopropanecarboxylic acid

To a solution of 1,1-cyclopropanecarboxylic acid (390 mg, 3.0 mmol, Aldrich) in THF (5 mL) at 0 °C was added triethylamine (0.418 mL, 3.0 mmol). The reaction mixture was stirred at 0 °C for 30 min and treated with thionyl chloride (0.219 mL, 3.0 mmol, Aldrich). The reaction mixture was stirred at 0 °C for an additional 30 min, and treated with a solution of 4-fluoroaniline (333 mg, 3.0 mmol, Aldrich) in 2 mL of THF. The reaction mixture was stirred at 0 °C for 2 h, then diluted with 100 mL of ethyl acetate and extracted with 1 N NaOH (10 mL). The aqueous phase was acidified with 1 N HCl to pH 1-2. The solid that formed was collected by filtration (508 mg, 76%). MS(ESI$^+$) *m/z* 224.2 $(M+H)^+$.

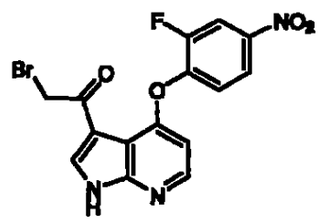
B) ***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-*N*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide**

Prepared in a similar manner as Step B of Example 251 (41 mg, 73%). ^{1}H NMR (DMSO-d_6) δ 11.97 (br s, 1H), 10.35 (s, 1H), 9.99 (s, 1H), 8.12 (d, 1H, $J = 5.5$ Hz), 7.85 (d, 1H, $J = 13.2$ Hz), 7.62 (m, 2H), 7.43 (m, 2H), 7.36 (t, 1H, $J = 9.4$ Hz), 7.14 (t, 2H, $J = 9.1$ Hz), 6.43 (d, 1H, $J = 5.5$ Hz), 6.29 (s, 1H), 1.46 (d, 4H, $J = 2.8$ Hz); MS(ESI$^+$) *m/z* 449.1 $(M+H)^+$.

EXAMPLE 253

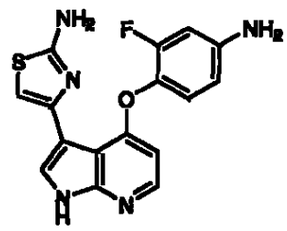


***N*-(4-(3-(2-Aminothiazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide**



A) **2-Bromo-1-(4-(2-fluoro-4-nitrophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)ethanone**

To a solution of 4-(2-fluoro-4-nitrophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridine (1.00 g, 3.66 mmol, Compound A of Example 132) in DCE (100 mL) at rt was added aluminum chloride (2.43 g, 18.3 mmol, Alfa Aesar). The reaction mixture was stirred at rt for 1 h and then treated with bromoacetyl chloride (7.32 mmol, Aldrich). The reaction mixture was then stirred at rt for 2 h and quenched by the addition of 100 mL of EtOAc, 30 mL of MeOH, and 30 mL of saturated aq. K_2HPO_4. This mixture was filtered through a pad of Celite®. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, eluting with 2-5% MeOH in dichloromethane) to afford the desired product (1.12 g, 78%) as a light yellow solid. MS(ESI$^+$) *m/z* 393.9 $(M + H)^+$.



B) **4-(4-(4-Amino-2-fluorophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)thiazol-2-amine**

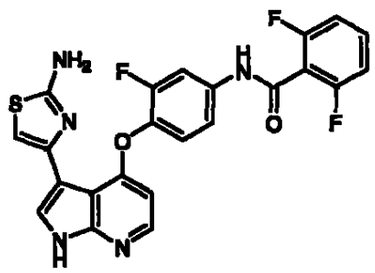
To a solution of 2-bromo-1-(4-(2-fluoro-4-nitrophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)ethanone (392 mg, 1.0 mmol) in acetic acid (10 mL) was added thiourea (228 mg, 3.0 mmol, Aldrich). The reaction mixture was stirred at room

temperature for 3 h, and then diluted with 50 mL of EtOAc. The reaction mixture was washed with saturated aq. $NaHCO_3$ solution and brine. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to give a light yellow solid. The solid was dissolved in a mixed solvent (20 mL of THF and 40 mL of MeOH). Ammonium chloride (267 mg, 5.0 mmol, EMD) and Zn dust (327 mg, 5.0 mmol, Aldrich).were added then added to the resulting solution. The reaction mixture was stirred at room temperature overnight, diluted with 100 mL of EtOAc and filtered through a pad of Celite®. The filtrate was concentrated *in vacuo* and the resulting residue was purified by preparative HPLC. The desired fractions were combined, neutralized with saturated aq. $NaHCO_3$ solution, and concentrated under reduced pressure. The solid that formed was collected by filtration (194 mg, 57% over two steps). MS(ESI$^+$) *m/z* 342.2 $(M + H)^+$.

D) ***N*-(4-(3-(2-Aminothiazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide**

Prepared in a similar manner as Step C of Example 242 (5.6 mg, 12%). ^1H NMR (CD_3OD) δ 8.60 (dd, 1H, *J* = 5.5, 1.7 Hz), 8.08 (d, 1H, *J* = 5.5 Hz), 7.90-7.88 (m, 2H), 7.67 (s, 1H), 7.45-7.42 (m, 2H), 7.29 (d, 1H, *J* = 5.5 Hz), 7.25-7.18 (m, 4H), 6.65 (t, 1H, *J* = 7.4 Hz), 6.43 (d, 1H, *J* = 6.1 Hz); MS(ESI$^+$) *m/z* 557.1 $(M + H)^+$.

EXAMPLE 254

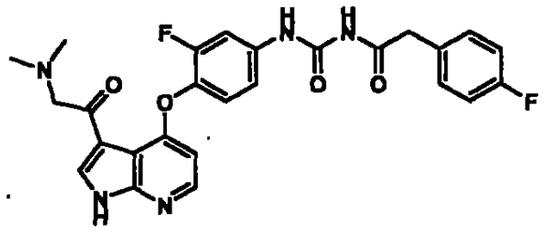


***N*-(4-(3-(2-Aminothiazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-2,6-difluorobenzamide, trifluoroacetic acid salt**

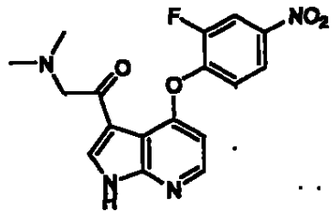
To a solution of 4-(4-(4-amino-2-fluorophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)thiazol-2-amine (20 mg, 0.06 mmol, Compound B of Example 253) in 0.5 mL of

pyridine at –20 °C was added a solution of 2,6-difluorobenzoylchloride (10.6 mg, 0.06 mmol, Aldrich) in 0.3 mL of dichloromethane. The reaction mixture was stirred at –20 °C for 30 min and quenched by the addition of MeOH (0.5 mL). The reaction mixture was concentrated *in vacuo* and the resulting residue was purified by preparative HPLC. The desired fractions were combined, concentrated under reduced pressure, and lyophilized to afford the desired product (TFA salt, 9.2 mg, 22%) as a white solid. ^{1}H NMR (CD_3OD) δ 8.10 (d, 1H, J = 6.1 Hz), 7.68 (s, 1H), 7.48-7.37 (m, 2H), 7.24 (t, 1H, J = 8.3 Hz), 7.05-7.01 (m, 3H), 6.86 (s, 1H), 6.46 (d, 1H, J = 5.5 Hz); MS(ESI$^+$) *m/z* 482.1 $(M+H)^+$.

EXAMPLE 255

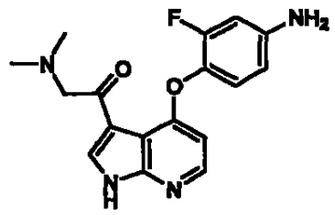


1-(4-(3-(2-(Dimethylamino)acetyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea



B) 2-(Dimethylamino)-1-(4-(2-fluoro-4-nitrophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)ethanone

To a solution of 2-bromo-1-(4-(2-fluoro-4-nitrophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)ethanone (96 mg, 0.24 mmol, Compound A of Example 253) in THF (5 mL) at 0 °C was added dimethylamine (1.0 M solution in THF, 0.72 mL, 0.72 mmol). The reaction mixture was stirred at 0 °C for 1 h and concentrated under reduced pressure to give the desired product (80 mg, 93%) as a light yellow solid, which was washed with cold water and air dried. MS(ESI$^+$) *m/z* 359.2 $(M+H)^+$.



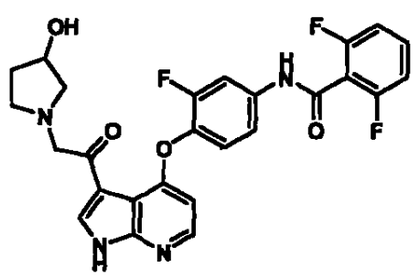
C) **1-(4-(4-Amino-2-fluorophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2-(dimethylamino)ethanone**

To a solution of 2-(dimethylamino)-1-(4-(2-fluoro-4-nitrophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)ethanone (80 mg, 0.22 mmol) in a mixed solvent (5 mL of THF and 5 mL of MeOH) were added ammonium chloride (64.2 mg, 1.2 mmol, EMD) and Zn dust (78.4 mg, 1.2 mmol, Aldrich). The reaction mixture was stirred at room temperature overnight, diluted with 30 mL of EtOAc and filtered through a pad of Celite®. The filtrate was concentrated *in vacuo* and the resulting residue was purified by preparative HPLC. The desired fractions were combined, neutralized with saturated aq. $NaHCO_3$ solution, and concentrated *in vacuo*. The solid that formed was collected by filtration (51 mg, 71%). MS(ESI$^+$) *m/z* 328.1 $(M+H)^+$.

D) **1-(4-(3-(2-(Dimethylamino)acetyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea**

Prepared in a similar manner as Step C of Example 132 (5.7 mg, 11%). ^{1}H NMR (CD_3OD) δ 10.67 (s, 1H), 8.27 (s, 1H), 8.08 (d, 1H, J = 6.1 Hz), 7.65 (d, 1H, J = 12.6 Hz), 7.24-7.16 (m, 4H), 6.96 (t, 2H, J = 8.8 Hz), 6.45 (d, 1H, J = 5.5 Hz), 4.74 (s, 2H), 3.60 (s, 2H), 2.86 (s, 6H); MS(ESI$^+$) *m/z* 508.2 $(M+H)^+$.

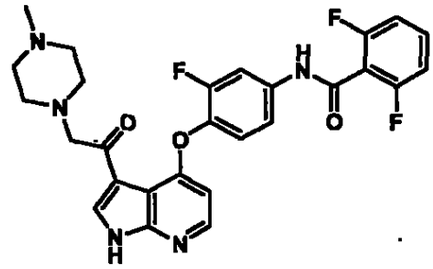
EXAMPLE 256



2,6-Difluoro-*N*-(3-fluoro-4-(3-(2-(3-hydroxypyrrolidin-1-yl)acetyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)benzamide

Prepared in a similar manner as Example 254. ^{1}H NMR (CD_3OD) δ 8.29 (d, 1H, J = 6.6 Hz), 8.13 (d, 1H, J = 5.5 Hz), 7.80 (dd, 1H, J = 12.7, 2.2 Hz), 7.46-7.38 (m, 2H), 7.23 (t, 1H, J = 9.1 Hz), 7.03 (t, 2H, J = 8.3 Hz), 6.53 (d, 1H, J = 5.5 Hz), 5.01-4.86 (m, 2H), 4.49-4.46 (m, 1H), 3.77-3.64 (m, 2H), 3.35-3.06 (m, 2H), 2.25-1.98 (m, 2H); MS(ESI$^+$) *m/z* 511.2 $(M+H)^+$.

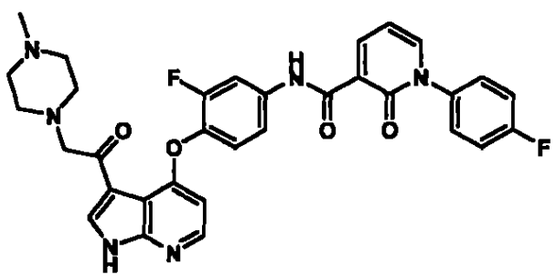
EXAMPLE 257



2,6-Difluoro-*N*-(3-fluoro-4-(3-(2-(4-methylpiperazin-1-yl)acetyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)benzamide

Prepared in a similar manner as Example 254. ^{1}H NMR (CD_3OD) δ 8.23 (s, 1H), 8.11 (d, 1H, J = 5.5 Hz), 7.79 (dd, 1H, J = 12.1, 2.2 Hz), 7.46-7.34 (m, 2H), 7.16 (t, 1H, J = 8.8 Hz), 7.03 (t, 2H, J = 8.3 Hz), 6.53 (d, 1H, J = 6.1 Hz), 4.11 (s, 2H), 3.21-2.92 (m, 8H), 2.76 (s, 3H); MS(ESI$^+$) *m/z* 524.3 $(M+H)^+$.

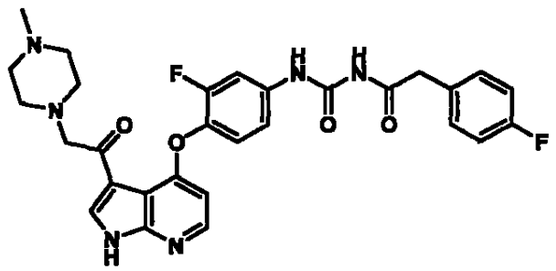
EXAMPLE 258



***N*-(3-Fluoro-4-(3-(2-(4-methylpiperazin-1-yl)acetyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide**

Prepared in a similar manner as Example 253. ^{1}H NMR (CD_3OD) δ 8.59 (dd, 1H, J = 7.2, 2.2 Hz), 8.53 (s, 1H), 8.08 (d, 1H, J = 5.5 Hz), 7.89-7.85 (m, 2H), 7.44-7.41 (m, 2H), 7.28-7.18 (m, 3H), 7.15 (t, 1H, J = 8.8 Hz), 6.65 (t, 1H, J = 6.7 Hz), 6.48 (d, 1H, J = 5.5 Hz), 4.13 (s, 2H), 3.21-2.89 (bm, 8), 2.76 (s, 3H); MS(ESI$^+$) *m/z* 599.2 $(M+H)^+$.

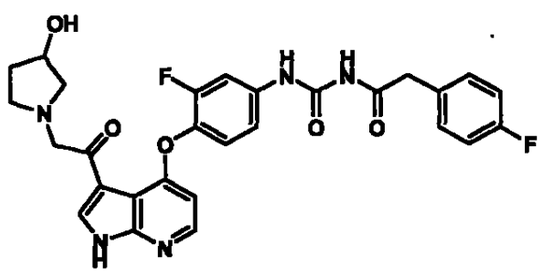
EXAMPLE 259



1-(3-Fluoro-4-(3-(2-(4-methylpiperazin-1-yl)acetyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea

Prepared in a similar manner as Example 255. ^{1}H NMR (CD_3OD) δ 8.28 (s, 1H), 8.12 (d, 1H, J = 6.1 Hz), 7.66 (dd, 1H, J = 10.1, 2.8 Hz), 7.28-7.16 (m, 4H), 6.97-6.92 (m, 3H), 6.51 (d, 1H, J = 6.1 Hz), 4.43 (s, 2H), 3.88 (s, 2H), 3.49 (s, 2H), 3.37-3.20 (m, 4H), 2.82 (s, 3H); MS(ESI$^+$) *m/z* 563.2 $(M+H)^+$.

EXAMPLE 260

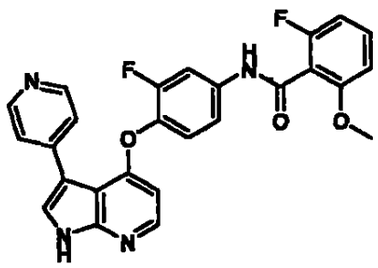


1-(3-Fluoro-4-(3-(2-(3-hydroxypyrrolidin-1-yl)acetyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea

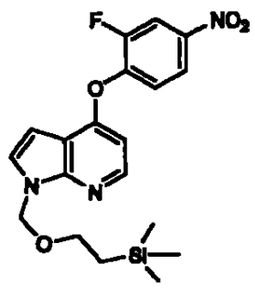
Prepared in a similar manner as Example 255. ^{1}H NMR (CD_3OD) δ 10.69 (s, 1H), 8.27 (d, 1H, J = 8.8 Hz), 8.09 (d, 1H, J = 5.5 Hz), 7.66 (d, 1H, J = 12.7 Hz), 7.27-7.16 (m, 4H), 6.98 (t, 2H, J = 8.8 Hz), 6.47 (d, 1H, J = 5.5 Hz), 4.99 (m, 1H),

4.49-4.44 (m, 2H), 3.90-3.68 (m, 2H), 3.62 (s, 2H), 3.37-3.09 (m, 2H), 2.15-1.92 (m, 2H); MS(ESI$^+$) *m/z* 550.1 $(M+H)^+$.

EXAMPLE 261

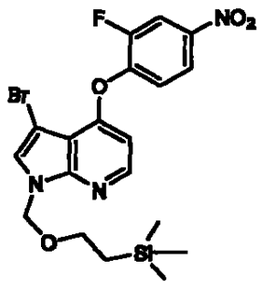


2-Fluoro-*N*-(3-fluoro-4-(3-(pyridin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)-6-methoxybenzamide



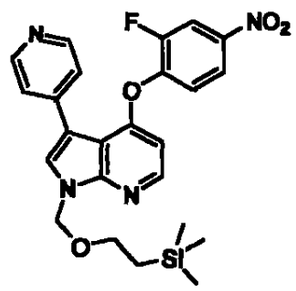
A) **4-(2-Fluoro-4-nitrophenoxy)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridine**

To a solution of 4-(2-fluoro-4-nitrophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridine (1.68 g, 6.15 mmol, Compound A of Example 132) in 20 mL of DMF at –40 °C was added sodium hydride (271 mg, 6.77 mmol, 60% in mineral oil, Aldrich). The reaction mixture was stirred at 0 °C for 30 min, cooled to –40 °C, and treated with 2-(trimethylsilyl)ethoxymethyl chloride (1.20 mL, 6.77 mmol, Aldrich). The reaction mixture was stirred at room temperature for 1 h, quenched by the addition of cold water (40 mL) and extracted with EtOAc (3 x 100mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give the desired product (2.40 g, 97%) as a brown solid. MS(ESI$^+$) *m/z* 404.2 $(M+H)^+$.



B) 3-Bromo-4-(2-fluoro-4-nitrophenoxy)-1-((2-(trimethylsilyl)ethoxy)methyl) -1*H*-pyrrolo[2,3-*b*]pyridine

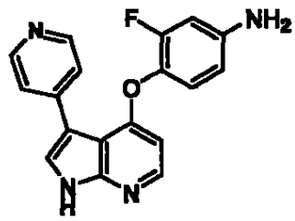
To a solution of 4-(2-fluoro-4-nitrophenoxy)-1-((2-(trimethylsilyl)ethoxy) methyl)-1*H*-pyrrolo[2,3-*b*]pyridine (2.40 g, 5.96 mmol) in 20 mL of acetonitrile at 0 °C was added a solution of NBS (1.01 g, 5.69 mmol, Aldrich) in 10 mL of acetonitrile. The reaction mixture was stirred at 0 °C for 30 min, quenched by the addition of cold water (50 mL), and extracted with EtOAc (3 x 120 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, eluting with dichloromethane) to afford the desired product (2.70 g, 94%) as a light yellow oil. MS(ESI^+) *m/z* 482.9 $(M + H)^+$.



C) 4-(2-Fluoro-4-nitrophenoxy)-3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy) methyl)-1*H*-pyrrolo[2,3-*b*]pyridine

A sealed tube was charged with a solution of 3-bromo-4-(2-fluoro-4-nitrophenoxy)-1-((2-(trimethylsilyl) ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridine (480 mg, 1.0 mmol) in toluene (5 mL), pyridin-4-ylboronic acid (246 mg, 2.0 mmol, Lancaster), 0.5 mL of ethanol, and potassium phosphate (1.0 mL, 2 M solution, 2.0 mmol). Argon was bubbled through the mixture for 15 minutes, and the reaction

mixture was treated with tetrakis(triphenylphosphine)Pd(0) (58 mg, 0.05 mmol, Strem). The tube was sealed and the mixture was heated at 95 °C for 18 h with vigorous stirring. The reaction mixture was then cooled to room temperature and diluted with EtOAc. The mixture was washed with saturated aq. $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, eluting with 2% MeOH in dichloromethane) to give the desired product (237 mg, 49%) as a thick brown oil. MS(ESI$^+$) *m/z* 481.1 $(M+H)^+$.



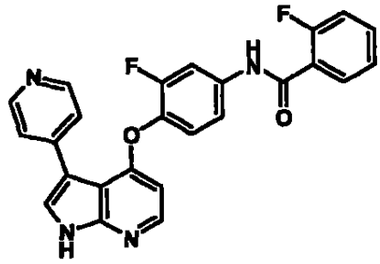
D) **3-Fluoro-4-(3-(pyridin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)benzenamine**

To a solution of 4-(2-fluoro-4-nitrophenoxy)-3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy) methyl)-1*H*-pyrrolo[2,3-*b*]pyridine (237 mg, 0.49 mmol) in a mixed solvent (8 mL of MeOH and 4 mL of THF) were added ammonium chloride (131 mg, 2.49 mmol, EMC) and zinc dust (163 mg, 2.49 mmol, Aldrich). The reaction mixture was stirred at room temperature for 3 h, diluted with EtOAc (40 mL), and filtered through a pad of Celite®. The filtrate was concentrated *in vacuo* to give a solid. MS(ESI$^+$) *m/z* 451.3 $(M+H)^+$. The solid was dissolved in 15 mL of THF and treated with TBAF (4 mL, 1.0 M solution in THF, Aldrich) and ethane-1,2-diamine (0.4 mL, Aldrich). The reaction mixture was refluxed for 16 h, cooled to room temperature, diluted with EtOAc, washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, eluting with 2-5% MeOH in dichloromethane) to afford the desired product (127 mg, 81% for two steps). MS(ESI$^+$) *m/z* 321.2 $(M+H)^+$.

E) **2-Fluoro-*N*-(3-fluoro-4-(3-(pyridin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)-6-methoxybenzamide**

Prepared in a similar manner as Example 254 (3.2 mg, 7%). ^{1}H NMR (DMSO-d_6) δ 12.92 (s, 1H), 10.80 (s, 1H), 8.72 (d, 2H, J = 7.2 Hz), 8.44 (s, 1H), 8.31 (d, 2H, J = 7.2 Hz), 8.16 (d, 2H, J = 5.5 Hz), 7.94-7.86 (m, 1H), 7.55-7.41 (m, 2H), 6.97-6.91 (m, 1H), 6.88 (t, 1H, J = 8.8 Hz), 6.45 (d, 1H, J = 5.5 Hz), 3.78 (s, 3H); MS(ESI$^+$) *m/z* 473.1 $(M+H)^+$.

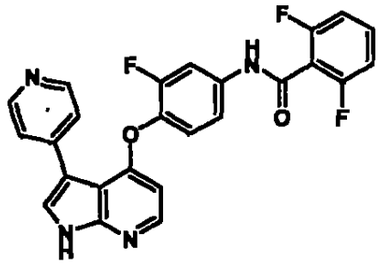
EXAMPLE 262



2-Fluoro-*N*-(3-fluoro-4-(3-(pyridin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)benzamide

Prepared in a similar manner as Example 261. ^{1}H NMR (DMSO-d_6) δ 12.97 (s, 1H), 10.76 (s, 1H), 8.78 (d, 2H, J = 8.8 Hz), 8.50 (s, 1H), 8.36 (d, 2H, J = 6.1 Hz), 8.23 (d, 1H, J = 5.5 Hz), 7.96 (d, 1H, J = 8.8 Hz), 7.70-7.54 (m, 4H), 7.39-7.35 (m, 2H), 6.50 (d, 1H, J = 5.5 Hz); MS(ESI$^+$) *m/z* 443.1 $(M+H)^+$.

EXAMPLE 263

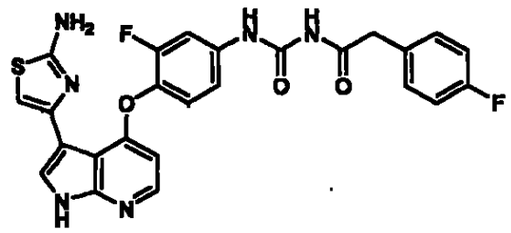


2,6-Difluoro-*N*-(3-fluoro-4-(3-(pyridin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)benzamide

Prepared in a similar manner as Example 261. ^{1}H NMR (DMSO-d_6) δ 12.89 (s, 1H), 11.10 (s, 1H), 8.70 (d, 2H, J = 6.6 Hz), 8.42 (s, 1H), 8.27 (d, 2H, J = 6.6 Hz),

8.16 (d, 1H, J = 5.5 Hz), 7.86 (d, 1H, J = 11.6 Hz), 7.58-7.48 (m, 3H), 7.23 (t, 2H, J = 8.3 Hz), 6.45 (d, 1H, J = 5.5 Hz); MS(ESI$^+$) m/z 461.1 $(M+H)^+$.

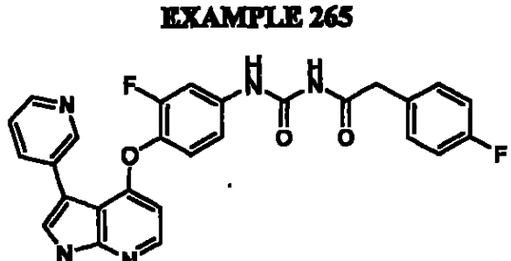
EXAMPLE 264



1-(4-(3-(2-Aminothiazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, trifluoroacetic acid salt

To a solution of 4-(4-(4-amino-2-fluorophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)thiazol-2-amine (34 mg, 0.1 mmol, Compound B of Example 253) in a mixed solvent (0.5 mL of DMF and 0.5 mL of THF) at rt was added a solution of 2-(4-fluorophenyl)acetyl isocyanate in toluene (0.4 M, 0.25 ml, 0.1 mmol, Compound C of Example 4). The reaction mixture was stirred at rt for 1 h, concentrated *in vacuo* and the resulting residue was purified by preparative HPLC. The desired fractions were combined, concentrated under reduced pressure, and lyophilized to afford the desired product (TFA salt, 21.2 mg, 28%) as a white solid. ^{1}H NMR (CD_3OD) δ 10.69 (s, 1H), 8.08 (d, 1H, J = 5.5 Hz), 7.68 (s, 1H), 7.66 (d, 1H, J = 12.1 Hz), 7.26-7.18 (m, 4H), 6.98 (t, 2H, J = 8.8 Hz), 6.84 (s, 1H), 6.42 (d, 1H, J = 6.1 Hz), 3.62 (s, 2H); MS(ESI$^+$) m/z 521.1 $(M+H)^+$.

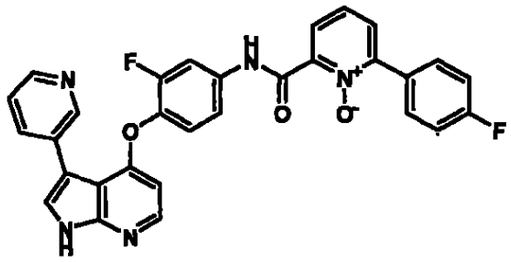
EXAMPLE 265



1-(3-Fluoro-4-(3-(pyridin-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea

Prepared in a similar manner as Example 264. ^{1}H NMR (DMSO-d_6) δ 12.71 (s, 1H), 11.04 (s, 1H), 10.61 (s, 1H), 9.18 (s, 1H), 8.84 (d, 1H, J = 8.3 Hz), 8.74 (d, 1H, J = 5.5 Hz), 8.20 (d, 1H, J = 5.5 Hz), 8.12 (s, 1H), 8.06 (dd, 1H, J = 8.3, 2.8 Hz), 7.78 (dd, 1H, J = 12.7, 2.2 Hz), 7.47 (t, 1H, J = 8.8 Hz), 7.40-7.34 (m, 3H), 7.16 (t, 2H, J = 8.8 Hz), 6.41 (d, 1H, J = 5.5 Hz), 3.75 (s, 2H); MS(ESI$^+$) m/z 500.1 $(M+H)^+$.

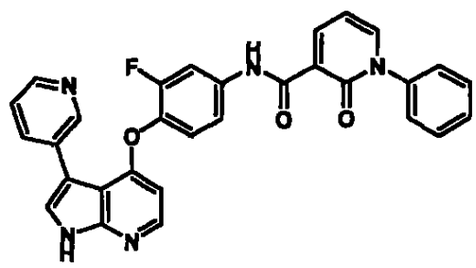
EXAMPLE 266



6-(4-Fluoro-phenyl)-1-oxy-pyridine-2-carboxylic acid [3-fluoro-4-(3-pyridin-3-yl-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-phenyl]-amide

Prepared in a similar manner as Example 241. ^{1}H NMR (DMSO-d_6) δ 13.58 (s, 1H), 12.50 (s, 1H), 9.10 (s, 1H), 8.66 (d, 1H, J = 5.5 Hz), 8.32 (dd, 1H, J = 8.2, 2.2 Hz), 8.19 (d, 1H, J = 5.5 Hz), 8.05-8.02 (m, 2H), 7.89-7.85 (m, 5H), 7.73 (t, 1H, J = 7.7 Hz), 7.60 (d, 1H, J = 8.8 Hz), 7.50 (t, 1H, J = 8.8 Hz), 7.38 (t, 2H, J = 8.8 Hz), 6.41 (d, 1H, J = 6.5 Hz); MS(ESI$^+$) m/z 536.2 $(M+H)^+$.

EXAMPLE 267

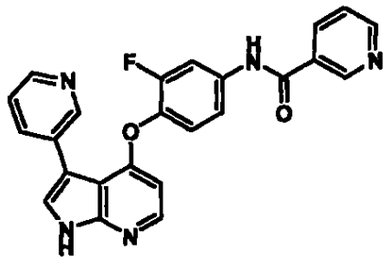


***N*-(3-Fluoro-4-(3-(pyridin-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide**

Prepared in a similar manner as Example 245. ^{1}H NMR (DMSO-d_6) δ 12.48 (s, 1H), 12.15 (s, 1H), 9.09 (s, 1H), 8.65-8.59 (m, 3H), 8.18 (d, 1H, J = 5.5 Hz), 8.15

(dd, 1H, J = 6.6, 2.2 Hz), 8.04-7.99 (m, 2H), 7.88 (m, 1H), 7.59-7.46 (m, 7H), 6.74 (t, 1H, J = 7.2 Hz), 6.40 (d, 1H, J = 5.5 Hz); MS(ESI$^+$) m/z 518.1 $(M+H)^+$.

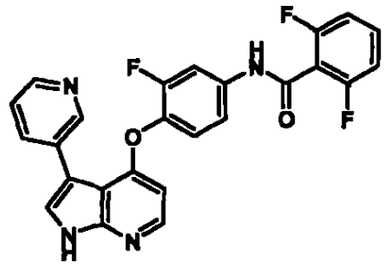
EXAMPLE 268



***N*-(3-Fluoro-4-(3-(pyridin-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)nicotinamide**

Prepared in a similar manner as Example 254. ^{1}H NMR (DMSO-d_6) δ 12.65 (s, 1H), 10.96 (s, 1H), 9.22 (s, 1H), 9.18 (s, 1H), 8.84 (t, 2H, J = 5.0 Hz), 8.74 (d, 1H, J = 5.5 Hz), 8.49 (d, 1H, J = 8.3 Hz), 8.21 (d, 1H, J = 5.5 Hz), 8.11 (d, 1H, J = 1.7 Hz), 8.08-8.01 (m, 2H), 7.73-7.69 (m, 2H), 7.54 (t, 1H, J = 8.8 Hz), 6.43 (d, 1H, J = 5.5 Hz); MS(ESI$^+$) m/z 426.2 $(M+H)^+$.

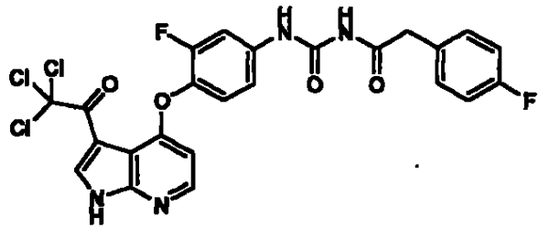
EXAMPLE 269



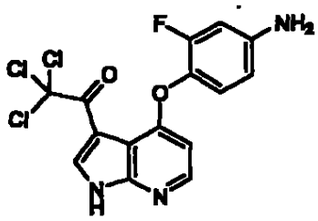
2,6-Difluoro-*N*-(3-fluoro-4-(3-(pyridin-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)benzamide

Prepared in a similar manner as Example 254. ^{1}H NMR (DMSO-d_6) δ 11.23 (s, 1H), 9.20 (d, 1H, J = 1.7 Hz), 8.87 (d, 1H, J = 8.3 Hz), 8.77 (d, 1H, J = 5.5 Hz), 8.23 (d, 1H, J = 5.5 Hz), 8.55 (s, 1H), 8.08 (dd, 1H, J = 8.2, 2.2 Hz), 7.90 (d, 1H, J = 13.7 Hz), 7.62-7.55 (m, 3H), 7.27 (t, 2H, J = 8.3 Hz), 6.50 (d, 1H, J = 5.5 Hz); MS(ESI$^+$) m/z 461.1 $(M+H)^+$.

EXAMPLE 270



1-(3-Fluoro-4-(3-(2,2,2-trichloroacetyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea



A) 1-(4-(4-Amino-2-fluorophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2,2,2-trichloroethanone

To a solution of 4-(2-fluoro-4-nitrophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridine (546 mg, 2.0 mmol, Compound A of Example 132) in 100 mL of dichloroethane at room temperature was added aluminum chloride (1.33 g, 10 mmol, Alfa Aesar). The reaction mixture was stirred at rt for 30 min, treated with trichloroacetyl chloride (0.34 mL, 3.0 mmol), and then stirred at 45 °C for 5 h. After cooling to 0 °C, ice water (30 mL) was added to the mixture and the pH was adjusted to 7-8 with aq. K_2HPO_4 solution. The mixture was then filtered through a pad of Celite®. The organic layer was dried ($MgSO_4$), concentrated *in vacuo* and the resulting residue was purified by flash chromatography (SiO_2, eluting with 2-7% MeOH in dichloromethane) to afford 2,2,2-trichloro-1-(4-(2-fluoro-4-nitrophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)ethanone (498 mg, 60%). MS(ESI$^+$) *m/z* 417.9 $(M+H)^+$.

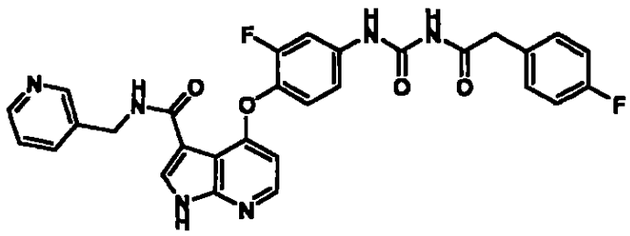
To a solution of the above intermediate (83 mg, 0.2 mmol) in a mixed solvent (3 mL of MeOH and 2 mL of THF) were added ammonium chloride (53.5 mg, 1.0 mmol, EMC) and zinc dust (65.4 mg, 1.0 mmol, Aldrich). The reaction mixture was stirred at room temperature for 3 h, diluted with EtOAc (10 mL), and filtered through

a pad of Celite®. The filtrate was concentrated *in vacuo* to give the desired product (78 mg, 100%) as a solid. MS(ESI$^+$) *m/z* 390.1, 392.1 $(M+H)^+$.

C) **1-(3-Fluoro-4-(3-(2,2,2-trichloroacetyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea**

Prepared in a similar manner as Example 264 (33 mg, 37%). ^{1}H NMR (DMSO-d_6) δ 13.18 (s, 1H), 11.02 (s, 1H), 10.57 (s, 1H), 8.62 (s, 1H), 8.25 (d, 1H, *J* = 5.5 Hz), 7.78 (dd, 1H, *J* = 10.5, 2.2 Hz), 7.38-7.35 (m, 3H), 7.28 (t, 1H, *J* = 9.4 Hz), 7.18 (t, 2H, *J* = 8.8 Hz), 6.52 (d, 1H, *J* = 5.5 Hz), 3.75 (s, 2H); MS(ESI$^+$) *m/z* 567.05 $(M+H)^+$.

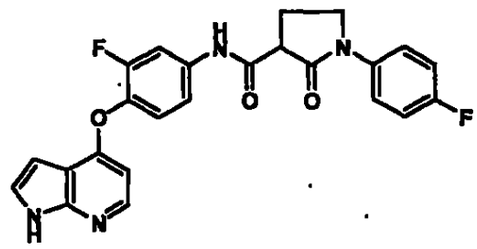
EXAMPLE 271



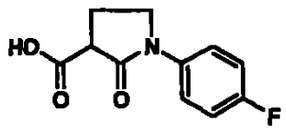
1-(4-(3-((Pyridin-3-ylmethyl)carbamoyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea

To a solution of 1-(3-fluoro-4-(3-(2,2,2-trichloroacetyl)-1*H*-pyrrolo[2,3-*b*]pyridine 4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea (7.0 mg, 0.012 mmol, Example 270) in 0.5 mL of DMF was added 3-(aminomethyl)pyridine (10 mg, 0.092 mmol, Aldrich). The reaction mixture was stirred at rt for 1h, and quenched by the addition of 1 mL of cold water. The precipitate that formed was collected by filtration, washed with cold water (1 mL) and cold acetonitrile (1 mL) and dried under vacuum to afford the desired product (4.3 mg, 64%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 12.38 (s, 1H), 11.03 (s, 1H), 10.57 (s, 1H), 8.48 (s, 1H), 8.40 (t, 1H, *J* = 5.5 Hz), 8.34 (d, 1H, *J* = 3.3 Hz), 8.11 (d, 1H, *J* = 5.5 Hz), 8.00 (s, 1H), 7.73 (d, 1H, *J* = 13.2 Hz), 7.65 (d, 1H, *J* = 7.7 Hz), 7.37-7.29 (m, 4H), 7.16 (t, 3H, *J* = 8.8 Hz), 6.34 (d, 1H, *J* = 5.5 Hz), 4.48 (d, 2H, *J* = 5.5 Hz), 3.74 (s, 2H); MS(ESI$^+$) *m/z* 567.1 $(M+H)^+$.

EXAMPLE 272



***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxopyrrolidine-3-carboxamide**



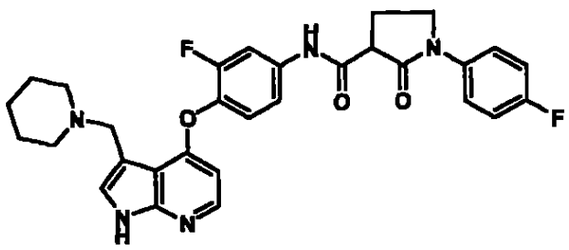
A) 1-(4-Fluorophenyl)-2-oxopyrrolidine-3-carboxylic acid

To a solution of 6,6-dimethyl-5,7-dioxaspiro[2,5]-octane-4,8-dione (1.02 g, 6.0 mmol, Aldrich) in 3 mL of DMF was added 4-fluorobenzenamine (666 mg, 6.0 mmol, Aldrich). The reaction mixture was stirred at rt overnight. The reaction mixture was poured into cold water (10 mL). The precipitate that formed was collected by filtration, washed with water, and dried under vacuum to afford the desired product (980 mg, 73%) as a tan solid. MS(ESI$^+$) *m/z* 224.3 $(M + H)^+$.

B) *N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxopyrrolidine-3-carboxamide

Prepared in a similar manner as Step B of Example 251 (98 mg, 49%). ^{1}H NMR (DMSO-d_6) δ 11.76 (s, 1H), 10.63 (s, 1H), 8.06 (d, 1H, J = 5.5 Hz), 7.86 (dd, 1H, J = 13.2, 2.2 Hz), 7.71-7.68 (m, 2H), 7.45-7.36 (m, 3H), 7.25 (t, 2H, J = 8.8 Hz), 6.38 (d, 1H, J = 6.5 Hz), 6.22 (dd, 1H, J = 3.3, 2.2 Hz), 3.94-3.89 (m, 2H), 3.77 (t, 1H, J = 8.5 Hz), 2.49-2.33 (m, 2H); MS(ESI$^+$) *m/z* 449.2 $(M + H)^+$.

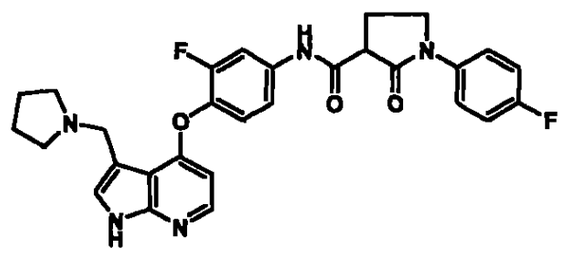
EXAMPLE 273



N-(3-Fluoro-4-(3-(piperidin-1-ylmethyl)-1H-pyrrolo[2,3-b]pyridin-4-yloxy)phenyl)-1-(4-fluorophenyl)-2-oxopyrrolidine-3-carboxamide, trifluoroacetic acid salt

To a solution of *N*-(4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxopyrrolidine-3-carboxamide (22.4 mg, 0.05 mmol, Compound B of Example 272) and paraformaldehyde (2.4 mg, 0.08 mmol) in a mixed solvent (1 mL of isopropanol and 0.2 mL of DMF) was added piperidine (8.5 mg, 0.1 mmol). The reaction mixture was heated at 85 °C for 7 h, concentrated *in vacuo*, and the resulting residue was purified by preparative HPLC. The desired fractions were lyophilized to give the desired product (TFA salt, 3.4 mg, 13%) as a white solid. ^{1}H NMR (CD_3OD) δ 8.15 (d, 1H, J = 5.5 Hz), 7.91 (dd, 1H, J = 11.0, 2.2 Hz), 7.67-7.63 (m, 3H), 7.48-7.38 (m, 2H), 7.15 (t, 2H, J = 8.8 Hz), 6.45 (d, 1H, J = 5.5 Hz), 4.64 (s, 2H), 3.99-3.95 (m, 2H), 3.81 (t, 1H, J = 8.8 Hz), 3.61-3.59 (m, 2H), 3.10-3.06 (m, 2H), 2.61-2.47 (m, 2H), 1.97-1.93 (m, 2H), 1.81-1.71 (m, 4H); MS(ESI$^+$) *m/z* 546.2 $(M+H)^+$.

EXAMPLE 274

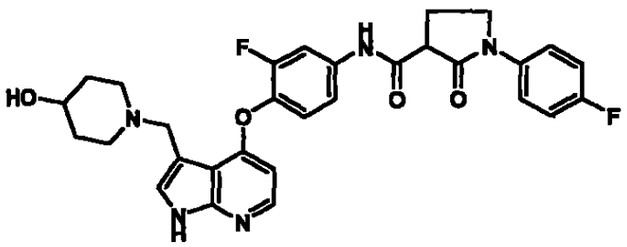


N-(3-Fluoro-4-(3-(pyrrolidin-1-ylmethyl)-1H-pyrrolo[2,3-b]pyridin-4-yloxy)phenyl)-1-(4-fluorophenyl)-2-oxopyrrolidine-3-carboxamide

Prepared in a similar manner as Example 273. ^{1}H NMR (DMSO-d_6) δ 12.13 (s, 1H), 10.62 (s, 1H), 8.04 (d, 1H, J = 5.5 Hz), 7.84 (dd, 1H, J = 13.2, 2.2 Hz), 7.65-

7.62 (m, 3H), 7.43-7.39 (m, 2H), 7.19 (t, 2H, J = 8.8 Hz), 6.25 (d, 1H, J = 6.5 Hz), 4.54 (d, 2H, J = 3.3 Hz), 3.91-3.85 (m, 2H), 3.72 (t, 1H, J = 8.5 Hz), 3.38-3.37 (m, 2H), 3.20-3.77 (m, 2H), 2.38-2.31 (m, 2H), 1.95-1.91 (m, 2H), 1.81-1.76 (m, 2H); MS(ESI$^+$) m/z 532.2 $(M + H)^+$.

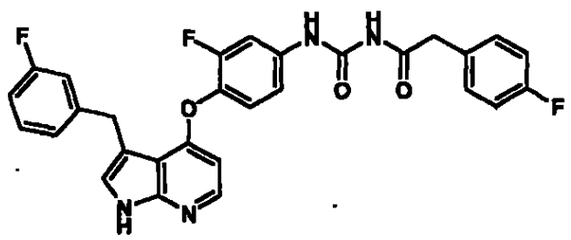
EXAMPLE 275



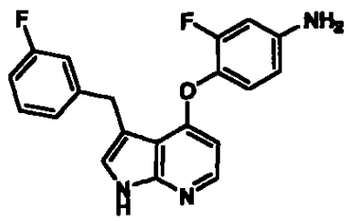
***N*-(3-Fluoro-4-(3-((4-hydroxypiperidin-1-yl)methyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)-1-(4-fluorophenyl)-2-oxopyrrolidine-3-carboxamide**

Prepared in a similar manner as Example 273. ^{1}H NMR (DMSO-d_6) δ 11.71 (s, 1H), 10.88 (s, 1H), 8.00 (d, 1H, J = 5.5 Hz), 7.79 (dd, 1H, J = 12.7, 2.2 Hz), 7.67-7.64 (m, 2H), 7.30-7.35 (m, 3H), 7.20 (t, 2H, J = 8.8 Hz), 6.30 (d, 1H, J = 6.5 Hz), 6.16 (s, 1H), 4.51 (d, 1H, J = 4.4 Hz), 3.83-3.79 (m, 2H), 3.38 (m, 1H), 3.70-2.69 (m, 5H), 2.28-2.19 (m, 3H), 1.65-1.62 (m, 2H), 1.37-1.26 (m, 2H); MS(ESI$^+$) m/z 562.2 $(M + H)^+$.

EXAMPLE 276



1-(4-(3-(3-Fluorobenzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea



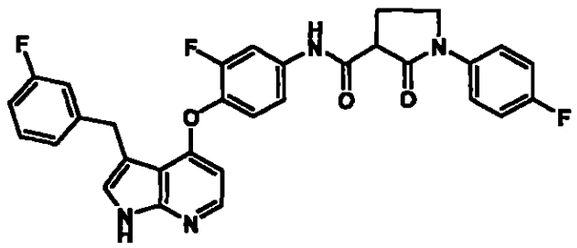
A) **4-(3-(3-Fluorobenzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorobenzenamine**

To a solution of 4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorobenzenamine (49 mg, 0.2 mmol, Compound B of Example 132) in 2 mL of methanol were added sodium hydroxide (40 mg, 1.0 mmol, EMD) and 3-fluorobenzaldehyde (62 mg, 0.5 mmol, Aldrich). The reaction mixture was stirred at rt for 16 h, poured into cold water (5 mL), and extracted with EtOAc (3 x 30 mL). The organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in 2 mL of dichloromethane, and treated with 1 mL of TFA and 0.2 mL of triethylsilane (Aldrich). The reaction mixture was stirred for 1 h and concentrated under reduced pressure. The residue was purified by preparative HPLC and the desired fractions were combined, concentrated *in vacuo*, neutralized with saturated aq. $NaHCO_3$ solution, and extracted with dichloromethane. The organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give the desired compound (12.1 mg, 35% over two steps). MS(ESI$^+$) *m/z* 351.4 $(M+H)^+$.

B) **1-(4-(3-(3-Fluorobenzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea**

Prepared in a similar manner as Example 264 (3.4 mg, 11%). ^{1}H NMR (DMSO-d_6) δ 11.58 (s, 1H), 10.96 (s, 1H), 10.49 (s, 1H), 7.95 (d, 1H, J = 5.5 Hz), 7.67 (dd, 1H, J = 11.6, 2.1 Hz), 7.31-6.67 (m, 12H), 6.10 (d, 1H, J = 5.5 Hz), 4.09 (s, 2H), 3.68 (s, 2H); MS(ESI$^+$) *m/z* 531.2 $(M+H)^+$.

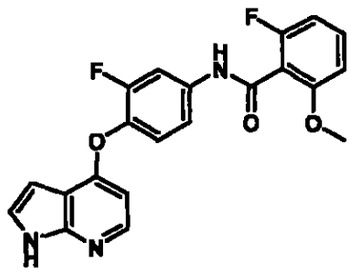
EXAMPLE 277



N-(4-(3-(3-Fluorobenzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxopyrrolidine-3-carboxamide

Prepared in a similar manner as Example 273. ^{1}H NMR (DMSO-d_6) δ 11.74 (s, 1H), 10.62 (s, 1H), 8.03 (d, 1H, J = 5.5 Hz), 7.84 (dd, 1H, J = 12.7, 2.2 Hz), 7.71-7.68 (m, 2H), 7.41 (d, 1H, J = 8.8 Hz), 7.30 (d, 1H, J = 1.7 Hz), 7.26-7.22 (m, 3H), 7.16 (t, 1H, J = 8.5 Hz), 7.08 (d, 1H, J = 7.7 Hz), 7.01 (d, 1H, J = 10.4 Hz), 6.94 (t, 1H, J = 8.8 Hz), 6.22 (d, 1H, J = 5.5 Hz), 4.17 (s, 2H), 3.94-3.90 (m, 2H), 3.76 (t, 1H, J = 8.5 Hz), 2.49-2.35 (m, 2H); MS(ESI$^+$) *m/z* 557.2 $(M+H)^+$.

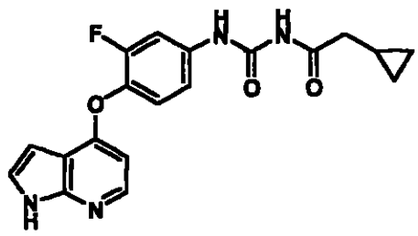
EXAMPLE 278



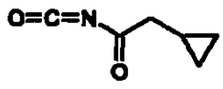
N-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-2-fluoro-6-methoxybenzamide

Prepared in a similar manner as Example 261 (12.1 mg, 31%). ^{1}H NMR (DMSO-d_6) δ 11.97 (s, 1H), 10.86 (s, 1H), 8.14 (d, 1H, J = 5.5 Hz), 7.92 (dd, 1H, J = 13.2, 2.2 Hz), 7.54-7.42 (m, 4H), 7.03 (d, 1H, J = 8.2 Hz), 6.95 (t, 1H, J = 8.8 Hz), 6.48 (d, 1H, J = 6.1 Hz), 6.35 (d, 1H, J = 1.4 Hz); MS(ESI$^+$) *m/z* 396.2 $(M+H)^+$.

EXAMPLE 279



1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-3-(2-cyclopropylacetyl)urea



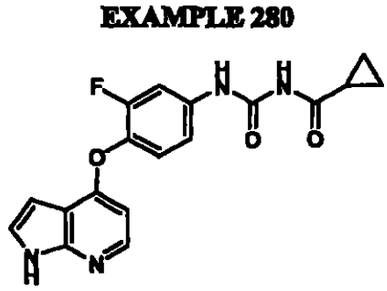
A) 2-Cyclopropylacetyl isocyanate

To a suspension of silver cyanate (435 mg, 3.0 mmol, Aldrich) in 10 mL of toluene was added cyclopropylacetyl chloride (313 mg, 3.0 mmol, Aldrich). The reaction mixture was refluxed for 2 h, cooled to rt and filtered. The filtrate was used as 0.3 M solution for next reaction.

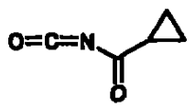
B) 1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-3-(2-cyclopropylacetyl)urea

Prepared in a similar manner as Example 264 (13.5 mg, 59%). ^{1}H NMR (CD_3OD) δ 8.03 (d, 1H, J = 5.5 Hz), 7.80-7.76 (m, 1H), 7.27-7.24 (m, 3H), 6.41 (d, 1H, J = 5.5 Hz), 6.38 (d, 1H, J = 3.9 Hz), 2.25 (d, 1H, J = 7.2 Hz), 0.64-0.59 (m, 2H), 0.28-0.23 (m, 2H); MS(ESI$^+$) *m/z* 369.2 $(M + H)^+$.

EXAMPLE 280



1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-3-(cyclopropanecarbonyl)urea



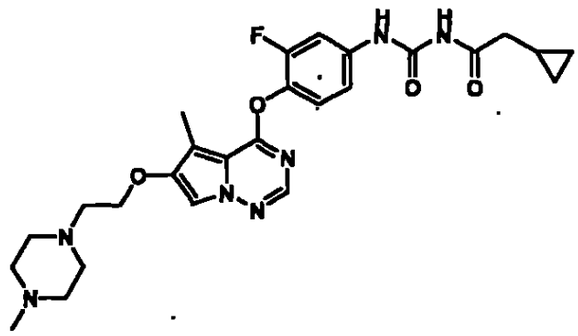
A) **Cyclopropanecarbonyl isocyanate**

Prepared in a similar manner as Step A of Example 279.

B) **1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-3-(cyclopropanecarbonyl)urea**

Prepared in a similar manner as Step B of Example 279 (17.2 mg, 60%). ^{1}H NMR (CD_3OD) δ 7.93 (d, 1H, J = 5.5 Hz), 7.57 (d, 1H, J = 13.8 Hz), 7.12-7.08 (m, 3H), 6.31 (m, 2H), 1.02 (m, 2H), 0.90 (m, 2H); MS(ESI$^+$) *m/z* 355.19 $(M+H)^+$.

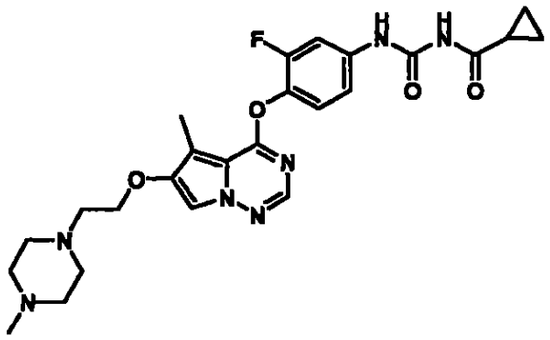
EXAMPLE 281



1-(2-Cyclopropylacetyl)-3-(3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)urea

Prepared in a similar manner as Example 264 using Compound B of Example 45 and Compound A of Example 279 (21.0 mg, 81%). ^{1}H NMR (CD_3OD) δ 7.81 (s, 1H), 7.74 (d, 1H, J = 5.5 Hz), 7.25 (m, 3H), 4.18 (t, 2H, J = 5.5 Hz), 3.35 (t, 2H, J = 1.7 Hz), 2.90 (t, 2H, J = 5.5 Hz), 2.74-2.54 (m, 4H), 2.45 (s, 3H), 2.33 (t, 4H, J = 2.8 Hz), 1.12 (m, 1H), 0.67-0.64 (m, 2H), 0.29-0.25 (m, 2H); MS(ESI$^+$) *m/z* 529.3 $(M+H)^+$.

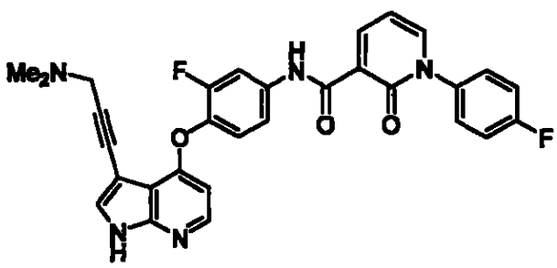
EXAMPLE 282



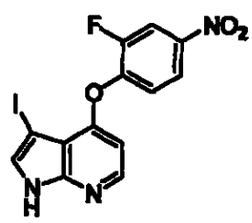
1-Cyclopropanecarbonyl-3-(3-fluoro-4-(5-methyl-6-(2-(4-methylpiperazin-1-yl)ethoxy)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)urea

Prepared in a similar manner as Example 264 using Compound B of Example 45 and Compound A of Example 280 (20.3 mg, 64%). ^{1}H NMR (CD_3OD) δ 10.85 (s, 1H), 7.70 (s, 1H), 7.76–7.72 (m, 2H), 7.22-7.14 (m, 2H), 4.14 (t, 2H, J = 5.5 Hz), 2.94 (t, 2H, J = 5.5 Hz), 2.89-2.60 (m, 4H), 2.78 (s, 3H), 2.34 (s, 4H), 1.70-1.67 (m, 1H), 0.99-0.95 (m, 2H), 0.91-0.86 (m, 2H); MS(ESI$^+$) *m/z* 512.3 $(M + H)^+$.

EXAMPLE 283

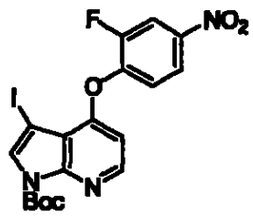


***N*-(4-(3-(3-(Dimethylamino)prop-1-ynyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, trifluoroacetic acid salt**



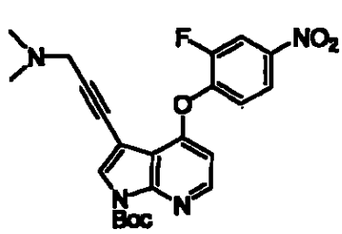
A) 4-(2-Fluoro-4-nitrophenoxy)-3-iodo-1*H*-pyrrolo[2,3-*b*]pyridine

A mixture of 4-(2-fluoro-4-nitrophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridine (550 mg, 2 mmol, Compound A of Example 132) and *N*-iodosuccinimide (450 mg, 2 mmol) in CH_2Cl_2 (50 mL) was stirred at rt for 1 h. The mixture was washed with brine, dried over $MgSO_4$, and passed through a short pad of silica gel, eluting with EtOAc. The filtrate was concentrated *in vacuo* to give the desired product (quantitative yield) as a yellow solid. LC/MS(ESI$^+$) *m/z* 400 $(M+H)^+$.



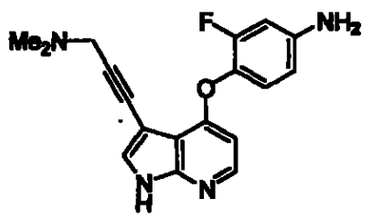
B) *tert*-Butyl 4-(2-fluoro-4-nitrophenoxy)-3-iodo-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate

To a solution of 4-(2-fluoro-4-nitrophenoxy)-3-iodo-1*H*-pyrrolo[2,3-*b*]pyridine (400 mg, 1 mmol) in DMF (10 mL) at –40 °C under N_2 was added NaH (60% in mineral oil, 1.2 mmol). The mixture was stirred at 0 °C for 20 min, and cooled to –40 °C. To this mixture, was added Boc_2O (330 mg, 1.5 mmol). The mixture was stirred at –40 °C for 1 h, diluted with 5% aq. sodium citrate solution, extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude compound was purified by flash column chromatography (silica gel, 20% EtOAc/ CH_2Cl_2) to give the desired compound (460 mg, 92%) as a yellow solid. LC/MS(ESI$^+$) *m/z* 500 $(M+H)^+$.



C) *tert*-Butyl 3-(3-(dimethylamino)prop-1-ynyl)-4-(2-fluoro-4-nitrophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate

A stream of Ar was bubbled through a mixture of *tert*-butyl 4-(2-fluoro-4-nitrophenoxy)-3-iodo-1*H*-pyrrolo[2,3-b]pyridine-1-carboxylate (200 mg, 0.4 mmol), *N,N*-dimethylprop-2-yn-1-amine (66 mg, 0.8 mmol), $Pd(dppf)_2Cl_2$:CH_2Cl_2 (33 mg, 0.04 mmol), and CuI (20 mg) in triethylamine (0.4 mL) and THF (3 mL) for 5 min. The reaction mixture was heated in a sealed tube at 70 °C for 2 h and the solvent was removed *in vacuo*. The crude compound was purified by flash column chromatography (silica gel, 5% MeOH/EtOAc) to afford the desired product (170 mg, 95%) as a yellow oil. LC/MS(ESI$^+$) *m/z* 455 $(M+H)^+$.



D) **4-(3-(3-(Dimethylamino)prop-1-ynyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorobenzenamine**

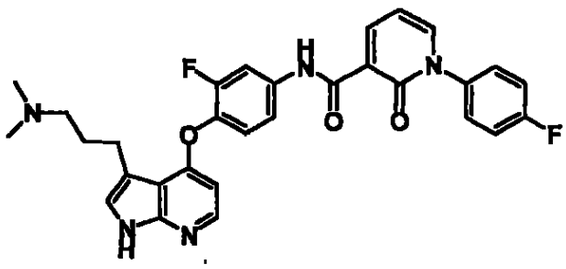
To a mixture of *tert*-butyl 3-(3-(dimethylamino)prop-1-ynyl)-4-(2-fluoro-4-nitrophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate (170 mg, 0.374 mmol) in THF (10 mL) and MeOH (10 mL), was added Zn powder (<10 micron, 500 mg) and NH_4Cl (500 mg). The reaction mixture was stirred at rt for 2 h, diluted with EtOAc, and filtered through a pad of Celite®. The filtrate was washed with sat. aq. KH_2PO_4 solution, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford the desired product (110 mg, 90%) as a yellow solid. LC/MS(ESI$^+$) *m/z* 325 $(M+H)^+$.

E) ***N*-(4-(3-(3-(Dimethylamino)prop-1-ynyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, trifluoroacetic acid salt**

To a mixture of 4-(3-(3-(dimethylamino)prop-1-ynyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorobenzenamine (33 mg, 0.1 mmol), 1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (46 mg, 0.2 mmol, Compound B of Example 242), and HATU (Perseptive Biosystems, 76 mg, 0.2 mmol) in DMF (1 mL), was added DIPEA (0.1 mL). The reaction mixture was stirred at rt overnight and

concentrated *in vacuo*. The crude compound was purified by preparative HPLC, and the appropriate fractions were lyophilized to afford the title compound (15 mg, TFA salt, 23%) as a yellow solid. ^{1}H NMR (CD_3OD) δ 8.73 (dd, 1H, J = 7.6, 2.4 Hz), 8.14 (d, 1H, J = 5.6 Hz), 8.00-8.16 (m, 2H), 7.74 (s, 1H), 7.54-7.60 (m, 2H), 7.30-7.47 (m, 4H), 6.78 (dd, 1H, J = 6.8, 6.8 Hz), 6.47 (d, 1H, J = 5.6 Hz), 4.30 (s, 2H), 2.99 (s, 6H); LC/MS (ESI$^+$) *m/z* 540 $(M+H)^+$.

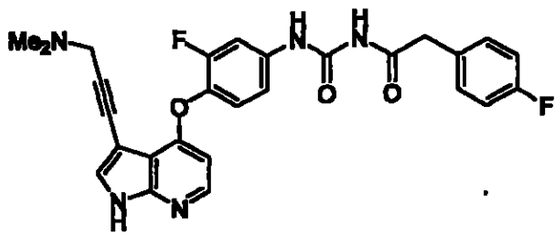
EXAMPLE 284



***N*-(4-(3-(3-(Dimethylamino)propyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, trifluoroacetic acid salt**

A mixture of *N*-(4-(3-(3-(dimethylamino)prop-1-ynyl)-1-(1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carbonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (32 mg, TFA salt, 0.037 mmol, obtained as a byproduct in Step E of Example 283), and Pd/C (10%, 100 mg) in MeOH (5 mL) was hydrogenated under 1 atm for 1 h. The mixture was bubbled through a stream of N_2 for 5 min, filtered through a pad Celite®. The filtrate was purified by prep-HPLC to afford the title compound as a white solid (10 mg, TFA salt, 39% yield). ^{1}H NMR (CD_3OD) δ 8.62 (dd, 1H, J = 7.2, 2.0 Hz), 8.04 (d, 1H, J = 6.4 Hz), 7.95 (dd, 1H, J = 12.8, 1.2 Hz), 7.90 (dd, 1H, J = 6.8, 2.4 Hz), 7.20-7.50 (m, 6H), 6.66 (t, 1H, J = 7.20 Hz), 6.43 (d, 1H, J = 6.4Hz), 3.11 (t, 2H, J = 8.0 Hz), 2.96 (t, 2H, J = 7.2 Hz), 2.77 (s, 6H), 2.11 (m, 2H); LC/MS(ESI$^+$) *m/z* 544 $(M+H)^+$.

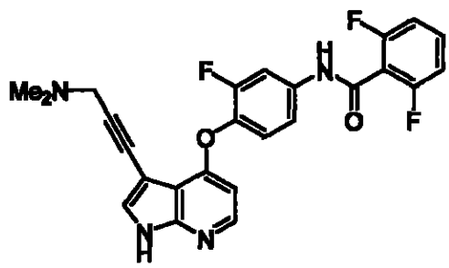
EXAMPLE 285



1-(4-(3-(3-(Dimethylamino)prop-1-ynyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, trifluoroacetic acid salt

To a solution of 4-(3-(3-(dimethylamino)prop-1-ynyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorobenzenamine (15 mg, 0.046 mmol, Compound D of Example 283) in THF (1.5 mL) was added 2-(4-fluorophenyl)acetyl isocyanate (0.05 mmol, Compound C of Example 4) at rt. The mixture was stirred for 1 h and concentrated *in vacuo*. The crude compound was purified by preparative HPLC to give the desired product (TFA salt, 12 mg, 42% yield) as a white solid. ^{1}H NMR (DMSO-d_6) δ 12.30 (s, 1H), 10.98 (s, 1H), 10.52 (s, 1H), 10.00 (s, 1H), 8.07 (d, 1H, J = 5.6 Hz), 7.74 (d, 1H, J = 2.4 Hz), 7.73 (dd, 1H, J = 12.4, 2.4Hz), 7.25-7.40 (m, 4H), 7.10 (m, 2H), 6.26 (d, 1H, J = 5.2 Hz), 4.21 (s, 2H), 3.68 (s, 2H), 2.43 (s, 6H); LC/MS(ESI$^+$) *m/z* 504 $(M+H)^+$.

EXAMPLE 286

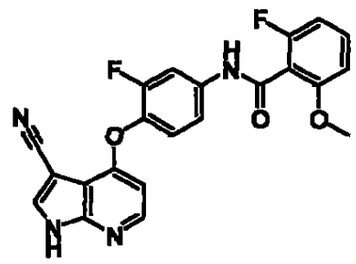


***N*-(4-(3-(3-(Dimethylamino)prop-1-ynyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-2,6-difluorobenzamide, trifluoroacetic acid salt**

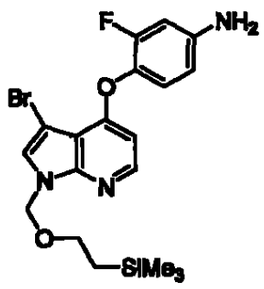
To a solution of 4-(3-(3-(dimethylamino)prop-1-ynyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorobenzenamine (15 mg, 0.046 mmol, Compound D of Example 283) and pyridine (0.05 mL) in CH_2Cl_2 (1.0 mL) at 0 °C, was added 2,6-difluorobenzoyl chloride (9 mg, 0.05 mmol). The mixture was stirred at 0 °C for 30 min and concentrated *in vacuo*. The crude compound was purified by preparative

HPLC to give the desired product (TFA salt, 11 mg, 41%) as a white solid. ^{1}H NMR (CD_3OD) δ 8.05 (d, 1H, J = 5.6 Hz), 7.82 (dd, 1H, J = 12.4, 2.4 Hz), 7.63 (s, 1H), 7.35-7.50 (m, 2H), 7.25 (t, 1H, J = 8.8 Hz), 7.00-7.06 (m, 2H), 6.38 (d, 1H, J = 5.6 Hz), 4.19 (s, 2H), 2.87 (s, 6H); LC/MS(ESI$^+$) m/z 465 $(M+H)^+$.

EXAMPLE 287

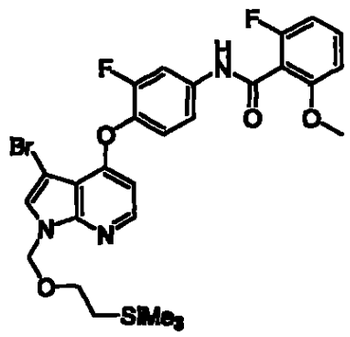


***N*-(4-(3-Cyano-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-2-fluoro-6-methoxybenzamide, hydrochloride salt**



A) 4-(3-Bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorobenzenamine

A mixture of 3-bromo-4-(2-fluoro-4-nitrophenoxy)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridine (626 mg, 1.3 mmol, Compound B of Example 261), zinc powder (1.0 g), and ammonium chloride (1.0 g) in THF (25 mL) and MeOH (25 mL) was stirred at rt overnight. The mixture was diluted with CH_2Cl_2 and filtered through a short pad of Celite®. The resulting solution was then concentrated under reduced pressure, and the residue was purified by flash column chromatography (silica gel, eluting with 30% EtOAc/CH_2Cl_2) to give the desired product (420 mg, 71%) as a clear oil. LC/MS(ESI$^+$) m/z 453 $(M+H)^+$.



B) ***N*-(4-(3-Bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-2-fluoro-6-methoxybenzamide**

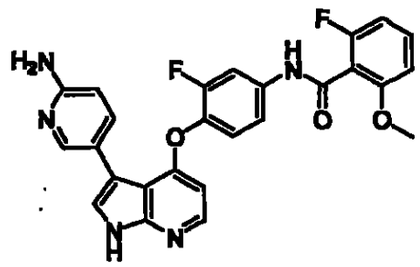
To a stirred solution of 4-(3-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorobenzenamine (400 mg, 0.85 mmol), 2-fluoro-6-methoxybenzoic acid (226 mg, 1.33 mmol), and HATU (641 mg, 1.33 mmol) in DMF (6 mL) was added DIPEA (387 mg, 3 mmol), followed by DMAP (50 mg). The resulting mixture was stirred at rt overnight, diluted with EtOAc, and washed with saturated aq. K_2HPO_4 solution and brine. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, eluting with 30% EtOAc/CH_2Cl_2) to give the desired product (370 mg, 72%) as a white solid. LC/MS(ESI$^+$) *m/z* 605 $(M+H)^+$.

C) ***N*-(4-(3-Cyano-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-2-fluoro-6-methoxybenzamide, hydrochloride salt**

A mixture of *N*-(4-(3-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-2-fluoro-6-methoxybenzamide (30 mg, 0.05 mmol), $Zn(CN)_2$ (17 mg, 0.15 mmol), $Pd(dppf)_2Cl_2$:CH_2Cl_2 (5 mg, Aldrich), Zn(OAc)2 (1 mg) and zinc powder (1 mg) in DMF (0.6 mL) was heated in a sealed tube at 120 °C for 15 h. The mixture was diluted with CH_2Cl_2, filtered through a pad of Celite® (CH_2Cl_2). The filtrate was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was treated with TBAF (1 M in THF, 1.0 mmol) and ethane-1,2-diamine (30 μL) in THF (3 mL). The mixture was refluxed for 15 h and concentrated *in vacuo*. The residue was purified by preparative HPLC. The desired fractions were lyophilized to give a white TFA salt, which was dissolved in small amount of MeOH/H_2O with 1 N HCl (0.1 mL). This

solution was then lyophilized to afford the title compound (HCl salt, 12 mg, 53%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 10.80 (s, 1H), 8.36 (d, 1H, J = 2.8 Hz), 8.14 (d, 1H, J = 5.6 Hz), 7.87 (dd, 1H, J = 12.8, 2.0 Hz), 7.37 (m, 3H), 6.95 (d, 1H, J = 8.4 Hz), 6.88 (t, 1H, J = 8.8 Hz), 6.41 (d, 1H, J = 5.2 Hz), 3.79 (s, 3H); LC/MS(ESI$^+$) *m/z* 421 $(M+H)^+$.

EXAMPLE 288

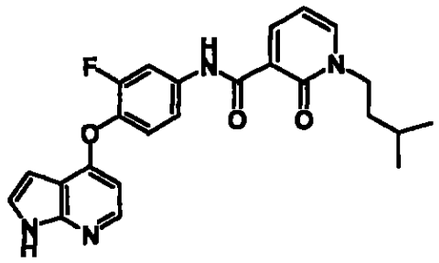


***N*-(4-(3-(6-Aminopyridin-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-2-fluoro-6-methoxybenzamide**

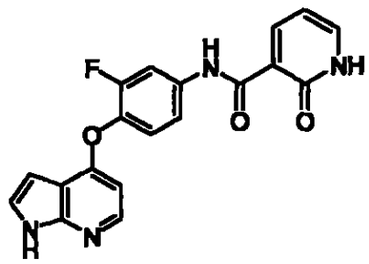
A mixture of *N*-(4-(3-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-2-fluoro-6-methoxybenzamide (50 mg, 0.08 mmol, Compound B of Example 287), 5-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)pyridin-2-amine (36 mg, 0.16 mmol, Oakwood), $Pd(PPh_3)_4$ (10 mg), and K_3PO_4 (2 M in H_2O, 0.32 mmol) in toluene (1 mL), EtOH (0.2 mL), and DME (0.4 mL) was purged with Ar for 10 min. The reaction mixture was heated at 95 °C for 2 h, diluted with EtOAc, and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a residue, which was treated with TBAF (1 M in THF, 1 mL), ethane-1,2-diamine (50 μL) in THF (3 mL) at reflux for 24 h. The mixture was diluted with EtOAc, washed with brine, dried with $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, 5% 2 M NH_3 in MeOH/CH_2Cl_2) to give the desired product, which was converted to the HCl salt by lyophilization with 1 N HCl in H_2O (white solid, 10 mg, 26% yield). ^{1}H NMR (CD_3OD) δ 8.32 (dd, 1H, J = 9.2, 2.0 Hz), 8.21 (d, 1H, J = 6.1 Hz), 8.15 (d, 1H, J = 2.0 Hz), 7.94 (dd, 1H, J = 12.7, 2.5 Hz), 7.70 (s, 1H), 7.44-7.50 (m, 2H), 7.36 (t, 1H, J = 8.7 Hz), 7.08 (d, 1H, J = 9.2 Hz), 6.98 (d, 1H, J = 8.7 Hz),

6.85 (t, 1H, J = 8.7 Hz), 6.56 (d, 1H, J = 5.6 Hz), 3.92 (s, 3H); LC/MS(ESI$^+$) *m/z* 488 $(M+H)^+$.

EXAMPLE 289



***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-1-isopentyl-2-oxo-1,2-dihydropyridine-3-carboxamide, trifluoroacetic acid salt**



A) *N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide

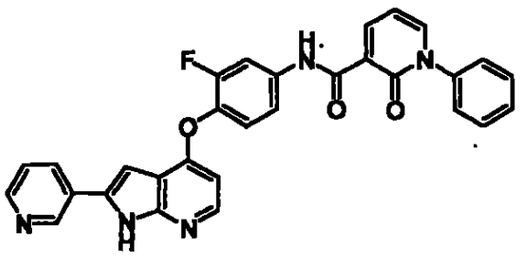
To a stirred solution of 4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorobenzenamine (24 mg, 0.1 mmol, Compound B of Example 132), 2-hydroxynicotinic acid (27 mg, 0.2 mmol), and HATU (76 mg, 0.2 mmol) in DMF (1 mL) was added DIPEA (0.1 mL) and DMAP (5 mg). The resulting mixture was stirred at rt for 2 h and concentrated *in vacuo*. The residue was was purified by preparative HPLC to give the desired product (8 mg, 22%) as a white solid. LC/MS(ESI$^+$) *m/z* 365 $(M+H)^+$.

B) *N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-1-isopentyl-2-oxo-1,2-dihydropyridine-3-carboxamide, trifluoroacetic acid salt

A mixture of *N*-(4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (8 mg, 0.02 mmol), Na_2CO_3 (50 mg), and 1-iodo-

3-methylbutane (50 mg) in DMF (1 *mL*) was stirred at rt overnight. The reaction mixture was concentrated *in vacuo* and the residue was was purified by preparative HPLC to give the desired product (TFA salt, 5 mg, 42%) as a white solid. ^{1}H NMR (CD_3OD) δ 12.50 (s, 1H), 8.46 (dd, 1H, J = 7.1, 2.0 Hz), 8.16 (d, 1H, J = 6.1 Hz), 7.90-8.00 (m, 2H), 7.38-7.44 (m, 2H), 7.33 (t, 1H, J = 8.7 Hz), 6.70 (d, 1H, J = 6.6 Hz), 6.51-6.57 (m, 2H), 4.08 (t, 2H, J = 7.6 Hz), 1.51-1.53 (m, 3H), 0.92 (d, 6H, J = 6.1 Hz); LC/MS(ESI$^+$) *m/z* 435 $(M+H)^+$.

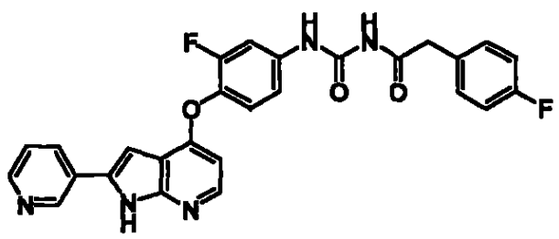
EXAMPLE 290



***N*-(3-Fluoro-4-(2-(pyridin-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide**

Prepared in a similar manner as Example 239 using 3-fluoro-4-(2-(pyridin-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)benzenamine (Compound E of Example 237) and 2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxylic acid. ^{1}H NMR (DMSO-d_6) δ 12.87 (s, 1H), 12.18 (s, 1H), 9.39 (s, 1H), 8.70-8.85 (m, 2H), 8.60 (d, 1H, J = 7.1 Hz), 8.00-8.25 (m, 3H), 7.94 (s, 1H), 7.30-7.75 (m, 8H), 6.77 (t, 1H, J = 6.6 Hz), 6.45 (d, 1H, J = 4.6 Hz), 4.21 (s, 2H), 3.68 (s, 2H), 2.43 (s, 6H); LC/MS(ESI$^+$) *m/z* 518 $(M+H)^+$.

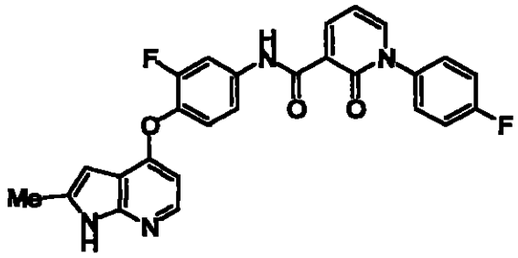
EXAMPLE 291



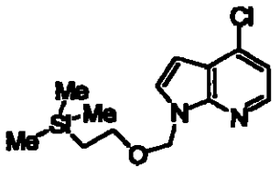
1-(3-Fluoro-4-(2-(pyridin-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea, hydrochloride salt

A mixture of 3-fluoro-4-(2-(pyridin-3-yl)-1*H*-pyrrolo[2,3-b]pyridin-4-yloxy)benzenamine (25 mg, 0.078 mmol, Compound E of Example 237) and 2-(4-fluorophenyl)acetyl isocyanate (0.09 mmol in toluene, Compound C of Example 4) in THF was stirred at rt for 1 h. The solvent was removed *in vacuo* and the residue was purified by preparative HPLC to afford the desired product (HCl salt, 18 mg, 40%) as a yellow solid. ^{1}H NMR (CD_3OD) δ 10.76 (s, 1H), 9.19 (s, 1H), 8.70 (d, 1H, J = 8.0 Hz), 8.66 (d, 1H, J = 5.2 Hz), 8.18 (d, 1H, J = 6.4 Hz), 8.00 (dd, 1H, J = 8.4, 5.6 Hz), 7.75 (dd, 1H, J = 13.2, 2.4 Hz), 7.10-7.35 (m, 4H), 6.90-7.03 -7.40 (m, 3H), 6.63 (d, 1H, J = 6.4 Hz); LC/MS(ESI$^+$) *m/z* 500 $(M+H)^+$.

EXAMPLE 292



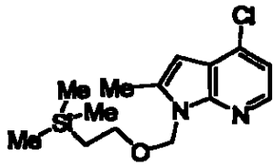
***N*-(3-Fluoro-4-(2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide**



A) 4-Chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridine

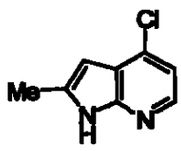
To a suspension of NaH (88 mg, 60% in mineral oil, 2.2 mmol) in DMF (1 mL) was added 4-chloro-1*H*-pyrrolo[2,3-*b*]pyridine (305 mg, 2 mmol, prepared according to Thibault, C. et al. *Org. Lett.* 2003, *5*, 5023) at room temperature with stirring. The mixture was stirred for 5 min and trimethylsilylethyl chloromethyl ether (350 mg, 2.1 mmol, Aldrich) was added. The mixture was stirred at room temperature

for 1 h, poured onto ice, and extracted with ethyl acetate (3 x 10 mL). The combined extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to give the crude product, which was purified by flash chromatograph (5% ethyl acetate in hexanes) to afford the title compound (300 mg, 1.06 mmol, 53%) as a liquid. ^1H NMR ($CDCl_3$) δ 8.28 (d, 1H, J = 5.5 Hz), 7.45 (d, 1H, J = 3.6 Hz), 7.18 (d, 1H, J = 5.5 Hz), 6.69 (d, 1H, J = 3.6 Hz), 5.74 (s, 2H), 3.60 (t, 2H, J = 6.8 Hz), 0.96 (t, 2H, J = 6.8 Hz), 0.07 (s, 9H); MS(ESI$^+$) *m/z* 283 and 285 (M + H, 1 Cl)$^+$.



B) **4-Chloro-2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridine**

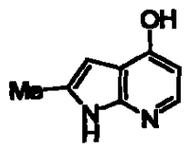
To a solution of 4-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridine (150 mg, 0.53 mmol) in THF (1 mL) at -78 °C under argon was added butyllithium (0.4 mL, 1.6 M in hexanes, 6.4 mmol) dropwise. The mixture was stirred at the same temperature for 5 min, and treated with iodomethane (0.1 mL). The mixture was warmed up to room temperature, quenched by the addition of saturated ammonium chloride solution, and extracted with ethyl acetate (3 x 10 mL). The combined extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product (150 mg, 95%), which was used for the next reaction. ^1H NMR ($CDCl_3$) δ 8.19 (d, 1H, J = 5.5 Hz), 7.14 (d, 1H, J = 5.5 Hz), 6.42 (s, 1H), 5.74 (s, 2H), 3.60 (t, 2H, J = 6.8 Hz), 2.61(s, 3H), 0.96 (t, 2H, J = 6.8 Hz), 0.07 (s, 9H); MS(ESI$^+$) *m/z* 297 and 299 (M + H, 1 Cl)$^+$.



C) **4-Chloro-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridine**

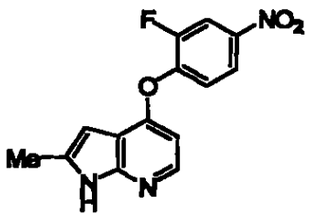
A mixture of 4-chloro-2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridine (296.5 mg, 1 mmol) and TBAF (5 mL, 1 M in THF, Aldrich)

was refluxed overnight. The THF was removed under reduced pressure and the residue was diluted with water (5 mL). The precipitate that formed was collected, washed with water and dried ($MgSO_4$) to afford the title compound (101 mg, 60%). ^1H NMR (CD_3OD) δ 7.99 (d, 1H, J = 5.5 Hz), 7.06 (d, 1H, J = 5.5 Hz), 6.23 (s, 1H), 2.46 (s, 3H); MS(ESI$^+$) *m/z* 167 and 169 $(M+H, 1\ Cl)^+$.



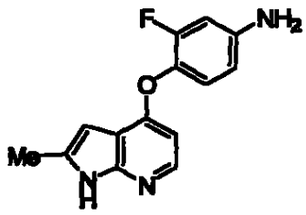
D) 2-Methyl-1*H*-pyrrolo[2,3-*b*]pyridin-4-ol

A mixture of 4-chloro-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (120 mg, 0.72 mmol) and sodium acetate (150 mg, 1.83 mmol) in acetic acid (1.5 mL) was microwaved at 200 °C for 40 minutes. The mixture was purified by preparative HPLC and the appropriate fractions were concentrated *in vacuo* and lyophilized to afford the title compound (90 mg, 47%). ^1H NMR (CD_3OD) δ 8.09 (d, 1H, J = 5.5 Hz), 6.80 (d, 1H, J = 5.5 Hz), 6.49 (s, 1H), 2.46 (s, 3H); MS(ESI$^+$) *m/z* 149 $(M+H)^+$.



D) 4-(2-Fluoro-4-nitrophenoxy)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridine

A mixture of 2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-4-ol (90 mg , TFA salt, 0.34 mmol), 3,4-difluoronitrobenzene (0.05 mL) and potassium carbonate (100 mg, 0.72 mmol) in DMF (1 mL) was stirred at 50 °C for 2 h. The mixture was diluted with water and extracted with ethyl acetate (3 x 5 mL). The combined extracts were washed with water, dried ($MgSO_4$) and concentrated *in vacuo* to afford the crude product, which was purified by preparative HPLC to give the title compound (45 mg, 46%). ^1H NMR (CD_3OD) δ 8.25 (dd, 2H, J = 10.4, 2.6 Hz), 8.12 (m, 1H), 8.04 (d, 1H, J = 5.5 Hz), 7.30 (t, 1H, J = 8.3 Hz), 6.67 (d, 1H, J = 5.5 Hz), 5.95 (s, 1H), 2.41 (s, 3H); MS(ESI$^+$) *m/z* 288 $(M+H)^+$.



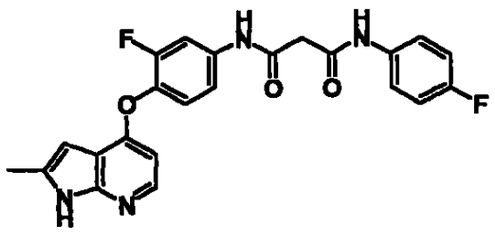
E) **3-Fluoro-4-(2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)benzenamine**

A mixture of 4-(2-fluoro-4-nitrophenoxy)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (43 mg, 0.15 mmol), zinc dust (50 mg, 0.75 mmol) and ammonium chloride (50 mg) in THF/Methanol (1/2, 0.6 mL) was stirred at room temperature for 1 h, filtered and concentrated *in.vacuo* to afford the desired product (35 mg, 90%), which was sufficiently pure to use in the subsequent reaction. ^{1}H NMR (DMSO-d_6) δ 11.71 (s, 1H), 8.04 (d, 1H, J = 5.5 Hz), 7.10 (t, 1H, J = 8.4 Hz), 6.64 (dd, 1H, J = 10.4, 2.6 Hz), 6.51 (m, 1H), 6.35 (d, 1H, J = 5.5 Hz), 5.95 (s, 1H), 5.50 (s 2H), 2.41 (s, 3H); MS(ESI$^+$) *m/z* 258 $(M + H)^+$.

F) ***N*-(3-Fluoro-4-(2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide**

A mixture of 3-fluoro-4-(2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)benzenamine (17 mg, 0.066 mmol), 1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (20 mg, 0.086 mmol) in DMF (0.5 mL) was stirred with BOP reagent (50 mg, 0.11 mmol) and triethylamine (0.01 mL) at 50 °C for 1 h. The reaction mixture was cooled to room temperature and diluted with water. The precipitate was collected and washed with water. The crude product was purified by preparative HPLC and the appropriate fractions were collected, neutralized and concentrated *in vacuo* to give the title compound (7.85 mg, 25%) as a solid. ^{1}H NMR (DMSO-d_6) δ 12.07 (s, 1H), 11.56 (s, 1H), 8.49 (d, 1H, J = 6.2 Hz), 8.12 (d, 1H, J = 6.2 Hz), 7.98 (dd, 1H, J = 10.4, 2.6 Hz), 7.95 (d, 1H, J = 5.5 Hz), 7.61 (m, 2H), 7.43 (m, 3H), 7.29 (t, 1H, J = 8.40 Hz), 6.72 (t, 1H, J = 6.2 Hz), 6.36 (d, 1H, J = 5.5 Hz), 5.88 (s, 1H), 2.32 (s, 3H); MS(ESI$^+$) *m/z* 473 $(M + H)^+$.

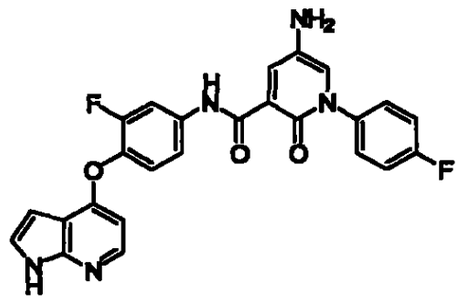
EXAMPLE 293



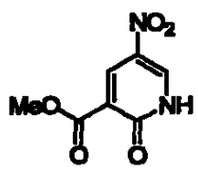
N^1-(3-Fluoro-4-(2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)-N^3-(4-fluorophenyl)malonamide, hydrochloride salt

To a mixture of 3-fluoro-4-(2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)benzenamine (20 mg, 0.078 mmol, Compound E of Example 292), 3-(4-fluorophenylamino)-3-oxopropanoic acid (20 mg, 1 mmol, Compound A of Example 25), and HATU (44 mg, 0.12 mmol) in DMF (0.5 mL) was added DIPEA (0.1 mL). The reaction mixture was stirred at rt for 2 h and concentrated *in vacuo*. The residue was purified by preparative HPLC to give the desired product (HCl salt, 12.5 mg, 34%) as a white solid. ^{1}H NMR (CD_3OD) δ 8.05 (d, 1H, J = 7.2 Hz), 7.79 (dd, 1H, J = 12.7, 2.8 Hz), 7.50-7.53 (m, 2H), 7.27-7.36 (m, 2H), 6.97 (m, 2H), 6.70 (d, 1H, J = 6.6 Hz), 6.20 (s, 1H), 3.47 (s, 2H), 2.40 (s, 3H); LC/MS(ESI$^+$) *m/z* 437 $(M+H)^+$.

EXAMPLE 294

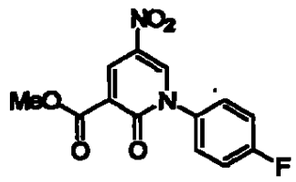


N-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-5-amino-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, hydrochloride salt



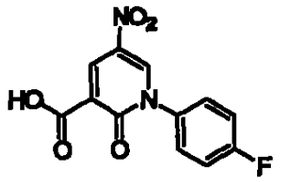
A) **Methyl 5-nitro-2-oxo-1,2-dihydropyridine-3-carboxylate**

To a solution of 2-hydroxy-5-nitronicotinic acid (0.80 g, 4.35 mmol, Combi-Blocks) in methanol (10 mL) at 0 °C was added thionyl chloride (1 mL) dropwise. The mixture was stirred at 0 °C for 1 h, then at 60 °C for 2 h. The excess methanol was removed under reduced pressure and the residue was neutralized with aqueous sodium bicarbonate solution. The solid was collected, washed with water and dried to afford the title compound (0.85 g, 99%). ^{1}H NMR (DMSO-d_6) δ 8.44 (s, 1H), 8.34 (s, 1H), 3.67 (s, 3H); MS(ESI$^+$) *m/z* 199 $(M+H)^+$.



B) Methyl 1-(4-fluorophenyl)-5-nitro-2-oxo-1,2-dihydropyridine-3-carboxylate

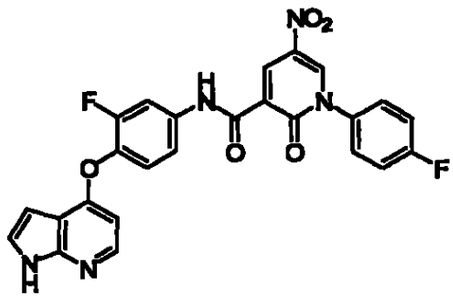
A mixture of methyl 5-nitro-2-oxo-1,2-dihydropyridine-3-carboxylate (850 mg, 4.29 mmol), 4-fluorophenylboronic acid (1.40 g, 10 mmol, Combi-Blocks) and copper acetate (200 mg, 1.1 mmol) in pyridine (1 mL) and dioxane (20 mL) was stirred at 80 °C for 4 h. The reaction mixture was cooled to room temperature and diluted with a solution of ammonia. The solid was collected, washed with water and dried to afford the title compound (656 mg, 52%). ^{1}H NMR (DMSO-d_6) δ 8.95 (d, 1H, J = 3.2 Hz), 8.80 (d, 1H, J = 3.2 Hz), 7.40 (m, 2H), 7.25 (m, 2H), 3.95 (s, 3H); MS(ESI$^+$) *m/z* 293 $(M+H)^+$.



C) 1-(4-Fluorophenyl)-5-nitro-2-oxo-1,2-dihydropyridine-3-carboxylic acid

A mixture of methyl 1-(4-fluorophenyl)-5-nitro-2-oxo-1,2-dihydropyridine-3-carboxylate (75 mg, 0.245 mmol) and 2 N NaOH solution (1 mL) was stirred at 80 °C for 2 h. The reaction mixture was cooled to rt and acidified with 1 N HCl solution.

The solid that formed was collected, washed with water and dried to afford the title compound (45 mg, 66%), which was used directly in the next reaction. ^{1}H NMR (DMSO-d_6) δ 13.41 (s, 1H), 9.28 (d, 1H, J = 3.2 Hz), 8.70 (d, 1H, J = 3.2 Hz), 7.60 (m, 2H), 7.41 (m, 2H); MS(ESI$^+$) m/z 279 $(M + H)^+$.



D) ***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-5-nitro-2-oxo-1,2-dihydropyridine-3-carboxamide**

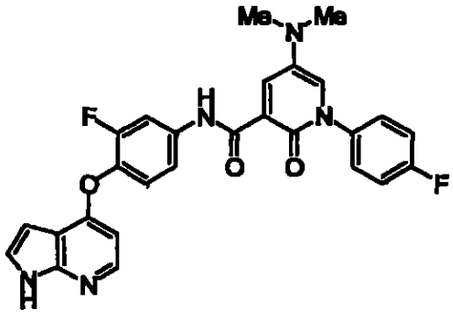
A mixture of 1-(4-fluorophenyl)-5-nitro-2-oxo-1,2-dihydropyridine-3-carboxylic acid (40 mg, 0.14 mmol) and 4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorobenzenamine (35 mg, 0.14 mmol, Compound B of Example 132) in DMF (1 mL) was stirred with BOP reagent (100 mg, 0.23 mmol) and triethylamine (0.1 mL) at 50 °C for 1 h. The reaction mixture was cooled to room temperature and diluted with water. The solid that formed was collected, washed with aqueous sodium bicarbonate solution, 1 N HCl solution, and water to afford the title compound (54 mg, 76%). ^{1}H NMR (DMSO-d_6) δ 12.19 (s, 1H), 11.04 (s, 1H), 9.37 (d, 1H, J = 2.6 Hz), 9.03 (d, 1H, J = 2.6 Hz), 8.18 (d, 1H, J = 5.5 Hz), 8.01 (dd, 1H, J = 10.2, 2.6 Hz), 7.71 (m, 2H), 7.61 (m, 1 H), 7.46 (m, 4H), 6.55 (d, 1H, J = 5.5 Hz), 6.36 (s, 1Hz); MS(ESI$^+$) m/z 504 $(M + H)^+$.

E) ***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-5-amino-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, hydrochloride salt**

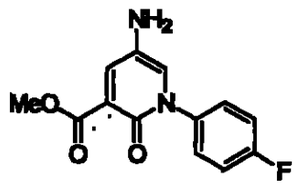
A solution of *N*-(4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-5-nitro-2-oxo-1,2-dihydropyridine-3-carboxamide (51 mg, 0.1 mmol) in DMF (1 mL) and ethanol (5 mL) was hydrogenated in the presence of Pd/C (10%, 10

mg) under hydrogen atmosphere for 4 h at room temperature. The reaction mixture was filtered and concentrated *in vacuo*. The residue was purified by preparative HPLC and the fraction containing the desired compound was collected and concentrated *in vacuo*. The product was converted to the HCl salt by adding 1 N HCl solution and lyophilizing to afford the title compound (7.6 mg, 15%) as a light yellow solid. ^{1}H NMR (CD_3OD) δ 8.56 (d, 1H, J = 3.2 Hz), 8.31 (d, 1H, J = 5.5 Hz), 8.08 (dd, 1H, J = 10.4, 2.6 Hz), 7.78 (m, 1H), 7.56 (m, 5H), 7.48 (m, 2H), 7.35 (t, 1H, J = 8.7 Hz), 6.90 (d, 1H, J = 5.5 Hz), 6.69 (s, 1H); MS(ESI$^+$) *m/z* 474 $(M+H)^+$.

EXAMPLE 295



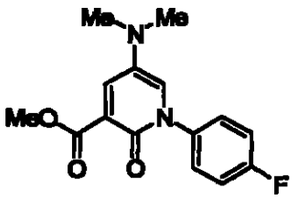
***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-5-(dimethylamino)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide**



A) Methyl 5-amino-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate

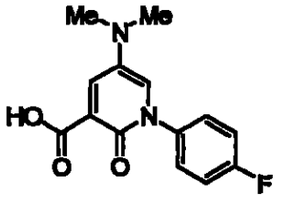
A mixture of methyl 1-(4-fluorophenyl)-5-nitro-2-oxo-1,2-dihydropyridine-3-carboxylate (1.46 g, 5 mmol, Compound B of Example 294), zinc dust (1.63 g, 25 mmol) and ammonium chloride (1.5 g, 28 mmol) in methanol/THF (1:1, 20 mL) was stirred at room temperature for 2 h. The reaction mixture was filtered and concentrated *in vacuo* to afford the desired product (1.30 g, 99%), which was used

directly in the next reaction without purification. ^{1}H NMR (CD_3OD) δ 8.08 (s, 1H), 7.41 (m, 2H), 7.29 (m, 3H), 3.84 (s, 3H); MS(ESI$^+$) *m/z* 263 $(M+H)^+$.



B) Methyl 5-(dimethylamino)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate

To a solution of methyl 5-amino-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (30 mg, 0.11 mmol) and formalin (37%, 0.1 mL) in acetic acid (1 mL) was added sodium triacetoxyborohydride (50 mg, 0.23 mmol). The reaction mixture was stirred at room temperature for 1 h and purified by preparative HPLC. The fractions containing the desired product were collected, neutralized and concentrated *in vacuo* to afford a solid. The solid was collected, washed with water and dried to give the title compound (25 mg, 77%). ^{1}H NMR (CD_3OD) δ 8.31 (d, 1H, J = 2.6 Hz), 7.41 (m, 2H), 7.26 (m, 3H), 3.89 (s, 3H), 2.79 (s, 6H); MS(ESI$^+$) *m/z* 291 $(M+H)^+$.



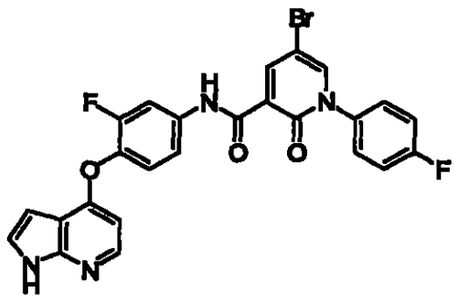
C) 5-(Dimethylamino)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid

The title compound was prepared from methyl 5-(dimethylamino)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (25 mg, 0.086 mmol) utilizing the procedure described in Step C of Example 294 (20 mg, 84%). ^{1}H NMR (CD_3OD) δ 8.31 (d, 1H, J = 2.6 Hz), 7.41 (m, 2H), 7.26 (m, 3H), 2.70 (s, 6H); MS(ESI$^+$) *m/z* 277 $(M+H)^+$.

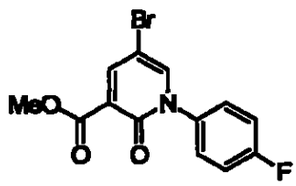
D) ***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-5-(dimethylamino)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide**

The title compound was prepared from 5-(dimethylamino)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (20 mg, 0.072 mmol) utilizing the procedure described in Step D of Example 294 (13.5 mg, 37%). ^{1}H NMR (DMSO-d_6) δ 12.54 (s, 1H), 11.79 (s, 1H), 8.45 (d, 1H, J = 3.2 Hz), 8.10 (d, 1H, J = 5.5 Hz), 8.01 (dd, 1H, J = 10.4, 2.6 Hz), 7.62 (m, 1H), 7.44 (m, 6H), 6.40 (d, 1H, J = 5.5 Hz), 6.24 (s, 1Hz), 2.82 (s, 6H); MS(ESI$^+$) *m/z* 502 $(M+H)^+$.

EXAMPLE 296

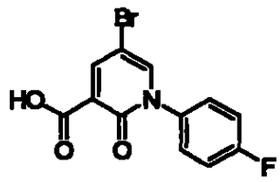


***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-5-bromo-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide**



A) **Methyl 5-bromo-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate**

The title compound was prepared from 5-bromo-2-hydroxynicotinic acid (Combi-Blocks) utilizing the procedures described in Steps A and B of Example 294 in 69% yield. ^{1}H NMR (DMSO-d_6) δ 8.29 (d, 1H, J = 3.2 Hz), 8.14 (d, 1H, J = 3.2 Hz), 7.50 (m, 2H), 7.37 (m, 2H), 3.75 (s, 3H); MS(ESI$^+$) *m/z* 326 and 328 (M + H, 1 Br)$^+$.



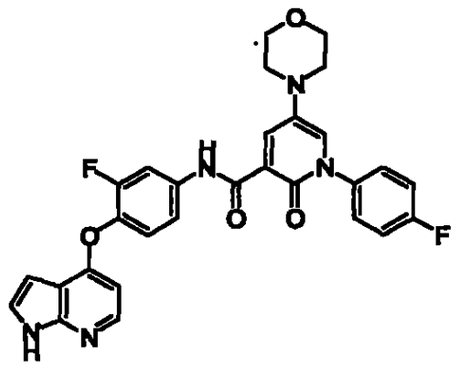
B) **5-Bromo-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid**

The title compound was prepared from methyl 5-bromo-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (65 mg, 0.2 mmol) utilizing the procedure described in Step C of Example 294 (55 mg, 88%). ^{1}H NMR (DMSO-d_6) δ 8.58 (d, 1H, J = 2.6 Hz), 8.44 (d, 1H, J = 2.6 Hz), 7.69 (m, 2H), 7.43 (t, 2H, J = 8.8 Hz); MS(ESI$^+$) m/z 312 and 314 (M + H, 1 Br)$^+$.

C) ***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-5-bromo-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide**

The title compound was prepared from 5-bromo-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (31.2 mg, 0.1 mmol) utilizing the procedure described in Step D of Example 294 (28 mg, 52%). ^{1}H NMR (DMSO-d_6) δ 11.93 (s, 1H), 11.80 (s, 1H), 8.53 (m, 2H), 8.01 (dd, 1H, J = 10.4, 2.6 Hz), 7.64 (m, 2H), 7.41 (m, 6H), 6.41 (br.s, 1H), 6.27 (s, 1H); MS(ESI$^+$) m/z 537 and 539 (M + H, 1 Br)$^+$.

EXAMPLE 297

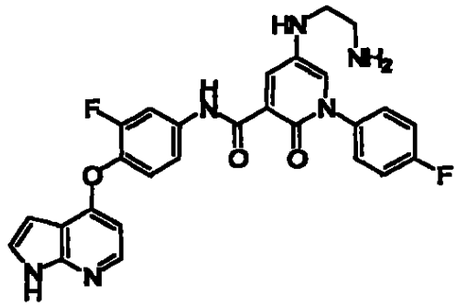


***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-5-morpholino-2-oxo-1,2-dihydropyridine-3-carboxamide**

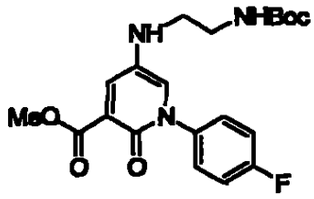
A mixture of *N*-(4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-5-bromo-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (40 mg, 0.074

mmol, Example 296) and morpholine (0.1 mL) in dimethylacetamide (1 mL) was microwaved at 160 °C for 30 minutes. The reaction mixture was cooled to room temperature and purified by preparative HPLC. The fractions containing the desired product were collected, neutralized and concentrated *in vacuo* to afford a solid. The solid was collected, washed with water and dried to give the title compound (7.5 mg, 18%). ^{1}H NMR (DMSO-d_6) δ 12.38 (s, 1H), 11.75 (s, 1H), 8.50 (d, 1H, J = 2.6 Hz), 8.06 (d, 1H, J = 5.5 Hz), 8.01 (dd, 1H, J = 10.4, 2.6 Hz), 7.60 (m, 2H), 7.41 (m, 6H), 6.41 (d, 1H, J = 5.5 Hz), 6.21 (s, 1H), 3.72 (m, 4H), 3.00 (m, 4H); MS(ESI$^+$) *m/z* 544 $(M+H)^+$.

EXAMPLE 298



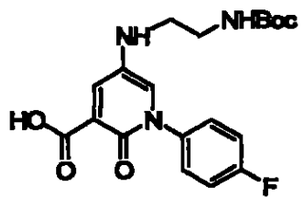
***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-5-(2-aminoethylamino)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide**



A) Methyl 5-(2-(*tert*-butoxycarbonyl)ethylamino)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate

To a solution of methyl 5-bromo-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (131 mg, 0.5 mmol, Compound A of Example 296) and *tert*-butyl 2-oxoethylcarbamate (159 mg, 1 mmol, Aldrich) in acetic acid (1 mL) was added sodium triacetoxyborohydride (212 mg, 1 mmol). The reaction mixture was stirred at room temperature for 1 h, quenched by adding water, and extracted with

ethyl acetate (3 x 10 mL). The combined organic extracts were washed with brine, aqueous sodium bicarbonate solution and dried. The solution was concentrated *in vacuo* and the residue was purified by flash column chromatography (SiO_2, 10% ethyl acetate in hexanes) to afford the title compound (60 mg, 30%) as a gel. ^{1}H NMR ($CDCl_3$) δ 7.90 (d, 1H, J = 2.6 Hz), 7.37 (m, 2H), 7.13 (m, 2H), 6.81 (d, 1H, J = 2.6 Hz), 3.88 (s, 3H), 3.30 (m, 2H), 3.10 (m, 2H), 1.46 (s, 9H); MS(ESI$^+$) *m/z* 406 $(M+H)^+$.



B) 5-(2-(*tert*-Butoxycarbonyl)ethylamino)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid

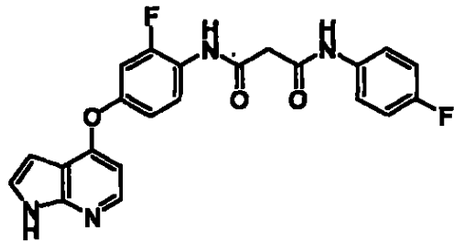
The title compound was prepared from methyl 5-(2-(*tert*-butoxycarbonyl)ethylamino)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (60 mg, 0.15 mmol) utilizing the procedure described in Step C of Example 294 (50 mg, 85%), which was used directly in the next reaction without further purification. ^{1}H NMR ($CDCl_3$) δ 8.26 (d, 1H, J = 2.6 Hz), 7.50 (m, 2H), 7.25 (m, 2H), 6.91 (d, 1H, J = 2.6 Hz), 3.30 (m, 2H), 3.10 (m, 2H), 1.46 (s, 9H); MS(ESI$^+$) *m/z* 392 $(M+H)^+$.

C) *N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridine-4-yloxy)-3-fluorophenyl)-5-(2-aminoethylamino)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide

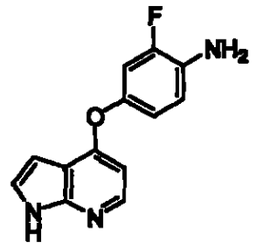
A mixture of 5-(2-(*tert*-butoxycarbonyl)ethylamino)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (50 mg, 0.13 mmol) and 4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorobenzenamine (40 mg, 0.16 mmol, Compound B of Example 132), BOP reagent (100 mg, 0.23 mmol) in DMF (1 mL) was stirred at 50 °C with triethylamine (0.1 mL) for 1 h. The reaction mixture was cooled to room temperature, diluted with water, and extracted with methylene chloride (3 x 10 mL).

The combined organic extracts were washed with water, dried and concentrated *in vacuo*. The residue was stirred with TFA (1 mL) at room temperature for 30 minutes. The TFA was removed and the residue was purified by preparative HPLC. The fraction containing the desired product was collected and concentrated *in vacuo*. The residue was converted to the HCl salt by adding 1 N HCl solution and lyophilizing to give the title compound (20 mg, 27%). ^{1}H NMR (CD_3OD) δ 8.35 (d, 1H, J = 2.6 Hz), 8.26 (d, 1H, J = 5.5 Hz), 8.01 (dd, 1H, J = 10.4, 2.6 Hz), 7.48 (m, 2H), 7.41 (m, 6H), 6.81 (d, 1H, J = 5.5 Hz), 6.60 (s, 1H), 3.26 (t, 2H, J = 6.1 Hz), 3.07 (t, 2H, J = 6.1 Hz); MS(ESI$^+$) *m/z* 517 $(M+H)^+$.

EXAMPLE 299



N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-2-fluorophenyl)-N^3-(4-fluorophenyl)malonamide, trifluoroacetic acid salt



A) 4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-2-fluorobenzenamine

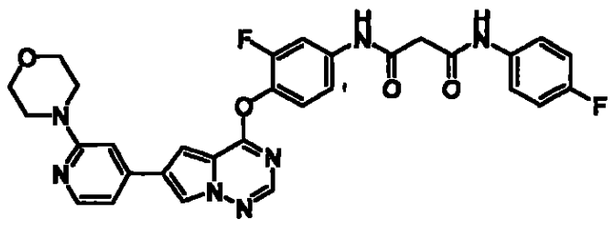
To a solution of 4-chloro-1*H*-pyrrolo[2,3-*b*]pyridine (50 mg, 0.33 mmol, prepared according to Thibault, C. et al. *Org. Lett.* **2003**, *5*, 5023) in NMP (0.5 mL) were added 4-amino-3-fluorophenol (51 mg, 0.40 mmol) and DIEA (0.1 mL, 0.57 mmol). The mixture was heated at 250 °C in a microwave oven for 1 h and then cooled to room temperature. To the mixture was added NaH (10 mg, 0.4 mmol) and the mixture was again heated at 250 °C for 3 h. After cooling, the mixture was diluted

with H_2O and extracted with EtOAc. The organic layer was washed with H_2O, brine, and dried over $MgSO_4$. After filtration and concentration *in vacuo*, the residue was purified by flash column chromatography (ISCO RediSep® silica gel cartridge) to give the title compound (15 mg, 19%). MS (ESI) *m/z* 244.1 $(M+H)^+$.

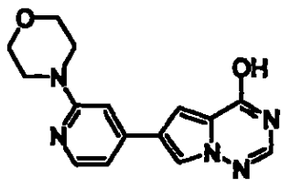
B) **N^1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-2-fluorophenyl)-N^3-(4-fluorophenyl)malonamide, trifluoroacetic acid**

To a solution of 4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-2-fluorobenzenamine (14 mg, 0.058 mmol) and 3-(4-fluorophenylamino)-3-oxopropanoic acid (12 mg, 0.06 mmol, Compound A of Example 25) in DMF (1 mL) were added DIEA (0.04 mL, 0.23 mmol) and TBTU (22 mg, 0.07 mmol). The reaction mixture was stirred at room temperature for 2 d and concentrated *in vacuo*. The residue was purified by preparative HPLC to give the title compound (18 mg, 74%). ^{1}H NMR (CD_3OD) δ 8.25 (d, 1H, J = 7.5 Hz), 8.19 (t, 1H, J = 7.5 Hz), 7.55 (m, 2H), 7.49 (d, 1H, J = 3.5 Hz), 7.25 (d, 1H, J = 8.0 Hz), 7.13 (d, 1H, J = 7.0 Hz), 7.01 (m, 2H), 6.84 (d, 1H, J = 7.0 Hz), 6.60 (d, 1H, J = 3.5 Hz), 3.60 (s, 2H); MS(ESI) *m/z* 423.1 $(M+H)^+$.

EXAMPLE 300

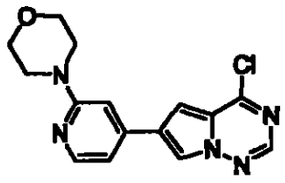


N^1-(3-Fluoro-4-(6-(2-morpholinopyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-N^3-(4-fluorophenyl)malonamide



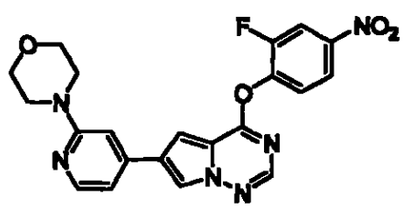
A) **6-(2-Morpholinopyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol**

To a solution of 6-bromopyrrolo[2,1-*f*][1,2,4]triazin-4-ol (100 mg, 0.47 mmol, prepared from methyl 4-bromo-1*H*-pyrrole-2-carboxylate: see, generally, Kitamura, C. and Yamashita, Y. *J. Chem. Soc. Perkin Trans.* 1, 1997, 1443, the disclosure of which is herein incorporated by reference, using a similar procedure outlined in the PCT Appl. WO 00/71129) and 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)morpholine (290 mg, 1.0 mmol) in DMF (2 mL) were added saturated aq. K_2CO_3 solution (2.0 mL) and $Pd(PPh_3)_4$ (60 mg, 0.05 mmol). The reaction mixture was purged with N_2 for 10 min and then was heated at 80 °C for 5 h and 100 °C for 12 h. After cooling, the mixture was diluted with H_2O and filtered to afford the crude product, which was triturated with DCM to provide the title compound (114 mg, 82% yield). MS(ESI) *m/z* 298.2 $(M+H)^+$.



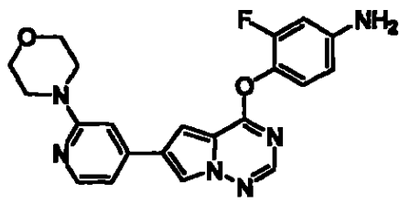
B) 4-Chloro-6-(2-morpholinopyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazine

To a suspension of 6-(2-morpholinopyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol (110 mg, 0.37 mmol) in toluene (100 mL) were added one drop of DMF and $POCl_3$ (30 mL). The flask was sealed and heated at 100 °C for 3 d. The reaction mixture was cooled to rt and concentrated *in vacuo*. The residue was then dissolved in DCM, neutralized with saturated aq. $NaHCO_3$ solution and the organic layer was separated. The aqueous layer was extracted with DCM (2 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford the desired product, which was used directly in the next step. MS(ESI) *m/z* 316.2/318.2 $(M+H)^+$.



C) **4-(2-Fluoro-4-nitrophenoxy)-6-(2-morpholinopyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazine**

To a suspension of the crude 4-chloro-6-(2-morpholinopyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazine in MeCN (5 mL) were added 2-fluoro-4-nitrophenol (59 mg, 0.37 mmol) and DABCO (45 mg, 0.4 mmol). The reaction mixture was stirred at room temperature for 2 h. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (ISCO RediSep® silica gel cartridge) to give the desired compound (54 mg, 33% yield in two steps). MS(ESI) *m/z* 437.2 $(M+H)^+$.



D) **3-Fluoro-4-(6-(2-morpholinopyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine**

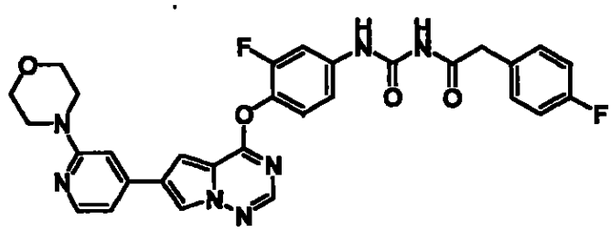
To a solution of 4-(2-fluoro-4-nitrophenoxy)-6-(2-morpholinopyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazine (54 mg, 0.12 mmol) in a mixture of THF (2.0 mL) and MeOH (2.0 mL) were added NH_4Cl (127 mg, 2.4 mmol) and Zn dust (78 mg, 1.2 mmol). The reaction mixture was stirred at room temperature for 3 h, filtered and concentrated *in vacuo*. The residue was purified by preparative HPLC to provide the desired product (40 mg, 82% yield). MS(ESI) *m/z* 407.19 $(M+H)^+$.

E) ***N*^{1}-(3-Fluoro-4-(6-(2-morpholinopyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-*N*^{3}-(4-fluorophenyl)malonamide**

To a solution of 3-fluoro-4-(6-(2-morpholinopyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine (15 mg, 0.037 mmol) and 3-(4-fluorophenylamino)-3-oxopropanoic acid (8 mg, 0.04 mmol, Compound A of Example 25) in DMF (1 mL) were added DIEA (0.1 mL, 0.57 mmol) and TBTU (13 mg, 0.04 mmol). The reaction mixture was stirred at room temperature overnight and then purified using preparative HPLC. The fraction containing the desired product

was collected and concentrated *in vacuo*. The residue was neutralized with 1 N NH_4OH and concentrated again. The solid that formed was filtered, washed with 1 N NH_4OH, dissolved in MeOH/H_2O, and lyophilized to give the title compound (8 mg, 37%). ^1H NMR (DMSO-d_6) δ 10.49 (s, 1H), 10.23 (s, 1H), 8.63 (s, 1H), 8.55 (s, 1H), 8.06 (s, 1H), 8.00 (d, 1H, J = 7.5 Hz), 7.70 (m, 1H), 7.50 (m, 2H), 7.30-7.45 (m, 3H), 7.04-7.17 (m, 3H), 6.85-6.92 (m, 2H), 3.36 (s, 4H), 3.44 (s, 6H); MS(ESI) *m/z* 586.2 $(M+H)^+$.

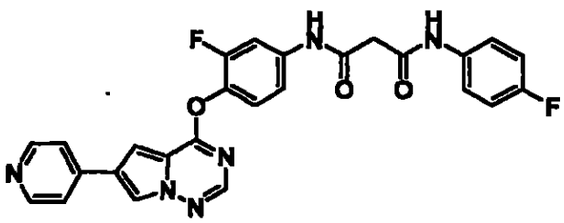
EXAMPLE 301



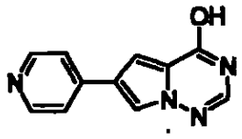
1-(3-Fluoro-4-(6-(2-morpholinopyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea

To a solution of 3-fluoro-4-(6-(2-morpholinopyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine (15 mg, 0.037 mmol, Compound D of Example 300) in THF (1 mL) were added DIEA (0.1 mL, 0.57 mmol) and 2-(4-fluorophenyl)acetyl isocyanate (0.347 M, 0.21 mL, 0.074 mmol, Compound C of Example 4). The reaction mixture was stirred at room temperature for 1 h and the precipitate was collected on a Buchner funnel and washed with toluene to give the title compound (10 mg, 46%). ^1H NMR (DMSO-d_6) δ 11.05 (s, 1H), 10.60 (s, 1H), 8.71 (s, 1H), 8.62 (s, 1H), 8.13 (s, 1H), 8.09 (d, 1H, J = 7.5 Hz), 7.80 (d, 1H, J = 8.0 Hz), 7.35-7.54 (m, 5H), 7.18 (t, 2H, J = 7.5 Hz), 6.91 (d, 1H, J = 8.0 Hz), 3.71-3.76 (m, 6H), 3.48-3.51 (m, 4H); MS(ESI) *m/z* 586.2 $(M+H)^+$.

EXAMPLE 302

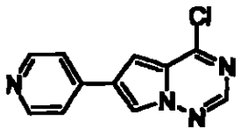


N^1-(3-Fluoro-4-(6-(pyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-N^3-(4-fluorophenyl)malonamide, trifluoroacetic acid salt



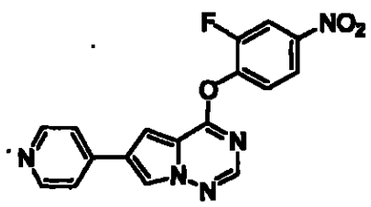
A) 6-(Pyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol

Following a similar procedure as described in Step A of Example 300, 6-(pyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol (100 mg, 0.47 mmol) was coupled with pyridin-4-ylboronic acid (172 mg, 1.40 mmol) to provide the title compound (72 mg, 72%). MS(ESI) *m/z* 213.2 $(M+H)^+$.



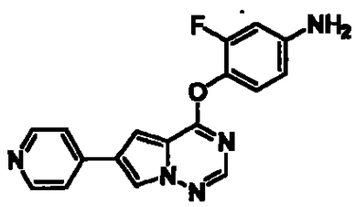
B) 4-Chloro-6-(pyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazine

Following a similar procedure as described in Step B of Example 300, 6-(pyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol (62 mg, 0.29 mmol) was converted to the title compound (30 mg, 45%). MS(ESI) *m/z* 231.1/233.1 $(M+H)^+$.



C) 4-(2-Fluoro-4-nitrophenoxy)-6-(pyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazine

Following a similar procedure as described in Step C of Example 300, 4-chloro-6-(pyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazine (37 mg, 0.16 mmol) was converted to the desired compound (50 mg, 89%). MS(ESI) *m/z* 352.2 $(M + H)^+$.



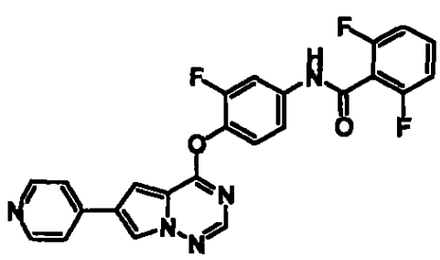
D) 3-Fluoro-4-(6-(pyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine

Following a similar procedure as described in Step D of example 300, 4-(2-fluoro-4-nitrophenoxy)-6-(pyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazine (50 mg, 0.14 mmol) was converted to the desired compound (50 mg, quantitative yield). MS(ESI) *m/z* 322.3 $(M+H)^+$.

E) N^1-(3-Fluoro-4-(6-(pyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-N^2-(4-fluorophenyl)malonamide, trifluoroacetic acid salt

Following a similar procedure as described in Step E of Example 300, 3-fluoro-4-(6-(pyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine (20 mg, 0.06 mmol) was converted to the title compound (8.5 mg, 28%). ^{1}H NMR (DMSO-d_6) δ 10.53 (s, 1H), 10.27 (s, 1H), 9.06 (s, 1H), 8.80 (d, 2H, J = 7.0 Hz), 8.30 (d, 2H, J = 6.0 Hz), 8.24 (s, 1H), 7.98 (s, 1H), 7.80 (d, 1H, J = 8.0 Hz), 7.60 (m, 2H), 7.35-7.45 (m, 2H), 7.16 (t, 2H, J = 8.0 Hz), 3.49 (s, 2H); MS(ESI) *m/z* 501.2 $(M + H)^+$.

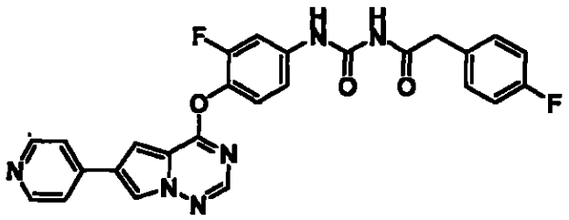
EXAMPLE 303



2,6-Difluoro-*N*-(3-fluoro-4-(6-(pyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)benzamide, trifluoroacetic acid salt

To a solution of 3-fluoro-4-(6-(pyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine (20 mg, 0.06 mmol, Compound D of Example 302) in DCM (1 mL) were added DIEA (0.1 mL, 0.57 mmol) and a solution of 2,6-difluorobenzoyl chloride in DCM (0.5 M, 0.14 mL, 0.07 mmol) at room temperature. The reaction mixture was stirred for 0.5 h and quenched with 1 N NH_4OH. The solution was then concentrated *in vacuo* and the residue was purified by preparative HPLC to give the title compound (15 mg, 54%). ^{1}H NMR (DMSO-d_6) δ 11.09 (s, 1H), 8.96 (s, 1H), 8.70 (m, 2H), 8.18 (s, 1H), 8.10 (br. s, 2H), 7.90 (s, 1H), 7.80 (d, 1H, J = 8.0 Hz), 7.45-7.55 (m, 3H), 7.23 (t, 2H, J = 8.0 Hz); MS(ESI) *m/z* 462.2 $(M+H)^+$.

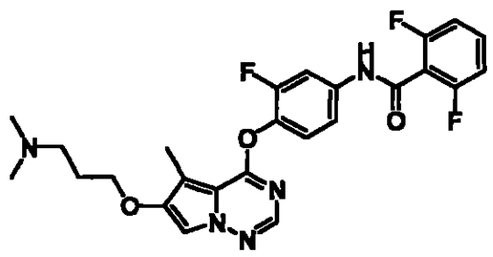
EXAMPLE 304



1-(3-Fluoro-4-(6-(pyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea, trifluoroacetic acid salt

Following a similar procedure as described in Example 301, 3-fluoro-4-(6-(pyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine (16 mg, 0.05 mmol, Compound D of Example 302) was converted to the title compound (6.5 mg, 26%). ^{1}H NMR (DMSO-d_6) δ 10.99 (s, 1H), 10.55 (s, 1H), 9.04 (s, 1H), 8.78 (d, 2H, J = 6.4 Hz), 8.31 (d, 2H, J = 6.4 Hz), 8.20 (s, 1H), 7.96 (s, 1H), 7.72 (m, 1H), 7.09-7.44 (m, 6H), 3.69 (s, 2H); MS(ESI) *m/z* 501.2 $(M+H)^+$.

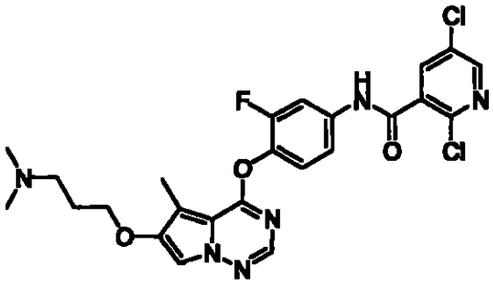
EXAMPLE 305



N-(4-(6-(3-(Dimethylamino)propoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)-2,6-difluorobenzamide, hydrochloride salt

Following a similar procedure as described in Example 134, 4-(6-(3-(dimethylamino)propoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorobenzenamine (36 mg, 0.1 mmol, Compound B of Example 32) was converted to the title compound (20 mg, 40%). ^{1}H NMR (DMSO-d_6) δ 11.17 (s, 1H), 10.40 (s, 1H), 8.00 (d, 2H, J = 4.0 Hz), 7.86 (d, 1H, J = 12.0 Hz), 7.65 (m, 1H), 7.51 (d, 2H, J = 5.0 Hz), 7.29 (t, 2H, J = 8.0 Hz), 4.15 (m, 2H), 3.24 (m, 2H), 2.80 (s, 6H), 2.40 (s, 3H), 2.18 (m, 2H); MS(ESI) *m/z* 500.3 $(M + H)^+$.

EXAMPLE 306

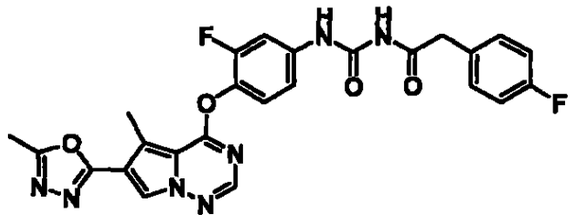


2,5-Dichloro-*N*-(4-(6-(3-(dimethylamino)propoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorophenyl)nicotinamide, hydrochloride salt

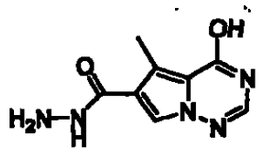
Following a similar procedure as described in Example 134, 4-(6-(3-(dimethylamino)propoxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)-3-fluorobenzenamine (36 mg, 0.1 mmol, Compound B of Example 32) was converted to the title compound (10 mg, 18%). ^{1}H NMR (DMSO-d_6) δ 11.12 (s, 1H), 10.50 (s, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 8.00 (s, 1H), 7.86 (d, 1H, J = 12 Hz), 7.52 (s, 1H), 7.38 (s, 1H), 7.25 (s, 1H), 7.12 (s, 1H), 4.12 (m, 2H), 3.26 (m, 2H), 2.78 (s, 6H), 2.41 (s, 3H), 2.20 (m, 2H); MS(ESI) *m/z* 533.2 $(M + H)^+$.

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EXAMPLE 307

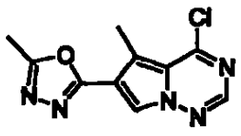


1-(3-Fluoro-4-(5-methyl-6-(5-methyl-1,3,4-oxadiazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea



A) 4-Hydroxy-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbohydrazide

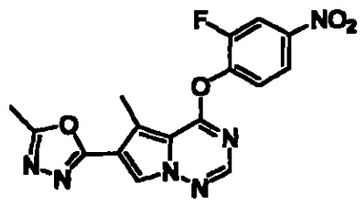
Ethyl 4-hydroxy-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate (467 mg, 2.11 mmol, preparation: See US Pat. No. 6,670,357) was dissolved in $N_2H_4 \cdot H_2O$/EtOH (4:1, 5 mL). The solution was heated at 88 °C for 4 h, cooled to rt, and concentrated *in vacuo* to give the title compound (450 mg, >95%). MS(ESI) *m/z* 208.1 $(M+H)^+$.



B) 4-Chloro-5-methyl-6-(5-methyl-1,3,4-oxadiazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine

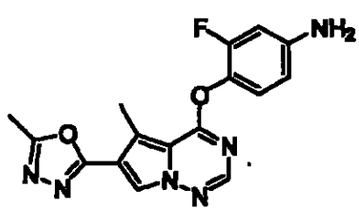
To a suspension of 4-hydroxy-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carbohydrazide (100 mg, 0.48 mmol) in $POCl_3$ (5 mL) was added AcOH (50 mg, 0.83 mmol). The reaction mixture was heated at 80 °C for 3 d, cooled to rt, and concentrated *in vacuo*. The resulting residue was dissolved in EtOAc and treated with sat. aq. $NaHCO_3$ solution, brine, and dried over $MgSO_4$. Filtration, followed by concentration, provide the title compound, which was used directly in next step. MS (ESI) *m/z* 250.1/252.1 $(M+H)^+$.

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C) **4-(2-Fluoro-4-nitrophenoxy)-5-methyl-6-(5-methyl-1,3,4-oxadiazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine**

Following a similar procedure as described in Step C of Example 300, 4-chloro-5-methyl-6-(5-methyl-1,3,4-oxadiazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine was converted to the title compound (50 mg, 28% in two steps). MS(ESI) *m/z* 371.2 $(M+H)^+$.



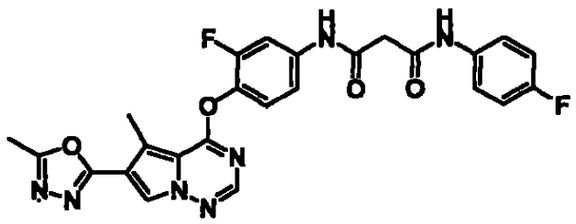
D) **3-Fluoro-4-(5-methyl-6-(5-methyl-1,3,4-oxadiazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine**

Following a similar procedure as described in Step D of Example 300, 4-(2-fluoro-4-nitrophenoxy)-5-methyl-6-(5-methyl-1,3,4-oxadiazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine (50 mg, 0.13 mmol) was converted to the title compound (45 mg, >95%). MS(ESI) *m/z* 341.2 $(M+H)^+$.

E) **1-(3-Fluoro-4-(5-methyl-6-(5-methyl-1,3,4-oxadiazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea**

Following a similar procedure as described for Example 301, 3-fluoro-4-(5-methyl-6-(5-methyl-1,3,4-oxadiazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine (20 mg, 0.06 mmol) was converted to the title compound (11 mg, 35%). ^{1}H NMR ($CDCl_3$) δ 10.80 (s, 1H), 8.69 (s, 1H), 8.18 (s, 1H), 7.96 (s, 1H), 7.70 (m, 1H), 7.10-7.30 (m, 6H), 3.75 (s, 2H), 2.92 (s, 3H), 2.64 (s, 3H); MS(ESI) *m/z* 520.2 $(M+H)^+$.

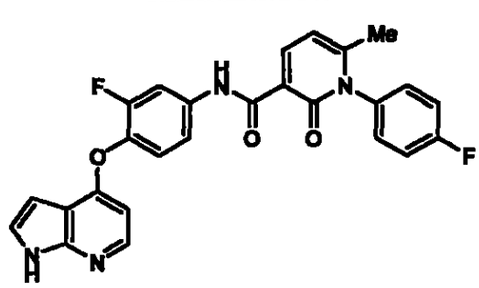
EXAMPLE 308



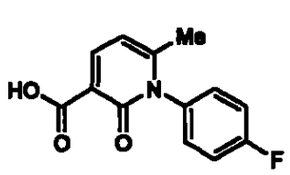
N[1]-(3-Fluoro-4-(5-methyl-6-(5-methyl-1,3,4-oxadiazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)phenyl)-*N*[3]-(4-fluorophenyl)malonamide

Following a similar procedure as described in Step E of Example 300, 3-fluoro-4-(5-methyl-6-(5-methyl-1,3,4-oxadiazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yloxy)benzenamine (20 mg, 0.06 mmol) was converted to the title compound (8 mg, 26%). ^{1}H NMR ($CDCl_3$) δ 9.26 (s, 1H), 8.47 (s, 1H), 8.21 (s, 1H), 7.96 (s, 1H), 7.80 (m, 1H), 7.50 (m, 2H), 7.10-7.30 (m, 4H), 3.60 (s, 2H), 2.93 (s, 3H), 2.69 (s, 3H); MS (ESI) *m/z* 520.1 $(M+H)^+$.

EXAMPLE 309



N-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide



A) 1-(4-Fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid

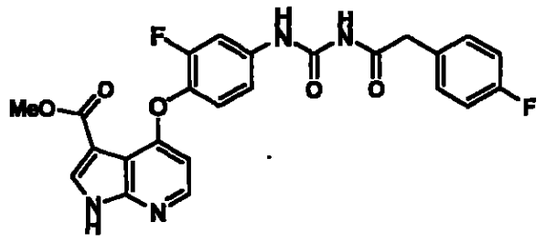
Prepared in a similar manner as Steps B and C of Example 294 using 2-hydroxy-6-methylnicotinic acid (Aldrich). ^{1}H NMR (DMSO-d_6) δ 8.41 (d, 1H, *J* =

6.5 Hz), 8.08 (s, 1H), 7.51-7.48 (m, 4H), 6.81 (d, 1H, *J* = 6.5 Hz), 2.10 (s, 3H); MS(ESI$^+$) *m/z* 248 $(M+H)^+$.

B) ***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide**

Prepared in a similar manner as Step D of Example 294 (21% yield). ^{1}H NMR (DMSO-d_6) δ 12.11 (s, 1H), 11.83 (s, 1H), 8.56 (d, 1H, *J* = 6.5 Hz), 8.13 (d, 1H, *J* = 5.5 Hz), 8.01 (dd, 1H, *J* = 10.4, 2.6 Hz), 7.56-7.50 (m, 7H), 6.78 (d, 1H, *J* = 6.5 Hz), 6.44 (d, 1H, *J* = 5.5 Hz), 6.30 (s, 1H), 2.14 (s, 3H); MS(ESI$^+$) *m/z* 473 $(M+H)^+$.

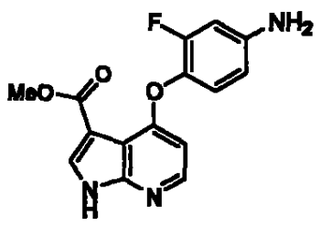
EXAMPLE 310



Methyl 4-(2-fluoro-4-(3-(2-(4-fluorophenyl)acetyl)ureido)phenoxy)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxylate

A) **Methyl 4-(2-fluoro-4-nitrophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxylate**

To a solution of 2,2,2-trichloro-1-(4-(2-fluoro-4-nitrophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)ethanone (490 mg, 1.17 mmol, See: Step A of Example 270) in a mixed solvent (10 mL of MeOH and 10 mL of THF) was added 1 N NaOH (10 mL, 10 mmol). The reaction mixture was stirred at room temperature for 3 h, and diluted with EtOAc (30 mL). The organic layer was washed with sat. aq. $NaHCO_3$, solution, dried and concentrated *in vacuo* to give the desired product (235 mg, 61%) as a light brown solid. MS(ESI$^+$) *m/z* 332.2 $(M+H)^+$.



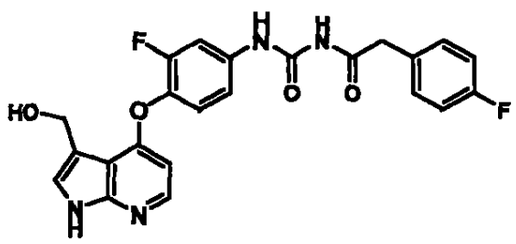
B) Methyl 4-(4-amino-2-fluorophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxylate

To a solution of methyl 4-(2-fluoro-4-nitrophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxylate (230 mg, 0.69 mmol) in a mixed solvent (10 mL of MeOH and 10 mL of THF) were added ammonium chloride (185 mg, 3.45 mmol) and zinc dust (226 mg, 3.45 mmol). The reaction mixture was stirred at room temperature overnight, diluted with EtOAc (50 ml), and filtered through a pad of Celite®. The filtrate was concentrated *in vacuo* to give the desired product (207 mg, 100%) as a yellow solid. MS(ESI$^+$) *m/z* 302.2 $(M+H)^+$.

C) Methyl 4-(2-fluoro-4-(3-(2-(4-fluorophenyl)acetyl)ureido)phenoxy)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxylate

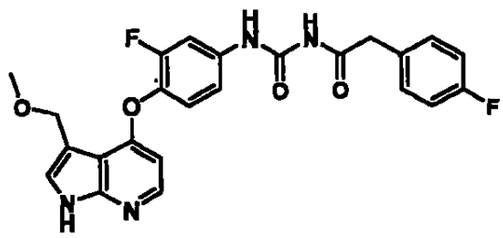
Prepared in a similar manner as Step C of Example 132 (61 mg, 36%). ^{1}H NMR (DMSO-d_6) δ 11.01 (s, 1H), 10.54 (s, 1H), 8.15 (s, 1H), 8.14 (d, 1H, J = 5.5 Hz), 7.74 (dd, 1H, J = 12.5, 2.2 Hz), 7.31-7.36 (m, 3H), 7.14-7.19 (m, 3H), 6.45 (d, 1H, J = 5.5 Hz), 3.73 (s, 2H), 3.69 (s, 3H). MS(ESI$^+$) *m/z* 481.1 $(M+H)^+$.

EXAMPLE 311



1-(3-Fluoro-4-(3-(hydroxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea

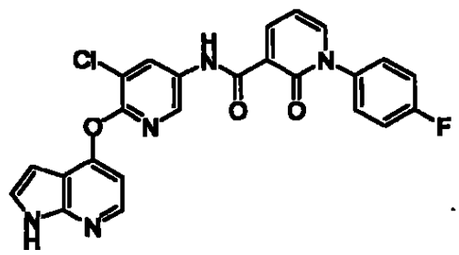
EXAMPLE 312



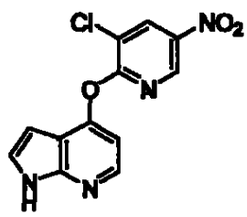
1-(3-Fluoro-4-(3-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea

To a solution of methyl 4-(2-fluoro-4-(3-(2-(4-fluorophenyl)acetyl)ureido) phenoxy)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxylate (19.2 mg, 0.04 mmol, Compound C of Example 310) in THF (1 mL) at 0 °C was added DIBAL-H (1.5 M soln in toluene, 133 µL, 0.2 mmol, Aldrich). The reaction mixture was stirred at 0 °C for 2 h, and quenched by adding 2 mL of methanol. The reaction mixture was concentrated *in vacuo* and purified by preparative HPLC. The desired fractions were combined, concentrated *in vacuo* and lyophilized to give a white solid. LC/MS indicated that the solid contained two compounds. The solid was purified again by flash column chromatography (ISCO RediSep® silica gel cartridge, eluting with 1-10% MeOH in dichloromethane) to afford Examples 311 and 312. For 1-(3-fluoro-4-(3-(hydroxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea (Example 311, 7.47 mg, 42%): ^{1}H NMR (DMSO-d_6) δ 11.47 (s, 1H), 10.94 (s, 1H), 10.49 (s, 1H), 7.92 (d, 1H, J = 5.5 Hz), 7.68 (dd, 1H, J = 13.2, 2.2 Hz), 7.31-7.19 (m, 5H), 7.09 (t, 2H, J = 8.8 Hz), 6.10 (d, 1H, J = 5.5 Hz), 4.68 (q, 1H, J = 5.5 Hz), 4.65 (d, 1H, J = 5.5 Hz),3.67 (s, 2H); MS(ESI$^+$) *m/z* 453.3 $(M+H)^+$. For 1-(3-Fluoro-4-(3-(methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea (Example 312): ^{1}H NMR (DMSO-d_6) δ 11.67 (s, 1H), 10.97 (s, 1H), 10.64 (s, 1H), 7.96 (d, 1H, J = 5.5 Hz), 7.68 (d, 1H, J = 12.5), 7.34-7.28 (m, 5H), 7.23 (t, 1H, J = 8.8 Hz), 7.01 (t, 2H, J = 8.8 Hz), 6.16 (d, 1H, J = 5.5 Hz), 4.54 (s. 2H), 3.70 (s, 2H), 3.18 (s, 3H); MS(ESI$^+$) *m/z* 467.2 $(M+H)^+$.

EXAMPLE 313

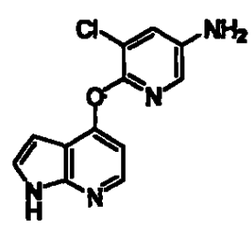


N-(6-(1H-Pyrrolo[2,3-b]pyridin-4-yloxy)-5-chloropyridin-3-yl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, trifluoroacetic acid salt



A) 4-(3-Chloro-5-nitropyridin-2-yloxy)-1H-pyrrolo[2,3-b]pyridine

To a solution of 1*H*-pyrrolo[2,3-*b*]pyridin-4-ol (210 mg, 1.56 mmol, see: Thibault, C. et al. *Org. Lett.* **2003**, *5*, 5023) in 3 mL of MeCN was added K_2CO_3 (240 mg, 1.74 mmol). The suspension was stirred for 10 min and treated with 2,3-dichloro-5-nitropyridine (270 mg, 1.40 mmol, see: Koch, V. and Schnatterer, S. *Synthesis*, **1990**, 499). The reaction mixture was stirred for 12 h and quenched with 20 mL of H_2O. The solution was extracted with EtOAc and the organic layer was washed with brine, and dried over $MgSO_4$. After filtration and concentration *in vacuo*, the residue was purified by flash column chromatography (ISCO RediSep® silica gel cartridge) to give the title compound (220 mg, 54%). MS (ESI) *m/z* 291.1 $(M + H)^+$.



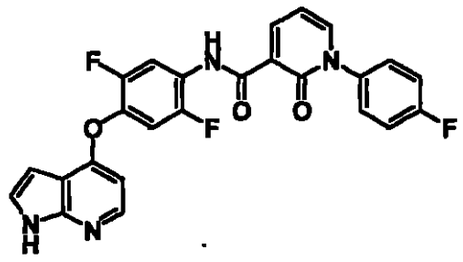
B) 6-(1H-Pyrrolo[2,3-b]pyridin-4-yloxy)-5-chloropyridin-3-amine

Following a similar procedure as described in Step B of Example 132, 4-(3-chloro-5-nitropyridin-2-yloxy)-1*H*-pyrrolo[2,3-*b*]pyridine (140 mg, 0.48 mmol) was reduced to the title compound (90 mg, 72%). MS(ESI) *m/z* 261.1 $(M+H)^+$.

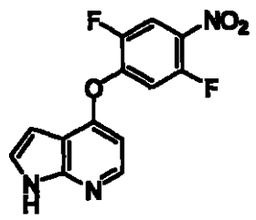
C) ***N*-(6-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-5-chloropyridin-3-yl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, trifluoroacetic acid salt**

Following a similar procedure as described in Step C of Example 242, 6-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-5-chloropyridin-3-amine, dihydrochloride (14 mg, 0.042 mmol) was converted to the title compound (5.0 mg, 20%). ^{1}H NMR (DMSO-d_6) δ 12.08 (s, 1H), 11.86 (s, 1H), 8.67 (d, 1H, J = 2.0 Hz), 8.57 (dd, 1H, J = 7.0, 2.0 Hz), 8.41 (d, 1H, J = 2.0 Hz), 8.18 (d, 1H, J = 5.5 Hz), 8.14 (dd, 1H, J = 6.5, 2.0 Hz), 7.60 (dd, 2H, J = 9.0, 5.0 Hz), 7.38-7.43 (m, 3H), 6.76 (d, 1H, J = 5.5 Hz), 6.73 (t, 1H, J = 7.0 Hz), 6.08 (m, 1H); MS(ESI) *m/z* 476.2 $(M+H)^+$.

EXAMPLE 314

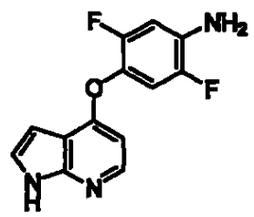


***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-2,5-difluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, trifluoroacetic acid salt**



A) **4-(2,5-Difluoro-4-nitrophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridine**

Following a similar procedure as described in Step A of Example 313 and using 1,2,4-trifluoro-5-nitrobenzene, 1*H*-pyrrolo[2,3-*b*]pyridin-4-ol (268 mg, 2.0 mmol) was converted to the title compound (230 mg, 40%). MS(ESI) *m/z* 292.2 $(M+H)^+$.



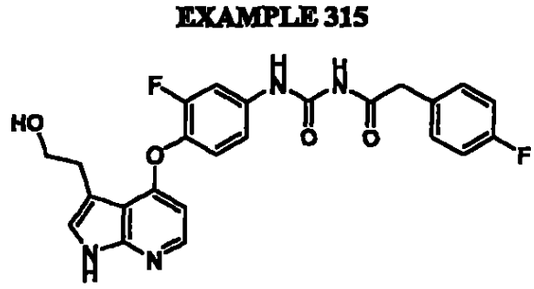
B) **4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-2,5-difluorobenzenamine**

Following a similar procedure as described in Step B of Example 132, 4-(2,5-difluoro-4-nitrophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridine (230 mg, 0.79 mmol) was converted to the title compound (34 mg, 17%). MS(ESI) *m/z* 262.2 $(M+H)^+$.

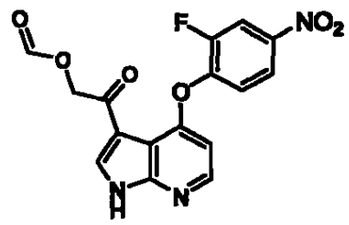
C) ***N*-(4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-2,5-difluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, trifluoroacetic acid**

Following a similar procedure as described in Step C of Example 242, 4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-2,5-difluorobenzenamine, dihydrochloride (14 mg, 0.042 mmol) was converted to the title compound (4.5 mg, 18%). ^{1}H NMR (DMSO-d_6) δ 12.42 (s, 1H), 11.86 (s, 1H), 8.61 (dd, 1H, J = 7.0, 2.0 Hz), 8.55 (dd, 1H, J = 12.5, 7.0 Hz), 8.15 (dd, 1H, J = 6.5, 2.0 Hz), 8.10 (d, 1H, J = 6.5 Hz), 7.57-7.62 (m, 3H), 7.40-7.44 (m, 3H), 6.75 (t, 1H, J = 7.0 Hz), 6.47 (d, 1H, J = 5.5 Hz), 6.29 (m, 1H); MS(ESI) *m/z* 477.2 $(M+H)^+$.

EXAMPLE 315

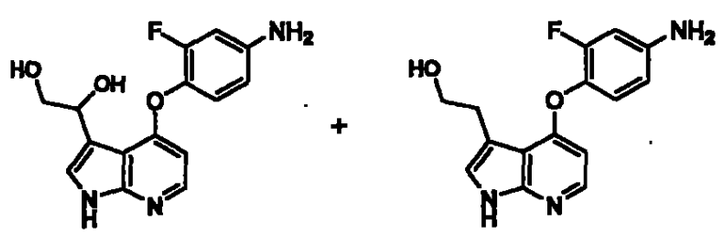


1-(3-Fluoro-4-(3-(2-hydroxyethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea



A) **2-(4-(2-Fluoro-4-nitrophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2-oxoethyl formate**

To a solution of 2-bromo-1-(4-(2-fluoro-4-nitrophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)ethanone (100 mg, 0.25 mmol, Compound A of Example 253) in 1 mL of DMF was added sodium formate (52 mg, 0.75 mmol, Aldrich). The reaction mixture was stirred at room temperature for 4 h, and diluted with sat. aq. K_2HPO_4 (2 mL). The precipitate that formed was collected by filtration, washed with cold H_2O (2 mL) and ether (5 mL), and dried under vacuum to afford the desired product (81 mg, 90%) as a light brown solid. MS(ESI$^+$) *m/z* 360.16 $(M + H)^+$.



B) **1-(4-(4-Amino-2-fluorophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)ethane-1,2-diol and 2-(4-(4-Amino-2-fluorophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)ethanol**

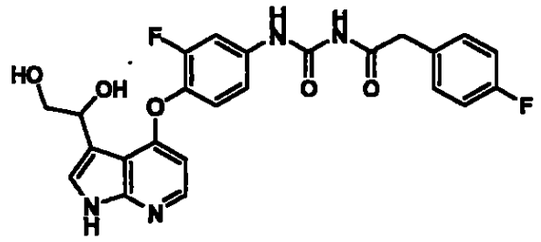
To a suspension of anhydrous aluminum hydride (266 mg, 2.0 mmol, Alfa Aesar) in 5 mL of 1,2 dimethoxyethane at 0 °C was added lithium aluminum hydride (1 M soln. in THF, 1.0 mL, 1.0 mmol). A solution of 2-(4-(2-fluoro-4-nitrophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2-oxoethyl formate (72 mg, 0.2 mmol) in 5 mL of 1,2-dimethoxyethane was added dropwise. The reaction mixture was stirred at rt for 2 h and quenched by the addition of 5 mL of cold water. The mixture was extracted with EtOAc (3 x 30 mL) and the combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo* and purified by flash column chromatography (ISCO RediSep®

silica gel cartridge, eluting with 2-10% MeOH in dichloromethane) to give 1-(4-(4-amino-2-fluorophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)ethane-1,2-diol (27 mg, 45%): MS(ESI$^+$) *m/z* 304.3(M + H)$^+$ and 2-(4-(4-amino-2-fluorophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)ethanol (10 mg, 18%): MS(ESI$^+$) *m/z* 288.3 (M + H)$^+$.

C) 1-(3-Fluoro-4-(3-(2-hydroxyethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea

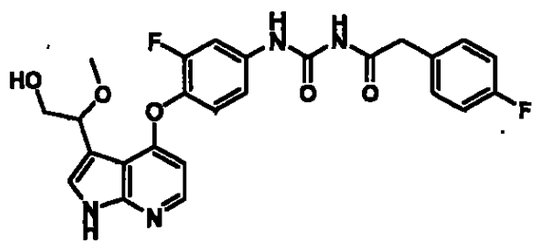
Prepared from 2-(4-(4-amino-2-fluorophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)ethanol using a similar procedure as described for Example 264 (4.5 mg, 28%). ^{1}H NMR (CD_3OD) δ 10.74 (s, 1H), 8.06 (d, 1H, *J* = 5.5 Hz), 7.74 (d, 1H, *J* = 12.1 Hz), 7.29-7.25 (m, 4H), 7.00-6.96 (m, 3H), 6.51 (d, 1H, *J* = 5.5 Hz), 3.80 (t, 2H, *J* = 6.6 Hz), 3.62 (s, 2H), 3.06 (t, 2H, *J* = 6.6 Hz); MS(ESI$^+$) *m/z* 467.3 (M + H)$^+$.

EXAMPLE 316



1-(4-(3-(1,2-Dihydroxyethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea

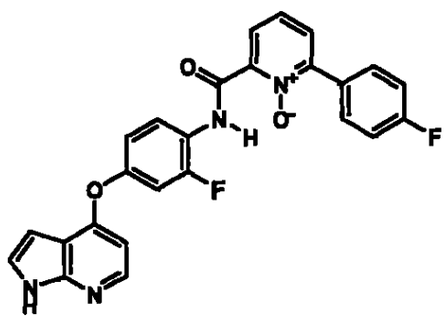
EXAMPLE 317



1-(3-Fluoro-4-(3-(2-hydroxy-1-methoxyethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea

Examples 316 and 317 were prepared from 1-(4-(4-amino-2-fluorophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)ethane-1,2-diol (see: Step B of Example 315) using a similar procedure as described for Example 264. The reaction mixture was concentrated *in vacuo* and purified by preparative HPLC. The desired fractions were combined, concentrated *in vacuo* and lyophilized to give a white solid. LC/MS indicated that the solid contained 1-(4-(3-(1,2-dihydroxyethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea and 1-(3-fluoro-4-(3-(2-hydroxy-1-methoxyethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea. The solid was purified again by flash column chromatography (ISCO RediSep® silica gel cartridge, eluting with 1-10% MeOH in dichloromethane) to afford two products: For 1-(4-(3-(1,2-dihydroxyethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea (6.3 mg, 16%); ^{1}H NMR (DMSO-d_6) δ 11.57 (s, 1H), 11.03 (s, 1H), 10.59 (s, 1H), 7.99 (d, 1H, J = 5.5 Hz), 7.77 (dd, 1H, J = 12.6, 2.2 Hz), 7.41-7.32 (m, 4H), 7.28 (d, 1H, J = 2.2 Hz), 7.18 (t, 1H, J = 8.8 Hz), 7.01 (t, 2H, J = 8.8 Hz), 6.15 (d, 1H, J = 5.5 Hz), 5.05 (m, 1H), 4.91 (d, 1H, J = 4.4 Hz), 4.60 (t, 1H, J = 5.8 Hz), 3.79-3.75 (m, 1H), 3.75 (s, 2H), 3.47-3.44 (m, 1H); MS(ESI$^+$) *m/z* 483.3 $(M+H)^+$. For 1-(3-fluoro-4-(3-(2-hydroxy-1-methoxyethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea (3.2 mg, 8%); ^{1}H NMR (CD_3OD) δ 8.05 (d, 1H, J = 5.5 Hz), 7.71 (d, 1H, J = 12.1 Hz), 7.37 (s, 1H), 7.28-6.25 (m, 4H), 6.98 (t, 1H, J = 8.2 Hz), 6.45 (d, 1H, J = 5.5 Hz), 3.81 (m, 1H), 3.73-3.71 (m, 2H), 3.63 (s, 2H), 3.34 (s, 3H); MS(ESI$^+$) *m/z* 497.2 $(M+H)^+$.

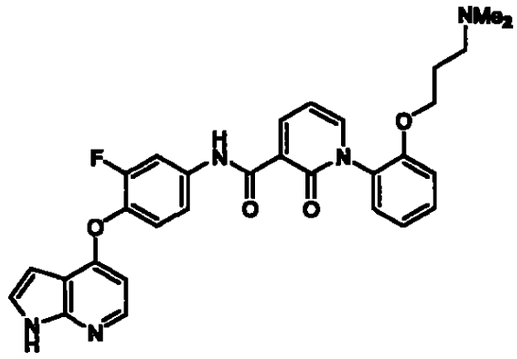
EXAMPLE 318



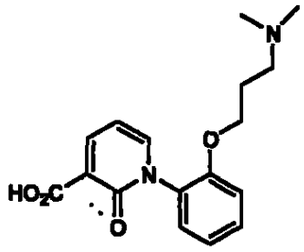
6-(4-Fluoro-phenyl)-1-oxy-pyridine-2-carboxylic acid [2-fluoro-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-phenyl]-amide

Prepared in a similar manner as Example 241. HPLC t_R = 3.328 min (YMC S5 ODS 4.6 x 50 mm, 10-90% aqueous methanol containing 0.2% H_3PO_4, 4 min gradient, monitored at 220 nm); MS(ESI$^+$) *m/z* 459.2 $(M+H)^+$.

EXAMPLE 319



***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-1-(2-(3-(dimethylamino)propoxy)phenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, hydrochloride salt**



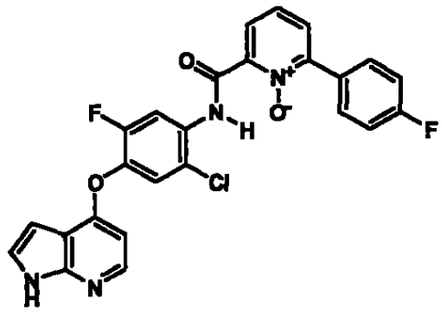
A) **1-(2-(3-(Dimethylamino)propoxy)phenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid**

Prepared in a similar manner as Steps A and B of Example 242. ^{1}H NMR (DMSO-d_6) δ 10.53 (br m, 1H), 8.51-8.53 (m, 1H), 8.18-8.20 (m, 1H), 7.48-7.51 (m, 2H), 7.30 (d, 1H, *J* = 7.96 Hz), 7.13-7.17 (m, 1H), 6.82 (t, 1H, *J* = 6.95 Hz), 4.11-4.18 (m, 2H), 2.66-2.68 (m, 2H), 2.67 (s, 6H), 1.98-2.05(m, 2H); HRMS(ESI), calculated: 317.1501, found: 317.1490.

B) ***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-3-fluorophenyl)-1-(2-(3-(dimethylamino)propoxy)phenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, hydrochloride salt**

Prepared in a similar manner as Step C of Example 242. ^{1}H NMR (CD_3OD) δ 8.62-8.65 (m, 1H), 8.23 (d, 1H, J = 6.90 Hz), 7.98-8.01 (m, 1H), 7.83-7.85 (m, 1H), 7.39-7.50 (m, 2H), 7.31-7.49 (m, 3H), 7.20 (d, 1H, J = 7.93), 7.10-7.13 (m, 1H), 6.80 (d, 1H, J = 6.72 Hz), 6.69 (t, 1H, J = 6.75 Hz), 6.59-6.60 (m, 1H), 4.12 (t, 2H, J = 5.61 Hz), 3.02-3.06 (m, 2H), 2.70 (s, 6H), 2.03-2.04 (m, 2H); HRMS(ESI), calculated: 542.2204, found: 542.2194.

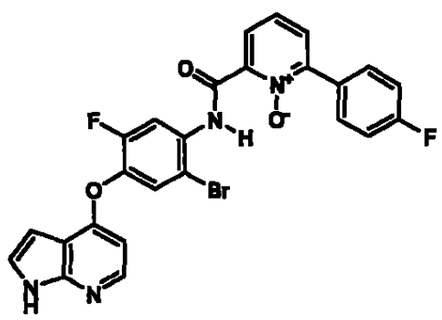
EXAMPLE 320



6-(4-Fluoro-phenyl)-1-oxy-pyridine-2-carboxylic acid [2-chloro-5-fluoro-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-phenyl]-amide

Prepared in a similar manner as Example 241. HPLC t_R = 3.293 min (Chromolith SpeedROD 4.6 x 50 mm, 10-90% aqueous methanol containing 0.1% TFA, 4 min gradient, monitored at 220 nm); MS(ESI$^+$) *m/z* 493 $(M + H)^+$.

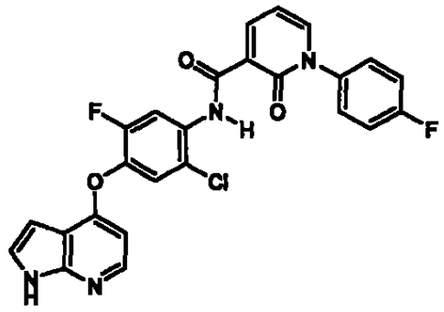
EXAMPLE 321



6-(4-Fluoro-phenyl)-1-oxy-pyridine-2-carboxylic acid [2-bromo-5-fluoro-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-phenyl]-amide

Prepared in a similar manner as Example 241. HPLC t_R = 3.371 min (Chromolith SpeedROD 4.6 x 50 mm, 10-90% aqueous methanol containing 0.1% TFA, 4 min gradient, monitored at 220 nm); MS(ESI$^+$) *m/z* 537 $(M + H)^+$.

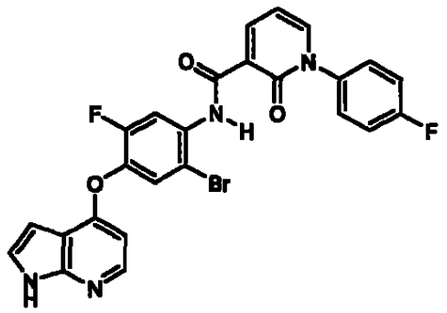
EXAMPLE 322



***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-2-chloro-5-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide**

Prepared in a similar manner as Step C of Example 242. HPLC t_R = 3.070 min (Chromolith SpeedROD 4.6 x 50 mm, 10-90% aqueous methanol containing 0.1% TFA, 4 min gradient, monitored at 220 nm); MS(ESI$^+$) *m/z* 493 $(M + H)^+$.

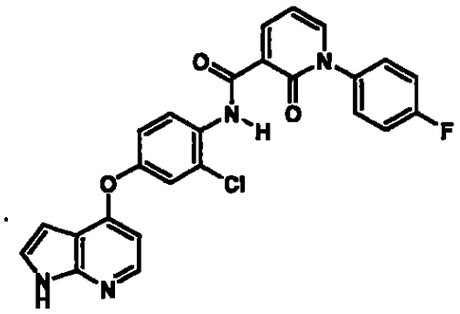
EXAMPLE 323



***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-2-bromo-5-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide**

Prepared in a similar manner as Step C of Example 242. HPLC t_R = 3.115 min (Chromolith SpeedROD 4.6 x 50 mm, 10-90% aqueous methanol containing 0.1% TFA, 4 min gradient, monitored at 220 nm); MS(ESI$^+$) *m/z* 538 $(M+H)^+$.

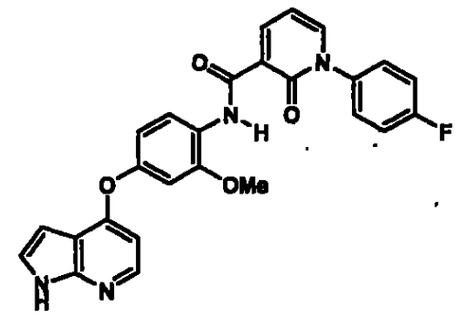
EXAMPLE 324



***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-2-chlorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide**

Prepared in a similar manner as Step C of Example 242. HPLC t_R = 2.946 min (Chromolith SpeedROD 4.6 x 50 mm, 10-90% aqueous methanol containing 0.1% TFA, 4 min gradient, monitored at 220 nm); MS(ESI$^+$) *m/z* 475 $(M+H)^+$.

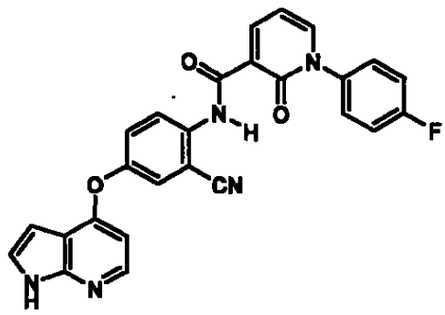
EXAMPLE 325



***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-2-methoxyphenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide**

Prepared in a similar manner as Step C of Example 242. HPLC t_R = 2.795 min (Chromolith SpeedROD 4.6 x 50 mm, 10-90% aqueous methanol containing 0.1% TFA, 4 min gradient, monitored at 220 nm); MS(ESI$^+$) *m/z* 471 $(M+H)^+$.

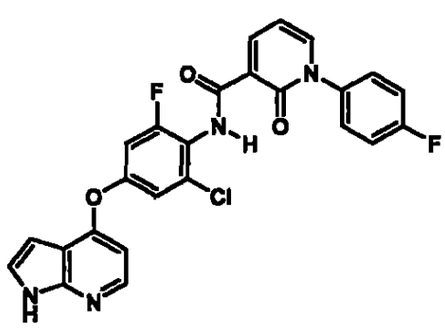
EXAMPLE 326



***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-2-cyanophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide**

Prepared in a similar manner as Step C of Example 242. HPLC t_R = 2.618 min (Chromolith SpeedROD 4.6 x 50 mm, 10-90% aqueous methanol containing 0.1% TFA, 4 min gradient, monitored at 220 nm); MS(ESI$^+$) *m/z* 466 $(M + H)^+$.

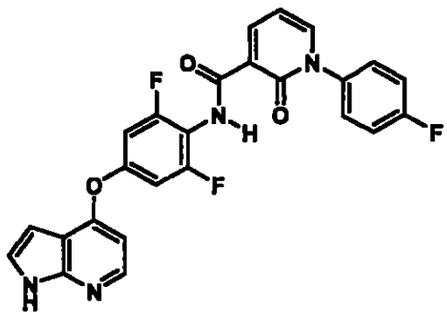
EXAMPLE 327



***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-2-chloro-6-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide**

Prepared in a similar manner as Step C of Example 242. HPLC t_R = 2.805 min (Chromolith SpeedROD 4.6 x 50 mm, 10-90% aqueous methanol containing 0.1% TFA, 4 min gradient, monitored at 220 nm); MS(ESI$^+$) *m/z* 493 $(M + H)^+$.

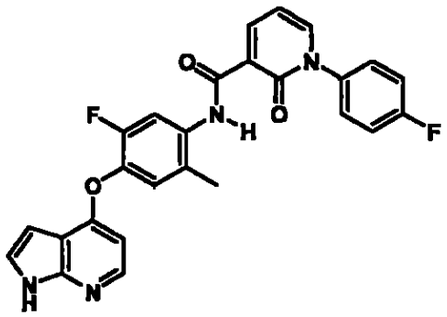
EXAMPLE 328



***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-2,6-difluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide**

Prepared in a similar manner as Step C of Example 242. HPLC t_R = 2.653 min (Chromolith SpeedROD 4.6 x 50 mm, 10-90% aqueous methanol containing 0.1% TFA, 4 min gradient, monitored at 220 nm); MS(ESI$^+$) *m/z* 477 $(M+H)^+$.

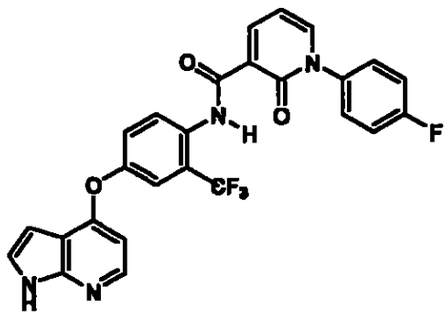
EXAMPLE 329



***N*-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yloxy)-2-methyl-4-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide**

Prepared in a similar manner as Step C of Example 242. HPLC t_R = 3.010 min (Chromolith SpeedROD 4.6 x 50 mm, 10-90% aqueous methanol containing 0.1% TFA, 4 min gradient, monitored at 220 nm); MS(ESI$^+$) *m/z* 473 $(M+H)^+$.

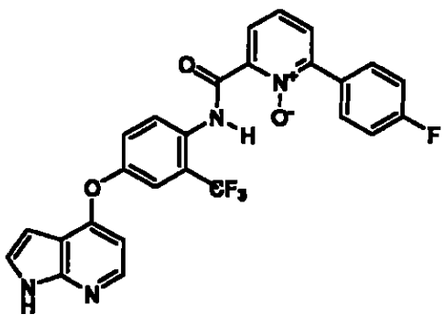
EXAMPLE 330



N-(4-(1H-Pyrrolo[2,3-b]pyridin-4-yloxy)-2-trifluoromethyl-phenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide

Prepared in a similar manner as Step C of Example 242. HPLC t_R = 2.943 min (Chromolith SpeedROD 4.6 x 50 mm, 10-90% aqueous methanol containing 0.1% TFA, 4 min gradient, monitored at 220 nm); MS(ESI$^+$) *m/z* 509 $(M+H)^+$.

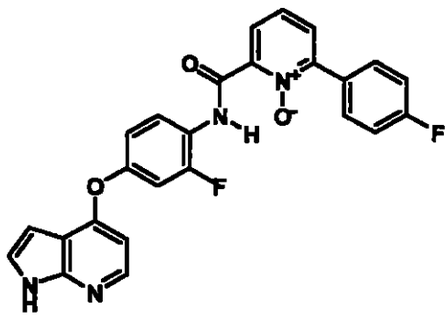
EXAMPLE 331



6-(4-Fluoro-phenyl)-1-oxy-pyridine-2-carboxylic acid [2-trifluoromethyl-4-(1H-pyrrolo[2,3-b]pyridin-4-yloxy)-phenyl]-amide

Prepared in a similar manner as Example 241. HPLC t_R = 3.205 min (Chromolith SpeedROD 4.6 x 50 mm, 10-90% aqueous methanol containing 0.1% TFA, 4 min gradient, monitored at 220 nm); MS(ESI$^+$) *m/z* 509 $(M+H)^+$.

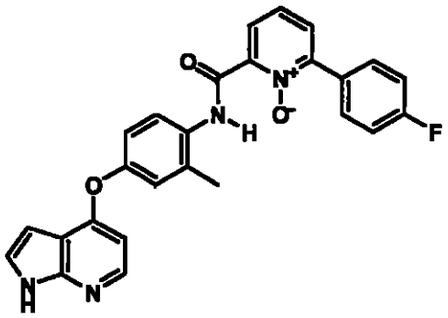
EXAMPLE 332



6-(4-Fluoro-phenyl)-1-oxy-pyridine-2-carboxylic acid [2-fluoro-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-phenyl]-amide

Prepared in a similar manner as Example 241. HPLC t_R = 1.103 min (YMC S5 ODS 4.6 x 50 mm, 10-90% aqueous methanol containing 0.1% H_3PO_4, 4 min gradient, monitored at 220 nm); MS(ESI$^+$) *m/z* 459 $(M + H)^+$.

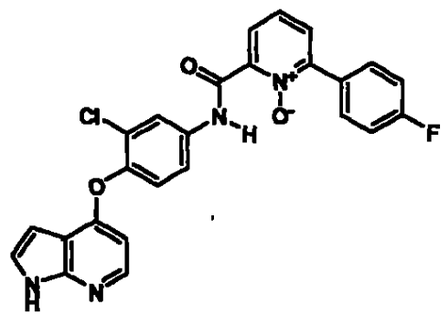
EXAMPLE 333



6-(4-Fluoro-phenyl)-1-oxy-pyridine-2-carboxylic acid [2-methyl-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-phenyl]-amide

Prepared in a similar manner as Example 241. HPLC t_R = 3.120 min (Chromolith SpeedROD 4.6 x 50 mm, 10-90% aqueous methanol containing 0.1% TFA, 4 min gradient, monitored at 220 nm); MS(ESI$^+$) *m/z* 455 $(M + H)^+$.

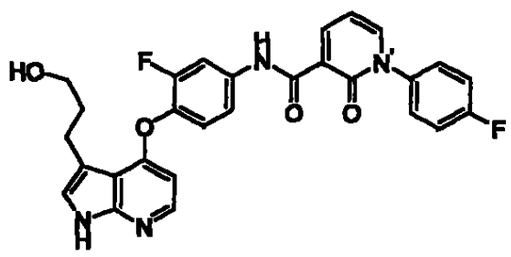
EXAMPLE 334



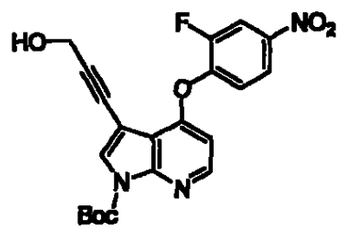
6-(4-Fluoro-phenyl)-1-oxy-pyridine-2-carboxylic acid [5-chloro-4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)-phenyl]-amide

Prepared in a similar manner as Example 241. HPLC t_R = 3.200 min (Chromolith SpeedROD 4.6 x 50 mm, 10-90% aqueous methanol containing 0.1% TFA, 4 min gradient, monitored at 220 nm); MS(ESI$^+$) *m/z* 475 $(M + H)^+$.

EXAMPLE 335



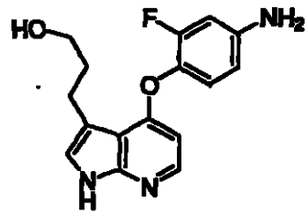
***N*-(3-Fluoro-4-(3-(3-hydroxypropyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide**



A) ***tert*-Butyl 4-(2-fluoro-4-nitrophenoxy)-3-(3-hydroxyprop-1-ynyl)-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate**

A stream of Ar was bubbled through a mixture of *tert*-butyl 4-(2-fluoro-4-nitrophenoxy)-3-iodo-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate (400 mg, 0.8 mmol,

Compound B of Example 283), propargyl alcohol (90 mg, 1.6 mmol), $Pd(dppf)_2Cl_2:CH_2Cl_2$ (66 mg, 0.08 mmol), and CuI (40 mg) in triethylamine (0.8 mL) and THF (6 mL) for 5 min. The reaction mixture was sealed in a tube and heated at 75 °C for 1h. The mixture was diluted with CH_2Cl_2 and washed with brine. The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, 30% EtOAc/ CH_2Cl_2) to afford the desired product (220 mg, 64% yield) as a yellow solid. LC/MS (ESI^+) *m/z* 428 $(M+H)^+$.



B) **3-(4-(4-Amino-2-fluorophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)propan-1-ol**

A mixture of *tert*-butyl 4-(2-fluoro-4-nitrophenoxy)-3-(3-hydroxyprop-1-ynyl)-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate (50 mg, 0.15 mmol) and 10% Pd/C (containing 50% H_2O, 120 mg) in THF (10 mL) and MeOH (2 mL) was hydrogenated at 1 atm for 5 h. The mixture was diluted with MeOH and filtered through a pad of Celite®. The crude mixture was purified by preparative HPLC to afford the desired product (6 mg, 13% yield) as a white solid. LC/MS (ESI^+) *m/z* 302 $(M+H)^+$.

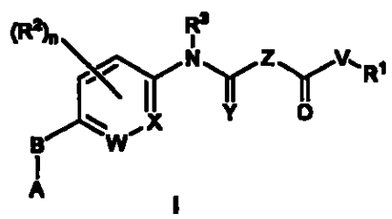
C) ***N*-(3-Fluoro-4-(3-(3-hydroxypropyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy)phenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide**

To a stirred mixture of 3-(4-(4-amino-2-fluorophenoxy)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)propan-1-ol (5 mg, 0.0166 mmol), 1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (5.8 mg, 0.025 mmol, Compound B of Example 242), and HATU (Perseptive Biosystems, 10 mg, 0.025 mmol) in DMF (0.5 mL), was added DIPEA (0.1 mL). The reaction mixture was stirred at rt for 2 h and concentrated *in vacuo*. The residue was purified by preparative HPLC to give the title

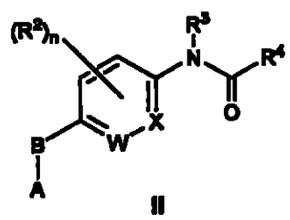
compound (6 mg, HCl salt, 66% yield) as a white solid. ^{1}H NMR (CD_3OD) δ 8.71 (dd, 1H, J = 7.2, 2.0 Hz), 8.22 (d, 1H, J = 6.8 Hz), 8.10 (dd, 1H, J = 12.4, 2.0 Hz), 8.00 (dd, 1H, J = 6.4, 2.0 Hz), 7.25-7.60 (m, 7H), 7.70-7.80 (m, 2H), 3.64 (t, 2H, J = 6.4 Hz), 3.05 (t, 2H, J = 7.2 Hz), 2.00 (m, 2H); LC/MS (ESI^+) *m/z* 517 $(M + H)^+$.

WE CLAIM:

1. A compound having the formula I or II



I



II

including pharmaceutically acceptable salts thereof, wherein:

R^1 is H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, arylalkyl, substituted arylalkyl, aryl, substituted aryl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, heteroaryl, substituted heteroaryl, heterocyclo, substituted heterocyclo, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, or substituted heterocycloalkyl;

each R^2 is independently, H, halogen, cyano, NO_2, OR^5, NR^6R^7, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclo, substituted heterocyclo, aryalkyl, substituted arylalkyl, heterocycloalkyl, or substituted heterocycloalkyl;

B is O, NR^8, S, SO, SO_2, CR^9R^{10};

V is NR^{11} or $-(CR^{47}R^{48})_p-$;

W or X are independently C or N;

Y is O, S, or NR^{12};

Z is $-CR^{13}R^{14}-$, $-(CR^{13}R^{14})_mNR^{15}-$;

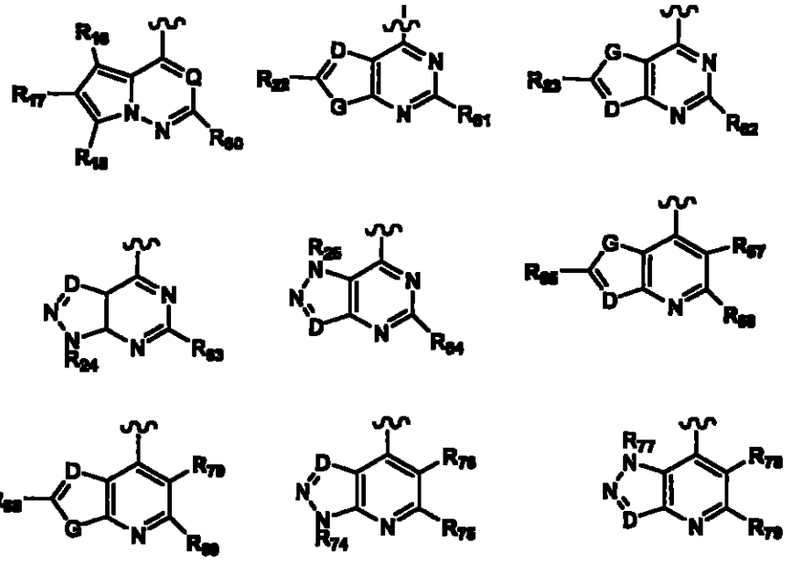
l is 0 to 4;

m is 0 to 2;

n is 0 to 4;

p is 0 to 4, provided that if p is 0, R^1 is not phenyl;

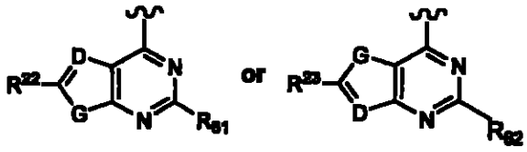
A is:



Q is CR^{19};

D is CR^{20} or N;

G is S, O or NR^{21}, provided that if A is



and G is S, R^4 is not a substituted phenyl group;

R^3, R^5, R^6, R^7, R^8, R^{11} and R^{15} are each independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, or substituted heterocycloalkyl;

R^4 is aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, or substituted heterocycloalkyl;

R^9 and R^{10} are independently H, halogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, or substituted heterocycloalkyl;

R^{12} is H, alkyl, substituted alkyl, CN, NO_2 or SO_2NH_2;

R^{13}, R^{14}, R^{15}, R^{47} and R^{48} are independently H, halogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclo, substituted heterocyclo or taken together to form a carbocyclic or heterocyclic ring of 3 to 8 atoms;

R^{16}, R^{17}, R^{18}, R^{20}, R^{22}, R^{23}, R^{60}, R^{61}, R^{62}, R^{63}, R^{64}, R^{65}, R^{66}, R^{67}, R^{68}, R^{69}, R^{70}, R^{75}, R^{76}, R^{78}, and R^{79}, are independently H, halogen, NO_2, cyano, OR^{26}, $NR^{27}R^{28}$, CO_2R^{29}, $C(O)NR^{30}R^{31}$, SO_2R^{32}, $SO_2NR^{33}R^{34}$, $NR^{35}SO_2R^{36}$, $NR^{37}C(O)R^{38}$, $NR^{39}CO_2R^{40}$, $-CO(CH_2)_1R^{41}$; $-CONH(CH_2)_1R^{42}$, alkylaminoalkyl, alkylaminoalkynyl, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_7 cycloalkyl, substituted C_3 to C_7 cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, hydroxyalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, arylalkyl, substituted arylalkyl, heterocycloalkyl, or substituted heterocycloalkyl;

R^{19} is H or cyano;

$R^{21}$and R^{24} are independently H, C_1 to C_6 alkyl or substituted C_1 to C_6 alkyl;

R^{25}, R^{74} and R^{77} are independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heterocycloalkyl, or substituted heterocycloalkyl

R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, R^{33}, R^{34}, R^{35}, R^{36}, R^{37}, R^{38}, R^{39}, R^{40}, R^{41}, and R^{42} are independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heterocycloalkyl, or substituted heterocycloalkyl.

2. The compound according to claim 1 wherein R^1 is an optionally substituted $C_1$to C_6 alkyl, alkenyl, alkynyl, optionally substituted C_3 to C_7 cycloalkyl, C_3 to C_7 heterocycloalkyl, optionally substituted phenyl, optionally substituted biphenyl, or a C_5 to C_{11} optionally substituted monocyclic or bicyclic heteroaryl.

3. The compound according to claim 2 wherein R^1 is selected from the group consisting of phenyl, optionally substituted with Cl, F, OCH_3, alkyl, alkenyl,

alkynyl, hydroxy, cyano, amido, phenoxy, CH_2CN, benzyl, $NHCO_2CH_3$; biphenyl, pyridyl, azepanyl, pyrazolyl, thiazolyl, indolyl, indazolyl, indenyl, cyclopropyl, isopropyl, phenylethyl, aminoalkyl, benzyl, amidoalkyl, morpholine, or furanylmethyl.

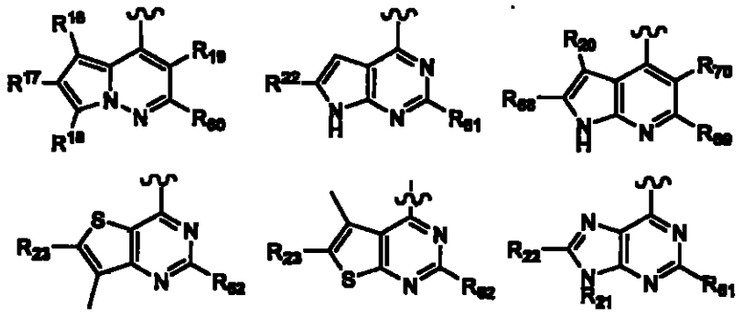
4. The compound according to claim 1 wherein R^2 is H, methyl, alkoxy, halo, haloalkyl, or cyano.

5. The compound according to claim 1 wherein R^4 is an optionally substituted phenyl, an optionally substituted pyridyl, an optionally substituted pyrrolidinyl, an optionally substituted pyridyl-N-oxy, or an optionally substituted pyridinone.

6. The compound according to claim 5 wherein said phenyl, pyridyl, pyridinone, or N-oxy pyridyl is substituted with hydroxyl, halo, C_1 to C_4alkyl, C_3 to C_7 cycloalkyl, $-COCH_3$, alkoxy, amino, heterocycloalkyl, aminoalkylamino, cyano, alkylthio, phenyl or alkylaminoalkoxy.

7. The compound according to claim 6 wherein said substituent is F, Br, Cl, methyl, pentyl, methoxy, phenyl, morpholinyl, NH_2, or $NHCHNH_2$.

8. The compound according to claim 1 wherein A is

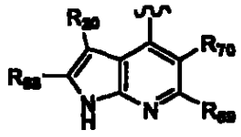


9. The compound according to claim 8 wherein R^{19} is H or CN; R^{16} and R^{17} are independently H, C_1 to C_4 alkyl, C_1 to C_4 alkoxy, or $-C(O)_2R^{29}$ wherein R^{29} is C_1 to C_4 alkyl; and R^{18} is H.

10. The compound according to claim 8 wherein R^{22} and R^{61} are H.

11. The compound according to claim 8 wherein R^{68}, R^{69} and R^{70} are H; R^{20} is C_1 to C_4 alkyl; alkenyl;, alkynyl; C_5 to C_6 heterocycloaryl; $CO(CH_2)_1R^{41}$, and R^{41} is C_1 to C_4 alkyl, haloalkyl, amino, alkylamino, C_5 to C_7 heterocycloalkyl, or C_5 to C_7 heteroaryl; $C(O)_2R^{29}$ wherein R^{29} is ethyl; CN; alkoxy; phenylmethyl; alkylaminoalkynyl; alkylaminoalkyl, hydroxyalkyl; or methoxyalkyl.

12. The compound according to claim 8 wherein A is



13. The compound according to claim 1 wherein Y is O or S.

14. The compound according to claim 1 wherein B is O.

15. The compound according to claim 1 wherein Z is $-CR^{13}R^{14}$ or NR^{15} wherein R^{13}, R^{14}, and R^{15} are each H or R^{13} and R^{14} together with the carbon to which they are attached form a cyclopropyl.

16. The compound according to claim 1 wherein R^4 is phenyl.

17. The compound according to claim 1 wherein R^4 is pyridyl.

18. The compound according to claim 1 wherein R^4 is pyrrolidinyl.

19. The compound according to claim 1 wherein R^4 is pyridyl-N-oxy.

20. The compound according to claim 1 wherein R^4 is pyridinone.

21. The compound according to claim 12 wherein R^{20} is $-COCH_2$-R, wherein R is amino, pyrrolidine, or piperazine.

22. The compound according to claim 12 wherein R^{20} is pyridine or thiazole.

23. The compound according to claim 12 wherein R^{20} is is $-COC(Cl)_3$, or $CONHCH_2$pyridine.

24. The compound according to claim 12 wherein R^{20} is CH_2piperidine, CH_2phenyl, -C≡C-amino, cyano, $-CO_2CH_3$, $-CH_2OH$, CH_2OMe, hydroxyethyl,-$CHOH(CH_2)_2OH$, or $CH(OCH_3)CH_3$.

25. The compound according to claim 1 having an IC50 value of less than about 5 μM.

26. The compound according to claim 1 having an IC50 value of less than about 1 μM.

27. A method for treating cancer comprising administering to a patient in need thereof, a pharmaceutically effective amount of a compound having the formula I or II according to claim 1.

28. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1 in a pharmaceutically acceptable carrier.

29. The method of claim 18, further comprising administering to said patient at least one other anticancer agent.

(12) SOLICITUD INTERNACIONAL PUBLICADA BAJO EL TRATADO DE COOPERACION EN MATERIA DE PATENTES (PCT)

(19) Organización Mundial de la Propiedad Intelectual: Oficina Internacional

CODIGO DE BARRAS

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(71) Solicitante *(para todos los estados designados, excepto EU)*: **BRISTOL-MYERS SQUIBB COMPANY** [US/US]; Route 206 y Province Line Road, Princeton, Nueva Jersey 08543-4000 (US).

(72) Inventores; e

(75) Inventor/Solicitante *(para Estados Unidos solamente)*: **BORZILLERI, Robert M.** [US/US]; 222 Riverwoods Drive, New Hope, Pennsylvania 18938 (US). **CHEN, Zhong** [CN/US]; 30 Kingston Terrace, Princeton, Nueva Jersey 08540 (US). **HUYNH, Tram N.** [US/US]; 26 Manley Road, Pennington, Nueva Jersey 08534 (US). **VACCARO, Wayne** [US/US]; 1706 Westover Road, Yardley, Pennsylvania 19067 (US). **CHEN, Xiao Tao** [US/US]; 3708 Powder Horn Drive, Furlong, Pennsylvania 18925 (US). **KIM, Kyoung S.** [US/US]; 252 Forest Lane, North Brunwick, Nueva Jersey 08902 (US). **CAI, Zhen-Wei** [US/US]; 36 Hills Drive, Belle Mead, Nueva Jersey 08502 (US).

(74) Apoderado: **GIBBONS, Maureen et al.**; Bristol-Myers Squibb Company, P.O. Box 4000, Princeton, Nueva Jersey 08543-4000 (US).

(81) Estados designados *(nacional)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Estados designados *(regional)*: patente ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), patente Euroasiática (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Patente europea (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), Patente OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Publicado:
- con reporte de búsqueda internacional
- antes del vencimiento de la fecha límite para enmendar las reivindicaciones y para republicarse en el caso de recibir las enmiendas

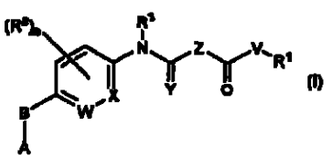
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Para códigos de dos letras y otras abreviaturas, refiérase a la "Guía de Notas en Códigos y Abreviaturas" que aparece al inicio de cada artículo regular de la Gaceta de PCT.

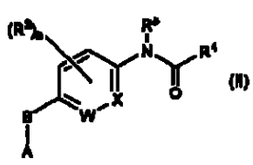
(54) TÍTULO: INHIBIDORES DE CINASA HETEROCICLICOS FUSIONADOS

(57) RESUMEN:

En general, la invención actual comprende compuestos de las Fórmulas I y II que incluyen sales farmacéuticamente aceptables de los mismos. Los compuestos de la invención son útiles como inhibidores de proteína cinasa y, por lo tanto, son útiles para el tratamiento contra el cáncer y otras enfermedades mediadas por la proteína cinasa.



(I)



(II)

TRATADO DE COOPERACION EN MATERIA DE PATENTES

De la AUTORIDAD EXAMINADORA PRELIMINAR INTERNACIONAL

Para: Véase forma PCT/ISA/220	**PCT** 282 **OPINION ESCRITA DE LA AUTORIDAD DE BÚSQUEDA INTERNACIONAL** (Regla 43bis.1 del PCT)
	Fecha de envío (día/mes/año): véase forma PCT/ISA/210 (segunda hoja)
Referencia de archivo de la solicitante o apoderado: Véase forma PCT/ISA/220	**PARA ACCIÓN ADICIONAL** Véase párrafo 2 a continuación

No. de solicitud internacional:	Fecha de presentación internacional (día/mes/año):	Fecha de prioridad (día/mes/año):
PCT/US2005/022682	28.06.2005	28.06.2004

Clasificación Internacional de Patente (CIP) o clasificación nacional y CIP:
INV. C07D487/04 C07D495/04 C07D471/04

Solicitante:
BRISTOL-MYERS SQUIBB COMPANY

1. Esta opinión contiene indicaciones relacionadas a los siguientes puntos:

- [X] Bloque No. I Base de la opinión
- [ ] Bloque No. II Prioridad
- [X] Bloque No. III Ausencia de formulación de opinión con respecto a novedad, actividad inventiva y posibilidad de aplicación industrial
- [ ] Bloque No. IV Carencia de unidad de la invención
- [X] Bloque No. V Declaración justificada en virtud de la Regla 43bis.1(a)(i) con respecto a novedad, actividad inventiva o posibilidad de aplicación industrial; citas y explicaciones que apoyan tal declaración
- [ ] Bloque No. VI Ciertos documentos citados
- [X] Bloque No. VII Ciertos defectos en la solicitud internacional
- [X] Bloque No. VIII Ciertas observaciones en la solicitud internacional

2. ACCIÓN ADICIONAL

Si se realiza una demanda de examen preliminar internacional, la presente opinión será considerada usualmente una opinión escrita de la Autoridad Examinadora Preliminar Internacional ("IPEA"). Sin embargo, esto no se aplica en donde la solicitante escoge una Autoridad diferente a la presente para que sea la IPEA y la IPEA escogida ha notificado a la Oficina Internacional, en virtud de la regla 66.1bis(b) que las opiniones escritas de esta Autoridad de Búsqueda Internacional no serán consideradas de esta manera.

Si se considera que esta opinión, como se estipula anteriormente, es una opinión escrita de la IPEA, se invita a la solicitante a presentar a la IPEA una opinión escrita junto con enmiendas, en donde sea apropiado, antes de la expiración de los tres meses a partir de la fecha de envío por correo de la forma PCT/ISA/220 o antes de la expiración de 22 meses a partir de la fecha de prioridad, lo que expire más tarde.

Para opciones adicionales, véase forma PCT/ISA/220.

3. Para detalles adicionales, véanse notas a la forma PCT/ISA/220.

Nombre y dirección de correspondencia de la ISA	Funcionario Autorizado
Oficina Europea de Patentes D-80298 Munich Tel. + 49 89 2399 - 0 Tx:523656 epmu d Fax: + 49 89 2399 - 4465	Wolf, C Teléfono No.: +49 89 2399-8285

Forma (PCT/ISA/237) (hoja de cubierta) (Enero 2004)

OPINIÓN ESCRITA DE LA AUT RIDAD DE BÚSQUEDA INTERNACIONAL

No. de solicitud internacional
PCT/US2005/022682

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Bloque No. I Base de la opinión

1. Con respecto al **idioma**, esta opinión se ha establecido en base de la solicitud internacional en el idioma en que se envió, a menos que se indique de otra forma en este punto.

☐ Esta opinión se ha establecido en base de una traducción del idioma original en el siguiente idioma, Que es el idioma de una traducción llevada a cabo para propósitos de búsqueda internacional (bajo las Reglas 12.3 y 23.1 (b)).

2. Con respecto a cualquier **secuencia de aminoácidos y/o nucleótidos** descrita en la solicitud internacional y necesaria para reivindicar la invención, esta opinión se estable en la base de:

a. tipo de material:

☐ Un listado de secuencias

☐ Tabla (s) relacionada (s) al listado de secuencias

b. formato del material:

☐ En forma escrita

☐ En forma compatible de computadora

c. fecha de envío/elaboración:

☐ Contenido en la solicitud internacional como se envió.

☐ Enviado junto con la solicitud internacional en forma compatible de computadora.

☐ Enviado subsecuentemente a esta Autoridad para propósitos de búsqueda.

3. ☐ Además, en caso de que más de una versión o copia de un listado de secuencias y/o tabla relacionada a esto se haya enviado o elaborado, las declaraciones requeridas de información en copias subsecuentes o adicionales debe ser idéntica de tal forma que la solicitud sea enviada o no vaya más allá de la solicitud como se envió, si es adecuado, debe elaborarse.

4. Comentarios adicionales:

OPINIÓN ESCRITA DE LA AUTORIDAD DE BÚSQUEDA INTERNACIONAL

No. de solicitud internacional
PCT/US2005/022682

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Bloque No. III No establecimiento de opinión con respecto a novedad, etapa inventiva y aplicación industrial

1. Las cuestiones en donde la invención reivindicada aparece por tener novedad, por involucrar una etapa inventiva (que no sea obvia) o por se aplicable industrialmente no se ha examinado con respecto de:

☐ La solicitud internacional en su totalidad

☒ Reivindicaciones Nos. **27, 29 con respecto a la aplicación industrial**

Porque:

☐ La solicitud internacional, o las reivindicaciones Nos. se relacionan al siguiente tema que no requiere de un examen preliminar internacional (*especifique*):

La descripción, reivindicaciones o figuras (a continuacion indique elementos particulares) o las reivindicaciones Nos. son tan imprecisas que no se pudo formular una opinión significativa (especifique):

☐ Las reivindicaciones, o las reivindicaciones Núms.- están tan mal apoyadas por la descripción que no se puede formular ninguna opinión significativa.

☒ No se ha establecido ningún reporte de búsqueda internacional para toda la solicitud o para las reivindicaciones Núms. **27, 29 con respecto a la aplicación industrial**

☐ El listado de nucleótidos o aminoácidos no cumple con la norma proporcionada en el Anexo C de las Instrucciones Administrativas en que:

la forma escrita	no ha sido otorgada no cumple con la norma
la forma legible por computadora	no ha sido otorgada no cumple con la norma

☐ Las tablas relacionadas con el listado de nucleótidos y/o aminoácidos, si sólo se encuentra en forma legible por computadora, no cumpla con los requerimientos técnicos proporcionados para el Anexo C-bis de las Instrucciones Administrativas.

☐ Ver hoja separada para más detalles.

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Bloque No. V Declaración justificada bajo el Artículo 43bis.1(a)(i) con respecto a novedad, etapa inventiva o aplicabilidad industrial; citas y explicaciones que apoyan esta declaración

1. Declaración

Novedad (N)	Sí: Reivindicaciones	
	No: Reivindicaciones	1-29
Etapa Inventiva (IS)	Sí: Reivindicaciones	
	No: Reivindicaciones	1-29
Aplicabilidad Industrial (IA)	Sí: Reivindicaciones	1-26,28
	No: Reivindicaciones	

2. Citas y explicaciones :

ver hoja separada

Bloque No. VII Ciertos defectos en la solicitud internacional

Se han observado los siguientes defectos en la forma o contenido de la solicitud internacional

ver hoja separada

Bloque No. VIII Ciertas observaciones de la solicitud internacional

Se hicieron las siguientes observaciones sobre la claridad de las reivindicaciones, descripción y figuras o sobre la cuestion de si las reivindicaciones están completamente apoyadas por la descripción:

ver hoja separada

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Con relación al Artículo III.

Regla 39.1(iv)PCT- Método de tratamiento del cuerpo humano o animal mediante terapia

Para la evaluación de las presentes reivindicaciones 27, 29 de si son industrialmente aplicables, no existe un criterio unificado en los Estados Contrayentes del PCT. La patentabilidad también puede ser dependiente de la formulación de las reivindicaciones. Por ejemplo, el EPO no reconoce como industrialmente aplicable el tema de las reivindicaciones para el uso de un compuesto en el tratamiento médico, pero, sin embargo, puede permitir reivindicaciones para un compuesto conocido para su primer uso en el tratamiento médico y el uso de éste para la elaboración de un medicamento para un nuevo tratamiento médico.

Con relación al Artículo V.

Los siguientes documentos se citan en el Reporte de Búsqueda Internacional:

D1: EP-A-1 415 987 (EISAI CO.,LTD) 6 de mayo de 2004 (06-05-2004)

D2: WO 01/09134 A (NOVARTIS AG; NOVARTIS-ERFINDUNGEN VERWALTUNGSGESSELLSCHAFT M.B.H; COLLI) 8 de febrero de 2001 (09-02-2001)

D3: WO 97/16452 A (NOVARTIS AG; ZIMMERMANN, JUERG; CAPRARO, HANS-GEORG; PETERLI, PATRICIA) 9 de mayo de 1997 (09-05-1997).

En vista de D1, el tema reivindicado no parece ser novedoso y carece de etapa inventiva (Artículos 33 (2) y (3) del PCT).

El documento D1 describe agentes con actividad antitumoral de la Fórmula II en la reivindicación 2 cuya fórmula general II se traslapa con la fórmula general reivindicada en la reivindicación 1 de la presente solicitud.

Los documentos D2 y D3 describen compuestos farmacológicamente activos de estructura similar que difieren de los compuestos como se reivindican en los sustitutos R^1 respectivamente R_1 como se definen en los documentos de la técnica anterior.

2. La evaluación de la etapa inventiva del tema reivindicado sólo puede basarse en

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el tema que es novedoso. Sin embargo, se ha de observar lo siguiente:

El problema técnico subyacente a la presente solicitud fué la estipulación de otros compuestos con actividad antitumoral.

Hasta el punto que el tema de la reivindicación es novedoso, está estructuralemente muy relacionado con el tema descrito en el documento D1. El experto puede esperar, al tratar de resolver el problema técnico, que estos compuestos estructuralmente similares exhiban un perfil farmacológico similar a la técnica anterior. Por lo tanto, la solución al problema técnico es obvio en vistad de D1.

Con relación al Artículo VIII.

La reivindicación 29 contiene una referencia a la reivindicación 18 que no es correcta.

Con relación al Artículo VIII.

1. Los términos "sustituido" en las reivindicaciones hacen el alcance reivindicado impreciso (Artículo 6 PCT).

2. Se le invita al Solicitante a indicar la razón de las estipulaciones en las reivindicaciones. Si se pretendió delimitar el tema reivindicado de otra técnica anterior no citada aún, se deberán indicar los documentos de referencia.

INHIBIDORES DE CINASA HETEROCICLICOS FUSIONADOS

CAMPO DE LA INVENCIÓN

La invención se refiere a compuestos que inhiben la actividad de proteína tirosina cinasa de receptores del factor de crecimiento como c-Met, haciéndolos, con ello, útiles como agentes anticancerígenos. Las composiciones farmacéuticas que comprenden estos compuestos, son también, útiles en el tratamiento contra enfermedades diferentes al cáncer, que se asocian con vías de transducción de señal que operan a través de los receptores del factor de crecimiento y antiangiogénesis tales como c-Met.

ANTECEDENTES DE LA INVENCIÓN

El factor de crecimiento de hepatocitos (HGF por sus siglas en inglés), también conocido como factor difractor (SF por sus siglas en inglés), por su habilidad para interrumpir la formación de colonias *in vitro*, es un citocina derivada del mesénquima que se sabe induce múltiples respuestas pleiotróficas en células normales y neoplásicas (Sonnenberg et al., *J. Cell Biol.* 123:223-235, 1993; Matsumoto et al., *Crit. Rev. Oncog.* 3:27-54, 1992 y Stoker et al., *Nature* 327: 239-242, 1987). Se sabe que estas respuestas incluyen proliferación tanto en células epiteliales como endoteliales, disociación de colonias epiteliales en células individuales, estimulación de motilidad (motogénesis) de células

epiteliales, supervivencia celular, inducción de morfogénesis celular (Montesano et. Al., *Cel* 67:901-908, 1991) y promoción de invasión (Stella et. Al. *Int. J. Biochem., Cell Biol* 12:1357-62, 1999 y Stuart et al., *Int. J. Exp. Path.* 81 :17-30, 2000), todos los procesos críticos subrayan metástasis. También se ha informado que HGF promueve la angiogénesis (Bussolino et al., *J. Cell. Biol.* 119:629-641, 1992). Además, HGF tiene una función crítica en la regeneración tisular, cicatrización de heridas y procesos embriónicos normales, de los cuales todos son dependientes tanto de la proliferación como motilidad celular.

HGF inicia estos procesos fisiológicos mediante un enlace de alta afinidad a su receptor cognado, el receptor tirosina cinasa de la proteína Met, un protooncogén identificado (Park et al., *Proc. Nat. Acad. Sci.* USA 84:6379-83, 1987 y Bottaro et al., *Science* 251:802-4, 1991). La forma madura de Met consiste de una α-subunidad externa altamente glicosilada así como de una β-subunidad con un gran dominio extracelular, un segmento transmembranal y un dominio citoplásmico de tirosina cinasa. La implicación del ligando indica la dimerización de Met, lo que resulta en un receptor activado autofosforilado. La activación de Met promueve las cascadas de transducción de señal como se define en la transfosforilación de residuos clave de tirosina citoplásmica responsables de reclutar múltiples proteínas efectoras (Furge

et al., *Oncogene* 19:5582-9, 2000). Estas incluyen la subunidad p85 de P13-cinasa, fosfolipasa Cγ (Gaul et al. *Oncogene* 19:1509-18, 2000), proteínas adaptadoras Grb2 y Shc, la proteína fosfatasa SHP2 y Gab1. Este último adaptador ha emergido como la principal molécula de acoplamiento en dirección 3′ que se convierte en tirosina fosforilada en respuesta a la ocupación de ligandos (Schaeper et al., *J. Cell. Biol.* 149:1419-32, 2000; Bardelli et al., *Oncogene* 18:1139-46, 1999 y Sachs et al., *J. Cell. Biol.* 150:1375-84, 2000). La activación de otras moléculas de señalización ha sido mencionada en células estimuladas con HGF, con más notoriedad, Ras, MAP cinasas, STAT, ERK-1, -2 y FAK (Tanimura et al., *Oncogene,* 19:5582-9, 2000). La función de varias de estas moléculas de señalización se ha establecido bien en la proliferación celular.

Met, también conocida como receptor del factor de crecimiento de hepatocitos (HGFR), se expresa predominantemente en células epiteliales pero también se ha identificado en células endoteliales, mioblastos, células hematopoiéticas y neuronas motrices. La sobreexpresión de HGF y la activación de Met han sido asociados con la manifestación y progresión de una variedad de diferentes tipos tumorales así como de la promoción de metástasis. La evidencia inicial que asocia Met con cáncer ha sido apoyada por la identificación de mutación de dominios cinasa antisentido, que predispone a los pacientes a carcinomas papilares renales (PRC) y carcinomas hepatocelulares (HCC) (Lubenski et al.,

Amer. J. Pathology, 155:517-26, 1999). Las formas mutadas de Met también han sido identificadas en cáncer ovárico, HCC infantil, carcinoma gástrico, carcinoma de células escamosas en cabeza y cuello, carcinoma pulmonar de células no pequeñas, metástasis colorrectal, (Christensen et al., *Cancer Res.*, 63:7345-55, 2003; Lee et al., *Oncogen,* 19:4947-53, 2000 y Direnzo et al., *Clin. Cancer Res.*, 1:147-54, 1995). Además, más evidencia que apoya la función de Met en cáncer se basa en la sobreexpresión de receptores HGF y Met en diversos tumores incluyendo carcinomas pancreáticos, ováricos y tiroideos. También se ha demostrado que se amplifica en metástasis hepático de carcinomas colorrectales (Rong et al. *Cancer Res.* 55:1963-1970, 1995; Rong et al. *Cancer Res.* 53:5355-5360, 1993; Kenworthy et al., *Br. J. Cancer* 66:243-247, 1992 y Scarpino et al. J. *Pathology* 189:570-575). Se ha descrito e identificado TPR-Met (una forma activada similar a BCR/Abl en CML) en carcinoma gástrico de humano (*PNAS* 88:4892-6, 1991). En pacientes con carcinoma invasivo de mama y en un estudio reciente en pacientes con carcinoma pulmonar de células no pequeñas, la expresión ya sea del receptor o el ligando es un predictor asociado a menor sobrevivencia, asociando aún más a Met con la progresión tumoral (Camp et al., *Cancer* 86:2259-65, 1999 y Masuya et al., *Br. J. Cancer,* 90:1555-62, 2004). En general, La mayoría de tumores y líneas de células tumorales en humanos de origen mesenquimatoso expresan inapropiadamente HGFR y/o HGF.

Diversos datos experimentales apoyan la función de HGF y Met en la invasión, crecimiento y progresión tumoral lo que conlleva

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ultimadamente a metástasis. Preclínicamente, la expresión transgénica de HGF da como resultado un fenotipo metastásico (Takayama et al., *PNAS*, 94:701-6, 1997 y un Met amplificado/sobreexpresado transforma espontáneamente a células NIH-3T3 (Cooper et al., *EMBO J.*, 5:2623-8, 1986).

Los agentes biológicos, como ribosimas, anticuerpos y ARN antisentido con especificidad de objetivo hacia HGF o Met han demostrado que inhiben tumorogénesis (Stabile et al., *Gene Therapy*, 11:325-35, 21004; Jiang et al., *Clin. Cancer Res.* 9:4274-81, 2003 y *Genetech* US 6,214,344, 2001). Por lo tanto, se espera que los pequeños moduladores de moléculas de cinasa selectivos hacia objetivos Met tengan efectos terapéuticos potenciales para el tratamiento contra el cáncer donde la activación del receptor Met tiene una función importante en el desarrollo y progresión de tumores primarios y metástasis secundaria. También se sabe que HGF regula la angiogénesis, un proceso crítico para la diseminación y crecimiento tumorales. Por lo tanto, existe el potencial para esta clase de moduladores para tener un impacto sobre las enfermedades dependientes de angiogénesis incluyendo, entre otras, retinopatía diabética, degeneración macular, obesidad y enfermedad inflamatoria como artritis reumatoide.

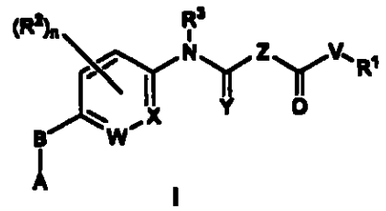
BREVE DESCRIPCIÓN DE LA INVENCIÓN

La presente invención concierne a compuestos que tienen

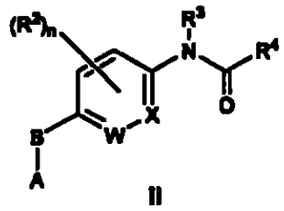
2ª PD

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las siguientes Fórmulas I y II:



I



II

que incluyen sales, enantiómeros, diastereómeros y solvatos farmacéuticamente aceptables de los mismos, en donde:

R^1 es H, alquilo, alquilo substituido, cicloalquilo, cicloalquilo substituido, arilalquilo, arilalquilo substituido, arilo, arilo substituido, alquenilo, alquenilo substituido, alquinilo, alquinilo substituido, heteroarilo, heteroarilo substituido, heterociclo, heterociclo substituido, heteroarilaquilo, heteroarilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido;

cada R^2 es independientemente, H, halógeno, ciano, NO_2, OR^5, NR^6R^7, alquilo, alquilo substituido, cicloalquilo, cicloalquilo substituido, arilo, arilo substituido, heteroarilo, heteroarilo substituido, heterociclo, heterociclo substituido, arilalquilo, arilalquilo substituido, heterocicloalquilo, o heterocicloalquilo substituido;

B es O, NR^8, S, SO, SO_2, CR^9R^{10};

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V es NR^{11} o $-(CR^{47}R^{48})_p-$;

W o X son independientemente C o N;

Y es O, S, o NR^{12};

Z es $-CR^{13}R^{14}-$, $-(CR^{13}R^{14})_mNR^{15}-$;

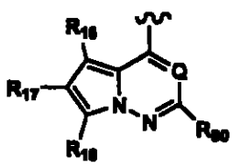
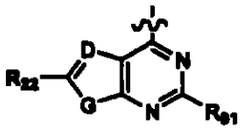
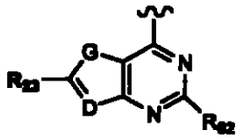
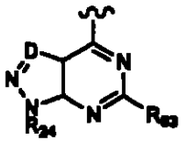
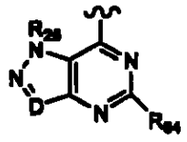
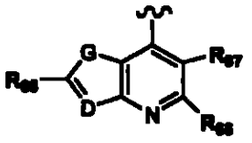
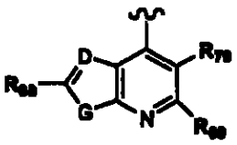
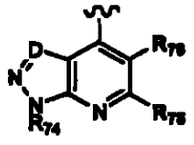
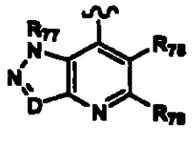
l tiene un valor de 0 a 4;

m tiene un valor de 0 a 2;

n tiene un valor de 0 a 4;

p tiene un valor de 0 a 4, con la condición de que si p es 0, R^1 no es fenilo;

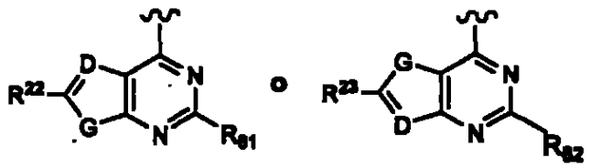
A es:

Q es CR^{19};

D es CR^{20} o N;

G es S, O o NR^{21}, con la condición de que si A es



y G es S, R^4 no es un grupo fenilo substituido;

R^3, R^5, R^6, R^7, R^8, R^{11} y R^{15} son cada uno independientemente H, alquilo, alquilo substituido, cicloalquilo, cicloalquilo substituido, arilo, arilo substituido, heteroarilo, heteroarilo substituido, heterocicloalquilo, o heterocicloalquilo substituido;

R^4 es arilo, arilo substituido, heteroarilo, heteroarilo substituido, heterocicloalquilo, o heterocicloalquilo substituido;

R^9 y R^{10} son independientemente H, halógeno, alquilo, alquilo substituido, cicloalquilo, cicloalquilo substituido, arilo, arilo substituido, heteroarilo, heteroarilo substituido, heterocicloalquilo, o heterocicloalquilo substituido;

R^{12} es H, alquilo, alquilo substituido, CN, NO_2 o SO_2NH_2;

R^{13}, R^{14}, R^{15}, R^{47} y R^{48} son independientemente H, halógeno, alquilo, alquilo substituido, cicloalquilo, cicloalquilo substituido, arilo, arilo substituido, heteroarilo, heteroarilo substituido, heterociclo,

heterociclo substituido o tomados juntos para formar un anillo heterocíclico o carbocíclico desde 3 a 8 átomos;

R^{16}, R^{17}, R^{18}, R^{20}, R^{22}, R^{23}, R^{60}, R^{61}, R^{62}, R^{63}, R^{64}, R^{65}, R^{66}, R^{67}, R^{68}, R^{69}, R^{70}, R^{75}, R^{76}, R^{78}, y R^{79}, son independientemente H, halógeno, NO_2, ciano, OR^{26}, $NR^{27}R^{28}$, CO_2R^{29}, $C(O)NR^{30}R^{31}$, SO_2R^{32}, $SO_2NR^{33}R^{34}$, $NR^{35}SO_2R^{36}$, $NR^{37}C(O)R^{38}$, $NR^{39}CO_2R^{40}$, $-CO(CH_2)_1R^{41}$; $-CONH(CH_2)_1R^{42}$, alquilaminoalquilo, alquilaminoalquinilo, alquilo C_1 a C_6, alquilo C_1 a C_6 substituido, cicloalquilo C_3 a C_7, cicloalquilo C_3 a C_7 substituido, alquenilo, alquenilo substituido, alquinilo, alquinilo substituido, hidroxialquilo, arilo, arilo substituido, heteroarilo, heteroarilo substituido, arilalquilo, arilalquilo substituido, heterocicloalquilo, o heterocicloalquilo substituido;

R^{19} es H o ciano;

R^{21} y R^{24} son independientemente H, alquilo C_1 a C_6 o alquilo C_1 a C_6 substituido;

R^{25}, R^{74} y R^{77} son independientemente H, alquilo, alquilo substituido, cicloalquilo, cicloalquilo substituido, arilo, arilo substituido, arilalquilo, arilalquilo substituido, heteroarilo, heteroarilo substituido, heterocicloalquilo, o heterocicloalquilo substituido

R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, R^{33}, R^{34}, R^{35}, R^{36}, R^{37}, R^{38}, R^{39}, R^{40}, R^{41}, y R^{42} son independientemente H, alquilo,

alquilo substituido, cicloalquilo, cicloalquilo substituido, arilo, arilo substituido, arilalquilo, arilalquilo substituido, heteroarilo, heteroarilo substituido, heterocicloalquilo, o heterocicloalquilo substituido.

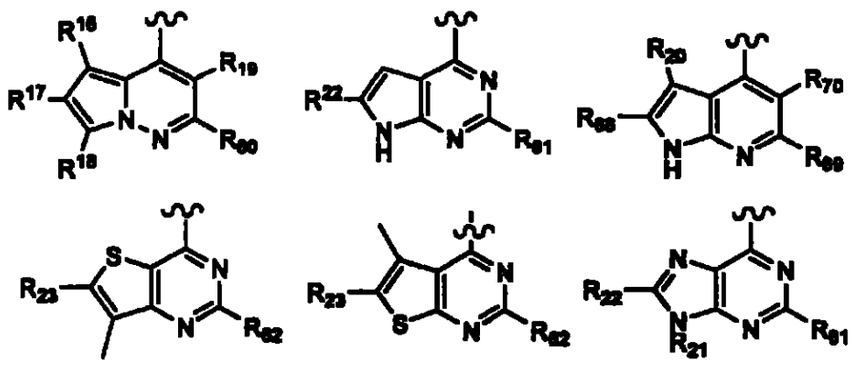
En algunas modalidades de la presente invención, R^1 es un alquilo C_1 a C_6 opcionalmente substituido, alquenilo, alquinilo, cicloalquilo C_3 a C_7 opcionalmente substituido, heterocicloalquilo C_3 a C_7, fenilo opcionalmente substituido, bifenilo opcionalmente substituido o un heteroarilo biciclico o monociclico C_5 a C_{11} opcionalmente substituido. Preferiblemente, R^1 es fenilo, opcionalmente substituido con al menos uno de Cl, F, OCH, t-butilo, alquenilo, alquinilo, hidroxi, amido, fenoxi, CH_2CN, bencilo, $NHCO_2CH_3$; bifenilo, piridilo, azepanilo, pirazolilo, tiazolilo, indolilo, indazolilo, indenilo, ciclopropilo, isopropilo, feniletilo, aminoalquilo, bencilo, amidoalquilo, morfolina y furanilmetilo.

En algunas modalidades de la presente invención, R^2 es alcoxi, halo o CN.

En algunas modalidades de la presente invención, R^4 es un fenilo opcionalmente substituido, un piridilo opcionalmente substituido, un pirrolidinilo opcionalmente substituido, un piridil-N-oxi opcionalmente substituido, o

una piridinona opcionalmente substituida, en donde el sustituto se selecciona, por ejemplo, de halo, alquilo C_1 a C_4, cicloalquilo C_3 a C_7, alcoxi, amino, heterocicloalquilo, aminoalquilamino. En algunas modalidades de la presente invención, el sustituto es F, Br, Cl, metilo, pentilo, metoxi, fenilo, morfolinilo, NH_2 o $NHCHNH_2$.

De conformidad con algunas modalidades de la presente invención, A es uno de los siguientes:



De conformidad a una modalidad de la presente invención, R^{19} es H o CN y R^{16}, R^{17} y R^{18} son independientemente H, alquilo C_1 a C_4, alcoxi C_1 a C_4, o $-C(O)_2R^{29}$ en donde R^{29} es alquilo C_1 a C_4.

De conformidad a una modalidad de la presente invención, R^{22} y R^{61} son H.

De conformidad a otra modalidad de la presente invención, R^{68}, R^{69} y R^{70} son H; R^{20} es alquilo C_1 a C_4; alquenilo; alquinilo; heterocicloarilo C_5 a C_6; $-CO(CH_2)_1R^{41}$,

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en donde R^{41} es alquilo C_1 a C_4; haloalquilo; amino; alquilamino; heterocicloalquilo C_5 a C_7; heteroarilo C_5 a C_7; o $C(O)_2R^{29}$ en donde R^{29} es etilo; CN; alcoxi; fenilmetilo; alquilaminoalquinilo; alquilaminoalquilo; o metoxialquilo.

De conformidad a una modalidad de la presente invención, Y es O u S.

De conformidad a una modalidad de la presente invención, B es O.

En algunas modalidad de la presente invención, Z es $-CR^{13}R^{14}$ o NR^{15} en donde R^{13}, R^{14} y R^{15} son cada uno H o R^{13} y R^{14} junto con el carbono al cual se enlazan forman un ciclopropilo.

La presente invención también concierne a composiciones farmacéuticas que comprenden cantidades terapéuticamente efectivas de un compuesto de la Fórmula I ó II, o una sal o solvato del mismo, junto con un portador farmacéuticamente aceptable.

La presente invención también proporciona métodos para el tratamiento contra el cáncer que comprende administrar a un paciente que necesita del mismo, una cantidad farmacéuticamente efectiva de un compuesto de fórmula I o II o una sal o solvato del mismo, que incluye opcionalmente administrar al paciente al menos un agente adicional anticáncer.

29X

300

DESCRIPCION DETALLADA DE LA INVENCIÓN

La presente invención proporciona compuestos de las fórmulas I y II antes definidas, composiciones farmacéuticas que emplean tales compuestos, métodos de elaboración y métodos de uso de tales compuestos.

Se enlistan a continuación las definiciones de diversos términos usados para describir los compuestos de la actual invención. Estas definiciones aplican a los términos como se usan a lo largo de la especificación (a menos que se limite de otra manera en instancias específicas) ya sea individualmente o como parte de un grupo mayor.

En esta descripción, el término "alquilo", por sí solo o como parte de otro grupo, se refiere a un radical derivado de alcano monovalente (hidrocarburo) que contiene de 1 a 12 átomos de carbono a menos que se defina de otra manera. Los grupos alquilo preferidos tienen desde 1 a 6 átomos de carbono. Un grupo alquilo es un grupo de hidrocarburos saturado, lineal, cíclico o ramificado, opcionalmente substituido. Los grupos alquilo pueden estar substituidos en cualquier punto disponible de enlace. Un grupo alquilo que está substituido con otro grupo alquilo, también se refiere como un "grupo alquilo ramificado". Los grupos alquilo ejemplares incluyen metilo, etilo, propilo, isopropilo, n-butilo, t-butilo, isobutilo, pentilo, hexilo, isohexilo, heptilo, 4,4-dimetilpentilo, octilo, 2,2,4-trimetilpentilo,

nonilo, decilo, undecilo, dodecilo, y los similares. Los sustitutos ejemplares incluyen pero no se limitan a uno o más de los grupos siguientes: alquilo, arilo, halo (tal como F, Cl, Br, I), haloalquilo (tal como CCl_3 o CF_3), alcoxi, alquiltio, hidroxi, carboxi (-COOH), alquiloxicarbonil (-C(O)R), alquilcarboniloxi (-OCOR), amino ($-NH_2$), carbamoil (-NHCOOR- o -OCONHR-), urea (-NHCONHR-) o tiol (-SH). En algunas modalidades preferidas de la presente invención, los grupos alquilo se substituyen con, por ejemplo, amino, heterocicloalquilo, tales como grupos morfolina, piperazina, piperidina, azetidina, hidroxilo, metoxi o heteroarilo tal como pirrolidina.

El término "alquenilo" en la presente, solo o como parte de otro grupo se refiere a un radical hidrocarburo lineal, ramificado o cíclico que contiene de dos a doce átomos de carbono y al menos un doble enlace carbono a carbono. Los grupos alquenilo también se pueden substituir en cualquier punto de enlace disponible. Los sustitutos ejemplares para los grupos alquenilo incluyen aquellos arriba enlistados para los grupos alquilo e incluyen especialmente grupos cicloalquilo C_3 a C_7 tales como ciclopropilo, ciclopentilo y ciclohexilo que se pueden substituir además con por ejemplo amino, oxo, hidroxilo, etc.

El término "alquinilo" en la presente, solo o como parte de otro grupo se refiere a un radical hidrocarburo lineal,

ramificado o cíclico que contiene de 2 a 12 átomos de carbono y al menos un triple enlace carbono a carbono. Los grupos alquinilo también se pueden substituir en cualquier punto disponible de enlace. Los sustitutos ejemplares para los grupos alquenilo incluyen aquellos arriba enlistados para los grupos alquilo tales como amino, alquilamino, etc.

Los números en el subíndice después del símbolo "C", definen la cantidad de átomos de carbono que puede contener un grupo particular. Por ejemplo "alquilo C_{1-6}", significa una cadena de carbono saturada ramificada o lineal, que tiene de uno a seis átomos de carbono; los ejemplos incluyen metilo, etilo, n-propilo, isopropilo, n-butilo, sec-butilo, isobutilo, t-butilo, n-pentilo, sec-pentilo, isopentilo, y n-hexilo. Dependiendo del contexto, "alquilo C_{1-6}" puede también referirse a alquileno C_{1-6} el cual forma puentes con dos grupos; los ejemplos incluyen propano-1,3-diilo, butano-1,4-diilo, 2-metilo-butano-1,4-diilo, etc. "Alquenilo C_{2-6}" significa una cadena de carbono lineal o ramificada que tiene al menos un doble enlace carbono, carbono, y que tiene de dos a seis átomos de carbono; los ejemplos incluyen etenilo, propenilo, isopropenilo, butenilo, isobutenilo, pentenilo, y hexenilo. Dependiendo del contexto, "alquenilo C_{2-6}", también se puede referir a alquendiilo C_{2-6} el cual se enlaza a dos grupos; los ejemplos incluyen 1,2-diilo (vinileno), 2-metilo-2-buteno-1,4-diilo, 2-hexeno-1,6-diilo, etc. "Alquinilo C_{2-6}"

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significa una cadena de carbono lineal o ramificada que tiene al menos un triple enlace carbono a carbono y de dos a seis átomos de carbono; los ejemplos incluyen etinilo, propinilo, butinilo, y hexinilo.

Los términos "alcoxi" o "alquiltio" en la presente, solos o como parte de otro grupo, denotan un grupo alquilo como se describe arriba, enlazado a través de una ligadura de oxígeno (-O-) o una ligadura de azufre (-S-) respectivamente.

El término "alcoxicarbonilo" en la presente, solo o como parte de otro grupo, denota un grupo alcoxi enlazado a través de un grupo carbonilo. Un radical alcoxicarbonilo está representado por la fórmula -C(O)OR, en donde el grupo R es un grupo alquilo C_{1-6} lineal o ramificado, cicloalquilo, arilo o heteroarilo.

El término "alquilcarbonilo" en la presente, solo o como parte de otro grupo, se refiere a un grupo alquilo enlazado a través de un grupo carbonilo o -C(O)R.

El término "alquilcarboniloxi" en la presente, solo o como parte de otro grupo, denota un grupo alquilcarbonilo que se enlaza a través de una ligadura de oxígeno.

El término "arilalquilo" en la presente, solo o como parte de otro grupo, denota un anillo aromático enlazado a un grupo alquilo (tal como bencilo) como se describe arriba.

El término "arilo" en la presente, solo o como parte de otro grupo, se refiere a anillos aromáticos bicíclicos o

monociclicos, por ejemplo fenilo, fenilo substituido y similares, así como grupos que están fusionados por ejemplo naftilo, fenantrenilo y similares. Un grupo arilo contiene así al menos un anillo que tiene al menos 6 átomos, con hasta cinco de estos anillos que están presentes, que contienen hasta 22 átomos en él, con dobles enlaces alternos (en resonancia) entre los átomos de carbono adyacentes o heteroátomos adecuados. Los grupos arilo se pueden substituir opcionalmente con uno o más grupos que incluyen pero no se limitan a halógeno, tales como Br, F o Cl, alquilo, tales como metilo, etilo, propilo, alcoxi, tales como metoxi o etoxi, hidroxi, carboxi, carbamoilo, alquiloxicarbonilo, nitro, alqueniloxi, trifluorometilo, amino, cicloalquilo, arilo, heteroarilo, ciano, alquilo $S(O)_m$ (m=0, 1,2), o tiol.

El término "amino" en la presente, solo o como parte de otro grupo se refiere a $-NH_2$. Un "amino" puede opcionalmente substituirse con uno o dos sustitutos, que pueden ser iguales o diferentes tal como alquilo, arilo, arilalquilo, alquenilo, alquinilo, heteroarilo, heteroarilalquilo, cicloheteroalquilo, cicloheteroalquilalquilo, cicloalquilo, cicloalquilalquilo, haloalquilo, hidroxialquilo, alcoxialquilo, tioalquilo, carbonilo o carboxilo. Estos sustitutos se pueden además substituir con un ácido carboxílico, cualquiera de los sustitutos alquilo o arilo aquí establecidos. En algunas modalidades, los grupos amino

se substituyen con carboxilo o carbonilo para formar derivados de N-acilo o N-carbamoilo.

El término "cicloalquilo" en la presente, solo o como parte de otro grupo, se refiere a anillos hidrocarburos completamente saturados y parcialmente insaturados, de 3 a 9, preferiblemente de 3 a 7 átomos de carbono. Además puede estar substituido un cicloalquilo. Un cicloalquilo substituido se refiere a tales anillos que tienen uno, dos, o tres sustitutos, seleccionados del grupo que consiste de halo, alquilo, alquilo substituido, alquenilo, alquinilo, nitro, ciano, oxo (=O), hidroxi, alcoxi, tioalquilo, $-CO_2H$, -C(=O)H, alquilo CO_2, -C(=O)alquilo, ceto =N-OH, =N-O-alquilo, arilo, heteroarilo, heterociclo, un cetal de cinco o seis miembros (esto es, 1,3-dioxolano o 1,3-dioxano), NR'R", -C(=O)NR'R", $-CO_2NR'R"$, -C(=O)NR'R", $-NR'CO_2R"$, -NR'C(=O)R", $-SO_2NR'R"$ y $-NR'SO_2R"$, en donde cada uno de R' y R" son independientemente seleccionados de hidrógeno, alquilo, alquilo substituido, y cicloalquilo o R' y R" juntos forman un anillo heterociclo o heteroarilo.

El término "heteroarilo" en la presente, solo o como parte de otro grupo, se refiere a grupos monocíclicos de 5 o 6 miembros aromáticos substituidos o no substituidos, grupos bicíclicos de 9 o 10 miembros y grupos tricíclicos de 11 a 14 miembros, que tienen al menos un heteroátomo (O, S o N) en al menos uno de los anillos. Cada anillo del grupo heteroarilo

que contiene un heteroátomo, puede contener uno o dos átomos de oxígeno o azufre, y/o desde uno hasta cuatro átomos de nitrógeno con la condición de que el número total de heteroátomos en cada anillo sea de cuatro o menos y cada anillo tenga al menos un átomo de carbono. Los anillos fusionados que completan los grupos bicíclicos y tricíclicos, pueden contener solamente átomos de carbono y pueden ser saturados, parcialmente saturados o insaturados. Los átomos de azufre o nitrógeno se pueden oxidar opcionalmente, y los átomos de nitrógeno se pueden cuaternizar opcionalmente. Los grupos heteroarilo que son bicíclicos o tricíclicos deben incluir al menos un anillo completamente aromático, pero el otro anillo o anillos fusionados pueden ser aromáticos o no aromáticos. El grupo heteroarilo se puede unir a cualquier átomo de nitrógeno o carbono disponible de cualquier anillo. El sistema de anillo de heteroarilo puede contener cero, uno, dos, o tres sustitutos, seleccionados del grupo que consiste de halo, alquilo, alquilo substituido, alquenilo, alquinilo, arilo, nitro, ciano, hidroxi, alcoxi, tioalquilo, $-CO_2H$, $-C(=O)H$, $-CO_2$-alquilo, $-C(=O)$alquilo, fenilo, bencilo, feniletilo, feniloxi, feniltio, cicloalquilo, cicloalquilo substituido, heterociclo, heteroarilo, $-NR'R''$, $-C(=O)NR'R''$, $-CO_2NR'R''$, $-C(=O)NR'R''$, $-NR'CO_2'R''$, $-NR'C(=O)R''$, $-SO_2NR'R''$, y $-NR'SO_2'R''$, donde cada uno de R' y R'' se selecciona independiente de hidrógeno, alquilo, alquilo substituido y

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cicloalquilo o R' y R" juntos forman un anillo de heterociclo o heteroarilo.

Los grupos heteroarilo monocíclicos ejemplares incluyen pirrolilo, pirazolilo, pirazolinilo, imidazolilo, oxazolilo, diazolilo, isoxazolilo, tiazolilo, tiadiazolilo, isotiazolilo, furanilo, tienilo, oxadiazolilo, piridilo, pirazinilo, pirimidinilo, piridazinilo, triazinilo y similares.

Los grupos heteroarilo bicíclicos ejemplares incluyen indolilo, benzotiazolilo, benzodioxolilo, benzoxaxolilo, benzotienilo, quinolinilo, tetrahidroisoquinolinilo, isoquinolinilo, benzimidazolilo, benzopiranilo, indolizinilo, benzofuranilo, cromonilo, cumarinilo, benzopiranilo, cinolinilo, quinoxalinilo, indazolilo, pirrolopiridilo, furopiridinilo, dihidroisoindolilo, tetrahidroquinolinilo, y similares.

Los grupos heteroarilo tricíclicos ejemplares incluyen carbazolilo, benzidolilo, fenantrolinilo, acridinilo, fenantridinilo, xantenilo y similares.

El término "heterocicloalquilo" en la presente solo o como parte de otro grupo, se refiere a un grupo cicloalquilo (no aromático) en el cual uno de los átomos de carbono en el anillo se reemplaza por un heteroátomo seleccionado de O, S, o N, y en el cual hasta tres átomos de carbono adicionales se pueden reemplazar por los heteroátomos. El término

"heterocicloalquilo", en la presente solo o como parte de otro grupo, se refiere a un sistema de anillo monocíclico saturado, estable o parcialmente insaturado que contiene de 5 a 7 miembros de anillo de átomos de carbono y otros átomos seleccionados de nitrógeno, azufre y/u oxígeno. Un anillo heterocíclico puede ser un anillo monocíclico de 5, 6 o 7 miembros y contiene uno, dos, o tres heteroátomos seleccionados de nitrógeno, oxígeno y/o azufre. El anillo heterocíclico se puede substituir opcionalmente lo cual significa que el anillo heterocíclico se puede substituir en una o más posiciones de anillo substituibles por uno o más grupos seleccionados independientemente de alquilo (preferiblemente alquilo inferior), heterocicloalquilo, heteroarilo, alcoxi (preferiblemente alcoxi inferior), nitro, monoalquilamino (preferiblemente un alquilamino inferior), dialquilamino (preferiblemente un dialquilamino inferior), ciano, halo, haloalquilo (preferiblemente trifluorometilo), alcanoilo, aminocarbonilo, monoalquilaminocarbonilo, dialquilaminocarbonilo, alquil amido (preferiblemente alquilamido inferior) alcoxialquilo (preferiblemente alcoxi inferior alquilo[inferior]), alcoxicarbonilo (preferiblemente un alcoxicarbonilo inferior), alquilcarboniloxi (preferiblemente un alquilcarboniloxi inferior), y arilo (preferiblemente fenilo), el arilo estando opcionalmente substituido por halo, alquilo inferior y grupos alcoxi

inferior. Ejemplos de tales grupos heterocicloalquilo incluyen piperazina, piperidina, morfolina, homomorfolina, tiomorfolina, pirrolidina y azetidina.

Un grupo heteroarilo o heterocicloalquilo puede ser también un anillo bicíclico de 8-11 miembros que consiste de átomos de carbono, y contiene uno, dos, o tres heteroátomos seleccionados de nitrógeno, oxígeno y/o azufre. Algunos anillos bicíclicos preferidos incluyen benzodioxol, quinoxalina, indolilo, y quinolinilo. El término "opcionalmente substituido" como se refiere a "heteroarilo" o heterocicloalquilo en la presente indica que el grupo heterociclilo se puede substituir en una o más posiciones substituibles del anillo, por uno o más grupos independientemente seleccionados de alquilo (preferiblemente alquilo inferior), alcoxi (preferiblemente alcoxi inferior), nitro, monoalquilamino (preferiblemente un alquilamino inferior), dialquilamino (preferiblemente un dialquilamino inferior), ciano, halo, haloalquilo (preferiblemente trifluorometilo), alcanoilo, aminocarbonilo, monoalquilaminocarbonilo, dialquilaminocarbonilo, alquil amido (preferiblemente alquilamido inferior) alcoxialquilo (preferiblemente alcoxi inferior[inferior]alquilo), alcoxicarbonilo (preferiblemente un alcoxicarbonilo inferior), alquilcarboniloxi (preferiblemente un alquilcarboniloxi inferior), y arilo (preferiblemente

fenilo), el arilo estando opcionalmente substituido por halo, alquilo inferior y grupos alcoxi inferior.

El término "heteroátomo" significa O, S o N, seleccionado en una base independiente. Se debe observar que cualquier heteroátomo con valencias no satisfechas, se supone que tiene un átomo de hidrógeno para satisfacer las valencias.

El término "halógeno" o "halo" se refiere a cloro, bromo, flúor o yodo seleccionados en una base independiente.

El término agente "anticancerígeno" incluye cualquier agente conocido que sea útil para el tratamiento contra el cáncer incluyendo 17α-Etinilestradiol, Dietilestilbestrol, Testosterona, Prednisona, Fluoximesterona, Dromostanolona propionato, Testolactona, Megestrolacetato, Metilprednisolona, Metil-testosterona, Prednisolona, Triamcinolona, clorotrianiseno, Hidroxiprogesterona, Aminoglutetimida, Estramustina, Medroxiprogesteronoacetato, Leuprolida, Flutamida, Toremifeno, Zoladex, inhibidores de la matriz de metaloproteinasa, inhibidores VEGF, que incluyen anticuerpos VEGF tales como Avastina y moléculas pequeñas tales como ZD6474 y SU6668, vatalanib, BAY-43-9006, SU11248, CP-547632 y CEP-7055 también se incluyen. Los anticuerpos Anti-Her2 de Genentech (tal

como Herceptina) también se pueden utilizar. Los inhibidores adecuados EGFR incluyen gefitinib, erlotinib y cetuximab. Los inhibidores Pan Her incluyen canertinib, EKB-569 y GW-572016. También se incluyen los inhibidores Src, dasatinib (BMS-354825) así como Casodex® (bicalutamida, Astra Zeneca), Tamoxifen, inhibidores de la MEK-1 cinasa, inhibidores de MAPK cinasa, inhibidores PI3 e inhibidores PDGF tales como imatinib. También se incluyen agentes antiangiogénicos y antivasculares los cuales por interrupción del flujo sanguíneo a los tumores sólidos, producen células de cáncer quiescentes al suprimirles la nutrición. La castración, que también produce carcinomas que dependen de andrógenos no proliferativos también se puede utilizar. También se incluyen los inhibidores IGF1R, inhibidores de tirosina cinasas no receptoras y receptoras e inhibidores de la señalización de integrina. Los agentes anticáncer adicionales incluyen agentes que estabilizan los microtúbulos tales como paclitaxel (también conocido como Taxol®), docetaxel (también conocido como Taxotere®), 7-O-metiltiometilpaclitaxel (descrito en la E.U.A. 5,646,176), 4-desacetil-4-metilcarbonatopaclitaxel, 3'-tert-butil-3'-N-tert-butiloxicarbonil-4-desacetil-3'-defenil-3'-N-

desbenzoil-4-O-metoxicarbonil-paclitaxel (descrito en USSN 09/712,352 presentada el 14 de Noviembre 2000), C-4 metil carbonato paclitaxel, 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]heptadecan-5,9-diona (descrita en WO 99/02514), [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]-heptadecan-5,9-diona (descrita en USP 6,262,094) y derivados de los mismos; y agentes disruptores de microtúbulos. También son adecuados los inhibidores CDK, un inhibidor del ciclo celular antiproliferativo, epidofilotoxina, una enzima antineoplástica, un inhibidor de topoisomerasa, procarbazina, mitoxantrona, complejos de coordinación del platino tales como cisplatina y carboplatina; modificadores de la respuesta biológica, inhibidores de crecimiento, agentes terapéuticos antihormonales, leucovorin, tegafur y factores del crecimiento hematopoyético.

Los agentes citotóxicos adicionales incluyen

melfalan, hexametil melamina, tiotepa, citarabina, idatrexato, trimetrexato, dacarbazina, L-asparaginasa, camptotecina, topotecan, bicalutamida, flutamida, leuprolida, derivados de piridobenzoindol, interferones e interleucinas.

La N-oxi piridina se refiere a un anillo de piridina que tiene un oxígeno substituido en el átomo N del anillo de piridina.

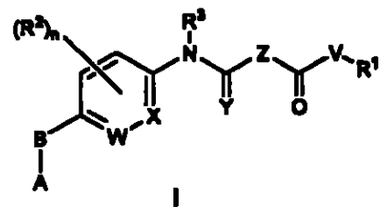
Cuando un grupo funcional se denomina "protegido", esto significa que el grupo está en una forma modificada para excluir reacciones colaterales indeseables en el sitio protegido. Los grupos protectores adecuados para los compuestos de la presente invención, se reconocerán de la solicitud actual tomando en cuenta el nivel de experiencia en la técnica, y con referencia a los libros de textos estándar tal como Greene, T. W. Et al., Protective Groups in Organic Synthesis, Wiley, N.Y. (1991).

Como se usa en la presente, el término "paciente" abarca todas las especies de mamíferos.

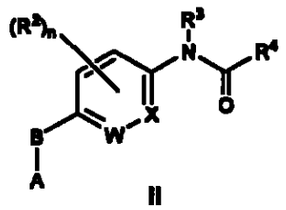
La frase "sales farmacéuticamente aceptables" como se usa en la presente, a menos que se indique de otra manera, incluye sales de grupos ácidos o básicos que pueden estar presentes en los compuestos de las Fórmulas I y II. Los compuestos de las Fórmulas I y II que son básicos en naturaleza pueden formar una amplia variedad de sales con

diversos ácidos orgánicos e inorgánicos. Los ácidos que se pueden usar para preparar sales de adición ácida farmacéuticamente aceptables de tales compuestos básicos de las Fórmulas I y II son aquellas que forman sales de adición ácidas no toxicas esto es, sales que contienen aniones farmacológicamente aceptables tales como sales de clorohidrato, bromohidrato, yodohidrato, nitrato, sulfato, bisulfato, fosfato, fosfato ácido, isonicotinato, acetato, lactato, salicilato, citrato, citrato ácido, tartrato, pantotenato, bitartrato, ascorbato, succinato, maleato, gentisinato, fumarato, gluconato, glucaronato, sacarato, formiato, benzoato, glutamato, metansulfonato, etansulfonato, bencenosulfonato, p-toluensulfonato y pamoato [esto es, 1,1'-metileno-bis-(2-hidroxi-3-naftoato)].

Los compuestos de la presente invención tienen la siguiente Fórmula I o II:



I



II

que incluyen sales farmacéuticamente aceptables de los mismos, en donde:

R^1 es H, alquilo, alquilo substituido, cicloalquilo, cicloalquilo substituido, arilalquilo, arilalquilo

substituido, arilo, arilo substituido, alquenilo, alquenilo substituido, alquinilo, alquinilo substituido, heteroarilo, heteroarilo substituido, heterociclo, heterociclo substituido, heteroarilalquilo, heteroarilalquilo substituido, heterocicloalquilo, o heterocicloalquilo substituido;

cada R^2 es independientemente, H, halógeno, ciano, NO_2, OR^5, NR^6R^7, alquilo, alquilo substituido, cicloalquilo, cicloalquilo substituido, arilo, arilo substituido, heteroarilo, heteroarilo substituido, heterociclo, heterociclo substituido, arilalquilo, arilalquilo substituido, heterocicloalquilo, o heterocicloalquilo substituido;

B es O, NR^8, S, SO, SO_2, CR^9R^{10};

V es NR^{11} o $-(CR^{47}R^{48})_p-$;

W o X son independientemente C o N;

Y es O, S, o NR^{12};

Z es $-CR^{13}R^{14}-$, $-(CR^{13}R^{14})_mNR^{15}-$;

l tiene un valor de 0 a 4;

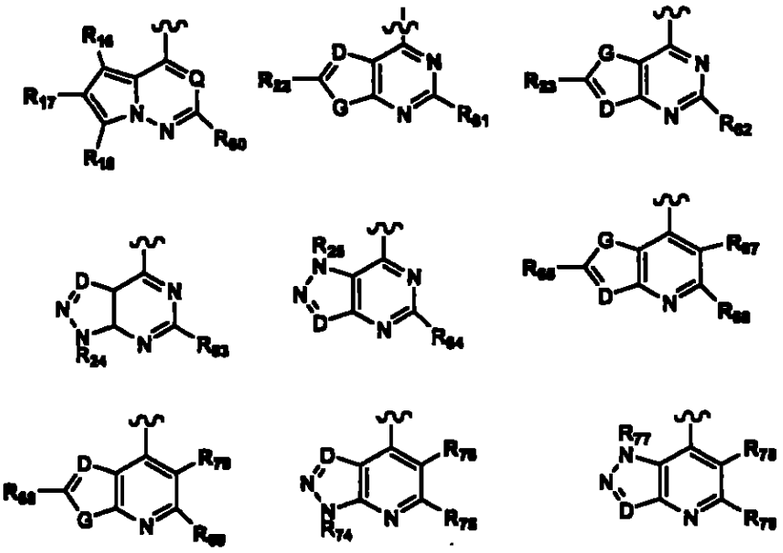
m tiene un valor de 0 a 2;

n tiene un valor de 0 a 4;

p tiene un valor de 0 a 4,

con la condición de que si p es 0, R^1 no es fenilo;

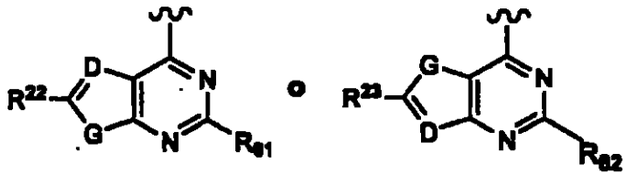
A es:



Q es CR^{19};

D es CR^{20} o N;

G es S, O u NR^{21}, con la condición de que si A es



y G es S, R^4 no es un grupo fenilo substituido;

R^3, R^5, R^6, R^7, R^8, R^{11} y R^{15} son cada uno independientemente H, alquilo, alquilo substituido, cicloalquilo, cicloalquilo substituido, arilo, arilo substituido, heteroarilo, heteroarilo substituido, heterocicloalquilo, o heterocicloalquilo substituido;

R^4 es arilo, arilo substituido, heteroarilo, heteroarilo

substituido, heterocicloalquilo, o heterocicloalquilo substituido;

R^9 y R^{10} son independientemente H, halógeno, alquilo, alquilo substituido, cicloalquilo, cicloalquilo substituido, arilo, arilo substituido, heteroarilo, heteroarilo substituido, heterocicloalquilo, o heterocicloalquilo substituido;

R^{12} es H, alquilo, alquilo substituido, CN, NO_2 o SO_2NH_2;

R^{13}, R^{14}, R^{15}, R^{47} y R^{48} son independientemente H, halógeno, alquilo, alquilo substituido, cicloalquilo, cicloalquilo substituido, arilo, arilo substituido, heteroarilo, heteroarilo substituido, heterociclo, heterociclo substituido o tomados juntos para formar un anillo heterocíclico o carbocíclico desde 3 a 8 átomos;

R^{16}, R^{17}, R^{18}, R^{20}, R^{22}, R^{23}, R^{60}, R^{61}, R^{62}, R^{63}, R^{64}, R^{65}, R^{66}, R^{67}, R^{68}, R^{69}, R^{70}, R^{75}, R^{76}, R^{78}, y R^{79}, son independientemente H, halógeno, NO_2, ciano, OR^{26}, $NR^{27}R^{28}$, CO_2R^{29}, $C(O)NR^{30}R^{31}$, SO_2R^{32}, $SO_2NR^{33}R^{34}$, $NR^{35}SO_2R^{36}$, $NR^{37}C(O)R^{38}$, $NR^{39}CO_2R^{40}$, $-CO(CH_2)_1R^{41}$; $-CONH(CH_2)_1R^{42}$, alquilaminoalquilo, alquilaminoalquinilo, alquilo C_1 a C_6, alquilo C_1 a C_6 substituido, cicloalquilo C_3 a C_7, cicloalquilo C_3 a C_7 substituido, alquenilo, alquenilo substituido, alquinilo, alquinilo substituido, hidroxialquilo, arilo, arilo substituido, heteroarilo, heteroarilo substituido,

arilalquilo, arilalquilo substituido, heterocicloalquilo, o heterocicloalquilo substituido;

R^{19} es H o ciano;

R^{21} y R^{24} son independientemente H, alquilo C_1 a C_6 o alquilo C_1 a C_6 substituido;

R^{25}, R^{74} y R^{77} son independientemente H, alquilo, alquilo substituido, cicloalquilo, cicloalquilo substituido, arilo, arilo substituido, arilalquilo, arilalquilo substituido, heteroarilo, heteroarilo substituido, heterocicloalquilo, o heterocicloalquilo substituido

R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, R^{33}, R^{34}, R^{35}, R^{36}, R^{37}, R^{38}, R^{39}, R^{40}, R^{41}, y R^{42} son independientemente H, alquilo, alquilo substituido, cicloalquilo, cicloalquilo substituido, arilo, arilo substituido, arilalquilo, arilalquilo substituido, heteroarilo, heteroarilo substituido, heterocicloalquilo, o heterocicloalquilo substituido.

La invención también proporciona un método para tratar una enfermedad proliferativa, tal como cáncer, para administrar a un paciente que necesite de tal tratamiento en una cantidad efectiva de un compuesto de la Fórmula I o II, como se define arriba.

En otra modalidad, la invención proporciona un método para el tratamiento contra una enfermedad proliferativa por medio de la modulación de la Met cinasa al administrar a un

paciente que necesita de tal tratamiento, una cantidad efectiva de un compuesto de fórmula I ó II como se define arriba, en combinación (simultáneamente o secuencialmente) con al menos algún otro agente anticancerígenos. En una modalidad preferida, la enfermedad proliferativa es cáncer.

La invención proporciona además composiciones farmacéuticas que comprenden compuestos que tienen la fórmula I ó II junto con un portador farmacéuticamente aceptable.

Más específicamente, los compuestos de las fórmulas I y II son útiles en el tratamiento contra una variedad de cánceres, incluyendo pero no limitado a los siguientes:

a) carcinoma incluyendo aquel de la vejiga, mama, colon, riñón, hígado, pulmón, incluyendo cáncer de pulmón de célula pequeña, esófago, vesícula biliar, ovario, páncreas estómago, cáncer cérvico, tiroides, próstata y piel incluyendo carcinoma de célula escamosa.

b) tumores hematopoyéticos de linaje linfoide incluyendo leucemia, leucemia linfocítica aguda, leucemia linfloblástica aguda, linfoma de células B, linfoma de células T, linfoma de Hodgkin, linfoma que no es Hodgkin, linfoma de célula vellosa, y linfoma de Burkett.

c) tumores hematopoyéticos de linaje mieloide incluyendo leucemias mielógenas agudas y crónicas, síndrome mielodisplástico y leucemia promielocítica.

d) tumores de origen mesenquimal, incluyendo

fibrosarcoma y rabdomiosarcoma.

e) tumores del sistema nervioso central y periférico incluyendo astrocitoma, neuroblastoma, glioma y schwanomas y

f) otros tumores incluyendo melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentosum, queratoctantoma, cáncer folicular de tiroides y sarcoma de Kaposi.

Debido al papel clave de las proteínas cinasas en la regulación de la proliferación celular en general, los inhibidores pueden actuar como agentes citoestáticos reversibles que pueden ser útiles en el tratamiento contra cualquier proceso de enfermedad que caracterice la proliferación celular anormal por ejemplo, hiperplasia prostática benigna, poliposis adenomatosa familial, neurofibromatosis, aterosclerosis, fibrosis pulmonar, artritis, psoriasis, glomerulonefritis, restenosis que sigue a la angioplastia o cirugía vascular, formación de cicatrices hipertróficas, enfermedad inflamatoria del intestino, rechazo de transplantes, choque endotóxico e infecciones fungales.

Los compuestos de Fórmulas I y II como moduladores de la apoptosis serán útiles en el tratamiento contra cáncer (incluido pero no limitado a aquellos tipos aquí mencionados arriba), infecciones virales (incluido pero no limitado al virus del herpes, virus de viruela, virus de Epstein-Barr, virus Sindbis y adenovirus), prevención del desarrollo del

SIDA en individuos infectados por VIH, enfermedades autoinmunes (incluido pero no limitado a lupus eritematoso sistémico, glomerulonefritis mediada autoinmune, artritis reumatoide, psoriasis, enfermedad inflamatoria del intestino y diabetes mellitus autoinmune, trastornos neurodegenerativos (incluido pero no limitado a enfermedad de Alzheimer, demencia relacionada con el SIDA, enfermedad de Parkinson, esclerosis lateral amiotrófica, retinitis pigmentosa, atrofia muscular espinal, y degeneración cerebelar), síndromes mielodisplásticos, anemia aplástica, lesión isquémica asociada con los infartos al miocardio, apoplejía y lesión por repurfusión, arritmia, aterosclerosis, enfermedades del hígado relacionadas con el alcohol o inducidas por toxina, enfermedades hematológicas (incluido pero no limitado a anemia crónica y anemia aplástica), enfermedades degenerativas de sistema músculo esqueletal (incluido pero no limitado a osteoporosis y artitris), rinosinusitis sensible a la aspirina, fibrosis quística, esclerosis múltiple, enfermedades del riñón y dolor por cáncer.

Los compuestos de Fórmulas I y II pueden modular el nivel de ARN celular y la síntesis del ADN. Estos agentes serían por lo tanto útiles en el tratamiento contra infecciones virales (incluido pero no limitado a VIH, virus de papiloma humano, virus de herpes, virus de la viruela, virus de Epstein-Barr, virus Sindbis y adenovirus).

Los compuestos de las Fórmulas I y II pueden ser útiles en el quimioprevención del cáncer. La quimioprevención se define como que inhibe el desarrollo de un cáncer invasivo por el bloqueo del inicio del evento mutagénico o al bloquear el avance de la células premalignas que ya han padecido una lesión o inhibir la recurrencia de tumores.

Los compuestos de Fórmulas I y II también pueden ser útiles en la angiogénesis de tumor y la metástasis.

Se ha encontrado que algunos compuestos de la presente invención, inhiben las proteína cinasas diferentes a Met, tales como aquellos en la familia Trk de las proteína cinasas.

Los compuestos de esta invención también pueden ser útiles en combinación (administrados juntos o secuencialmente) con tratamientos conocidos para el cáncer tales como terapia por radiación o con agentes citotóxicos o citoestáticos, tales como por ejemplo, pero no limitado a, agentes interactivos del ADN, tales como cisplatina o doxorubicina, inhibidores de topoisomerasa II tales como etopósido, inhibidores de topoisomerasa I tales como CPT-11 o topotecan; agentes de interacción de tubulina, tales como paclitaxel, docetaxel o las epotilonas (por ejemplo, ixabepilona), ya sea que se presenten naturalmente o sintéticos; agentes hormonales, tales como tamoxifen; inhibidores de la timidilato sintasa, tales como el 5-

fluorouracil; y antimetabolitos, tales como metotrexato, otros inhibidores de la tirosina cinasa tales como Iressa y OSI-774; inhibidores de la angiogénesis; inhibidores EGF; inhibidores VEGF; inhibidores CDK; inhibidores SRC; inhibidores c-Kit; inhibidores Her ½ y anticuerpos monoclonales dirigidos contra receptores del factor de crecimiento tales como erbitux (EGF) y herceptin (Her2).

Las composiciones farmacéuticas que contienen el ingrediente activo pueden estar en una forma adecuada para uso oral, por ejemplo, como tabletas, trociscos, grageas, suspensiones acuosas o aceitosas, polvos dispersables o gránulos, emulsiones, cápsulas duras o suaves o jarabes o elixires. Las composiciones pretendidas para uso oral se pueden preparar de acuerdo con cualquier método conocido en el arte, para la fabricación de composiciones farmacéuticas y tales composiciones pueden contener uno o más agentes seleccionados del grupo que consiste de agentes edulcorantes, agentes saborizantes, agentes colorantes, y agentes conservadores, con objeto de proporcionar preparaciones con buen sabor y presentables farmacéuticamente. Las tabletas contienen un ingrediente activo en mezcla con excipientes farmacéuticamente aceptables no tóxicos que son adecuados para la fabricación de tabletas. Estos excipientes pueden ser por ejemplo, diluyentes inertes tales como carbonato de calcio, carbonato de sodio, lactosa, fosfato de calcio, o

fosfato de sodio, agentes de granulación y desintegración por ejemplo, celulosa microcristalina, croscarmelosa de sodio, almidón de maíz o ácido algínico, agentes de enlace por ejemplo, almidón, gelatina, polivinilpirrolidona, o acacia y agentes lubricantes por ejemplo estearato de magnesio, ácido esteárico o talco. Las tabletas pueden estar sin recubrir o se pueden recubrir por técnicas conocidas para ocultar el sabor desagradable del fármaco o retrasar la desintegración y absorción en el tracto gastrointestinal y con ello provocar una acción sostenida durante un periodo prolongado. Por ejemplo se puede emplear un material que oculta el sabor soluble en agua tal como hidroxipropil-metilcelulosa o hidroxipropil-celulosa o un material que retrasa el tiempo tal como etil celulosa, butirato del acetato de celulosa.

Las formulaciones para uso oral también pueden presentarse como cápsulas de gelatina dura en donde el ingrediente activo se mezcla con un diluyente sólido inerte, por ejemplo, carbonato de calcio, fosfato de calcio o caolín, o como cápsula de gelatina suave en donde el ingrediente activo se mezcla con un portador soluble en agua tal como polietilenglicol o un medio aceitoso, por ejemplo, aceite de cacahuate, parafina líquida, o aceite de olivo.

Las suspensiones acuosas contienen el material activo en mezcla con excipientes apropiados para la fabricación de suspensiones acuosas. Tales excipientes son agentes de

suspensión, por ejemplo carboximetil celulosa de sodio, metil celulosa, hidroxipropilmetil-celulosa, alginato de sodio, polivinil-pirrolidona, goma de tragacanto y goma de acacia; agentes dispersantes o humectantes pueden ser una fosfatida que se presenta naturalmente, por ejemplo, lecitina o productos de condensación de óxido de alquileno con ácidos grasos, por ejemplo, estearato de polioxietileno, o productos de condensación de óxido de etileno con alcoholes alifáticos de cadena larga, por ejemplo, heptadecaetilen-oxicetanol o productos de condensación de óxido de etileno con ésteres parciales derivados de ácidos grasos y un hexitol tal como monooleato de polioxietilen sorbitán, o productos de condensación de óxido de etileno con ésteres parciales derivados de ácidos grasos y anhídridos de hexitol, por ejemplo, monooleato de polietilen sorbitán. Las suspensiones acuosas también pueden contener uno o más conservadores, por ejemplo, etilo o n-propil p-hidroxibenzoato, uno o más agentes colorantes y uno o más agentes saborizantes y uno o más agentes edulcorantes tales como sacarosa, sacarina o aspartame.

Las suspensiones aceitosas pueden formularse al suspender el ingrediente activo en aceite vegetal, por ejemplo, aceite de cacahuate, aceite de olivo, aceite de ajonjolí o aceite de coco, o un aceite mineral tal como parafina líquida. Las suspensiones aceitosas pueden contener

un agente espesante, por ejemplo, cera de abeja, parafina dura, o alcohol cetílico. Los agentes edulcorantes tales como aquellos establecidos arriba, y agentes saborizantes pueden agregarse para proporcionar una preparación oral de buen sabor. Estas composiciones pueden conservarse por la adición de un antioxidante tal como hidroxianisol butilado o alfa-tocoferol.

Los polvos y gránulos dispersables apropiados para la preparación de una suspensión acuosa por la adición de agua proporcionan el ingrediente activo en mezcla con un agente dispersante o humectante, agente de suspensión y uno o más conservadores. Los agentes dispersantes o humectantes apropiados y agentes de suspensión se ejemplifican por aquellos ya mencionados arriba. Los excipientes adicionales, por ejemplo, agentes edulcorantes, saborizantes y colorantes también pueden presentarse. Estas composiciones pueden conservarse por la adición de un antioxidante tal como ácido ascórbico.

Las composiciones farmacéuticas de la invención también pueden estar en forma de emulsiones de aceites en agua. La fase aceitosa puede ser un aceite vegetal por ejemplo, aceite de olivo o aceite de cacahuate o un aceite mineral, por ejemplo, parafina líquida o mezclas de estos. Los agentes emulsificantes adecuados pueden ser fosfatidas que se presentan naturalmente, por ejemplo, lecitina de frijol de

soya o ésteres parciales derivados de ácidos grasos y anhídridos de hexitol, por ejemplo, monooleato de sorbitán y productos de condensación de los ésteres parciales con óxido de etileno por ejemplo, monooleato de polioxietilen sorbitán. Las emulsiones también pueden contener edulcorantes, agentes saborizantes, conservadores y antioxidantes.

Se pueden formular los jarabes y elixires con agentes edulcorantes por ejemplo, glicerol, propilen glicol, sorbitol o sacarosa. Tales formulaciones también pueden contener un emulgente, o conservador, agentes saborizantes y colorantes, y antioxidantes.

Las composiciones farmacéuticas pueden estar en forma de soluciones acuosas inyectables. Entre los vehículos y solventes adecuados aceptables que se pueden emplear están el agua, solución de Ringer, y solución isotónica de cloruro de sodio.

La preparación inyectable estéril también puede ser una microemulsión de aceite en agua inyectable estéril, en donde se disuelve el ingrediente activo en la fase aceitosa. Por ejemplo, el ingrediente activo se puede disolver primero en una mezcla de aceite de soya y de lecitina. La solución aceitosa luego se introduce en una mezcla de agua y de glicerol y se procesa para formar una microemulsión.

Las soluciones inyectables o microemulsiones se pueden introducir en el torrente sanguíneo de un paciente por

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inyección local de bolo. Alternativamente puede ser ventajoso administrar la solución o la microemulsión en una forma tal que se mantenga una concentración constante en circulación del compuesto actual. Con objeto de mantener tal concentración constante, se puede utilizar un dispositivo de suministro intravenoso continuo. Un ejemplo de tal dispositivo es el Deltec CADD-PLUS.TM. modelo 5400 de bomba intravenosa.

Las composiciones farmacéuticas pueden estar en forma de una suspensión oleaginosa o acuosa inyectable estéril para administración intramuscular y subcutánea. Esta suspensión se puede formular de acuerdo al arte conocido, usando aquellos agentes de dispersión o humectantes adecuados y agentes de suspensión que han sido mencionados anteriormente. La preparación inyectable estéril puede ser también una solución inyectable estéril o una suspensión en un diluyente o solvente no tóxico parenteralmente aceptable por ejemplo, como una solución en 1,3-butanodiol. Además se emplean convencionalmente los aceites fijos estériles como un solvente o un medio de suspensión. Para este propósito se puede emplear cualquier aceite fijo blando incluyendo mono o diglicéridos sintéticos. Además los ácidos grasos tal como el ácido oleico encuentran uso en la preparación de inyectables.

Los compuestos de las fórmulas I y II también se pueden administrar en forma de supositorios para administración

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rectal del fármaco. Estas composiciones se pueden preparar al mezclar el fármaco con un excipiente no irritante adecuado que es sólido a temperaturas ordinarias, pero es líquido a la temperatura rectal, y se fundirá por lo tanto en el recto para liberar el fármaco. Tales materiales incluyen manteca de cacao, gelatina glicerinada, aceites vegetales hidrogenados, mezclas de polietilenglicoles de diversos pesos moleculares y ésteres de ácidos grasos del polietilenglicol.

Para uso local, se emplean cremas, ungüentos, soluciones o suspensiones etc., que contienen el compuesto de fórmula I (Para propósitos de esta aplicación, la aplicación tópica debe incluir lavados bucales y gargarismos).

Los compuestos de la presente invención se pueden administrar en forma intranasal, por medio del uso tópico de vehículos intranasales adecuados y dispositivos de suministro, o por medio de vías transdermales, usando aquellas formas de parches para la piel transdermales bien conocidos por aquellos de experiencia ordinaria en la técnica. Para administrarse en forma de un sistema de suministro transdermal, la administración de dosis será por supuesto continua más que intermitente a lo largo del régimen de dosis. Los compuestos de la presente invención también se pueden suministrar como un supositorio que emplea bases tal como manteca de cacao, gelatina glicerinada, aceites vegetales hidrogenados, mezclas de polietilenglicoles de diversos pesos moleculares, y ésteres de ácidos grasos del polietilenglicol.

Cuando se administra un compuesto de conformidad con esta

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invención en un sujeto humano, la dosis diaria se determinará normalmente por el médico que recete con la dosis que varía generalmente de acuerdo con la edad, peso, sexo y respuesta del paciente en lo individual, así como la severidad de los síntomas del paciente.

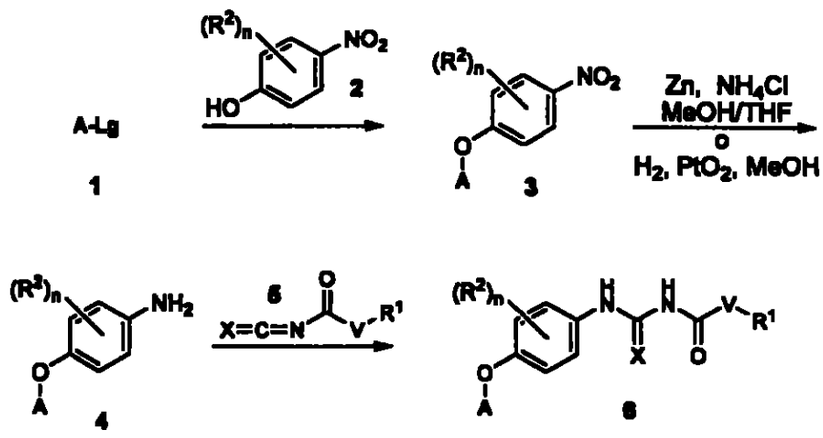
Si se formula como una dosis fija, tales productos de combinación emplean los compuestos de esta invención dentro del intervalo de dosis antes descrito, y el otro agente o tratamiento farmacéuticamente activo dentro de su intervalo de dosis aprobado. Los compuestos de fórmulas I y II también se pueden administrar secuencialmente con agentes citotóxicos o anticáncer conocidos cuando es inadecuada una formulación de combinación. La invención no se limita en la secuencia de administración; los compuestos de las fórmulas I y II se puede administrar previo o después de la administración de los agentes anticáncer o citotóxicos conocidos.

Ciertos compuestos de las fórmulas I y II se pueden preparar generalmente de acuerdo a los siguientes Esquemas de Reacción 1-16. Los compuestos se sintetizan fácilmente usando métodos sintéticos conocidos por aquellos expertos en la técnica. Los tautómeros y los solvatos (por ejemplo, hidratos) de los compuestos de las fórmulas I y II también están dentro del alcance de la presente invención. Se conocen generalmente en el arte los métodos de solvatación. De esta manera los compuestos de la invención actual pueden estar en forma libre o hidratada y se pueden obtener por los métodos ejemplificados por los siguientes Esquemas de Reacción.

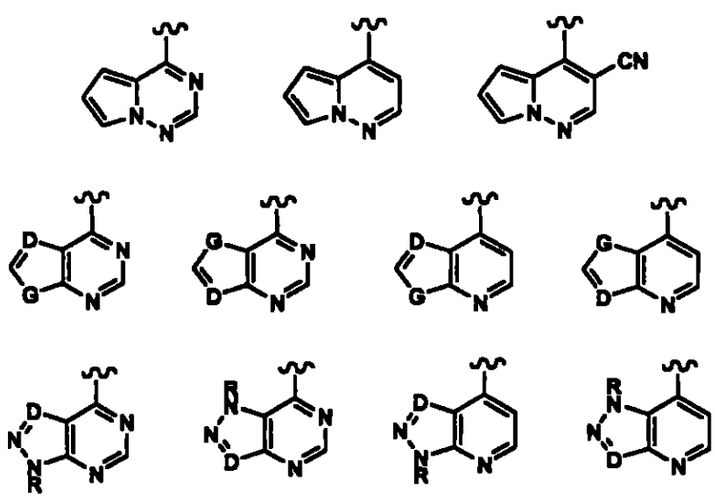
En general, los heterociclos fusionados deseados se pueden preparar usando las vías sintéticas detalladas en los Esquemas de Reacción 1-3. El grupo residual (Lg) tal como un halógeno (o triflato) de un heterociclo (A por lo cual las posiciones abiertas se pueden substituir opcionalmente) 1, se puede desplazar con un fenol 2 substituido para suministrar el éter 3 (Esquema de Reacción 1). Los grupos A-Lg se pueden preparar se acuerdo con los procedimientos generales detallados en por ejemplo, Hunt, J. T et al. WO 00/071129; Hunt, J. T. et al. J. Med. Chem. 2004, 47, 4054-4059; Leftheris, K. et al. WO 02/040486; Mastalerz, H. et al. WO 03/042172; Dyckman, A. et al., WO 03/091229; Vite, G. D. et al. WO 04/054514; Salvati, M.E. et al. WO 03/082208; Thibault, C et al. Org. Lett. 2003, 5, 5023-5025; Zhang, Z et al., J. Org. Chem. 2002, 67, 2345-2347; Itoh, T et al. J. Heterocyclic Chem. 1982, 19, 513-517; Tedder, M. E. et al. Bioorg. Med. Chem. Lett. 2004, 14, 3165-3168; Dorn, H. et al. J, Parkt Chem. 1982, 324, 557; Sanghvi. Y. S. et al. J. Med. Chem. 1989, 32, 945-951; Temple, C. Jr et al. J. Org., Chem. 1972, 37, 3601-3604, Hurst J. et al. EP119774; Hurst J. et al. EP151962; Ward, R. W et al. EP152910; Luzzio, M.J. et al WO 01/094353; Marx, M.A. et al. WO 03/000194; Boschelli. D.H. et al. WO 04/048386; He, M., et al. WO 05/021554; Barker, J.M. et al. J. Chem, Res., Synopses 1986, 4, 122-123, las descripciones de las cuales se incorporan en la presente como referencia. La reducción del grupo nitro del intermediario 3 con por ejemplo, polvo de zinc y cloruro de amonio o catalizador de Adam (óxido de platino (IV)) en condiciones de hidrogenación catalítica puede

resultar en la anilina 4. El tratamiento de la anilina 4 con un isocianato 5(X = O) o isotiocianato 5(X = S) resulta en la acilurea deseada o la aciltiourea 6, respectivamente.

ESQUEMA DE REACCIÓN 1



A =



Lg = grupo residual, tal como halógeno.

X = O, o S

G es O, S, o NR^{21}

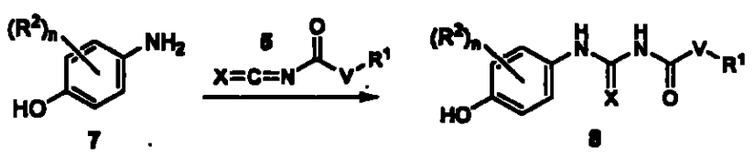
D es CR^{20} o N

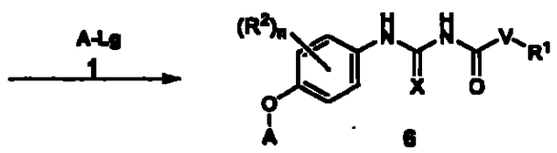
V= es como se define arriba

Alternativamente, la anilina 7 adecuadamente substituida se puede tratar con un isocianato 5 (X = O) o isotiocianato 5 (X = S) para dar el fenol 8 (Esquema de Reacción 2).

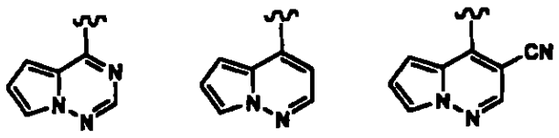
La reacción del intermediario 8 con un heterociclo (A-Lg)1 puede proporcionar el compuesto deseado 6.

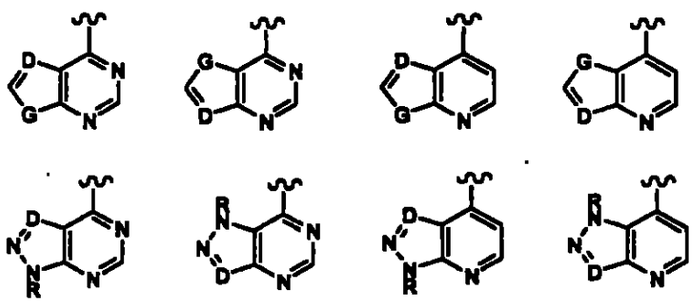
ESQUEMA DE REACCIÓN 2





A=





Lg = grupo residual, tal como halógeno.

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X = O, o S

G es O, S, o NR^{21}

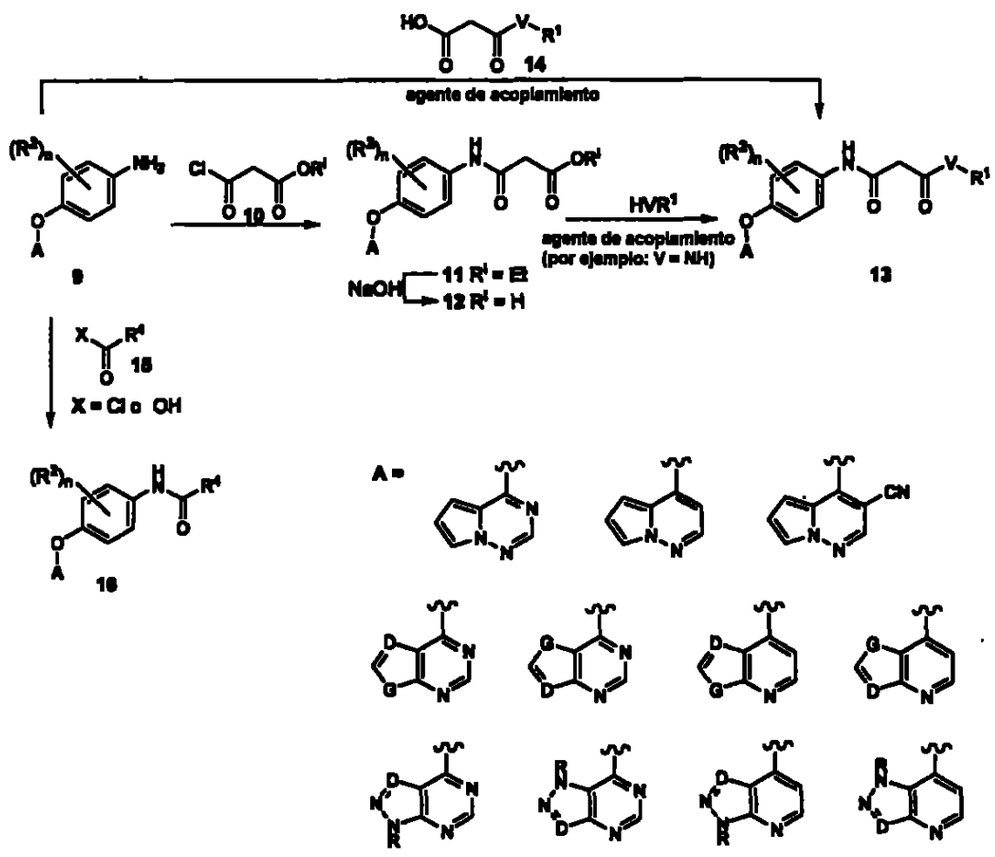
D es CR^{20} o N

V= es como se define arriba

En general, los derivados de amida descritos en la invención se pueden preparar usando la química detallada en el Esquema de Reacción 3. Por ejemplo, la anilina 9 (derivada del Esquema de Reacción 1) se puede acilar con el compuesto 10 para proporcionar la amida 11. La hidrólisis del éster con por ejemplo, hidróxido de sodio puede resultar en el ácido carboxílico 12. El compuesto 13 deseado puede luego obtenerse del intermediario 12 usando condiciones de formación conocidas del enlace amida. Alternativamente, la anilina 9 se puede convertir directamente al compuesto 13 usando ácido carboxílico 14 y un agente de acoplamiento tal como clorohidrato de benzotriazol-1-iloxitris(trimetilamino)fosfonio hexafluorofosfato, 1-(dimetilaminopropil)-3-etilcarbodiimida o bromotripirrolidinfosfonio hexafluorofosfato. El tratamiento de anilina 9 con el cloruro de ácido 15 (X = Cl) o un ácido carboxílico 15 (X = OH) y un reactivo de acoplamiento puede proporcionar amidas del tipo 16.

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ESQUEMA DE REACCIÓN 3



G es O, S, o NR^{21}

D es CR^{20} o N

V= como se define arriba

Un derivado heterocíclico substituido por ejemplo, un compuesto de pirrolotriazina 26a/b (Esquema de Reacción 5) se puede preparar usando las vías sintéticas detalladas en los Esquemas de Reacción 4 y 5. Ésteres carboxílicos en donde R puede ser un alquilo o un arilo (tal como fenilo) 17 pueden

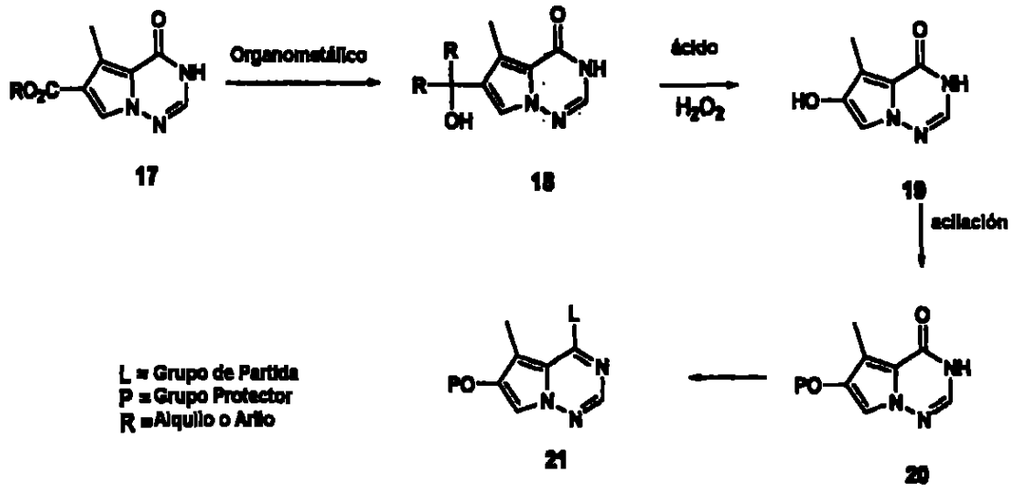
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hacer contacto con no menos de 2 equivalentes de un agente organometálico de alquilo o arilo tal como reactivo Grignard, organolitio, organozinc, etc. para producir el alcohol terciario 18 (Esquema de Reacción 4). La reacción se lleva a cabo generalmente en un solvente de éter tal como tetrahidrofurano, éter de dibutilo o éter de dietilo o cualquier otro solvente no reactivo tal como benceno, tolueno, o hexano, por ejemplo. El alcohol terciario 18 se puede tratar con una mezcla de ácido en presencia de peróxido de hidrógeno o peróxidos orgánicos tales como t-butilhidroperóxido, hidroperóxido de cumeno para afectar la reconfiguración para la hidroxipirrolotriazina 19. Casi cualquier ácido se puede usar como catalizador para la reconfiguración oxidante, la reacción se ha demostrado con ácidos orgánicos, ácidos minerales y ácidos Lewis. Algunos ácidos que se han usado para este tipo de reacción incluyen el ácido p-toluensulfónico ácido metansulfónico, ácido fórmico, ácido sulfúrico, ácido nítrico, BF_3-OEt_2 ácido trifluoroacético, zeolitas ácidas, y resinas de intercambio de iones ácidos. La concentración del ácido se puede variar, la concentración y resistencia del ácido se usa para controlar la cinética de la reacción. La

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concentración del peróxido se puede variar desde 30-50%. Cualquier agente reductor que reaccione para descomponer al peróxido de hidrógeno se puede usar en el apagado de esta reacción, incluyendo pero no limitado al metabisulfito de sodio, sulfito ácido de sodio, tiosulfato de sodio, hidrosulfito de sodio. Se puede usar una diversidad de bases mientras se apaga la reacción para controlar el pH. Puede reaccionar la hidroxipirrolotriazina 19 con una diversidad de reactivos acilantes para resultar en 20 (en donde por ejemplo, P puede ser el éster de pivalato). El compuesto 20 puede hacer contacto con un agente de halogenación adecuado (por ejemplo, oxicloruro de fósforo $POCl_3$) para resultar 21 (L = Cl). Se pueden usar otros reactivos para efectuar esta transformación además de $POCl_3$ incluyendo PCl_5 mezclas de $PCl_5/POCl_3$, $PhP(O)Cl_2$, $SOCl_2$. Usualmente se utiliza una amina para catalizar la reacción incluyendo Et_3N, $PhNMe_2$, DABCO, etc. Adicionalmente, las formamidas tales como por ejemplo, N,N-dimetilformamida y alquilamidas tal como N-metilpirrolidinona pueden también usarse para catalizar la reacción. La reacción puede correr en cualquier solvente inerte al agente halogenante incluyendo benceno, tolueno, THF, etc.

ESQUEMA DE REACCIÓN 4

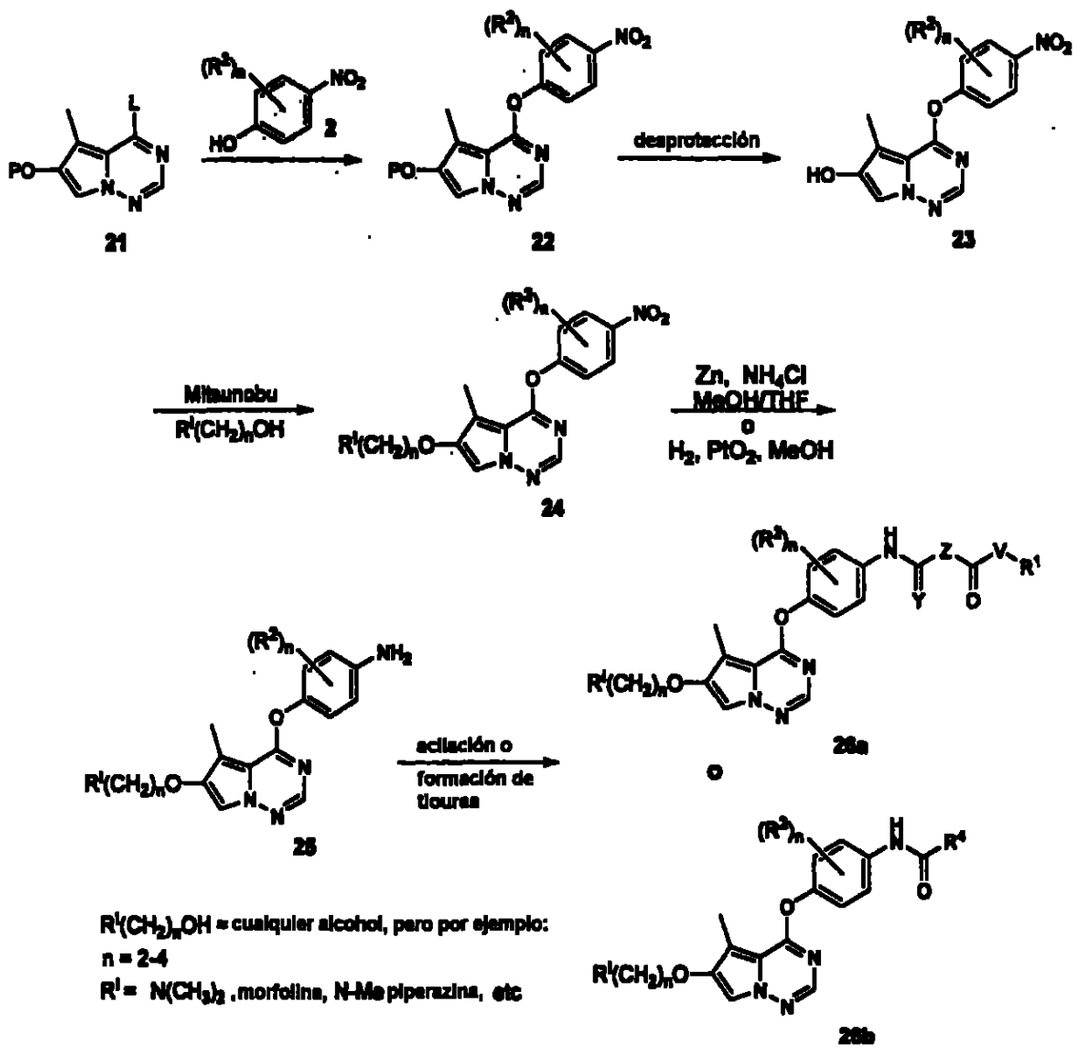


17 18 19 20 21

El imidato 21 adecuadamente protegido (Esquema de Reacción 5) se puede tratar con un fenol 2 opcionalmente sustituido para suministrar el intermediario 22. El fenol 23, derivado de la desprotección del compuesto 22 (usando hidróxido de sodio en el caso en donde P= pivalato) se puede convertir al éter 24 por medio de una reacción Mitsunobu con un alcohol. La reducción del sustituto nitro de 24 usando las mismas condiciones antes descritas en el Esquema de Reacción 1 puede ensamblar la anilina 25. La conversión de la anilina 25 a la acilurea, aciltiourea o amida deseada 26a/b puede lograrse usando la química previamente descrita en los Esquemas de Reacción 1 y 3.

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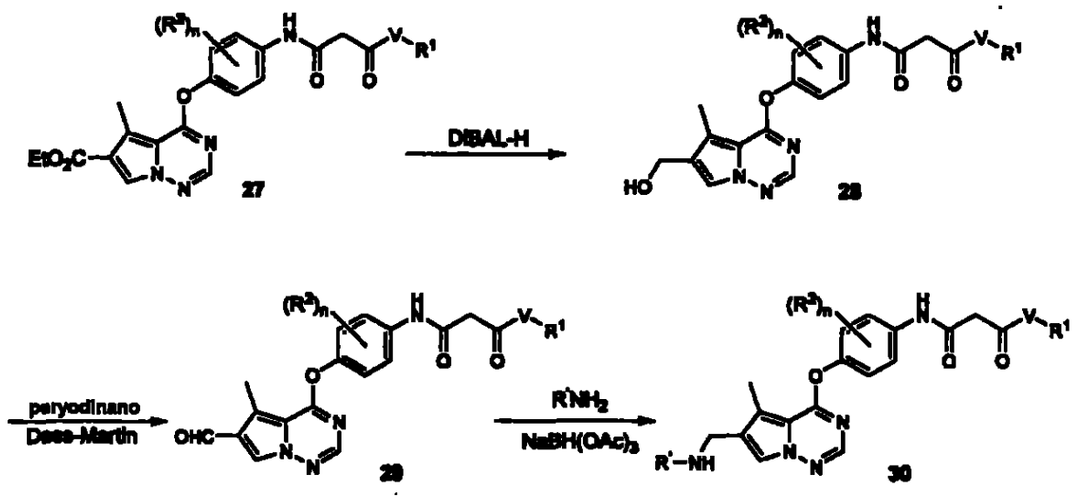
ESQUEMA DE REACCIÓN 5



Los compuestos de amina 30 se pueden preparar usando la química descrita en el Esquema de Reacción 6. La reducción del éster 27 con por ejemplo, el hidruro de diisobutilaliminio (DIBAL-H) puede proporcionar el alcohol 28. La oxidación del compuesto 28 con por ejemplo, periodinano Dess-Martin (1,1,1-tris(acetiloxi)-1,1-dihidro-1,2-benziodoxol-3-(1H)-ona) puede resultar en el aldehído 29. La aminación

reductora del aldehído 29 con una amina adecuadamente substituida en presencia de un agente reductor tal como triacetoxiborohidruro de sodio puede resultar en la amina deseada 30.

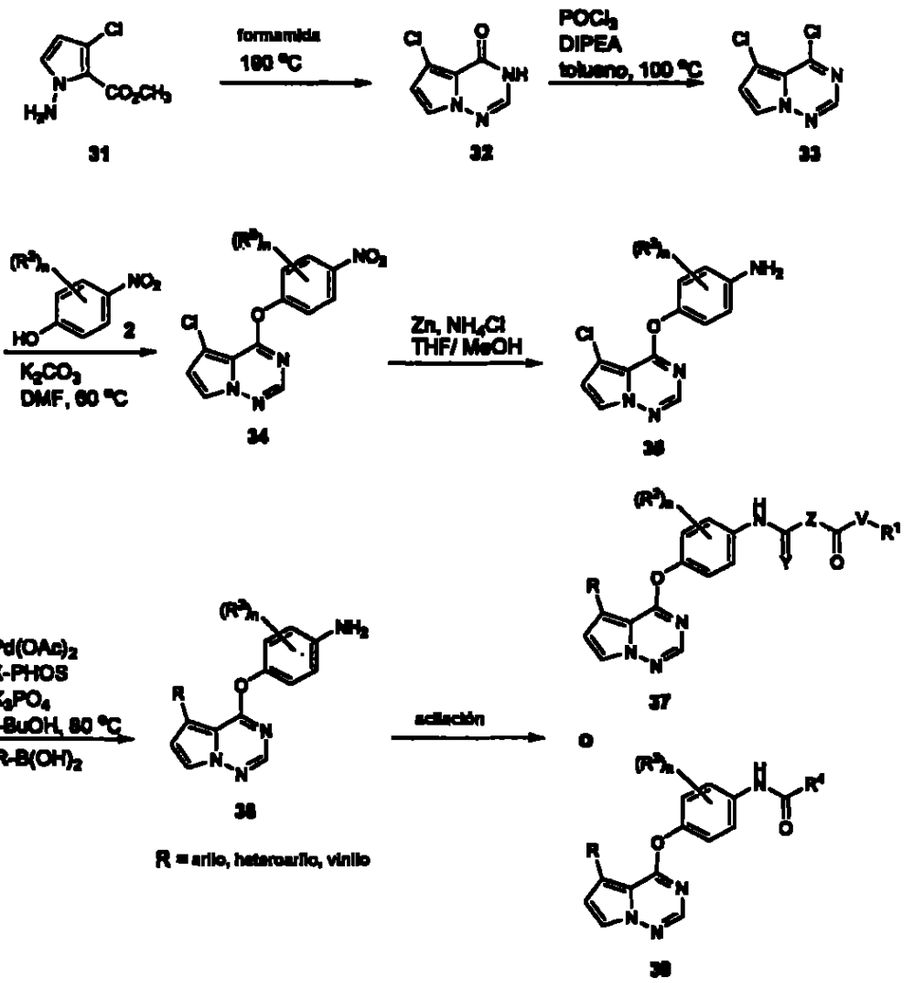
ESQUEMA DE REACCIÓN 6



Diversos sustitutos, tales como los grupos arilo, heteroarilo, o vinilo opcionalmente substituidos se pueden introducir en la posición 5 del anillo pirrol[2,1-*f*][1,2,4]triazina usando la química detallada en el Esquema de Reacción 7. El derivado de aminopirrol 31 puede ciclizarse en presencia de formamida para producir 5-cloropirrolo[2,1-*f*][1,2,4]triazin-4(3H)-ona(32). El tratamiento del intermediario 32 con $POCl_3$ en la presencia de una base, tal como una base Hunig a temperaturas elevadas puede producir 4,5-dicloropirrolo[2,1-*f*][1,2,4]triazina (33). El acoplamiento de un fenol 2 adecuadamente substituido con el compuesto 33 en presencia de una base tal como carbonato de potasio puede proporcionar el intermediario 34. El grupo

nitro de 34 se puede reducir usando polvo de zinc y cloruro de sodio para generar la anilina 35. Las reacciones de acoplamiento mediadas por paladio con diversos ácidos borónicos puede proporcionar el intermediario 36, que se puede convertir a los compuestos deseados 37 o 38 usando la química antes descrita.

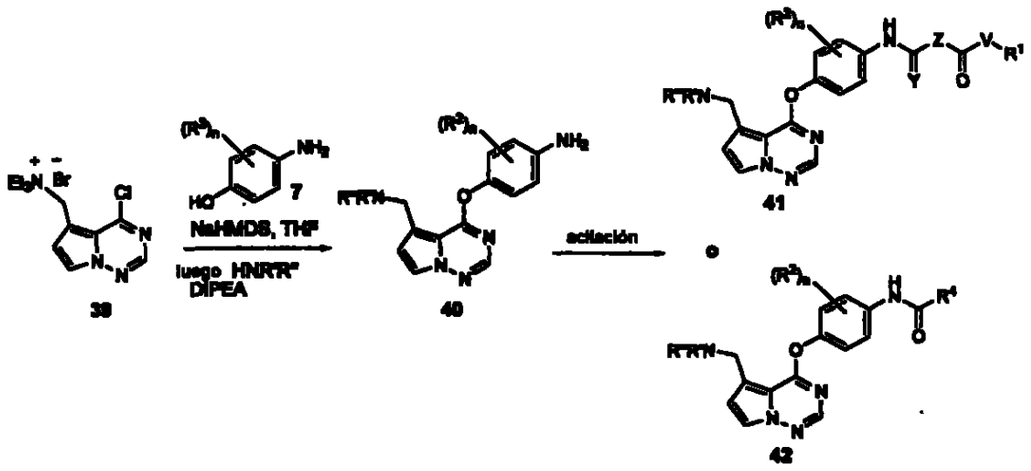
ESQUEMA DE REACCIÓN 7



La substitución en la posición 5 del anillo

pirrol-[2,1-f][1,2,4]triazina puede también lograrse por el acoplamiento de la sal de trietilamonio 39 con un fenol 7 adecuadamente substituido seguido por el tratamiento con una amina (HNR'R") en presencia de una base tal como una base Hunig para resultar la anilina 40 (Esquema de Reacción 8). La anilina 40 se puede procesar además como se describe previamente para producir los compuestos deseados 41 o 42.

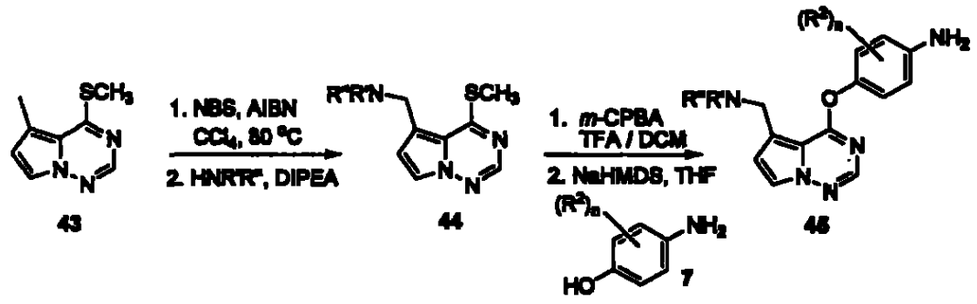
ESQUEMA DE REACCIÓN 8



Alternativamente, la 5-metil-4-(metiltio)pirrol[2,1-f][1,2,4]triazina(43) se puede bromar con por ejemplo, N-bromosuccinimida (NBS) y 2,2'-azobisisobutironitrilo (AIBN) en tetracloruro de carbono a temperaturas elevadas (Esquema de Reacción 9). El tratamiento del intermediario de bromuro con una amina (HNR'R") en presencia de una base tal como

base Hunig puede proporcionar el intermediario 44. La oxidación del grupo tiometilo de 44 se puede lograr con por ejemplo, ácido 3-cloroperbenzoico (m-CPBA). El tratamiento del intermediario de sulfona con el fenóxido generado del compuesto 7 y sodio bis(trimetilsililo)amida (NaHMDS) proporcionar el intermediario de anilina 45.

ESQUEMA DE REACCIÓN 9

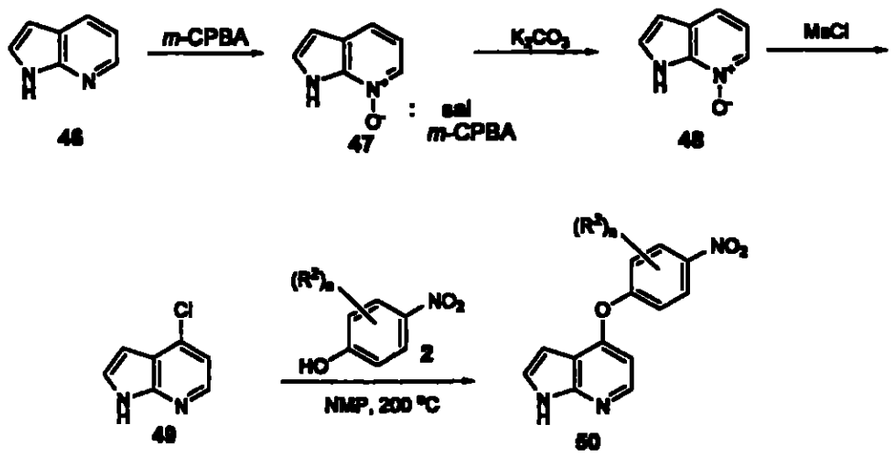


El intermediario de pirrol[2,3-b]piridina 50 se puede usar en la química detallada en el Esquema de Reacción 10. 4-Cloro-1H-pirrol[2,3-b]piridina (49) se puede obtener a partir de 1H-pirrol[2,3-b]piridina (46) comercialmente disponible usando la secuencia sintética descrita por Thibault C. y colaboradores (Org. Lett. 2003, 5, 5023-5025) que se ilustran en el Esquema de Reacción 10. El tratamiento del intermediario 49 con el fenol 2 a temperaturas elevadas puede proporcionar el intermediario clave

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50, que se puede convertir a los compuestos deseables usando la química descrita en los Esquemas de Reacción 1 y 3.

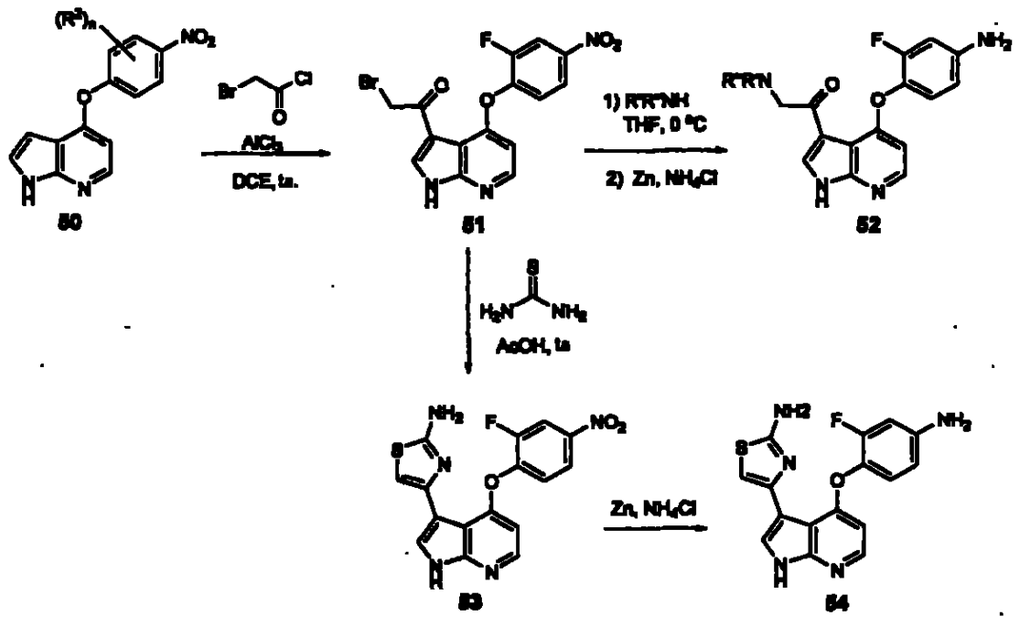
ESQUEMA DE REACCIÓN 10



La incorporación de varios sustitutos en la posición 3 del anillo pirrol[2,3-b]piridina se puede lograr usando la química descrita en los Esquemas de Reacción 11 y 12. Por ejemplo, la acilación del intermediario 50 con cloruro de 2-bromoacetilo en presencia de tricloruro de aluminio pueden proporcionar el compuesto 51 (Esquema de Reacción 11). El tratamiento del intermediario 51 con una amina (R"R'NH) o tiourea, seguido por la reducción posterior con polvo de zinc y cloruro de amonio puede proporcionar las anilinas 52 y 54 respectivamente.

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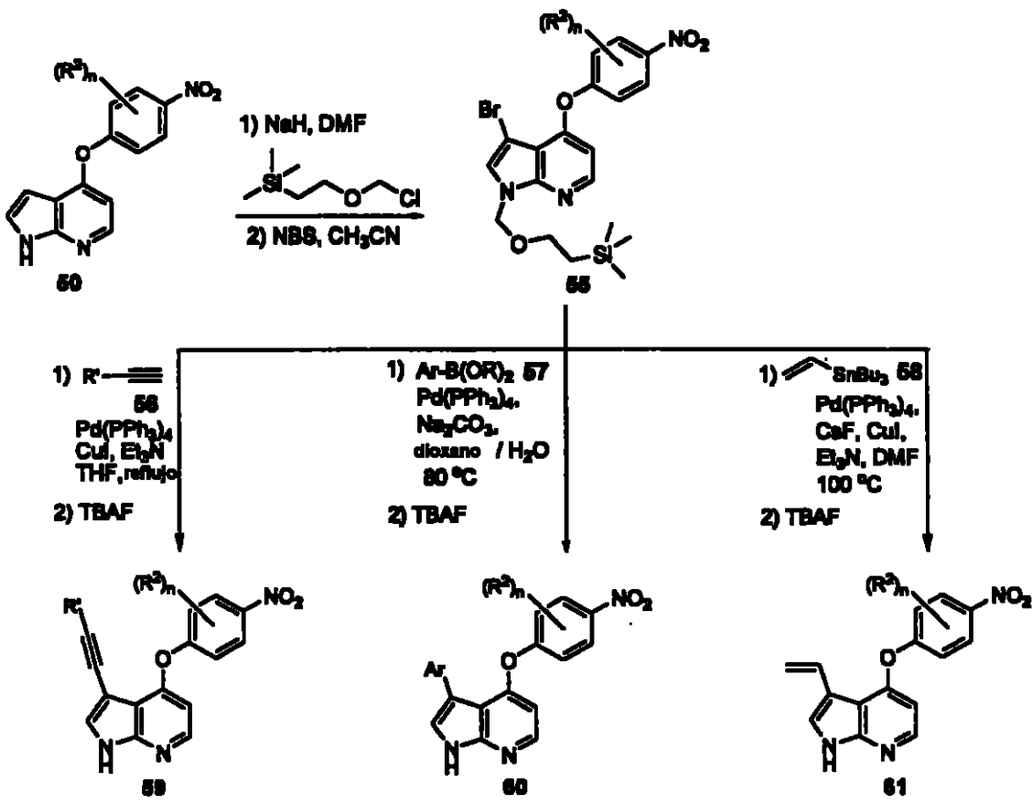
ESQUEMA DE REACCIÓN 11



Alternativamente, la protección del compuesto 50 con por ejemplo, (2-(clorometoxi)etil)trimetilsilano en presencia de una base tal como hidruro de sodio seguido por bromación con NBS se proporciona el intermediario 55 (Esquema de Reacción 12). El bromuro 55 luego se puede tratar con los alquinos substituidos 56, aril boronatos/ácidos arilborónicos 57 o vinilestananos 58 en presencia de un catalizador de paladio y/o cobre para resultar los intermediarios 59-61 respectivamente. La eliminación del grupo protector 59-61 con fluoruro de tetrabutil amonio (TBAF) seguido por la reducción de los grupos nitro puede proporcionar los intermediarios correspondientes de anilina que se puede acilar usando la química previamente descrita en los Esquemas de Reacción 1 y

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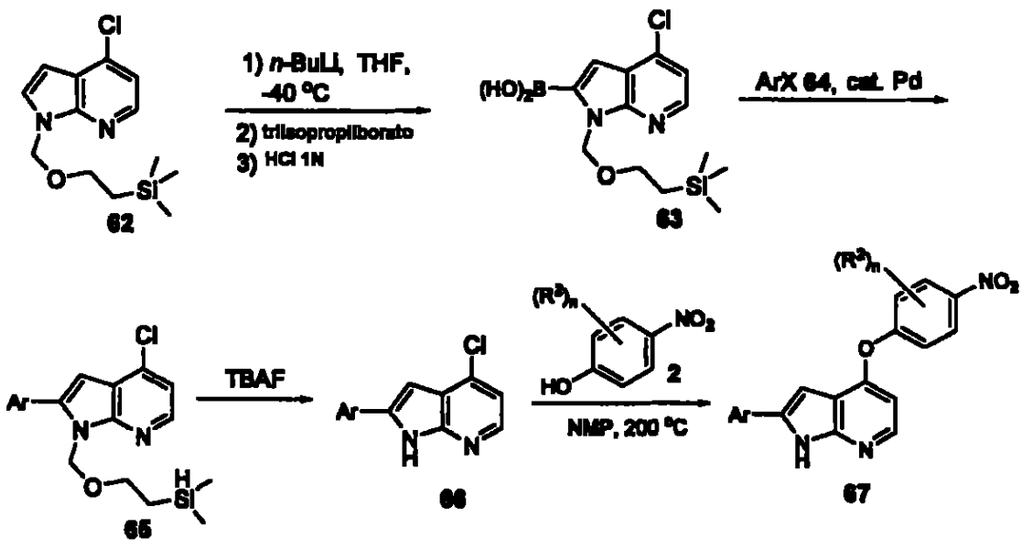
ESQUEMA DE REACCIÓN 12



La incorporación de diversos sustitutos en la posición 2 del núcleo de pirrol[2,3-b]piridina se puede lograr usando la química detallada en los Esquemas de Reacción 13 y 14. El derivado de azaindol protegido 62, derivado del compuesto 49 (Esquema de Reacción 10) se puede tratar a n-butillitio a baja temperatura seguido por triisopropilborato (Esquema de Reacción 13). El intermediario requerido luego se puede hidrolizar para generar el ácido borónico 63. El acoplamiento del ácido borónico 63 con diversos haluros de arilo o heteroarilo 64 se puede lograr

usando un catalizador de paladio para producir el intermediario 65. La eliminación del grupo protector 65 con TBAF puede producir el compuesto 66, que se puede tratar con el fenol 2 a temperatura elevada para proporcionar el intermediario 67. El compuesto 67 se puede además modificar para resultar los compuestos deseados usando la química similar antes descrita.

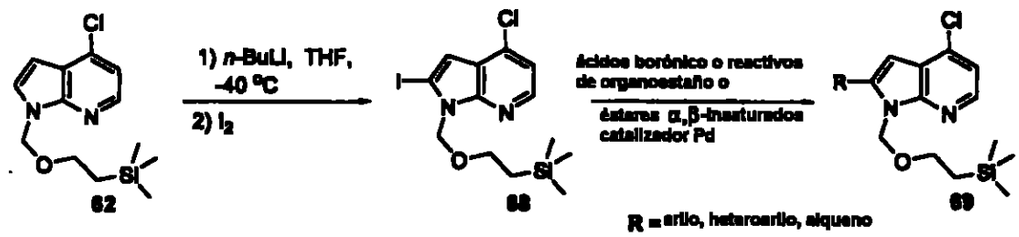
ESQUEMA DE REACCIÓN 13



Alternativamente, el compuesto 62 se puede convertir al yoduro 68 usando la química descrita en el Esquema de Reacción 14. El intermediario 68 se puede acoplar con una diversidad de reactivos tales como ácidos borónicos, organoestananos u olefinas

substituidas en presencia de un catalizador de un metal de transición [esto es., $Pd(OAc)_2$-cf. Chi, S. M. et al. Tetrahedron Lett. 2000, 9198-922] para dar 69. El intermediario 69 se puede convertir a los análogos deseados usando química previamente descrita.

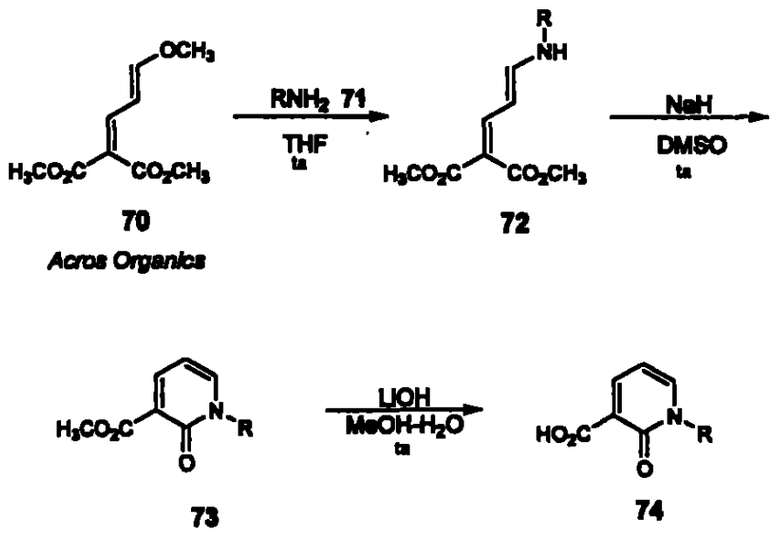
ESQUEMA DE REACCIÓN 14



El intermediario de piridinona 74 se puede obtener por un proceso de dos etapas que comienza con el (E)-dimetil 2-(3-metoxialilideno)malonato (70) comercialmente disponible (Esquema de Reacción 15). Así, el tratamiento del compuesto 70 con una amina o anilina 71 a temperatura ambiente puede proporcionar el intermediario 72, que luego se puede ciclizar el presencia de una base, tal como hidruro de sodio en dimetil sulfóxido para generar 73. La hidrólisis de intermediario 73 en condiciones básicas puede proporcionar el intermediario deseado de piridinona 74 que se puede acoplar a diversas anilinas como se describe en los Esquemas de Reacción antes mencionados.

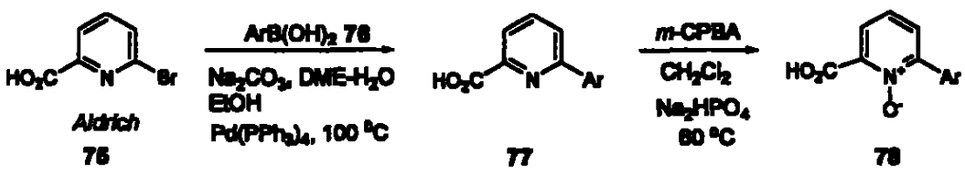
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ESQUEMA DE REACCIÓN 15



El intermediario de piridil N-óxido 78 (Esquema de Reacción 16) se puede obtener por un proceso de dos etapas en el cual el ácido 6-bromopicolínico comercialmente disponible (75) se acopla con ácido borónico o borinato 76 en presencia de un catalizador de paladio 0 y carbonato de sodio seguido por oxidación del intermediario 77 a temperatura elevada. El intermediario 78 luego se puede acoplar a diversas anilinas como se escribe en los Esquemas de Reacción antes mencionados.

ESQUEMA DE REACCIÓN 16



Los siguientes ejemplos y preparaciones describen la

forma y el proceso de elaboración y uso de la invención y son ilustrativas más que limitantes. Se deben entender que pueden haber otras modalidades que caigan dentro del alcance y espíritu de la invención como se define por las reivindicaciones anexas.

ENSAYOS

Las propiedades farmacológicas de los compuestos de esta invención se pueden confirmar por diversos ensayos farmacológicos. Los ensayos farmacológicos ejemplificados que siguen se han llevado a cabo con los compuestos de conformidad con la invención y/o sus sales farmacéuticamente aceptables.

Ensayo de Met cinasa

Reactivos	Concentración final de mezcla del substrato
Solución de reserva	
Tris-HCl, (1M, pH 7.4)	20 mM
$MnCl_2$ (1M)	1 mM
DTT(1M)	1 mM
BSA (100 mg/ml)	0.1 mg/ml
$PolyGlu_4$/tyr (10 mg/ml)	0.1 mg/mL
ATP (1mM)	1 µM
γ-ATP (10µCi/µl)	0.2 µCi/ml

solución amortiguadora — mezcla de enzima

20ul 1M DTT — 4ul GST/Met enzima(3.2 mg/ml)= 10ng/rxn

200ul 1M Tris-HCL, pH 7.4 — qs 12 ml solución amortiguadora

20ul 100mg/ml BSA

qs 20 ml H_2O

Las mezclas de incubación empleadas para el ensayo de Met cinasa contienen el substrato sintético polyGlu:Tyr, (4:1), ATP, ATP-γ-^{33}P y la solución amortiguadora que contiene Mn^{++} y/o Mg^{++}, DTT, BSA, y solución amortiguadora Tris. Se incuban las reacciones por 60 minutos a 27°C y se detiene por la adición de ácido tricloroacético frío (TCA) hasta una concentración final del 4%. Se recolectan los precipitados de TCA sobre placas unifiltro GF/C (Packard Instrument Co., Meriden, CT) usando un cosechador universal Filtermate (Packard Instrument Co., Meriden, CT) y los filtros se cuantifican usando un contador de escintilación líquida de 96 pozos TopCount (Packard Instrument Co., Meriden, CT). Las curvas de respuesta de dosis se generan para determinar la concentración requerida para inhibir el 50% de la actividad de cinasa (IC_{50}). Se disuelven los compuestos a 10 mM en sulfóxido de dimetilo (DMSO) y se evalúan a seis concentraciones cada una por cuadruplicado. La concentración final de DMSO en el ensayo es 1%. Los valores IC_{50} se derivan por un análisis de regresión no lineal y tienen un coeficiente de varianza (SD/media, n=6)= 16%.

Los compuestos de la invención inhiben la enzima de Met cinasa con valores IC_{50} entre 0.01 a 100 μM. Los compuestos preferidos tienen los valores IC_{50} menores de 1.0μM y más preferiblemente menores de aproximadamente 0.5 μM.

Los siguientes ejemplos y preparaciones describen la forma y el proceso de elaboración y uso de la invención y son ilustrativas más que limitantes. Se debe entender que pueden haber otras modalidades que caigan dentro del alcance y espíritu de la invención como se define por las reivindicaciones anexas.

EJEMPLOS

Todas las reacciones se llevan a cabo con agitación magnética continua bajo una atmósfera de nitrógeno o argón secos. Todas las evaporaciones y concentraciones se llevaron a cabo en un rotoevaporador a presión reducida. Se usaron reactivos comerciales como se recibieron sin purificación adicional. Los solventes fueron grados anhidros comerciales y se usaron sin secado y purificación adicional. Se llevó a cabo la cromatografía instantánea usando gel de sílice (Emerck Kieselgel 60, 0.040-0.060 mm).

La CLAR (RP) de fase inversa analítica se efectuó usando una columna Phenomenex Luna C18 S5 4.6 mm x 50 mm o una columna YMC S5 ODS 4.6 x 50 mm. En cada caso se

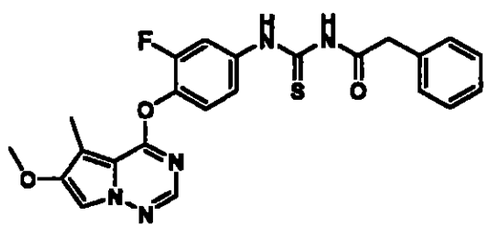
utilizó un gradiente lineal de 4 min (desde 100% A: %0 B a 0% A: 100% B) con el siguiente sistema de fase móvil: A= 90% H_2O/MeOH + 0.2% H_3PO; B= 90% MeOH/H_2O + 0.2% H_3PO_4 a una relación de flujo = a 4 mL/min y una detección a 220 nm.

La CLAR RP de fase inversa preparativa se llevó a cabo con una elución de gradiente lineal usando mezclas de H_2O/MeOH amortiguadas con ácido trifluoroacético al 0.1% y la detección a 220 nm en una de las siguientes columnas: Shimadzu S5 ODS-VP 20 x 100 mm (relación de flujo = 9 mL min), o YMC S10 ODS 50 x 500 mm (relación de flujo = a 50 mL/min), o YMC S10 ODS 30 X 500 MM (relación de flujo = 20 mL/min).

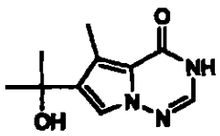
Todos los productos finales se caracterizaron por ^1H RMN, RP CLAR, ionización de electrorocío (ESI MS) y/o ionización a presión atmosférica (API MS) por espectrometría de masas. Los espectros ^1H RMN se obtuvieron en un instrumento 500 MHz JEOL o un instrumento 400 MHz Bruker. Los espectros ^{13}C RMN se grabaron a 100 o 125 MHz. Las resistencias de campo se expresan de unidades de δ (partes por millón, ppm) con relación de picos de solvente y las multiplicidades de picos se designan como siguen: s, singlete, d, doblete, dd, doblete de doblete, dm, doblete de mutipletes , t, triplete, q, cuarteto, br s, singlete amplio, m, multiplete.

Se usan las siguientes abreviaturas para reactivos comúnmente usados: Boc o BOC: t-butil carbamato; Fmoc: 9H-fluorenilmetil carbamato; NMM: N-metilmorfolina; Ms: metansulfonil; DIEA o DIPEA: diisopropiletilamina o base Hunig; NMP: N-metilpirrolidinona; BOP reactivo: benzotriazol-1-iloxitris(trimetilamino)fosfonio hexafluorofosfato; DCC: 1,3-diciclohexilcarbodiimida; EDCI; clorohidrato de 1-(dimetilaminopropil)-3-etilcarbodiimida; RT temperatura ambiente; t_R; tiempo de retención; h hora(s); min: minuto(s); PyBrOP: hexafluorofosfato de bromotripirrolidinofosfonio: TBTU: O-(1H-benzotriazol-1-il)-N,N,N',N'-tetrametiluronio tetrafluoroborato; DMAP: 4-N,N-dimetilaminopiridina; HOBt: hidroxibenzotriazol; HATU: O-(7-azabenzotriazol-1-il)-N,N,N'N'-tetrametiluronio hexafluorofosfato; DIBAL-H: hidruro de diisobutilaluminio; $Na(OAc)_3BH$: triacetoxiborohidruro de sodio; HOAc: ácido acético; TFA: ácido trifluoracético; LiHMDS: litio bis(trimetilsilil)amida; m-CPBA: m-cloro: ácido 3-cloroperbenzoico; AIBN: 2,2-azobisisobutironitrilo; DMSO: dimetil sulfóxido; MeCN: acetonitrilo; MeOH: metanol; EtOAc: acetato de etilo; DMF: formamida de dimetilo; THF: tetrahidrofurano: DCE; 1,2-dicloroetano; Et_2O: éter de dietilo.

EJEMPLO 1



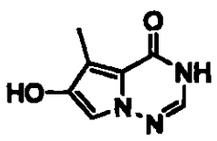
1-(3-Fluoro-4-(6-metoxi-5-metilpirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-3-(2-fenilacetil)tiourea



A) 6-(1-Hidroxi-1-metil-etil)-5-metil-3H-pirrolo[2,1-f]1,2,4]triazin-4-ona

Una mezcla de 1.9 kg de éster de etilo del ácido 5-metil-4-oxo-3,4-dihidro-pirrolo[2,1-f][1,2,4]triazin-6-carboxílico, preparado generalmente de conformidad con el procedimiento descrito en Solicitud de Patente de los Estados Unidos No. de Serie 09/573829, y 17.9 kg de THF se preparó bajo una atmósfera inerte y se enfrió a -10°C. A esta mezcla se le agregó 14.2 kg de cloruro de metilmagnesio como una solución 3 M en THF a una relación para mantener la temperatura de reacción <35°C. La mezcla de reacción se mantiene a 25-45°C hasta su finalización, luego se enfrió a 0°C. Una solución de 9.9 kg de cloruro de amonio en 36.7 kg de agua se preparó y se enfrió a 5°C. La mezcla de reacción orgánica se le agregó a la solución de cloruro de amonio a

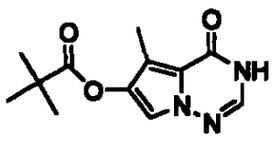
una relación para mantener la temperatura interna < 15°C. Las fases se permitieron que reposen y la fase acuosa inferior se drenó completamente y se volvió a extraer con 9.5 kg de THF adicional. A las fases orgánicas combinadas se le agregó 8.6 kg de EtOAc y la mezcla se lavó con 7.6 kg de solución de cloruro de sodio acuoso saturado. La mezcla de reacción se filtró, luego el solvente se retiró in vacuo (temperatura <40°C) hasta aproximadamente 1/3 del volumen original. Se agregó EtOAc adicional con destilación continua hasta que el nivel de THF fue <7%. La mezcla espesa resultante se enfrió a 0-5°C, luego el sólido se colectó por filtración. La torta húmeda se lavó con EtOAc frío (-10°C), luego se secó in vacuo a 40°C para producir 1.5 kg de 6-(1-hidroxi-1-metil-etil)-5-metil-3H-pirrolo[2,1-f]1,2,4]triazin-4-ona con una pureza de 96-99%.



B) 6-Hidroxi-5-metil-3H-pirrolo[2,1-f][1,2,4]triazin-4-ona

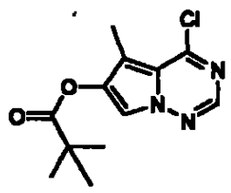
Un matraz de fondo redondo, de 3 cuellos, de un litro se equipó con agitador mecánico y un baño de enfriamiento de hielo/acetona. A esto se le cargó 20 g de 6-(1-hidroxi-1-metil-etil)-5-metil-3H-pirrolo[2,1-f][1,2,4]triazin-4-ona, 235 mL de THF y 47 mL peróxido de hidrógeno acuoso al 50%. Se observó una exotermia desde -7°C a 7.3°C se observó y la

mezcla se volvió una solución. A esto se le agregó una solución previamente enfriada de 28.5 mL de agua y 63 mL de ácido metansulfónico durante 40 minutos, manteniendo la temperatura entre -5°C y -0.7°C. La solución se agitó a -2°C por 95 minutos hasta que la CLAR indicó que la reacción se completó; la mezcla de reacción se apagó, mientras se mantiene a -2°C, al agregar en porciones a una solución enfriada de 28.5 mL de agua, 89 g de $NaHSO_3$ y 128 mL de hidróxido de amonio acuoso al 28% durante 40 minutos, a 15°C a 25°C. La mezcla se agitó a temperatura ambiente durante 20 minutos; el pH fue 6.80 y la prueba de peróxido fue negativa. Las capas se separaron y la capa acuosa se extrajo con 100 mL de THF. Las dos capas orgánicas se combinaron y se concentraron, se retiró 280 mL de solvente. A la mezcla espesa gruesa se le agregó 250 mL de agua y la concentración continuó hasta que 88 mL de solvente se retiró. La mezcla espesa se filtró y la torta se lavó con 25 mL de agua dos veces y luego 25 mL de acetonitrilo. Se secó por succión en el filtro hasta un peso constante para proporcionar 12.51 g de 6-hidroxi-5-metil-3H-pirrolo[2,1-f][1,2,4]triazin-4-ona, 75.9% de rendimiento, 96.5% de pureza.



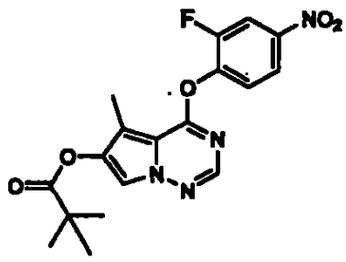
C) éster de 5-metil-4-oxo-3,4-dihidro-pirrolo[2,1-f][1,2,4]triazin-6-ilo del ácido 2,2-dimetil-propiónico

Una mezcla de 2.9 kg de 6-hidroxi-5-metil-3H-pirrolo[2,1-f][1,2,4]triazin-4-ona, 4.6 kg de diisopropiletilamina y 17.0 kg de THF se enfrió a 0-10°C, luego se trató con 2.6 kg de cloruro de pivaloilo a una relación para mantener la temperatura < 20°C. La mezcla se agitó hasta que la reacción se completó por CLAR, luego 17.8 kg de tolueno se le agregó, seguido por 20.6 kg de solución de fosfato diácido de potasio acuosa al 15%. Las fases se separaron y la orgánica se lavó con 10.2 kg de agua. La fase orgánica se filtró, luego se destiló bajo vacío con una temperatura máxima de 65°C. Puede agregarse tolueno adicional y la destilación continuó hasta que la concentración de THF fue <8%, y el volumen de reactor total se redujo a 31 L. La mezcla espesa resultante se enfrió a 20-25°C y se trató con 20.3 kg de heptano durante 1.5 hora. La mezcla espesa se enfrió a 0-5°C y se mantiene durante 1 hora, luego el sólido se colectó por filtración y se secó para proporcionar 4.0 kg de éster de 5-metil-4-oxo-3,4-dihidro-pyirolo[2,1-f][1,2,4]triazin-6-ilo del ácido 2,2-dimetil-propiónico con una pureza de 95-99%.



D) 4-Cloro-5-metilpirrolo[2,1-f][1,2,4]triazin-6-ilo pivalato

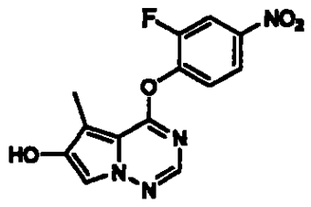
A una mezcla de 5-metil-4-oxo-3,4-dihidropirrolo[2,1-f][1,2,4]triazin-6-ilo pivalato (300 mg, 1.20 mmol), oxicloruro de fósforo (2.0 mL, 21.4 mmol) y DIEA (0.5 mL, 2.80 mmol) se le agregó tolueno (10 mL). La reacción se calentó a 110°C durante 4 horas y luego se enfrió hasta temperatura ambiente. La mezcla se diluyó con acetato de etilo (10 mL) y agua (5 mL). La capa orgánica se separó y se secó con sulfato de sodio, se concentró in vacuo y se purificó por cromatografía instantánea en gel de sílice (eluyendo con 1 - 25% EtOAc/CH_2Cl_2 para dar el compuesto del título (250 mg, 78%) como un sólido blanco.



E) 4-(2-Fluoro-4-nitrofenoxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-6-il pivalato

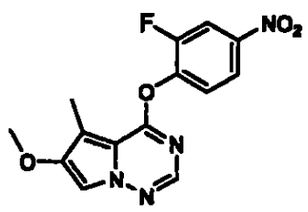
A una mezcla de 4-cloro-5-metilpirrolo[2,1-f][1,2,4]triazin-6-ilo pivalato (250 mg, 0.94 mmol), 2-

fluoro-4-nitrofenol (176 mg, 1.12 mmol, Aldrich) y K_2CO_3 (154 mg, 1.12 mmol) se le agregó DMF (5 mL). La reacción se agitó a temperatura ambiente durante 24 horas. La reacción se apagó con agua (5 mL) y CH_2Cl_2 (10 mL). La capa orgánica se separó, se secó con sulfato de sodio, se concentró in vacuo, y se purificó por cromatografía instantánea en gel de sílice (eluyendo con 1 - 25% EtOAc/CH_2Cl_2) para dar el compuesto del título (160 mg, 44%) como un sólido blanco.



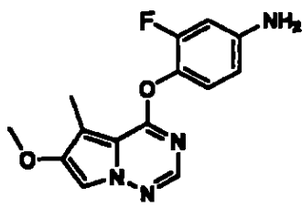
F) 4-(2-Fluoro-4-nitrofenoxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-6-ol

A una solución de 4-(2-fluoro-4-nitrofenoxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-6-ilo pivalato (80 mg, 0.2 mmol) en THF (1 mL) se le agregó una solución de NaOH en MeOH/H_2O (0.2 mL, 1 M). La solución se volvió roja instantáneamente. Después de 5 minutos, la reacción se apagó con EtOAc (5 mL) y H_2O (5 mL). La capa orgánica se separó, se secó con sulfato de sodio y se concentró in vacuo para dar el compuesto del título (52 mg, 85%) como un sólido amarillo.



G) 4-(2-Fluoro-4-nitrofenoxi)-6-metoxi-5-metilpirrolo[2,1-f][1,2,4]triazina

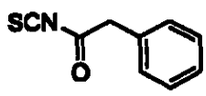
A una solución de 4-(2-fluoro-4-nitrofenoxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-6-ol (52 mg, 0.17 mmol) en DMF (2 mL) se le agregó Cs_2CO_3 (65 mg, 0.2 mmol) y la mezcla se agitó a temperatura ambiente durante 10 minutos. Una solución de yoduro de metilo en DMF (0.2 mL, 0.2 mmol, 1 M) se le agregó y la solución de reacción se agitó a temperatura ambiente durante 2 horas. La reacción se apagó con EtOAc (5 mL) y H_2O (5 mL). La capa orgánica se separó, se secó con sulfato de sodio y se concentró in vacuo para dar el compuesto del título (35 mg, 65%) como un sólido amarillo.



H) 3-Fluoro-4-(6-metoxi-5-metilpirrolo[2,1-f][1,2,4]triazin-4-iloxi)bencenamina

A una solución de 4-(2-fluoro-4-nitrofenoxi)-6-metoxi-5-metilpirrolo[2,1-f][1,2,4]triazina (35 mg, 0.11 mmol) en THF (1.0 mL) se le agregó MeOH (1.0 mL) seguido por Zn (100 mg, 1.5 mmol) y NH_4Cl (43 mg, 0.80 mmol). La reacción se calentó

a 60°C durante 3 horas. La solución se filtró a través de Celite® y se concentró in vacuo. La mezcla de producto se purificó por un cartucho SCX (eluyendo con amoniaco en metanol (2 M) para dar el compuesto del título (15 mg, 50%) como un sólido blanco.



I) 2-Fenil-1-tiocianatoetanona

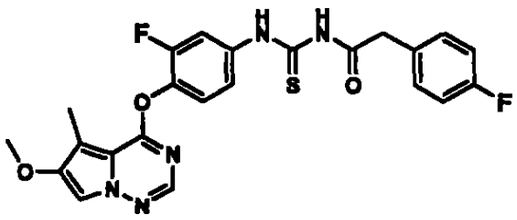
A una solución de NaSCN (49 mg, 0.60 mmol) en EtOAc (2 mL) se le agregó cloruro de fenilacetilo (0.066 mL, 0.50 mmol, Aldrich) para proporcionar una solución 0.25 M de 2-fenil-1-tiocianatoetanona. Después de 10 minutos, se determinó que la reacción estaba completa al hacer reaccionar una alícuota de la mezcla de reacción con 4-(feniloxi)anilina para formar el correspondiente tiocianato que se detectó por CLEM (ESI$^+$) m/z 363 $(M + H)^+$. La 2-fenil-1-tiocianatoetanona se usó directamente sin aislado o purificación adicional.

J) 1-(3-Fluoro-4-(6-metoxi-5-metilpirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-3-(2-fenilacetil)tiourea

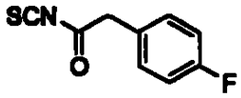
A una solución de 3-fluoro-4-(6-metoxi-5-metilpirrolo[2,1-f][1,2,4]triazin-4-iloxi)bencenamina (7.5 mg, 0.026 mmol) en CH_2Cl_2 (1 mL) se le agregó una solución de 2-fenil-1-tiocianatoetanona (0.133 mL, 0.033 mmol, 0.25 M en

acetato de etilo). La reacción se agitó a temperatura ambiente durante 20 minutos, se concentró in vacuo y se purificó por cromatografía instantánea en gel de sílice (eluyendo con 1 - 25% EtOAc/CH_2Cl_2) para dar el compuesto del título (6.1 mg, 50%) como un sólido amarillo pálido. ^1H RMN ($CDCl_3$) δ 8.51 (s, 1H), 7.87 (m, 1H), 7.83 (s, 1H), 7.47 (m, 5H), 7.31 (m, 4H), 3.89 (s, 3H) 3.74 (d, 2H, J= 10.5 Hz), 2.44 (s, 3H); EM(ESI$^+$) m/z 466 $(M + H)^+$.

EJEMPLO 2



1-(3-Fluoro-4-(6-metoxi-5-metilpirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)tiourea



A) 2-(4-Fluorofenil)-1-tiocianatoetanona

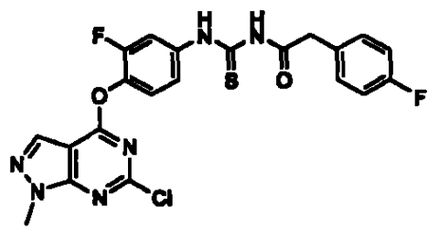
A una solución de NaSCN (49 mg, 0.60 mmol) en EtOAc (2 mL) se le agregó cloruro de 4-fluorofenilacetilo (0.066 mL, 0.50 mmol, Aldrich). La reacción se agitó a temperatura ambiente durante 1 hora para dar una solución 0.25 M de 2-(4-fluorofenil)-1-tiocianatoetanona en EtOAc, la cual se usó directamente sin purificación adicional.

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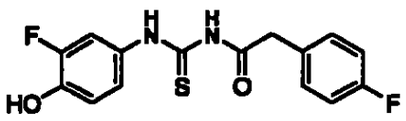
B) 1-(3-Fluoro-4-(6-metoxi-5-metilpirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)tiourea

El compuesto del título se preparó a partir de la 3-fluoro-4-(6-metoxi-5-metilpirrolo[2,1-f][1,2,4]triazin-4-iloxi)bencenamina y 2-(4-fluorofenil)-1-tiocianatoetanona en una manera similar como se describe por los Compuestos H y J del Ejemplo 1. ^{1}H RMN ($CDCl_3$) δ 8.49 (s, 1H), 7.88 (m, 1H), 7.83 (s, 1H), 7.45 (s, 1H), 7.28 (m, 5H), 7.12 (m, 2H), 3.89 (s, 3H), 3.71 (s, 2H) 2.44 (s, 3H); EM(ESI+) m/z 484 $(M + H)^+$.

EJEMPLO 3



1-(4-(6-Cloro-1-metil-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)tiourea



A) 1-(3-Fluoro-4-hidroxifenil)-3-(2-(4-fluorofenil)acetil)tiourea

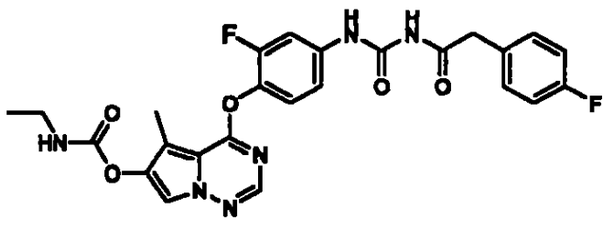
A una solución de 4-amino-2-fluorofenol (50 mg, 0.3

mmol, Indofine Chemical Co.) en CH_2Cl_2 (5 mL) se le agregó una solución 0.25 M de 2-(4-fluorofenil)-1-tiocianatoetanona (preparada usando un proceso similar para la síntesis del Compuesto A del Ejemplo 2) en EtOAc (1.6 mL, 0.4 mmol). La reacción se agitó a temperatura ambiente durante 20 minutos, se concentró in vacuo y se purificó por cromatografía instantánea en gel de sílice (eluyendo con 1-25% EtOAc/CH_2Cl_2) para dar el compuesto del título (100 mg, 95%) como un sólido blanco.

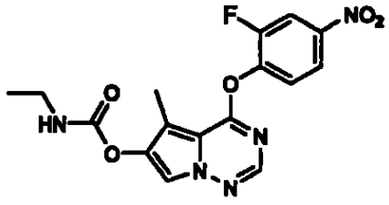
B) 1-(4-(6-Cloro-1-metil-1H-pirazolo[3,4-d]pirimidin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)tiourea

A una mezcla de 1-(3-fluoro-4-hidroxifenil)-3-(2-(4-fluorofenil)acetil)tiourea (24 mg, 0.075 mmol), 4,6-dicloro-1-metil-1H-pirazolo[3,4-d]pirimidina (15.3 mg, 0.075 mmol, preparación: J. Org. Chem. 1958, 23, 852, la descripción de la cual se incorpora en la presente para referencia) y K_2CO_3 (10 mg, 0.075 mmol) se le agregó DMF (2 mL). La reacción se agitó a temperatura ambiente durante 24 horas. La reacción se apagó con agua (2 mL) y CH_2Cl_2 (5mL). La capa orgánica se separó, se secó con sulfato de sodio, se concentró in vacuo y se purificó por CLAR preparativa de fase inversa para dar el compuesto del título (22.9 mg, 60%) como un sólido blanco. EM(ESI$^+$) m/z 457 $(M + H)^+$.

EJEMPLO 4

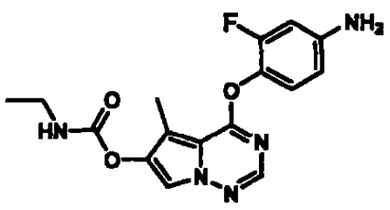


4-(2-Fluoro-4-(3-(2-(4-fluorofenil)acetil)ureido)fenoxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-6-ilo etilcarbamato



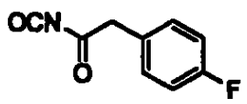
A) 4-(2-Fluoro-4-nitrofenoxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-6-ilo etilcarbamato

A una mezcla de 4-(2-fluoro-4-nitrofenoxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-6-ol (25 mg, 0.082 mmol, Compuesto F del Ejemplo 1), DIEA (0.017 mL, 0.1 mmol) en CH_2Cl_2 (5 mL) se le agregó isocianato de etilo (0.078 mL, 0.1 mL) y se agitó a temperatura ambiente durante 2 horas. La reacción se apagó con agua (5 mL). La capa orgánica se separó, se secó y se concentró in vacuo. La mezcla se purificó por cromatografía instantánea (1-5% Metanol/CH_2Cl_2 para dar el compuesto del título (12.5 mg, 32%) como un sólido blanco.



B) 4-(4-amino-2-fluorofenoxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-6-ilo etilcarbamato

A una solución de 4-(2-fluoro-4-nitrofenoxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-6-ilo etilcarbamato (12.5 mg, 0.033 mmol) en etanol (2 mL) se le agregó Zn (20 mg, 0.3 mmol) y NH_4Cl (20 mg, 0.37 mmol). La reacción se agitó a temperatura ambiente durante 1 hora, se filtró a través de Celite® y se concentró in vacuo para dar el compuesto del título (8 mg, 70%) como un sólido blanco.



C) 2-(4-Fluorofenil)acetil isocianato

A una solución/suspensión de 4-fluorofenilacetamida (77 mg, 0.50 mmol, ver generalmente, J. Med. Chem. 2003, 46, 4333-4341, la descripción de la cual se incorpora en la presente para referencia) en dicloroetano (2 mL) se le agregó cloruro de oxalilo (0.175 mL, 2.00 mmol). La reacción se calentó a 80°C durante 24 horas, y luego 70°C durante dos días. En este momento, la mayoría de los sólidos se han disuelto y la reacción fue amarilla. El análisis CL/EM encontró un pico con un peso molecular de 211 correspondiente

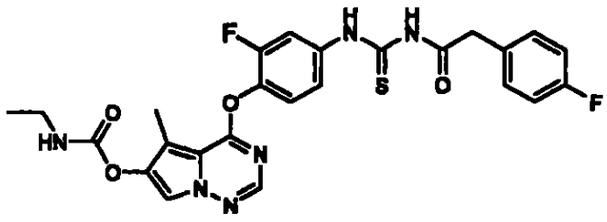
al 2-(4-fluorofenil)acetilcarbamato de metilo, que resulta del apagado del isocianato con metanol. La reacción se concentró in vacuo para dar una mezcla espesa amarilla. La mezcla espesa se volvió a disolver en dicloroetano (2 mL) y nuevamente se concentró in vacuo. El residuo resultante se volvió a disolver nuevamente en dicloroetano (2 mL) para dar una solución 0.25 M de 2-(4-fluorofenil)acetil isocianato en dicloroetano, el cual se usó directamente en reacciones posteriores.

D) 4-(2-Fluoro-4-(3-(2-(4-fluorofenil)acetil)ureido)fenoxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-6-ilo etilcarbamato

A una solución de 4-(4-amino-2-fluorofenoxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-6-ilo etilcarbamato (10 mg, 0.029 mmol) en CH_2Cl_2 (1 mL) se le agregó una solución de 2-(4-fluorofenil)acetil isocianato (2 mL, 0.25 M en dicloroetano). La reacción se agitó a temperatura ambiente durante 1 hora, El análisis CL/EM indica el consumo del carbamato inicial. La mezcla se concentró in vacuo y el residuo se suspendió en metanol y se filtró para dar el compuesto del título. El filtrado se purificó por cromatografía instantánea para proporcionar más del compuesto del título como un sólido amarillo pálido (rendimiento combinado 5.9 mg, 40%). ^1H RMN ($CDCl_3$) δ 10.63 (s, 1H), 8.42

(s, 1H), 7.88 (s, 1H), 7.82 (s, 1H), 7.67 (dd, 1H, J= 12.1, 2.2 Hz), 7.28 (m, 4H), 7.10 (m, 2H), 3.73 (s, 3H), 3.36 (m, 2H), 2.48 (s, 3H), 1.26 (m, 3H); EM(ESI$^+$) m/z 525 (M + H)$^+$.

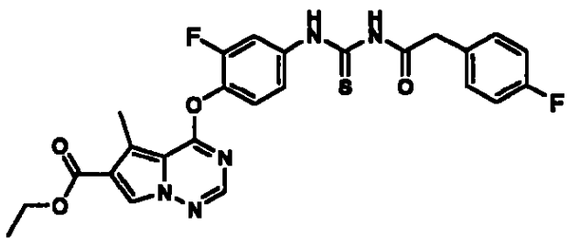
EJEMPLO 5



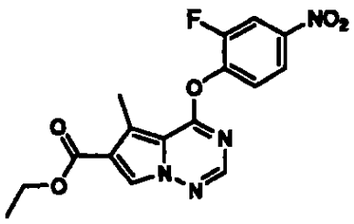
4-(2-Fluoro-4-(3-(2-(4-fluorofenil)acetil)tioureido)fenoxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-6-ilo etilcarbamato

A una solución de 4-(4-amino-2-fluorofenoxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-6-ilo etilcarbamato (8 mg, 0.023 mmol, preparación del Compuesto B del Ejemplo 4) en CH_2Cl_2 (1 mL) se le agregó una solución de 2-(4-fluorofenil)-1-tiocianatoetanona (0.120 mL, 0.025 mmol, 0.25 M en acetato de etilo, Compuesto A del Ejemplo 2). La reacción se agitó a temperatura ambiente durante 1 hora, se concentró in vacuo y se purificó por cromatografía instantánea en gel de sílice (eluyendo con 1 - 25% EtOAc/CH_2Cl_2) para dar el compuesto del título (5.4 mg, 43%) como un sólido amarillo pálido. ^{1}H RMN ($CDCl_3$) δ 12.41 (s, 1H), 8.58 (s, 1H), 7.88 (m, 3H), 7.28 (m, 5H), 7.12 (m, 2H), 3.72 (s, 2H), 3.37 (m, 2H), 2.46 (m, 3H), 1.26 (m, 3H); EM(ESI$^+$) m/z 541 (M + H)$^+$.

EJEMPLO 6

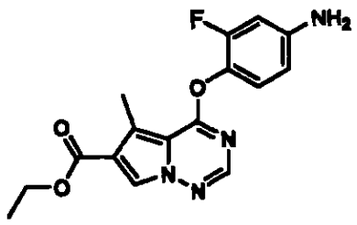


4-(2-fluoro-4-(3-(2-(4-fluorofenil)acetil)tioureido)fenoxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-6-carboxilato de etilo



A) 4-(2-fluoro-4-nitrofenoxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-6-carboxilato de etilo

A una mezcla del 4-cloro-5-metilpirrolo[2,1-f][1,2,4]triazin-6-carboxilato de etilo (24 mg, 0.10 mmol, preparación: Ver, patente E.U.A. No. 6,670,357, especialmente el Ejemplo 61, la descripción de la cual se incorpora en la presente para referencia), 2-fluoro-4-nitrofenol (20 mg, 0.125 mmol) y K_2CO_3 (28 mg, 0.20 mmol) se le agregó DMF (0.5 mL). La reacción se calentó a 70°C durante 20 minutos, se enfrió hasta temperatura ambiente y 2 mL de agua se le agregó. La mezcla se filtró, el sólido se lavó con agua, y se secó para dar el compuesto del título (36 mg, 100%) como un sólido amarillo ligero.



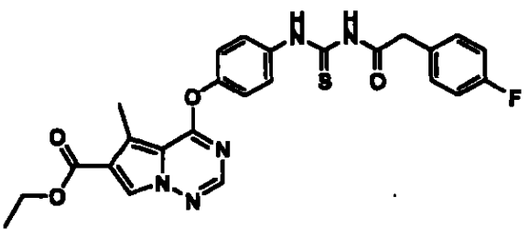
B) 4-(4-amino-2-fluorofenoxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-6-carboxilato de etilo

A una solución de 4-(2-fluoro-4-nitrofenoxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-6-carboxilato de etilo (36 mg, 0.1 mmol) en THF (1.0 mL) se le agregó MeOH (0.7 mL) seguido por Zn (130 mg, 2.0 mmol) y NH_4Cl (53 mg, 1.0 mmol). La reacción se calentó a 70°C durante la noche. El análisis CL/EM indicó mayormente materia prima. La solución se agitó vigorosamente y luego se calentó hasta 75°C. El análisis CL/EM después de 4 horas mostró el producto deseado y muchos otros picos. La reacción se filtró a través de un filtro grueso, y el filtrado se concentró para dar 55 mg de un residuo café. El residuo se suspendió en THF y se pasó a través de un filtro CLAR resultando en un filtrado claro. El filtrado se concentró in vacuo para dar 54 mg del compuesto del título como una mezcla cruda que se usó en la siguiente etapa sin purificación adicional.

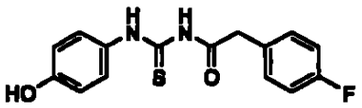
C) 4-(2-fluoro-4-(3-(2-(4-fluorofenil)acetil)tioureido)fenoxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-6-carboxilato de etilo

A una suspensión de 4-(4-amino-2-fluorofenoxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-6-carboxilato de etilo (54 mg) en CH_2Cl_2 (0.6 mL) se le agregó una solución de 2-(4-fluorofenil)-1-tiocianatoetanona (0.5 mL, 0.12 mmol, 0.25 M en acetato de etilo Compuesto A del Ejemplo 2). La reacción se agitó a temperatura ambiente durante 15 minutos, el análisis CL/EM indicó mayormente materia prima. La reacción se entibió a 45°C, después de 30 minutos la mayoría de la suspensión se había disuelto para dar una solución turbia. El análisis CL/EM indicó principalmente el producto deseado. La reacción se agitó a temperatura ambiente durante 2h adicionales, se evaporó hasta secar, y purificó por cromatografía en columna eluyendo con 1-7% acetato de etilo/diclorometano para el compuesto del título (9 mg, 17% rendimiento global para 3 etapas) como un sólido blanco. ^1H RMN($CDCl_3$) δ 12.45 (s,1H), 8.66 (s,1H), 8.18 (s,1H), 7.92 (dd, 1H,J=11.4, 2.4 Hz), 7.90 (s, 1H), 7.41 (m, 1H), 7.29 (m. 3H), 7.12 (m, 2H), 4.38 (q, 2H, J=7.1 Hz), 3.73 (s, 2H), 2.82 (s, 3H), 1.40 (t, 3H, J=7.1 Hz); EM(ESI^+) m/z 526 $(M + H)^+$.

EJEMPLO 7



4-(4-(3-(2-(4-fluorofenil)acetil)tioureido)fenoxi)-5-metilpirrolo(2,1-f][1,2,4]triazin-6-carboxilato de etilo



A) 1 -(2-(4-Fluorofenil)acetil)-3-(4-hidroxifenil)tiourea

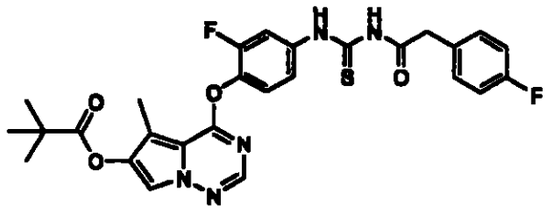
A una solución de 4-amino-fenol (11 mg, 0.1 mmol, Aldrich) en CH_2Cl_2 (0.55 mL) se le agregó una solución de 2-(4-fluorofenil)-1-tiocianatoetanona (0.5 mL, 0.125 mmol, 0.25 M en acetato de etilo, Compuesto A del Ejemplo 2). La reacción se agitó a temperatura ambiente durante 10 minutos, El análisis CL/EM indicó la formación del compuesto del título. La mezcla de reacción cruda se usó directamente en la siguiente reacción.

B) 4-(4-(3-(2-(4-fluorofenil)acetil)tioureido)fenoxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-6-carboxilato de etilo

A una solución a temperatura ambiente de 4-cloro-5-metilpirrolo[2,1-f][1,2,4]triazin-6-carboxilato de etilo (7.2 mg, 0.03 mmol) (para preparación ver Pat. E.U.A. 6,670,357, la descripción de la cual se incorpora en la presente para

referencia) y DABCO (7 mg, 0.06 mmol) en acetonitrilo (0.5 mL) se le agregó 1-(2-(4-fluorofenil)acetil)-3-(4-hidroxifenil)tiourea (0.5 mL, 0.05 mmol). La reacción se agitó a temperatura ambiente. Después de 30 minutos, el análisis CL/EM indicó principalmente producto. La reacción se agitó a temperatura ambiente durante la noche. La mezcla se evaporó hasta secar. La purificación por cromatografía en gel de sílice (elución con 1% metanol/diclorometano) proporcionó el producto deseado contaminado con impurezas. Una segunda purificación por cromatografía en gel de sílice (1-6% acetato de etilo/diclorometano) nuevamente no retiró todas las impurezas. La mezcla sólida resultante se lavó con metanol y se secó para proporcionar el compuesto del título (6 mg, 39%) como un sólido amarillo. ^{1}H RMN ($CDCl_3$) δ 12.32 (s, 1H), 8.62 (s, 1H), 8.16 (s, 1H), 7.91 (s, 1H), 7.76 (m, 2H), 7.29 (m, 4H), 7.12 (m, 2H), 4.38 (q. 2H, J=7.1 Hz), 3.72 (s, 2H), 2.82 (s, 3H), 1.40 (t, 3H,J=7.1 Hz); EM(ESI$^+$) m/z 508 $(M + H)^+$.

EJEMPLO 8

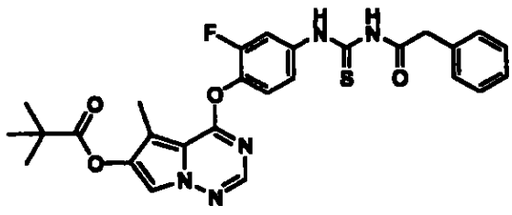


4-(2-Fluoro-4-(3-(2-(4-fluorofenil)acetil)tioureido)fenoxi)-5-metilpirrolo[2,1-f] [1,2,4]triazin-6-ilo pivalato

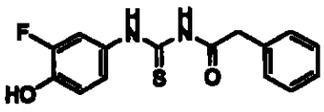
A una mezcla de 1-(3-fluoro-4-hidroxifenil)-3-(2-(4-

fluorofenil)acetil)tiourea (60 mg, 0.19 mmol, Compuesto A del Ejemplo 3), 4-cloro-5-metilpirrolo[2,1-f][1,2,4]triazin-6-ilo pivalato (50 mg, 0.19 mmol, Compuesto D del Ejemplo 1) y 1,4-diazabiciclo[2.2.2]octano (DABCO, 21.3 mg, 0.19 mmol) se le agregó MeCN (5 mL). La reacción se agitó a temperatura ambiente durante 1 hora y se concentró in vacuo. El residuo se purificó por cromatografía instantánea (eluyendo con 1-15% MeOH / CH_2Cl_2) para dar el compuesto del título (91 mg, 86 %) como un sólido blanco. ^1H RMN ($CDCl_3$) δ 12.40 (s, 1H), 8.54 (s, 1H), 7.87 (m, 3H), 7.29 (m, 4H), 7.12 (m, 2H), 3.71 (s, 2H), 2.43 (s, 3H), 1.39 (s, 9H); EM(ESI$^+$) m/z 554 $(M + H)^+$.

EJEMPLO 9



4-(2-Fluoro-4-(3-(2-fenilacetil)tioureido)fenoxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-6-ilo pivalato



A) 1-(3-Fluoro-4-hidroxifenil)-3-(2-fenilacetil)tiourea

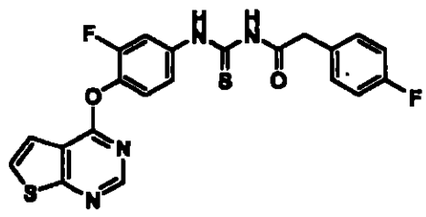
A una solución de 4-amino-3-fluorofenol (50 mg, 0.3 mmol) en CH_2Cl_2 (2 mL) se le agregó una solución de 2-fenil-1-

tiocianatoetanona (2 mL, 0.4 mmol, 0.2M en acetato de etilo, Compuesto I del Ejemplo 1). La reacción se agitó a temperatura ambiente durante 20 minutos, El análisis CL/EM indicó la formación del compuesto del título. La mezcla se concentró para dar un residuo que se usó sin purificación adicional.

B) 4-(2-Fluoro-4-(3-(2-fenilacetil)tioureido)fenoxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-6-ilpivalato

Se cargó un vial con 4-cloro-5-metilpirrolo[2,1-f][1,2,4]triazin-6-ilo pivalato (13.3 mg, 0.19 mmol, Compuesto D del Ejemplo 1), 1-(3-fluoro-4-hidroxifenil)-3-(2-fenilacetil)tiourea (16 mg, 0.05 mmol), carbonato de cesio (punta de espátula) y DMF (2 mL) y se calentó a 100°C durante 26 horas. La mezcla se concentró in vacuo. El residuo se purificó por cromatografía instantánea para dar el compuesto del título (6.2 mg, 25 %) como un sólido blanco. ^{1}H RMN ($CDCl_3$) δ 12.46 (s, 1H), 8.50 (s, 1H), 7.88 (m, 3H), 7.40 (m, 4H), 7.31 (m, 2H), 3.75 (s, 3H), 2.44 (s, 3H), 1.40 (s, 9H); EM(ESI+) m/z 536 $(M + H)^+$.

EJEMPLO 10

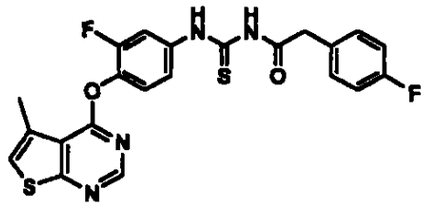


1-(4-(4a,7a-Dihidrotieno[2,3-d]pirimidin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)tiourea

A una mezcla de 1-(3-fluoro-4-hidroxifenil)-3-(2-(4-

fluorofenil)acetil)tiourea (24 mg, 0.075 mmol, Compuesto A del Ejemplo 3), 4-cloro-5-tieno[2,3-d]pirimidina (12.8 mg, 0.075 mmol, disponible comercialmente) y 1,4-diazabiciclo[2.2.2]octano (DABCO, 8.4 mg, 0.075 mmol) se le agregó MeCN (2 mL). La reacción se agitó a temperatura ambiente durante 4 horas y se concentró in vacuo. El residuo se purificó por CLAR preparativa de fase inversa para dar el compuesto del título (13.8 mg, 40%) como un sólido blanco. ^{1}H RMN ($CDCl_3$) δ 12.41 (s, 1H), 8.62 (s, 1H), 8.53 (s, 1H), 7.93 (dd, 1H, J=13.8, 2.2 Hz), 7.56 (m. 2H) 7.46 (m, 1H), 7.29 (m, 3H), 7.12 (m, 2H), 3.73 (s, 2H); EM(ESI$^+$) m/z 457 $(M + H)^+$.

EJEMPLO 11

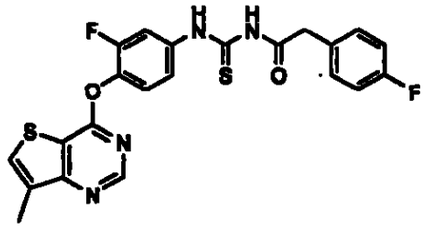


1-(3-Fluoro-4-(5-metil-4a,7a-dihidrotieno[2,3-d]pirimidin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)tiourea

En una forma similar a la que se describe para la preparación del Ejemplo 10, el compuesto del título se preparó a partir de 4-cloro-5-metiltieno[2,3-d]pirimidina y 1-(3-fluoro-4-hidroxifenil)-3-(2-(4-fluorofenil)acetil)tiourea disponible comercialmente (24 mg, 0.075 mmol, Compuesto A del Ejemplo 3). ^{1}H RMN ($CDCl_3$) δ 12.42

(s, 1H), 8.67 (s, 1H), 8.53 (s, 1H), 7.88 (dd, 1H, J=13.8. 2.2 Hz), 7.43 (s, 1H), 7.32 (m, 3H), 7.09 (m, 3H), 3.72 (S, 2H), 2.67 (s, 3H); EM(ESI$^+$) m/z 471 $(M + H)^+$.

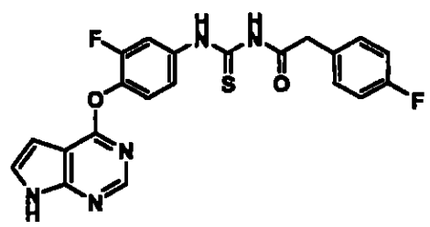
EJEMPLO 12



1-(3-Fluoro-4-(7-metil-4a,7a-dihidrotieno[3,2-d]pirimidin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)tiourea

A una mezcla de 1-(3-fluoro-4-hidroxifenil)-3-(2-(4-fluorofenil)acetil)tiourea (24 mg, 0.075 mmol, Compuesto A del Ejemplo 3), 4-cloro-7-metiltieno[3,2-d]pirimidina (13.8 mg, 0.075 mmol, disponible comercialmente) y 1,4-diazabiciclo[2.2.2]octano (DABCO, 8.4 mg, 0.075 mmol) se le agregó MeCN (2 mL). La reacción se agitó a temperatura ambiente durante 4 horas y se concentró in vacuo. El residuo se purificó por CLAR preparativa de fase inversa para dar el compuesto del título (11.2 mg, 31%) como un sólido blanco. ^{1}H RMN ($CDCl_3$) δ 12.45 (s, 1H), 8.79 (s, 1H), 8.61 (s, 1H), 7.93 (dd, 1H, J=13.8, 2.2 Hz), 7.46 (s, 1H), 7.43 (m, 1H), 7.28 (m, 3H), 7.12 (m, 2H), 3.72 (s, 2H), 2.51 (s, 3H); EM(ESI$^+$) m/z 471 $(M + H)^+$.

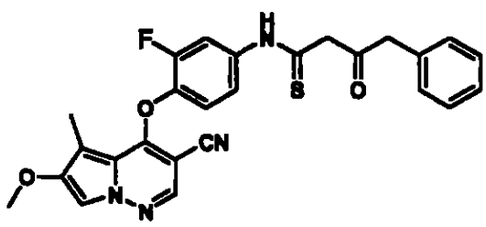
EJEMPLO 13



1-(4-(7,7a-Dihidro-4aH-pirrolo[2,3-d]pirimidin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)tiourea

A una mezcla de 1-(3-fluoro-4-hidroxifenil)-3-(2-(4-fluorofenil)acetil)tiourea (24 mg, 0.075 mmol, Compuesto A del Ejemplo 3), 4-cloro-7H-pirrolo[2,3-d]pirimidina (11 mg, 0.075 mmol, disponible comercialmente) y 1,4-diazabiciclo[2.2.2]octano (DABCO, 8.4 mg, 0.075 mmol) se le agregó MeCN (2 mL). La reacción se agitó a temperatura ambiente durante 4 horas y se concentró in vacuo. El residuo se purificó por CLAR preparativa de fase inversa para dar el compuesto del título (5.3 mg, 16%) como un sólido blanco. ^{1}H RMN ($CDCl_3$) δ 12.46 (s, 1H), 8.48 (s, 1H), 8.44 (s, 1H), 7.95 (dd, 1H, J=11.6, 2.8 Hz), 7.43 (m, 1H), 7.34 (m, 1H), 7.29 (m, 4H), 7.13 (ap. T, 2H, J=8.6 Hz), 6.80 (s, 1H), 3.72 (s, 2H); EM(ESI$^+$) m/z 440 $(M + H)^+$.

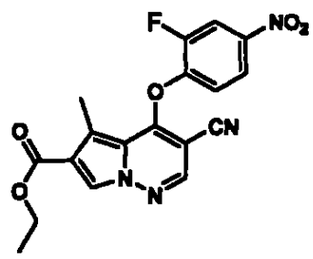
EJEMPLO 14



N(4-(3-Ciano-6-metoxi-5-metilH-pirrolo[1,2-b]piridazin-4-

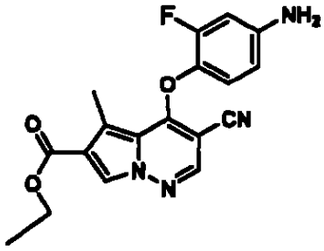
iloxi)-3-fluorofenil)-3-oxo-4-fenilbutanotioamida

380



A) 3-ciano-4-(2-fluoro-4-nitrofenoxi)-5-metilH-pirrolo[1,2-b]piridazin-6-carboxilato de etilo

A una mezcla de 4-cloro-3-ciano-5-metilH-pirrolo[1,2-b]piridazin-6-carboxilato de etilo (500 mg, 1.90 mmol, ver solicitud de Pat. E.U.A. No. 2004/063712, especialmente el Ejemplo 1, la descripción de la cual se incorpora en la presente para referencia en su totalidad), 2-fluoro-4-nitrofenol (361 mg, 2.3 mmol) y K_2CO_3 (315 mg, 2.3 mmol) se le agregó DMF (5 mL). La reacción se agitó a temperatura ambiente durante 2 horas. La reacción se apagó con agua (5 mL). La mezcla se filtró y el sólido se lavó con agua, se secó para dar el compuesto del título (630 mg, 86%) como un sólido amarillo ligero.

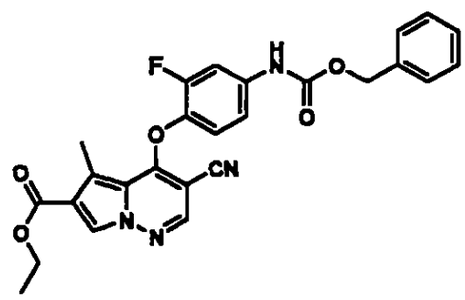


B) 4-(4-amino-2-fluorofenoxi)-3-ciano-5-metilH-pirrolo[1,2-b]piridazin-6-carboxilato de etilo

A una solución de 3-ciano-4-(2-fluoro-4-nitrofenoxi)-5-

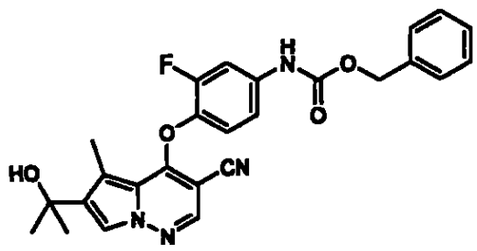
381

metilH-pirrolo[1,2-b]piridazin-6-carboxilato de etilo (630 mg, 1.64 mmol) en THF (5 mL) se le agregó MeOH (5 mL) seguido por Zn (200 mg, 3.0 mmol) y NH_4Cl (200 mg, 3.7 mmol). La reacción se calentó a 60°C durante 2 horas, se filtró y se concentró in vacuo. El filtrado se purificó por un cartucho SCX (eluyendo con amoniaco 2M en MeOH) para dar el compuesto del título (420 mg, 72%) como un sólido blanco.



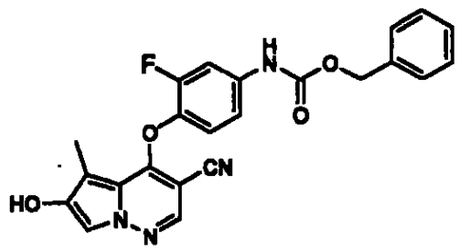
C) 4-(4-(benciloxicarbonil)-2-fluorofenoxi)-3-ciano-5-metilH-pirrolo[1,2-b]piridazin-6-carboxilato de etilo

A una solución de 4-(4-amino-2-fluorofenoxi)-3-ciano-5-metilH-pirrolo[1,2-b]piridazin-6-carboxilato de etilo (420 mg, 1.19 mmol) en CH_2Cl_2 (10 mL) se le agregó carbonato de potasio (200 mg. 1.43 mmol) y cloroformiato de bencilo (0.261 mL, 1.43 mmol). La solución se agitó a temperatura ambiente durante 24 horas. La solución se filtró, se concentró in vacuo y se recristalizó a partir de $EtOAc/CH_2Cl_2$ para dar el compuesto del título (490 mg, 84%) como un sólido blanco.



D) 4-(3-ciano-6-(2-hidroxipropan-2-il)-5-metilH-pirrolo[1,2-b]piridazin-4-iloxi)-3-fluorofenilcarbamato de bencilo

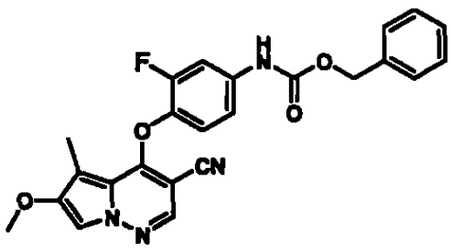
Una solución de 4-(4-(benciloxicarbonil)-2-fluorofenoxi)-3-ciano-5-metilH-pirrolo[1,2-b]piridazin-6-carboxilato de etilo (123 mg, 0.25 mmol) en THF (5 mL) se enfrió hasta 0°C. Una solución de bromuro de metilmagnesio (0.336 mL, 1.00 mmol, 3 M en THF) se le agregó y la solución se agitó a temperatura ambiente durante 30 minutos. Más bromuro de metilmagnesio (0.336 mL, 1.00 mmol, 3 M en THF) se le agregó, y la solución se calentó hasta 60°C durante 30 minutos. El acetato de etilo (10 mL) y agua (5 mL) se le agregó y la capa orgánica se lavó, se separó, se secó y se concentró in vacuo. La mezcla se purificó por cromatografía instantánea (20 - 50% EtOAc en CH_2Cl_2) para dar el compuesto del título (97 mg, 81%) como un sólido blanco.



E) 4-(3-ciano-6-hidroxi-5-metilH-pirrolo[1,2-b]piridazin-4-iloxi)-3-fluorofenilcarbamato de bencilo

A una solución de 4-(3-ciano-6-(2-hidroxipropan-2-

il)-5-metilH-pirrolo[1,2-6]piridazin-4-iloxi)-3-fluorofenilcarbamato de bencilo (97 mg, 0.2 mmol) en CH_2Cl_2 (2 mL) se le agregó a una solución previamente mezclada de peróxido de hidrógeno (0.033 mL) en agua y dieterato de trifluoruro de boro (0.570 mL) a -5°C. Después de 10 minutos, la reacción se apagó con solución de sulfato de sodio, se secó, se concentró in vacuo y el residuo se recristalizó con EtOAc y hexano para dar el compuesto del título (70 mg, 80%) como un sólido blanco.



F) 4-(3-ciano-6-metoxi-5-metilH-pirrolo[1,2-b]piridazin-4-iloxi)-3-fluorofenilcarbamato de bencilo

A una solución de 4-(3-ciano-6-hidroxi-5-metilH-pirrolo[1,2-b]piridazin-4-iloxi)-3-fluorofenilcarbamato de bencilo (25 mg, 0.06 mmol) en DMF (1 mL) se le agregó carbonato de cesio (39 mg. 0.12 mmol) y yoduro de metilo (0.05 mL, 0.072 mmol). La solución se agitó a temperatura ambiente durante 2 horas. El agua (1 mL) se le agregó y el producto se extrajo con acetato de etilo (2x5 mL), se secó y se concentró para dar el compuesto del título (20 mg, 74%)

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como un sólido blanco.



G) 4-(4-Amino-2-fluorofenoxi)-6-metoxi-5-metilH-pirrolo[1,2-b]piridazin-3-carbonitrilo

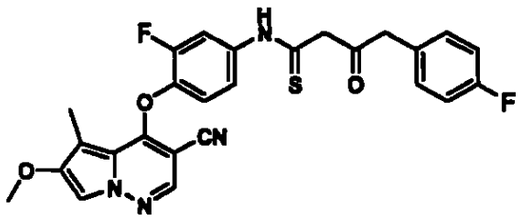
A una solución de 4-(3-ciano-6-metoxi-5-metilH-pirrolo[1,2-b]piridazin-4-iloxi)-3-fluorofenilcarbamato de bencilo (20 mg, 0.045 mmol) en etanol (3 mL) se le agregó paladio en carbono al 10% (20 mg) y la mezcla se agitó bajo un globo de hidrógeno durante 2 horas. La solución se filtró a través de una almohadilla de Celite® y se concentró in vacuo para dar el compuesto del título (12 mg, 85%).

H) N-(4-(3-Ciano-6-metoxi-5-metilH-pirrolo[1,2-b]-piridazin-4-iloxi)-3-fluorofenil)-3-oxo-4-fenilbutantioamida

A una solución de 4-(4-amino-2-fluorofenoxi)-6-metoxi-5-metilH-pirrolo[1,2-b]piridazin-3-carbonitrilo (6 mg, 0.02 mmol) en CH_2Cl_2 (1 mL) se le agregó una solución de 2-fenil-1-tiocianatoetanona (0.1 mL, 0.025 mmol, 0.25 M en acetato de etilo, Compuesto F del Ejemplo 1). La reacción se agitó a temperatura ambiente durante 20 minutos, se concentró in vacuo y se purificó por cromatografía instantánea en gel de sílice (eluyendo con 1 - 25% EtOAc/CH_2Cl_2) para proporcionar el

compuesto del título (3.90 mg, 40%) como un sólido amarillo pálido. ^{1}H RMN (CD_3OD) δ 8.01 (d, 1H, J= 12.7 Hz), 7.86 (s, 1H), 7.72 (s, 1H), 7.19 (m, 5H), 6.75 (m, 2H), 3.79 (s, 3H), 3.20 (m, 2H), 2.18 (s, 3H); EM(ESI$^+$) m/z 490 $(M + H)^+$.

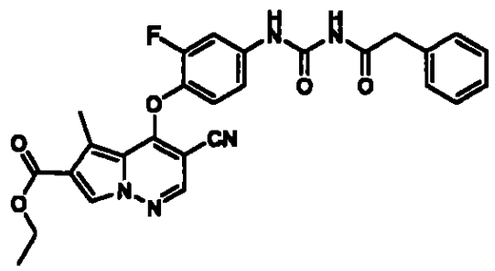
EJEMPLO 15



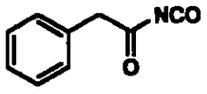
N-(4-(3-ciano-6-metoxi-5-metilH-pirrolo[1,2-b]piridazin-4-iloxi)-3-fluorofenil)-4-(4-fluorofenil)-3-oxobutanetioamida

El compuesto del título se preparó a partir de 4-(4-amino-2-fluorofenoxi)-6-metoxi-5-metilH-pirrolo[1,2-b]piridazin-3-carbonitrilo (Compuesto G del Ejemplo 14) y 2-(4-fluorofenil)-1-tiocianatoetanona (Compuesto A del Ejemplo 2) por el procedimiento descrito para el Compuesto H del Ejemplo 14. ^{1}H RMN (CD_3OD) δ 8.08 (dd, 1H, J = 12.7, 1.7 Hz), 7.95 (s, 1H), 7.80 (s, 1H), 7.34 (m, 3H), 7.19 (m, 1H), 7.04 (s, 2H), 6.87 (m, 2H), 3.89 (s, 3H), 3.30 (m, 2H), 2.27 (s, 3H); EM(ESI$^+$) m/z 508 $(M + H)^+$.

EJEMPLO 16



3-ciano-4-(2-fluoro-4-(3-(2-fenilacetil)ureido)fenoxi)-5-metilH-pirrolo[1,2-b]piridazin-6-carboxilato de etilo



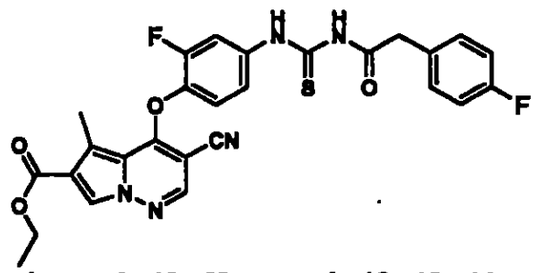
A) 2-Fenilacetil isocianato

A una suspensión de 2-fenilacetamida (68 mg, 0.5 mmol) en dicloroetano (2 mL) se le agregó cloruro de oxalilo (0.175 mL, 2.0 mmol). La suspensión se disolvió rápidamente y se formó una nueva suspensión. El análisis CL/EM de la mezcla de reacción después de 5 minutos, indicó que nada del producto deseado se formó. La mezcla se entibió hasta 80°C, la CL/EM después de 30 minutos indicó una pequeña cantidad del producto. La reacción se calentó a 70°C durante 2 días y se volvió mayormente clara. El análisis CL/EM indica mayormente producto. La mezcla se agitó y se calentó a 80°C durante otras 4 horas. Casi todo el sólido amarillo en las paredes del recipiente de reacción se disolvió. La mezcla se concentró in vacuo. El residuo se disolvió en dicloroetano (1.5 mL), se concentró, y se volvió a disolver en dicloroetano (2 mL). La solución resultante 0.25 M se usó sin purificación adicional.

B) 3-ciano-4-(2-fluoro-4-(3-(2-fenilacetil)ureido)fenoxi)-5-metilH-pirrolo[1,2-b]piridazin-6-carboxilato de etilo

A una solución de 4-(4-amino-2-fluorofenoxi)-3-ciano-5-metilH-pirrolo[1,2-b]piridazin-6-carboxilato de etilo (7 mg, 0.02 mmol, Compuesto B del Ejemplo 14) en diclorometano (0.3 mL) se le agregó una solución de isocianato de 2-fenilacetilo (0.04 mmol, 0.25 M. en dicloroetano). La reacción se agitó a temperatura ambiente y se monitoreó por CL/EM. Después de 2 horas, toda la materia prima se ha consumido. La mezcla se concentró y el residuo se purificó por cromatografía en gel de sílice (1-10% acetato de etilo/diclorometano) para dar el compuesto del título (8 mg, 78%) como un sólido amarillo. ^{1}H RMN ($CDCl_3$) δ 10.77 (s, 1H), 8.51 (s, 1H), 8.21 (s, 1H), 7.86 (s, 1H), 7.73 (dd, 1H, J= 12.2, 2.2 Hz), 7.43 - 7.21 (m, 7H), 4.37 (q, 2H, J = 7.1 Hz), 3.76 (s, 2H), 2.80 (s, 3H), 1.40 (t, 3H, J= 7.1 Hz); EM(ESI$^+$) m/z 516 $(M + H)^+$.

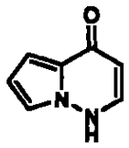
EJEMPLO 17



3-ciano-4-(2-fluoro-4-(3-(2-(4-fluorofenil)acetil)tioureido)fenoxi)-5-metilH-pirrolo[1,2-b]piridazin-6-carboxilato de etilo

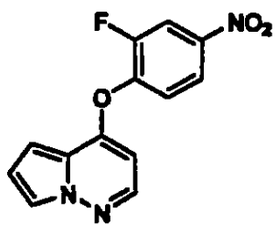
A una solución de 4-(4-amino-2-fluorofenoxi)-3-ciano-5-

dar el 2-((1H-pirrol-1-ilamino)metilen)malonato de dietilo crudo. A este intermediario se le agregó éter de difenilo (2 mL). La reacción se colocó bajo nitrógeno y se calentó a 220°C durante 2 horas, mientras se permite que el etanol formado en la reacción se destile completamente. La reacción se enfrió hasta temperatura ambiente y se purificó por cromatografía instantánea en gel de sílice (eluyendo con 100% CH_2Cl_2) para dar el compuesto del título (1.03 g, 71%) como un sólido amarillo.



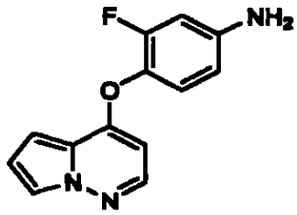
B) Pirrolo[1,2-6]piridazin-4(1H)-ona

Una mezcla de 4-oxo-1,4-dihidropirrolo[1,2-b]piridazin-3-carboxilato de etilo (206 mg, 1.0 mmol), NaCl (64 mg, 1.1 mmol), agua (0.054 mL, 3.0 mmol) y DMSO (2 mL) se calentó a 150°C durante 3 horas. Al final de la reacción, el DMSO se destiló completamente y el residuo se purificó por cromatografía instantánea en gel de sílice (eluyendo con 1 - 10% EtOAc/CH_2Cl_2) para dar el compuesto del título (90 mg, 67%) como un sólido amarillo ligero.



C) 4-(2-Fluoro-4-nitrofenoxi)H-pirrolo[1,2-b]piridazina

A una mezcla de pirrolo[1,2-b]piridazin-4(1H)-ona (13.4 mg, 0.10 mmol), 3,4-difluoronitrobenceno (24 mg, 0.15 mmol) y 1,4-diazabiciclo[2.2.2]octano (DABCO, 22 mg, 0.20 mmol) se le agregó MeCN (0.7 mL). La reacción se calentó a 70°C durante 72 horas y se concentró in vacuo. El residuo se purificó por cromatografía instantánea en gel de sílice (eluyendo con 100% CH_2Cl_2) para dar el compuesto del título (20 mg, 73%) como un sólido amarillo.



D) 4-(H-Pirrolo[1,2-b]piridazin-4-iloxi)-3-fluorobencenamina

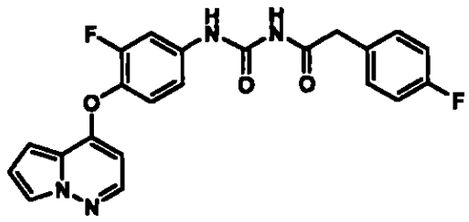
A una solución de 4-(2-fluoro-4-nitrofenoxi)H-pirrolo[1,2-b]piridazina (17 mg, 0.062 mmol) en THF (1.2 mL) se le agregó MeOH (0.8 mL) seguido por Zn (100 mg, 1.5 mmol) y NH_4Cl (43 mg, 0.80 mmol). La reacción se calentó a 70°C durante 90 minutos y se concentró in vacuo. Al residuo se le agregó CH_2Cl_2 (2 mL) y unas gotas de Et_3N. El sólido se disolvió parcialmente y la mezcla se filtró. El filtrado se concentró in vacuo y se purificó por cromatografía instantánea en gel de sílice (eluyendo con 1 - 6% EtOAc/CH_2Cl_2) para dar el compuesto del título (15

mg, 99%) como un sólido blanco.

E) 1-(4-(H-Pirrolo[1,2-b]piridazin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)tiourea

A una solución de 4-(H-pirrolo[1,2-b]piridazin-4-iloxi)-3-fluorobencenamina (7 mg, 0.03 mmol) en CH_2Cl_2 (0.3 mL) se le agregó una solución 0.25 M de isocianato (0.16 mL, 0.04 mmol, 0.25 M en acetato de etilo, Compuesto A del Ejemplo 2) en EtOAc. La reacción se agitó a temperatura ambiente durante 20 minutos, se concentró in vacuo y se purificó por cromatografía instantánea en gel de sílice (eluyendo con 1 - 5% EtOAc/CH_2Cl_2) para dar el compuesto del título (12 mg, 95%) como un sólido amarillo pálido. ^{1}H RMN ($CDCl_3$) δ 12.46 (s, 1H), 8.67 (s, 1H), 7.92 (dd, 1H, J = 11.5, 2.4 Hz), 7.85 (d, 1H,J=5.3Hz), 7.77 (dd, 1H, J=2.6, 1.5 Hz), 7.39 (m, 1H), 7.28 (m, 3H), 7.13 (m, 2H), 6.83 (dd, 1H, J= 4.3, 2.6 Hz), 6.74 (dd, 1H, J= 4.3, 1.5 Hz), 5.70 (d, 1H, J= 5.3 Hz), 3.73 (s, 2H); EM(ESI$^+$) m/z 439 $(M + H)^+$.

EJEMPLO 20



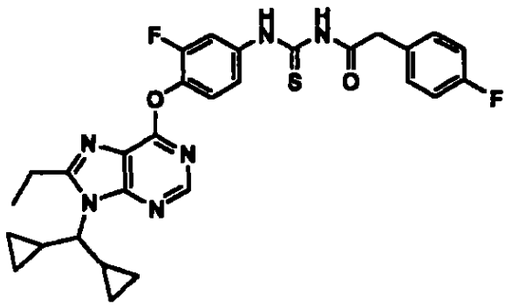
1-(4-(H-Pirrolo[1,2-b]piridazin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea

A una solución de la 4-(H-pirrolo[1,2-b]piridazin-4-

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iloxi)-3-fluorobencenamina (5 mg, 0.02 mmol, Compuesto D del Ejemplo 19) en CH_2Cl_2 (0.3 mL) se le agregó una solución de 2-(4-fluorofenil)acetil isocianato (0.16 mL, 0.04 mmol, 0.25 M en diclorometano, Compuesto C del Ejemplo 4). La reacción se agitó a temperatura ambiente durante 2 horas, se concentró in vacuo y se purificó por cromatografía instantánea en gel de sílice (eluyendo con 1 - 15% $EtOAc/CH_2Cl_2$) para dar el compuesto del título (5.5 mg, 63%) como un sólido amarillo pálido. ^1H RMN ($CDCl_3$) δ 10.68 (s, 1H), 8.69 (s, 1H), 7.83 (d, 1H,J=5.3 Hz), 7.77 (dd, 1H, J = 2.6, 1.5 Hz), 7.68 (dd, 1H, J= 11.5, 2.4 Hz), 7.33 - 7.17 (m, 4H), 7.09 (m, 2H), 6.82 (dd, 1H, J= 4.3, 2.6 Hz), 6.74 (dd, 1H, J = 4.3, 1.5 Hz), 5.69 (d, 1H, J= 5.3 Hz), 3.76 (s, 2H); EM(ESI^+) m/z 423 $(M + H)^+$.

EJEMPLO 21



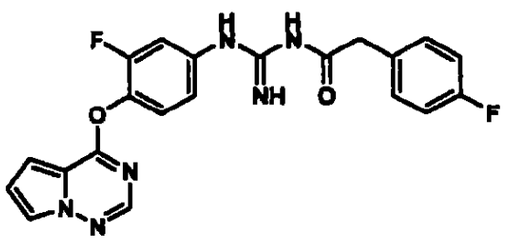
1-(4-(9-(diciclopropilmetil)-8-etil-9H-purin-6-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)tiourea

A una mezcla de 1-(3-fluoro-4-hidroxifenil)-3-(2-(4-

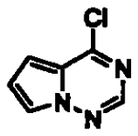
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fluorofenil)acetil)tiourea (24 mg, 0.075 mmol, Compuesto A del Ejemplo 3), 6-cloro-9-(diciclopropilmetil)-8-etil-9H-purina (20.7 mg, 0.075 mmol, Solicitud PCT WO 99/01454, Patente E.U.A. 6,143,743, ejemplo 831, la descripción de las cuales se incorpora en la presente para referencia) y 1,4-diazabiciclo[2.2.2]octano (DABCO, 8.4 mg, 0.075 mmol) se le agregó MeCN (2 mL). La reacción se agitó a temperatura ambiente durante 4 horas y se concentró in vacuo. El residuo se purificó por CLAR preparativa de fase inversa para dar el compuesto del título (15.3 mg, 36%) como un sólido blanco. ^{1}H RMN ($CDCl_3$) δ 12.43 (m, 1H), 8.48 (m, 1H), 8.40 (m, 1H), 7.92 (m, 1H), 7.28 (m, 4H), 7.13 (m, 2H), 3.72 (s, 2H), 3.34 (m, 3H), 1.53 (m, 3H), 0.81 (m, 2H), 0.46 (m, 4H), 0.23 (m, 2H); EM(ESI$^+$) m/z 489 $(M + H)^+$.

EJEMPLO 22



1-(3-Fluoro-4-(pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)guanidina

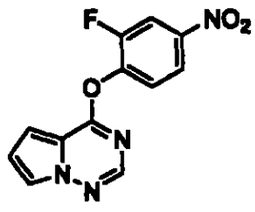


A) 4-Cloropirrolo[2,1-f][1,2,4]triazina

A una solución de pirrolo[2,1-f][1,2,4]triazin-4-ol

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(3.70 g, 27.4 mmol, ver generalmente, Solicitud PCT WO 2000/071129 la descripción de la cual se incorpora en la presente para referencia en su totalidad) en 40 mL de tolueno a temperatura ambiente se le agregó 4.77 mL (27.4 mmol) de diisopropiletilamina seguido por 7.70 mL (82.6 mmol) de oxicloruro de fósforo. La mezcla de reacción se calentó a 100°C durante 18 horas. Después de enfriar hasta temperatura ambiente, la reacción se agregó lentamente a una solución de solución de $NaHCO_3$ acuosa al 5% (100 mL) a 0°C. Una vez completada la adición, la mezcla bifásica se permitió agitar a temperatura ambiente durante 30 minutos. La capa acuosa se extrajo con EtOAc (3 x 100 mL) y los extractos orgánicos agrupados se lavaron con salmuera (100 mL), se secaron sobre $MgSO_4$ anhidro, y se concentraron in vacuo para dar el producto crudo (4.10 g, 97%) como un sólido amarillo. ^1H RMN ($CDCl_3$) δ 8.14 (s, 1H), 7.80 (dd, 1H, J= 2.4, 1.5 Hz), 6.91 (m, 2H).

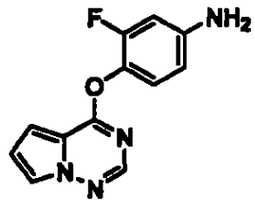


B) 4-(2-Fluoro-4-nitrofenoxi)pirrolo[2,1-f][1,2,4]triazina

La 4-cloropirrolo[2,1-f][1,2,4]triazina (4.1g, 27 mmol), 2-fluoro-4-nitrofenol (5.0 g, 32 mmol), y carbonato de

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potasio (7.4 g, 53 mmol) en 100 mL de dimetilformamida se agitó a 60°C durante 15 horas. Después de enfriar hasta temperatura ambiente, la mezcla de reacción se filtró a través de un tapón de gel de sílice con EtOAc. El filtrado se concentró in vacuo y el producto crudo resultante se purificó por cromatografía instantánea en gel de sílice (SiO_2, EtOAc/Hexano 1:4) para dar el compuesto del título (4.25 g, 58%) como un sólido blanco. ^1H RMN ($CDCl_3$) δ 8.09 (m, 2H), 7.88 (s, 1H), 7.77 (dd, 1H, J= 2.6, 1.2 Hz), 7.46 (t, 1H, J= 7.6 Hz), 6.98 (dd, 1H, J= 4.6, 1.4 Hz), 6.84 (dd, 1H, J =4.5, 2.6 Hz); ^{13}C RMN ($CDCl_3$) δ 160.6, 154.3 (J= 254 Hz), 146.5, 145.8, 144.8 (J= 12.9 Hz), 125.0, 121.7, 120.7, 114.5, 113.9, 113.6 (J= 23.2 Hz), 103.6.



C) 3-Fluoro-4-(pirrolo[2,1-f][1,2,4]triazin-4-iloxi)bencenamina (4)

A una solución de 4-(2-fluoro-4-nitrofenoxi)pirrolo[2,1-f][1,2,4]triazina (4.25 g, 15.5 mmol) en 40 mL de tetrahidrofurano y 60 mL de metanol a 0°C se le agregó polvo de zinc (3.04 g, 46.5 mmol, <10 micrones) seguido por cloruro de amonio (2.49 g, 46.5 mmol). La mezcla se agitó a

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temperatura ambiente durante la noche. El polvo de zinc adicional (6.08 g, 93 mmol) y cloruro de amonio (5.0 g, 93 mmol) se agregaron y la reacción se permitió agitar a temperatura ambiente durante 4 horas. La mezcla heterogénea se filtró a través de una almohadilla delgada de Celite® con metanol y el filtrado se concentró in vacuo. La purificación por cromatografía instantánea en gel de sílice (SiO_2, EtOAc/Hexano 1:1) dio el compuesto del título (3.5 g, 92%) como una espuma amarilla. ^1H RMN ($CDCl_3$) δ 7.92 (s, 1H), 7.70 (dd, 1H, J= 2.5, 1.6 Hz), 6.98 (t, 1H, J= 8.5 Hz), 6.92 (dd, 1H, J= 4.4, 1.4 Hz), 6.77 (m, 1H), 6.42 (m, 2H), 3.71 (br s, 2H); EM(ESI$^+$) m/z 245.2$(M+H)^+$.

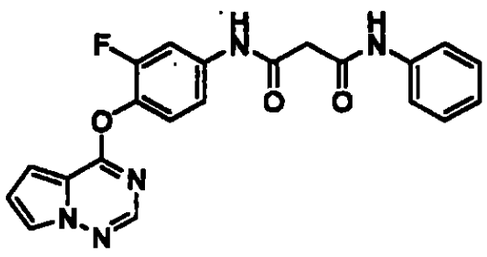
D) 1-(3-Fluoro-4-(pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)guanidina

A un tubo de ensayo que contiene 3-fluoro-4-(pirrolo[2,1-f][1,2,4]triazin-4-iloxi)bencenamina (20 mg, 0.082 mmol) y 1-(2-(4-fluorofenil)acetil)-2-metilisotiourea (20 mg, 0.086 mmol) se le agregó 0.3 mL de tolueno seguido por diisopropiletilamina (15 µL, 0.086 mmol). La reacción se agitó a 110°C durante 6 horas. Se agregaron porciones adicionales de 1-(2-(4-fluorofenil)-acetil)-2-metilisotiourea (20 mg, 0.086 mmol) y diisopropiletilamina (15 µL, 0.086 mmol). Después de agitar a 110°C durante la noche, la reacción se enfrió hasta temperatura ambiente y se purificó

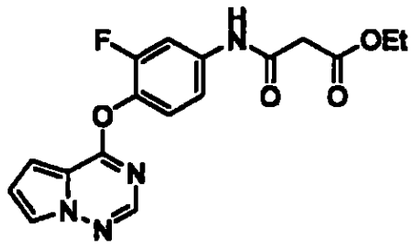
144 396

directamente por cromatografía instantánea en gel de sílice (SiO_2, EtOAc/Hexano 1:1) para dar el compuesto del título como un sólido blanco. El sólido se trató con HCl 4 N en dioxano a 0°C durante 30 minutos. La solución se concentró in vacuo para dar la sal HCl del compuesto del título (15 mg, 40%) como un polvo blanco. ^{1}H RMN ($CDCl_3$) δ 13.8 (br s, 1H), 11.5 (brs, 1H), 9.48 (brs, 1H), 7.85 (s, 1H), 7.78 (dd, 1H, J = 2.5, 1.4 Hz), 7.30 (m, 5H), 7.01 (m, 3H), 6.85 (m, 1H); EM(ESI$^+$) m/z 423.1 (M+ H)$^+$.

EJEMPLO 23



N^1-(3-Fluoro-4-(pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-N^3-fenilmalonamida

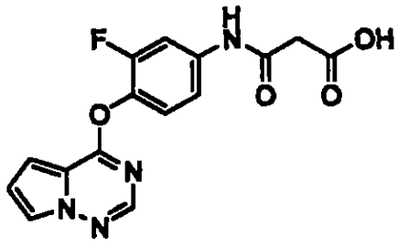


A) 3-(3-fluoro-4-(pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenilamino)-3-oxopropanoato de etilo

A una solución de 3-fluoro-4-(pirrolo[2,1-

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f][1,2,4]triazin-4-iloxi)bencenamina (112 mg, 0.459 mmol, Compuesto C del Ejemplo 22) en cloruro de metileno (4 mL) a 0°C se le agregó 96 µL (0.55 mmol) de diisopropiletilamina seguido por 61 µL (0.48 mmol) de 3-cloro-3-oxopropanoato de etilo. La reacción se agitó a 0°C durante 1 hora y luego se apagó con 10 mL de solución de $NaHCO_3$ saturada. La capa acuosa se extrajo con cloroformo (3x15 mL). Los extractos orgánicos combinados se secaron sobre Na_2SO_4 anhidro y se concentraron in vacuo para dar el producto crudo como un aceite amarillo que se solidificó durante el reposo (180 mg). ^1H RMN ($CDCl_3$) δ 9.45 (br s, 1H), 7.89 (s, 1H), 7.71 (dd, 1H, J= 2.5, 1.5 Hz), 7.68 (dd, 1H, J = 11.8, 2.2 Hz), 7.18 (m, 2H), 6.93 (dd, 1H, J= 4.4, 1.4 Hz), 6.78 (dd, 1H, J= 4.4, 2.6 Hz), 4.19 (q, 2H, J= 7.2 Hz), 3.41 (s, 2H), 1.25 (t, 3H, J= 7.2 Hz); EM(ESI$^+$) m/z 359.1 $(M + H)^+$.



B) ácido 3-(3-Fluoro-4-(pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenilamino)-3-oxopropanoico

A una solución del 3-(3-fluoro-4-(pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenilamino)-3-oxopropanoato de etilo crudo anterior (180 mg) en etanol (10 mL) a 0°C se le agregó

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solución de NaOH acuoso 1 N (10 mL). Después de agitar a 0°C durante 3 horas, la reacción se lavó con 20 mL de EtOAc. La capa de EtOAc nuevamente se extrajo con 20 mL de solución de NaOH acuoso 1 N. La solución acuosa combinada se hizo ácida hasta pH 5 con solución de HCl acuosa 1 N. La capa acuosa se extrajo con EtOAc (3 x 30 mL). Los extractos orgánicos combinados se secaron sobre Na_2SO_4 anhidro y se concentró in vacuo para dar el ácido crudo el cual se usó sin purificación adicional (150mg). EM(ESI$^+$) m/z 331.1 $(M^+H)^+$.

C) N^1-(3-Fluoro-4-(pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-N^3-fenilmalonamida

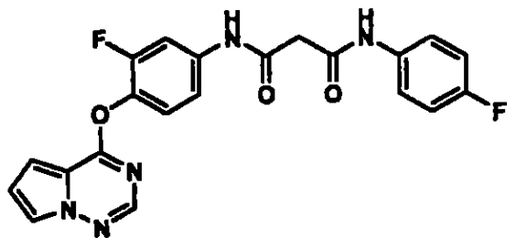
Una solución de ácido 3-(3-fluoro-4-(pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenilamino)-3-oxopropanoico (17 mg, 0.052 mmol), reactivo BOP (34 mg, 0.077 mmol), 4-metilmorfolina (28 µL, 0.26 mmol), y anilina (4.7 µL, 0.052 mmol) en dimetilformamida (0.5 mL) se agitó a temperatura ambiente durante 16 horas. La reacción se diluyó con EtOAc (4 mL) y se lavó con agua, solución de LiCl acuosa al 10%, y salmuera (1 x 3 mL de cada uno). La solución orgánica se secó sobre Na_2SO_4 anhidro y luego se concentró in vacuo. La purificación por cromatografía instantánea en gel de sílice (SiO_2, EtOAc/Hexano 7:3) dio el compuesto deseado como un sólido blanco. El producto se liofilizó con acetonitrilo/agua para dar el compuesto del título (12 mg, 57%) como un polvo blanco. ^{1}H RMN ($CDCl_3$) δ 9.23 (br s, 1H), 8.22 (br s, 1H),

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7.90 (s, 1H), 7.72 (m, 1H), 7.46 (d, 1H, J = 8.2 Hz), 7.20 (m, 7H), 6.95 (m, 1H), 6.78 (m, 1H), 3.47 (s, 2H); EM(ESI$^+$) m/z 406.1 $(M + H)^+$.

EJEMPLO 24



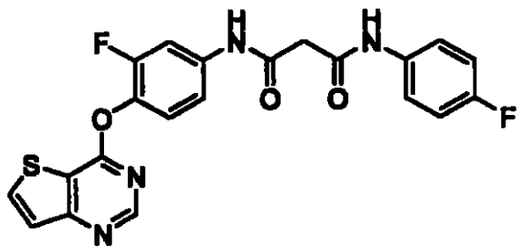
N^1-(3-Fluoro-4-(pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-N^3-(4-fluorofenil)malonamida

Una solución de ácido 3-(3-fluoro-4-(pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenilamino)-3-oxopropanoico (18 mg, 0.55 mmol, Compuesto B del Ejemplo 23), reactivo BOP (36 mg, 0.082 mmol), 4-metilmorfolina (30 µL, 0.27 mmol), y 4-fluoroanilina (5.2 µL, 0.055 mmol) en dimetilformamida (0.5 mL) se agitó a temperatura ambiente durante 16 horas. La reacción se diluyó con EtOAc (4 mL) y se lavó con agua, solución de LiCl acuoso al 10%, y salmuera (1 x 3 mL de cada uno). La solución orgánica se secó sobre Na_2SO_4 anhidro y luego se concentró in vacuo. La purificación por cromatografía instantánea en gel de sílice (SiO_2, EtOAc/Hexano 7:3) dio el compuesto deseado como un sólido blanco. El producto se liofilizó con acetonitrilo/agua para dar el compuesto del título (14 mg, 61%) como un polvo blanco. ^{1}H RMN ($CDCl_3$) δ 9.28 (br s, 1H), 8.64 (br s, 1H), 7.89 (s, 1H), 7.73 (dd, 1H, J= 2.5, 1.5 Hz), 7.69 (dd, 1H, J= 11.6, 1.9 Hz), 7.42 (m, 3H), 7.21 (m,

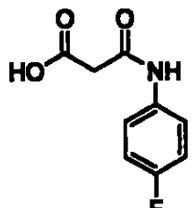
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1H), 6.97 (m, 3H), 6.80 (dd, 1H, J= 4.5, 2.6 Hz), 3.49 (s, 2H); EM(ESI$^+$) m/z 424.1 (M+ H)$^+$.

EJEMPLO 25



N^1-(3-Fluoro-4-(tieno[3,2-d]pirimidin-4-iloxi)fenil)-N^3-fluorofenil)malonamida



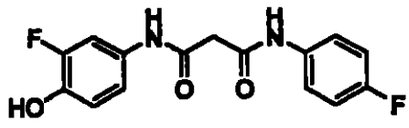
A) ácido 3-(4-fluorofenilamino)-3-oxopropanoico

A una solución de 3-cloro-3-oxopropanoato de etilo (5.0 mL, 40 mmol, Aldrich) en cloruro de metileno (100 mL) a 0°C se le agregó diisopropiletilamina (8.4 mL, 48 mmol) seguido por 4-fluoroanilina (3.6 mL, 38 mmol, Aldrich). La reacción se agitó a temperatura ambiente durante la noche y luego se apagó con 100 mL de una solución $NaHCO_3$ saturada. La capa acuosa se extrajo con cloroformo (3 x 100 mL). Los extractos orgánicos combinados se secaron sobre Na_2SO_4 anhidro y se concentró in vacuo para dar el producto crudo como un aceite amarillo que se solidificó en reposo (10 g). ^{1}H RMN ($CDCl_3$) δ

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9.30 (br s, 1H), 7.55 (m, 2H), 7.05 (t, 2H, J = 8.8 Hz), 4.28 (q, 2H, J = 7.2 Hz), 3.49 (s, 2H), 1.35 (t, 3H, J = 7.1 Hz); EM(ESI$^+$) m/z 226.1$(M+H)^+$.

El éster anterior se disolvió en 100 mL de etanol y se enfrió hasta 0°C. Una solución de NaOH acuoso 1 N (100 mL) se le agregó y la reacción se agitó a 0°C durante 1 hora. La reacción se concentró para retirar el etanol. La solución acuosa se extrajo con EtOAc (50 mL) y luego se hace ácida con solución de HCl acuosa 1 N. La solución acuosa se extrajo con EtOAc (5 x 100 mL). Los extractos orgánicos combinados se secaron sobre Na_2SO_4 anhidro y se concentró in vacuo para dar el producto crudo (6.31 g, 84%) como un sólido amarillo el cual se usó sin purificación adicional. ^{1}H RMN (DMSO-d_6) δ 12.9 (br s, 1H), 10.3 (br s, 1H), 7.59 (m, 2H), 7.16 (t, 2H, J = 8.9 Hz), 3.34 (s, 2H); EM(ESI$^+$) m/z 198.4 $(M+H)^+$.



B) N^1-(3-Fluoro-4-hidroxifenil)-N^3-(4-fluorofenil)malonamida

A una solución de 2-fluoro-4-nitrofenol (1.00 g, 6.37 mmol) en 4 mL de tetrahidrofurano y 6 mL de metanol a 0°C se le agregó polvo de zinc (2.08 g, 31.8 mmol, <10 micrones) seguido por cloruro de amonio (1.70 g, 31.8 mmol). La mezcla se agitó a temperatura ambiente durante la noche. La mezcla

heterogénea se filtró a través de una almohadilla delgada de Celite® con metanol y el filtrado se concentró in vacuo para dar un sólido café el cual se usó sin purificación adicional (656 mg, 81%).

El ácido 3-(4-fluorofenilamino)-3-oxopropanoico (197 mg, 1.00 mmol) se disolvió en 4 mL de dimetilformamida. La trietilamina (140 µL, 1.00 mmol) se le agregó y la solución se enfrió hasta 0°C. El 4-amino-2-fluorofenol (127 mg, 1.00 mmol, Aldrich) se le agregó seguido por reactivo BOP (442 mg, 1.00 mmol). La reacción se permitió que se entibiara hasta temperatura ambiente y luego se agitó a temperatura ambiente durante 3 horas. La mezcla de reacción se concentró para retirar el cloruro de metileno, y se le agregó agua para precipitar el producto. La filtración y trituración con agua dio el compuesto del título (211 mg, 69%) como un sólido blanco. ^{1}H RMN (CD_3OD) δ 7.61 (m, 2H), 7.51 (dd, 1H, J = 13, 2.5 Hz), 7.08 (m, 3H), 6.88 (t, 1H, J = 9.4 Hz), 3.51 (s, 2H); EM(ESI$^+$) m/z 307.4 $(M+H)^+$.

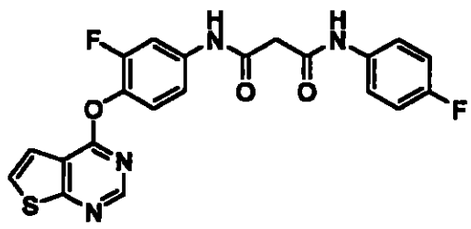
C) N^1-(3-Fluoro-4-(tieno[3,2-d]pirimidin-4-iloxi)fenil)-N^3-(4-fluorofenil)malonamida

La N^1-(3-fluoro-4-hidroxifenil)-N^3-(4-fluorofenil)malonamida (46 mg, 0.15 mmol), 4-clorotieno[3,2-d]pirimidina (17 mg, 0.10 mmol), carbonato de cesio (49 mg, 0.15 mmol), y cloruro de cobre (I) (10 mg, 0.10 mmol) se

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colocaron en un tubo de ensayo. El tubo se selló, se hizo fluir con nitrógeno, se cargó con 1-metil-2-pirrolidinona (0.3 mL) seguido por 2,2,6,6-tetrametil-3,5-heptanodiona (4.0 µL, 0.02 mmol). La reacción se agitó a 120°C durante 2 horas. La mezcla de reacción se purificó por CLAR preparativa. La fracción apropiada se concentró para retirar el metanol y la solución acuosa resultante se hizo básica con solución de $NaHCO_3$ saturada (5 mL). La solución acuosa se extrajo con EtOAc (3 x 10mL) y los extractos orgánicos combinados se secaron sobre Na_2SO_4 anhidro y se concentraron in vacuo para dar el producto deseado como un aceite incoloro. La liofilización con metanol/agua dio el compuesto del título (23 mg, 52%) como un sólido blanco. ^1H RMN (CD_3OD) δ 8.54 (s, 1H), 8.21 (d, 1H, J= 5.5 Hz), 7.69 (dd, 1H, J = 12.4, 2.0 Hz), 7.49 (m, 3H), 7.27 (m, 2H), 6.96 (t, 2H, J= 8.9 Hz), 3.47 (s, 2H); EM(ESI$^+$) m/z 441.1 $(M + H)^+$.

EJEMPLO 26



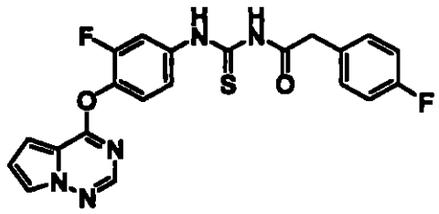
N^1-(3-Fluoro-4-(tieno[2,3-b]pirimidin-4-iloxi)fenil)-N3-(4-fluorofenil)malonamida

La N^1-(3-fluoro-4-hidroxifenil)-N^3-(4-fluorofenil)malonamida (46 mg, 0.15 mmol, Compuesto B del Ejemplo 25), 4-clorotieno[2,3-d]pirimidina (17 mg, 0.10 mmol),

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carbonato de cesio (49 mg, 0.15 mmol), y cloruro de cobre (I) (10 mg, 0.10 mmol) se colocaron en un tubo de ensayo. El tubo se selló, se hizo fluir con nitrógeno, se cargó con 1-metil-2-pirrolidinona (0.3 mL) seguido por 2,2,6,6-tetrametil-3,5-heptanodiona (4.0 µL, 0.02 mmol). La reacción se agitó a 120°C durante 1 hora. La mezcla de reacción se purificó por CLAR preparativa. La fracción apropiada se concentró para retirar el metanol y la solución acuosa resultante se hizo básica con solución de $NaHCO_3$ saturada (5 mL). La solución acuosa se extrajo con EtOAc (3x10 mL) y los extractos orgánicos combinados se secaron sobre Na_2SO_4 anhidro y se concentraron in vacuo para dar el producto deseado como un aceite incoloro. La liofilización con metanol/agua dio el compuesto del título (27 mg, 61 %) como un sólido blanco. ^1H RMN (DMSO-d_6) δ 10.7 (s, 1H), 10.4 (s, 1H), 8.77 (s, 1H), 8.15 (d, 1H, J= 5.9 Hz), 7.95 (dd, 1H, J= 12.8, 2.0 Hz), 7.85 (d, 1H, J= 5.9 Hz), 7.77 (m, 2H), 7.54 (m, 2H), 7.30 (t, 2H, J= 8.8 Hz), 3.48 (s, 2H); EM(ESI$^+$) m/z 441.1 $(M + H)^+$.

EJEMPLO 27

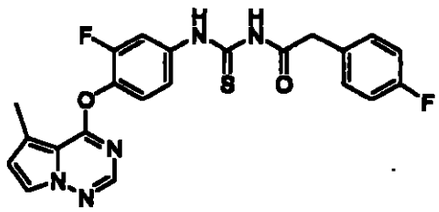


1-(3-Fluoro-4-(pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-3-(2-(4-fluorofenil)-acetil)tiourea

A una solución homogénea de tiocianato de sodio (21 mg,

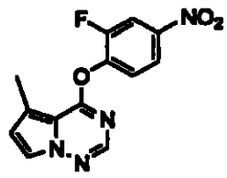
0.26 mmol) en acetato de etilo (1 mL), a temperatura ambiente bajo una atmósfera de nitrógeno, se le agregó cloruro de 4-fluorofenil-acetilo (28 µL, 0.20 mmol). La mezcla se agitó durante 30 minutos antes de agregarse directamente a una solución homogénea de 3-fluoro-4-(pirrolo[2,1-f][1,2,4]-triazin-4-iloxi)bencenamina (37 mg, 0.15 mmol, Compuesto C del Ejemplo 22) en diclorometano anhidro (3 mL), bajo una atmósfera de nitrógeno. La mezcla se agitó a temperatura ambiente durante 4 horas antes de concentrarse in vacuo. La purificación por (Merck KGaA, 230-400 tamaño de partícula de malla) cromatografía instantánea en gel de sílice, eluyendo con cloroformo, proporciona el compuesto del título (55 mg, 83%). ^{1}H RMN ($CDCl_3$) δ 12.41 (s, 1H), 8.50 (s, 1H), 7.97 (s, 1H), 7.92 (m, 1H), 7.81 (m, 1H), 7.42 (m, 1H), 7.35-7.25 (m, 3H), 7.17-7.10 (m, 2H), 7.05-7.02 (m, 1H), 6.85-6.90 (m, 1H), 3.72 (s, 2H); EMAR(ESI), 440.0993 $(M + H)^+$ calculado, 440.0988 $(M + H)^+$ encontrado.

EJEMPLO 28



1-(3-Fluoro-4-(5-metilpirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)tiourea

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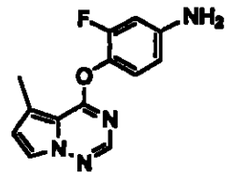


A) 4-(2-Fluoro-4-nitrofenoxi)-5-metilpirrolo(2,1-f][1,2,4]triazina

A una mezcla de 4-cloro-5-metilpirrolo[2,1-f][1,2,4]triazina (3.37 g, 20.11 mmol, Solicitud PCT WO 2000/071129, Solicitud de Patente E.U.A. 2003/0186982, la descripción de las cuales se incorpora en la presente para referencia) y 2-fluoro-4-nitrofenol (3.48 g, 22.12 mmol) en DMF anhidro (100 mL), agitada durante 5 minutos bajo una atmósfera de nitrógeno, se le agregó carbonato de potasio anhidro (6.11 g, 44.24 mmol). La mezcla se calentó a 60°C durante 15 horas antes de agregar 2-fluoro-4-nitrofenol (1.00 g, 6.37 mmol) y la agitación continuó a 60°C durante 4.5 horas. La mezcla se enfrió hasta temperatura ambiente, se diluyó con diclorometano, se lavó secuencialmente con agua y cloruro de litio acuoso al 10%, se secó sobre sulfato de magnesio anhidro y se concentró in vacuo para proporcionar un sólido color marrón. La purificación por (Merck KGaA, 230-400 tamaño de partícula de malla) cromatografía instantánea gel de sílice, eluyendo con cloroformo, proporciona el compuesto del título (4.19 g, 72%) como un sólido amarillo pálido. ^{1}H RMN ($CDCl_3$) δ 8.20-8.13 (m, 2H), 7.83 (s, 1H), 7.73 (d, 1H, J= 2.6 Hz); 7.58-7.53 (m, 1H), 6.69 (d, 1H, J = 2.4 Hz), 2.62

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(s, 3H); EMAR(ESI), 289.0737 $(M + H)^+$ calculado, 289.0733 $(M + H)^+$ encontrado.



B) 3-Fluoro-4-(5-metilpirrolo[2,1-f][1,2,4]triazin-4-iloxi)bencenamina

A una mezcla heterogénea de 4-(2-fluoro-4-nitrofenoxi)-5-metilpirrolo[2,1-f][1,2,4]triazina (3.04 g, 10.55 mmol) en metanol anhidro (60 mL) y tetrahidrofurano anhidro (40 mL), a temperatura ambiente bajo atmósfera de nitrógeno, se le agregó polvo de zinc (6.90 g, 105 mmol) y cloruro de amonio (5.64g, 105 mmol). La mezcla se agitó durante 7 horas antes de que el catalizador se filtrara completamente y el filtrado se concentró in vacuo hasta un sólido amarillo pálido el cual se dividió entre cloroformo y agua. La capa acuosa luego se extrajo dos veces con cloroformo. Las capas de cloroformo combinadas se lavaron con agua, se secó sobre sulfato de magnesio anhidro y se concentró in vacuo para proporcionar el compuesto del título (2.51 g, 92%) como un sólido. ^1H RMN ($CDCl_3$) δ 7.86 (s, 1H), 7.64 (d, 1H, $J_.$ = 2.6 Hz); 7.08-7.03 (m, 1H), 6.61 (d, 1H, J= 2.4 Hz), 6.55-6.45 (m, 2H), 3.78 (s, 2H), 2.60 (s, 3H); EMAR(ESI), 259.0995 $(M + H)^+$ calculado,

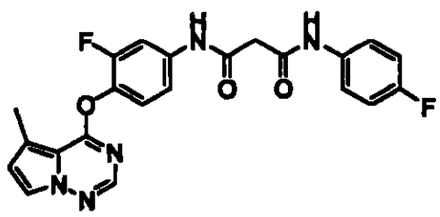
408

259.0997 $(M + H)^+$ encontrado.

C) 1-(3-Fluoro-4-(5-metilpirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)tiourea

La 3-fluoro-4-(5-metilpirrolo[2,1-f][1,2,4]triazin-4-iloxi)bencenamina (39 mg, 0.15 mmol) se convirtió al compuesto del título (42 mg, 62%) en una manera similar a la preparación del Ejemplo 27. ^{1}H RMN ($CDCl_3$) δ 12.41 (s, 1H), 8.48 (s, 1H), 7.92-7.82 (m, 2H), 7.68 (d, 1H, J = 2.5 Hz), 7.39-7.27 (m, 4H), 7.15-7.10 (m, 2H), 6.64 (d, 1H, J = 2.3 Hz), 3.72 (s, 2H), 2.60 (s, 3H); EMAR(ESI), 454.1149 $(M + H)^+$ calculado, 454.1154 $(M + H)^+$ encontrado.

EJEMPLO 29



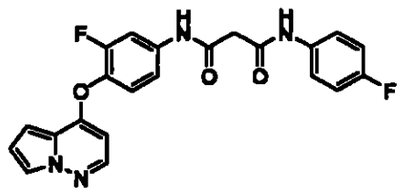
N^1-(3-Fluoro-4-(5-metilpirrolo[2,1-f][1,2,4]triazin-4-f]oxi)fenil)-N3-(4-fluoro-fenil)malonamida

A una solución homogénea de 3-fluoro-4-(5-metilpirrolo[2,1-f][1,2,4]triazin-4-iloxi)bencenamina (52 mg, 0.20 mmol, Compuesto B del Ejemplo 28) y ácido 3-(4-fluorofenilamino)-3-oxopropanoico (39 mg, 0.20 mmol, Compuesto A del Ejemplo 25) en DMF anhidro (2 mL), a temperatura ambiente bajo atmósfera de nitrógeno, se le agregó diisopropiletilamina

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(52 µL, 0.30 mmol). La mezcla se agitó durante 5 minutos antes de agregar tetrafluoroborato de o-benzotriazol-1-il-N,N,N',N'-tetrametiluronio (96 mg, 0.30 mmol) se le agregó en una porción. La mezcla se agitó durante 17.5 horas antes de concentrar la reacción in vacuo para retirar los volátiles. El residuo resultante se diluyó con acetato de etilo y se lavó dos veces con cloruro de litio acuoso al 10% antes de concentrarse in vacuo. La purificación por (Merck KGaA, 230-400 tamaño de partícula de malla) cromatografía instantánea en gel de sílice, eluyendo con 1% metanol en cloroformo, proporciona un sólido blanco opaco que se trituró y sonicó en presencia de éter de etilo anhidro (3 mL). El compuesto del título (66 mg, 75%) se aisló por filtración como un sólido blanco. ^{1}H RMN ($CDCl_3$) δ 9.28 (s, 1H), 8.67 (s, 1H), 7.83 (s, 1H), 7.80-7.73 (m, 1H), 7.67 (d, 1H, J = 2.5 Hz), 7.54-7.49 (m, 2H), 7.28-7.26 (m, 2H), 7.10-7.02 (m, 2H), 6.64 (d, 1H, J = 2.3 Hz), 3.56 (s, 2H), 2.60 (s, 3H); EMAR(ESI), 436.1221 $(M + H)^+$ calculado, 436.1230 $(M + H)^+$ encontrado.

EJEMPLO 30



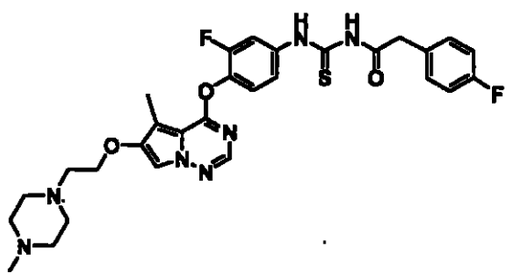
N^1-(4-H-Pirrolo[1,2-b]piridazin-4-iloxi)-3-fluorofenil)-N^3-fluorofenil)malonamida

Una solución de 4-(H-pirrolo[1,2-b]piridazin-4-iloxi)-3-

410

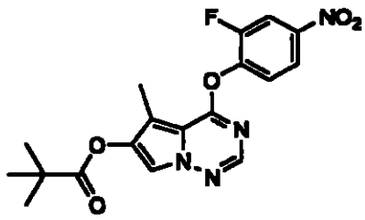
fluorobencenamina (51 mg, 0.21 mmol, Compuesto D del Ejemplo 19) en DMF (1 mL) se trató con ácido 3-(4-fluorofenilamino)-3-oxopropanoico (41 mg, 0.21 mmol, Compuesto A del Ejemplo 25), DIPEA (42 µL, 0.25 mmol) y TBTU (81 mg, 0.25 mmol) y la mezcla se agitó a temperatura ambiente durante 16 horas. La mezcla se concentró in vacuo para retirar el DMF y el residuo se dividió entre EtOAc (2 mL) y solución de bicarbonato de sodio saturada (2 mL). La fase de EtOAc se lavó con LiCl acuoso al 10% (2 mL), salmuera (2 mL), se secó ($MgSO_4$) y se concentró in vacuo. El producto crudo se trituró dos veces con EtOAc y dos veces con MeOH para dar el compuesto del título (17 mg, 19%) como un sólido blanco opaco. ^1H RMN (DMSO-d_6) δ 10.56 (s, 1H), 10.28 (s, 1H), 8.01, (d, 1H,J = 5.4 Hz), 7.92-7.91 (m, 1H), 7.65-7.62 (m, 2H), 7.48-7.44 (m, 2H), 7.22-7.15 (m, 3H), 6.86 (dd, 1H, J = 4.2, 2.7 Hz), 6.72 (dd, 1H, J = 4.4, 1.4 Hz), 5.81 (d, 1H,J = 5.4Hz), 3.51 (s, 2H); EM(ESI$^+$) m/z 423.3 $(M+H)^+$.

EJEMPLO 31



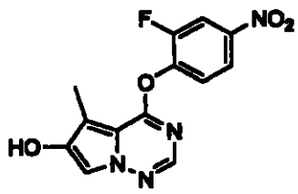
1-(3-Fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-f]-[1,2,4]triazin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)tiourea, sal de bis-clorohidrato

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A) 4-(2-Fluoro-4-nitrofenoxi)-5-metilpirrolo[2,1-f][1,2,4]-triazin-6-ilo pivalato

A una solución homogénea de 4-cloro-5-metilpirrolo[2,1-f][1,2,4]triazin-6-ilo pivalato (1.00 g, 3.74 mmol, Compuesto D del Ejemplo 1) y 2-fluoro-4-nitrofenol (588 mg, 3.74 mmol) en acetonitrilo anhidro (25 mL), a temperatura ambiente bajo una atmósfera de nitrógeno, se le agregó DABCO (462 mg, 4.12 mmol). La mezcla luego se calentó a 50°C durante 3 horas. La mezcla se enfrió hasta temperatura ambiente, luego se dividió entre cloroformo y cloruro de amonio acuoso saturado. La capa acuosa se extrajo dos veces con cloroformo. Las capas orgánicas combinadas se lavaron una vez cada una con cloruro de amonio acuoso saturado y cloruro de sodio acuoso saturado, se secaron sobre sulfato de magnesio anhidro y se concentraron in vacuo para proporcionar un sólido amarillo pálido el cual se usó en la siguiente etapa sin purificación adicional. EM(ESI$^+$) m/z 389.1 $(M + H)^+$.

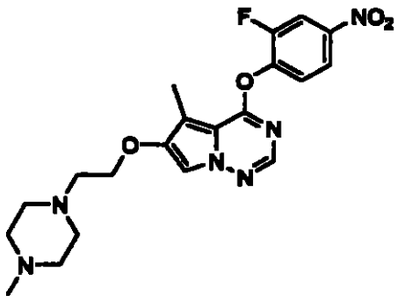


B) 4-(2-Fluoro-4-nitrofenoxi)-5-metilpirrolo[2,1-f][1,2,4]-triazin-6-ol

A una mezcla heterogénea de 4-(2-fluoro-4-nitrofenoxi)-

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5-metilpirrolo[2,1-f][1,2,4]-triazin-6-ilo pivalato (1.45 g, 3.74 mmol) en etanol absoluto (19 mL), a temperatura ambiente bajo una atmósfera de nitrógeno, se le agregó hidróxido de sodio acuoso 1 N. La mezcla de reacción se agitó a temperatura ambiente durante 1.5 hora antes de neutralizar hasta pH 7 con clorohidrato acuoso 1 N. La mezcla de reacción se concentró para retirar el etanol, antes de dividir entre acetato de etilo y agua. La capa acuosa se extrajo dos veces con acetato de etilo. Los extractos orgánicos combinados se lavaron dos veces con agua, una vez con cloruro de sodio acuoso saturado, se secaron sobre sulfato de magnesio anhidro y se concentraron in vacuo. La purificación por (Merck KGaA, 230-400 tamaño de partícula de malla) cromatografía instantánea en gel de sílice, eluyendo con 2:1 hexano/acetato de etilo, proporcionó el compuesto del título (602 mg, 53% para las Etapas A-B) como un sólido amarillo. ^{1}H RMN ($CDCl_3$) δ 8.20-8.12 (m, 2H), 7.84 (s, 1H), 7.58-7.53 (m, 1H), 7.53 (s, 1H), 4.76 (s, 1H), 2.48 (s, 3H); EM(ESI$^+$) m/z 305.2 $(M + H)^+$.

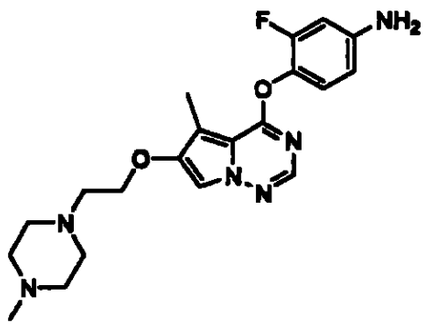


C) 4-(2-Fluoro-4-nitrofenoxi)-5-metil-6-(2-(4-metilpiperazin-1-il)-etoxi)pirrolo[2,1-f][1,2,4]triazina

A una mezcla homogénea de 4-(2-fluoro-4-nitrofenoxi)-

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5-metilpirrolo[2,1-f][1,2,4]-triazin-6-ol (100 mg, 0.33 mmol) y trifenilfosfina (129 mg, 0.49 mmol) en 4 mL de 1:1 diclorometano anhidro/tetrahidrofurano anhidro, se enfrió hasta 0°C bajo una atmósfera de nitrógeno, se le agregó gota a gota una mezcla de 2-(4-metilpiperazin-1-il)etanol (71 mg, 0.49 mmol) y diisopropilazodicarboxilato (0.10 µL, 0.49 mmol) en 2 mL de 1:1 diclorometano anhidro/tetrahidrofurano anhidro. La mezcla se agitó y se permitió que se entibiara hasta temperatura ambiente. La reacción se agitó durante veinte horas antes de concentrarse in vacuo. El residuo se purificó por CLAR preparativa (YMC S10 ODS, 30 x 500 mm, 30 minutos gradiente a partir de 50% hasta 90% de metanol acuoso con TFA al 0.1%). Las fracciones apropiadas se combinaron, se neutralizaron con bicarbonato de sodio acuoso saturado, y luego se concentró in vacuo para retirar el metanol. La mezcla se extrajo con cloroformo (3x10 mL). Las capas orgánicas combinadas se lavaron una vez cada una con agua y salmuera, se secaron sobre sulfato de magnesio anhidro, y se concentraron in vacuo para proporcionar el compuesto del título (34 mg, 24%) como un sólido amarillo. ^{1}H RMN ($CDCl_3$) δ 8.20-8.10 (m, 2H), 7.82 (s, 1H), 7.58-7.52 (m, 1H), 7.49 (s, 1H), 4.16 (t, 2H, J= 5.7 Hz), 2.87 (t, 2H, J= 5.7 Hz), 2.80-2.40 (m, 8H), 2.45 (s, 3H), 2.31 (s, 3H); EM(ESI$^+$) m/z 431.3 $(M + H)^+$.



D) 3-Fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-f]-[1,2,4]triazin-4-iloxi)bencenamina

La 4-(2-Fluoro-4-nitrofenoxi)-5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-f][1,2,4]triazina (20 mg, 0.05 mmol) se convirtió al compuesto del título (16 mg, 87%) en una manera similar a la preparación del Compuesto B del Ejemplo 28. ^{1}H RMN ($CDCl_3$) δ 7.86-7.83 (m, 1H), 7.50-7.38 (m, 2H), 7.09-7.00 (m, 1H), 6.56-6.45 (m, 1H), 4.14 (t, 2H, J= 5.5 Hz), 2.99-2.38 (m, 18H); EM(ESI$^+$) m/z 401.4 $(M + H)^+$.

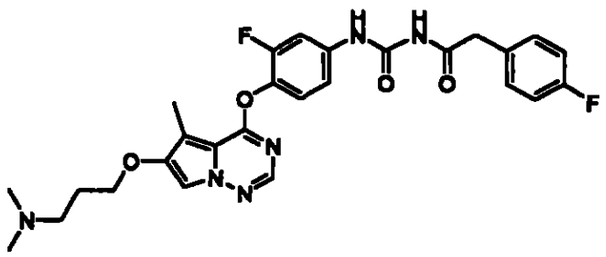
E) 1-(3-Fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)tiourea, sal de bis-clorohidrato

La 3-fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-f][1,2,4]-triazin-4-iloxi)bencenamina (18 mg, 0.05 mmol) se convirtió al

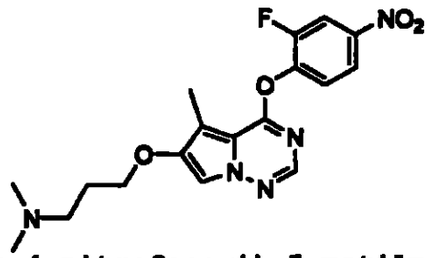
415

compuesto del título (7 mg, 26%) en una manera similar a la preparación del Ejemplo 27. El tratamiento con ácido clorhídrico acuoso 1 N (0.05 mL, 0.05 mmol), seguido por la liofilización, resulta en el compuesto del título como un sólido amarillo pálido (5 mg, 64%). ^{1}H RMN (CD_3OD) δ 8.06-7.99 (m, 2H), 7.83 (s, 1H), 7.79 (s, 1H), 7.48-7.30 (m, 4H), 7.13-7.02 (m, 2H), 4.56-4.45 (m, 2H), 3.87-3.59 (m, 4H), 3.09-2.44 (m, 15H); EMAR(ESI), 596.2255 $(M + H)^+$ calculado, 596.2261 $(M + H)^+$. encontrado.

EJEMPLO 32



1-(4-(6-(3-(Dimetilamino)propoxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea, sal de clorohidrato



A) 3-(4-(2-Fluoro-4-nitrofenoxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-6-iloxi)-N,N-dimetilpropan-1-amina

A una mezcla de trifenilfosfina unida al polímero (3

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mmol de trifenilfosfina por 1 g de resina, 583 mg, 1.75 mmol) en tetrahidrofurano anhidro (5 mL), a 0°C bajo una atmósfera de nitrógeno, se le agregó dietilazodicarboxilato (138 µL, 0.87 mmol) gota a gota por medio de una jeringa. La mezcla se agitó durante 15 minutos antes de 3-dimetil-aminopropanol (103 µL, 0.87 mmol) se le agregó. Después de 30 minutos a 0°C, 4-(2-fluoro-4-nitrofenoxi)-5-metilpirrolo[2,1-f][1,2,4]-triazin-6-ol (133 mg, 0.44 mmol, Compuesto B del Ejemplo 31) se le agregó, y la mezcla se permitió que se entibiara lentamente hasta temperatura ambiente. Después de 14.5 horas, la resina se retiró por filtración y se enjuagó con 1:1 metanol/tetrahidrofurano. El filtrado combinado se concentró in vacuo hasta un residuo amarillo el cual se usó en la siguiente etapa sin purificación adicional. EM(ESI$^+$) m/z 390.2 $(M + H)^+$.

B) 4-(6-(3-(Dimetilamino)propoxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-4-iloxi)-3-fluorobencenamina

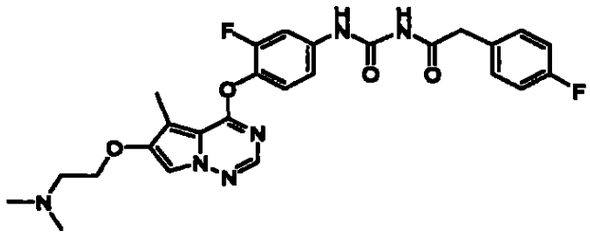
La 3-(4-(2-fluoro-4-nitrofenoxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-6-iloxi)-N,N-dimetilpropan-1-amina (170 mg, 0.44 mmol) se convirtió al compuesto del título en una manera similar a la preparación del Compuesto B del Ejemplo 28. El sólido amarillo resultante se usó en la siguiente etapa sin purificación adicional. EM(ESI$^+$) m/z 360.3 $(M + H)^+$.

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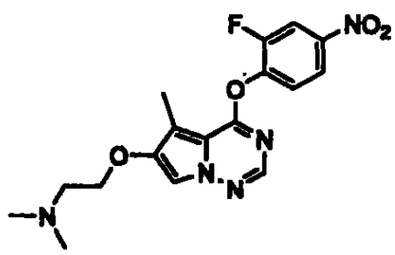
C) 1-(4-(6-(3-(Dimetilamino)propoxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea, sal de clorohidrato

La 4-(6-(3-(Dimetilamino)propoxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-4-iloxi)-3-fluorobencenamina (12 mg, 0.03 mmol) se convirtió al compuesto del título (2.5 mg, 13%) en una manera similar a la preparación del Compuesto E del Ejemplo 31, excepto que el isocianato de 2-(4-fluorofenil)-acetilo (0.10 mL, 0.04 mmol, Compuesto C del Ejemplo 4) se usó en lugar de isocianato de bencenesulfonilo. ^{1}H RMN (CD_3OD) δ 10.77 (s, 1H), 7.80 (s, 1H), 7.69 (s, 1H), 7.40-7.23 (m, 5H), 7.11-7.02 (m, 3H), 4.15-4.12 (m, 2H), 3.71 (s, 2H), 3.41-3.36 (m, 2H), 2.97 (s, 6H), 2.44 (s, 3H), 2.31-2.22 (m, 2H); EMAR(ESI), 539.2218 $(M + H)^+$ calculado, 539.2218 $(M + H)^+$ encontrado.

EJEMPLO 33

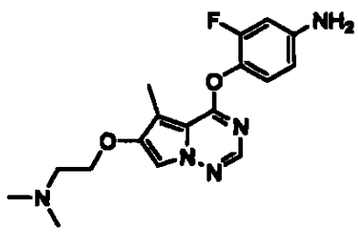


1-(4-(6-(2-(Dimetilamino)etoxi)-5-metilpirrolo(2,1-f][1,2,4]triazin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea, sal de clorohidrato



A) 2-(4-(2-Fluoro-4-nitrofenoxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-6-iloxi)-N,N-dimetiletanamina

El 4-(2-Fluoro-4-nitrofenoxi)-5-metilpirrolo[2,1-f][1,2,4]-triazin-6-ol (91 mg, 0.30 mmol, Compuesto B del Ejemplo 31) se convirtió al compuesto del título en una manera similar a la preparación del Compuesto A del Ejemplo 32, excepto que la N,N-dimetiletanolamina (75 u,L, 0.75 mmol) se usó en lugar de 3-dimetilaminopropanol y el diisopropilazodicarboxilato (148 µL, 0.75 mmol) se usó en lugar de dietilazodicarboxilato. El residuo se purificó por CLAR preparativa (YMC S10 ODS, 30 x 500 mm, 30 minutos gradiente a partir de 70% hasta 90% de metanol acuoso con TFA al 0.1%). Las fracciones apropiadas se combinaron, se neutralizaron con bicarbonato de sodio acuoso saturado, y luego se concentró in vacuo para retirar el metanol. La mezcla se extrajo con cloroformo (3 x 10mL). Las capas orgánicas combinadas se lavaron una vez cada una con agua y salmuera, se secaron sobre sulfato de magnesio anhidro, y se concentraron in vacuo para proporcionar el compuesto del título (22 mg, 19%) como un sólido. EM(ESI$^+$) m/z 376.2 $(M+H)^+$.



B) 4-(6-(2-(Dimetilamino)etoxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-4-iloxi)-3-fluorobencenamina

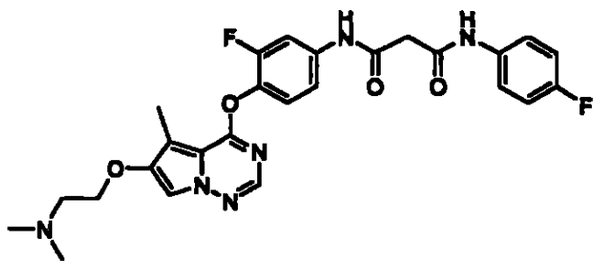
La 2-(4-(2-Fluoro-4-nitrofenoxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-6-iloxi)-N,N-dimetiletanamina (22 mg, 0.06 mmol) se convirtió al compuesto del título (20 mg, 100%) en una manera similar a la preparación del Compuesto B del Ejemplo 28. El vidrio amarillo resultante se usó en la siguiente etapa sin purificación adicional. EM(ESI$^+$) m/z 346.3 $(M + H)^+$.

C) 1-(4-(6-(2-(Dimetilamino)etoxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea, sal de clorohidrato

La 4-(6-(2-(Dimetilamino)etoxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-4-iloxi)-3-fluorobencenamina (20 mg, 0.06 mmol) se convirtió al compuesto del título (6.5 mg, 19%) en una manera similar a la preparación del Compuesto C del Ejemplo 32. ^{1}H RMN (CD_3OD) δ 10.79 (s, 1H), 7.84 (s, 1H), 7.77 (s, 1H), 7.40-7.21 (m, 5H), 7.10-6.97 (m, 3H), 4.43-4.39 (m, 2H), 3.71 (s, 2H), 3.68-3.62 (m, 2H), 3.03 (s, 6H), 2.48 (s, 3H); EMAR(ESI), 525.2062 $(M + H)^+$ calculado, 525.2079 $(M + H)^+$ encontrado.

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EJEMPLO 34

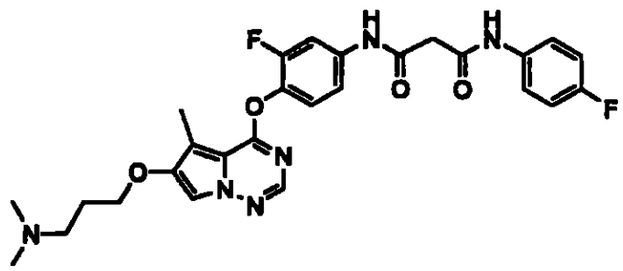


N^1-(4-(6-(2-(Dimetilamino)etoxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-4-iloxi)-3-fluorofenil)-N^3-(4-fluorofenil)malonamida, sal de clorohidrato

La 4-(6-(2-(Dimetilamino)etoxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-4-iloxi)-3-fluorobencenamina (35 mg, 0.10 mmol, Compuesto B del Ejemplo 33) se convirtió al compuesto del título (4.2 mg, 8%) en una manera similar a la preparación del Ejemplo 29, excepto que el PyBroP (52 mg, 0.11 mmol) se usó en lugar de tetrafluoroborato de o-benzotriazol-1-il-N,N,N',N'-tetrametil-uronio. El tratamiento con ácido clorhídrico acuoso 1 N (1 mL, 1 mmol), seguido por la liofilización, resulta en el compuesto del título (1.7 mg, 38%) como un sólido amarillo pálido. ^{1}H RMN (CD_3OD) δ 7.83 (s, 1H), 7.77 (s, 1H), 7.62-7.58 (m, 2H), 7.40-7.27 (m, 5H), 7.09-7.04 (m, 2H), 4.43-4.41 (m, 2H), 3.70-3.54 (m, 4H), 3.04 (s, 6H), 2.50 (s, 3H); EMAR(ESI), 525.2062 $(M + H)^+$ calculado, 525.2059 $(M + H)^+$ encontrado.

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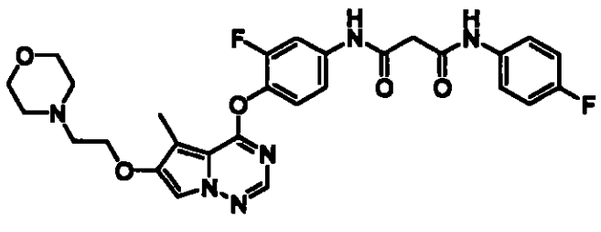
EJEMPLO 35



N^1-(4-(6-(3-(Dimetilamino)propoxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-4-iloxi)-3-fluorofenil)-N^3-(4-fluorofenil)malonamida, sal de clorohidrato

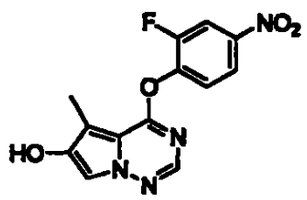
La 4-(6-(3-(dimetilamino)propoxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-4-iloxi)-3-fluorobencenamina (54 mg, 0.15 mmol, Compuesto B del Ejemplo 32) se convirtió al compuesto del título (13 mg, 15%) en una manera similar a la preparación del Ejemplo 34. ^{1}H RMN (CD_3OD) δ 7.83-7.75 (m, 2H), 7.67 (s, 1H), 7.63-7.57 (m, 2H), 7.39-7.27 (m, 2H), 7.09-7.02 (m, 2H), 4.18-4.13 (m, 2H), 3.58 (s, 2H), 3.42-3.36 (m, 2H), 2.96 (s, 6H), 2.48-2.42 (m, 4H), 2.32-2.25 (m, 2H); EMAR(ESI), 537.2062 $(M-H)^-$ calculado, 537.2073 $(M-H)^-$ encontrado.

EJEMPLO 36



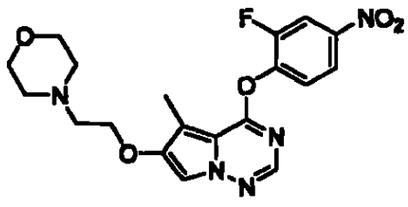
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N^1-(3-Fluoro-4-(5-metil-6-(2-morfolinoetoxi)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-N^3-(4-fluorofenil)malonamida, sal de clorohidrato



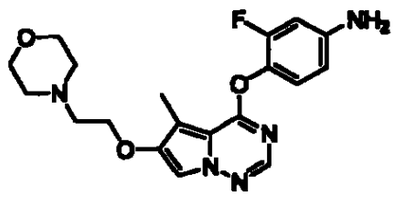
A) 4-(2-Fluoro-4-nitrofenoxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-6-ol

A una solución de 4-(2-fluoro-4-nitrofenoxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-6-ilo pivalato (2.40 g, 6.19 mmol, Compuesto E del Ejemplo 1) en una mezcla de 20 mL de THF y 30 mL de EtOH, se le agregó NaOH 1 N (12 mL, 12 mmol) gota a gota a temperatura ambiente. La solución resultante se permitió agitar durante 45 minutos, por tal tiempo, el análisis CLAR indica el final de la reacción. La reacción se apaga de este modo con 13 mL de HCl 1 N. Después de que el solvente orgánico se retiró a presión reducida, el producto se precipitó y se colectó a través de filtración. El producto obtenido es 4-(2-fluoro-4-nitrofenoxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-6-ol (1.65 g, 88%). EM(ESI$^+$) m/z 305.1 $(M + H)^+$.



B) 4-(2-Fluoro-4-nitrofenoxi)-5-metil-6-(2-morfolinetoxi)pirrolo[2,1-f][1,2,4]triazina

A una solución de 4-(2-fluoro-4-nitrofenoxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-6-ol (55 mg, 0.18 mmol), 2-morfolinetanol (47 mg, 0.36 mmol), y PPh_3 enlazado al polímero (3.0 mmol/g, 167 mg, 0.50 mmol) en 1 mL de THF a temperatura ambiente se le agregó DIAD (72 mg, 0.36 mmol). La mezcla se agitó durante 1 hora y el análisis CLAR indicó que la mayoría de la materia prima desapareció. El polímero se filtró a través de Celite® y el filtrado se concentró y se purificó por CLAR preparativa para proporcionar el compuesto del título (50 mg, 67%). EM(ESI+) m/z 418.2 $(M + H)^+$.



C) 3-Fluoro-4-(5-metil-6-(2-morfolinetoxi)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)bencenamina

A una solución de 4-(2-fluoro-4-nitrofenoxi)-5-metil-6-(2-morfolinetoxi)pirrolo[2,1-f][1,2,4]triazina (54 mg, 0.13 mmol) en una mezcla de 0.8 mL de THF y 1.2 mL de MeOH, se

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agregaron NH_4Cl (70 mg, 1.3 mmol) y polvo de Zn (85 mg, 1.3 mmol). La suspensión se permitió agitar a temperatura ambiente durante 2 horas. Tanto el análisis CLAR como el análisis de CL-EM indica el final de la reacción y el sólido se filtró así completamente. Después de la concentración del filtrado, el residuo se tomó en MeOH al 10% en CH_2Cl_2. La solución luego se filtró nuevamente y el filtrado se concentró in vacuo para proporcionar el compuesto del título (50 mg, 92%). EM(ESI$^+$) m/z 388.4 $(M + H)^+$.

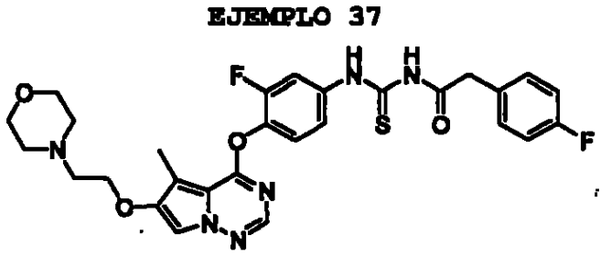
D) N^1-(3-Fluoro-4-(5-metil-6-(2-morfolinetoxi)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-N^3-(4-fluorofenil)malonamida, sal de clorohidrato

A una solución de 3-fluoro-4-(5-metil-6-(2-morfolinetoxi)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)bencenamina (16 mg, 0.041 mmol), ácido 3-(4-fluorofenilamino)-3-oxopropanoico (12 mg, 0.06 mmol, Compuesto A del Ejemplo 25) en 1 mL de THF se agregaron DIEA (0.04 mL) y PyBrOP (32 mg, 0.06 mmol) a temperatura ambiente. La reacción se permitió agitar durante el fin de semana y el análisis de CL-EM indica la formación del producto, no obstante que todavía quedó algo de materia prima. La solución se sometió directamente a purificación CLAR preparativa y la fracción CLAR que contiene el producto deseado se pasó a través de un cartucho de extracción Waters

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Oasis® MCX 20cc 500mg LP y se lavó con MeOH para retirar el TFA. Después de esto, el cartucho se eluyó con NH_3 7 N en MeOH y la solución de amoniaco se concentró a presión reducida hasta secarse. El residuo luego se suspendió en una mezcla de MeOH y H_2O y unas gotas de HCl 1 N se le agregaron. La suspensión se volvió una solución clara y se congeló en un baño de acetona-hielo seco. La solución congelada luego se liofilizó para proporcionar el compuesto del título (20 mg, 80%). ^1H RMN (CD_3OD) δ 7.71 (m, 2H), 7.60 (s, 1H), 7.53 (m, 2H), 7.28 (m, 2H), 7.00 (m, 2H), 4.13 (s, 2H), 3.67 (s, 4H), 2.80 (s, 2H), 2.58 (s, 4H), 2.37 (s, 3H); EM(ESI$^+$) m/z 567.2 $(M + H)^+$.

EJEMPLO 37

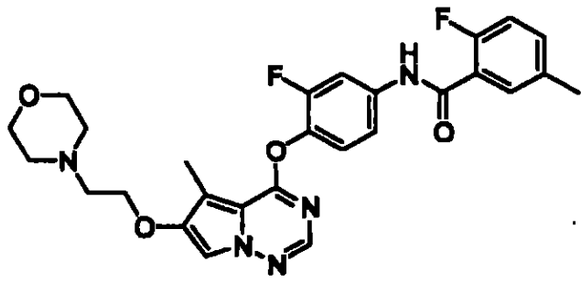


1-(3-Fluoro-4-(5-metil-6-(2-morfolinetoxi)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)tiourea, sal de clorohidrato

A una solución de 3-fluoro-4-(5-metil-6-(2-morfolinetoxi)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)bencenamina (30 mg, 0.072 mmol, Compuesto C del Ejemplo 36) en 1 mL de THF se le agregó 2-(4-fluorofenil)etanoilo

isotiocianato (19 mg, 0.1 mmol, Compuesto A del Ejemplo 2). La solución se permitió agitar a temperatura ambiente durante 2 horas y el análisis CLAR indica el final de la reacción. La reacción luego se apagó con NH_3 en propanol y la solución resultante se cargó en una CLAR preparativa para purificarse. Siguiendo un procedimiento de trabajo similar al del Compuesto D del Ejemplo 36, el compuesto del título (13 mg, 30%) se obtiene como la sal HCl. ^{1}H RMN (DMSO-d_6) δ 12.45 (s, 1H), 11.85 (s, 1H), 11.50 (br s, 1H), 8.15 (s, 1H), 8.10 (s, 1H), 7.90 (d, 1H), 7.50 (m, 2H), 7.40 (m, 2H), 7.20 (m, 2H), 4.50 (br s, 2H), 4.00 (m, 2H), 3.85 (s, 2H), 3.25-3.70 (m, 8H), 2.40 (s, 3H); EM(ESI$^+$) m/z 583.2 $(M + H)^+$.

EJEMPLO 38

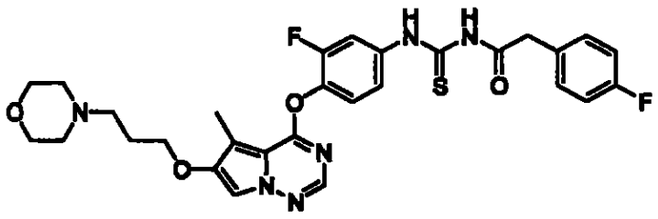


2-Fluoro-N-(3-fluoro-4-(5-metil-6-(2-morfolinetoxi)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-5-metilbenzamida, sal de clorohidrato

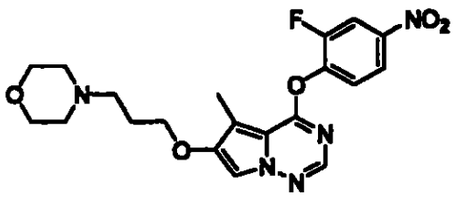
Siguiendo un procedimiento similar al de la síntesis del Compuesto D del Ejemplo 36, 3-fluoro-4-(5-metil-6-(2-morfolinetoxi)pirrolo[2,1-f][1,2,4]triazin-4-

iloxi)bencenamina (16 mg, 0.042 mmol, Compuesto C del Ejemplo 36) se convirtió al compuesto del título (5.6 mg, 23%) como la sal HCl. ^{1}H RMN (CD_3OD) δ 7.85 (d, 1H), 7.80 (s, 1H), 7.69 (s, 1H), 7.55 (m, 1H), 7.50 (m, 1H), 7.35 (m, 2H), 7.13 (m. 1H), 4.22 (m, 2H), 3.73 (m, 4H), 2.88 (m, 2H), 2.66 (m, 4H), 2.44 (s, 3H), 2.38 (s, 3H); EM(ESI$^+$) m/z 262.3 $(M + H)^+$.

EJEMPLO 39



1-(3-Fluoro-4-(5-metil-6-(3-morfolinopropoxi)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)tiourea, sal de clorohidrato

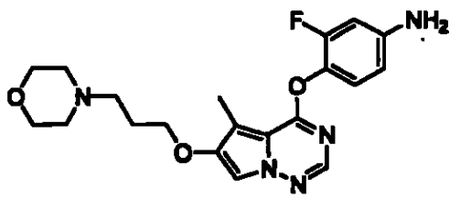


A) 4-(2-Fluoro-4-nitrofenoxi)-5-metil-6-(3-morfolinopropoxi)pirrolo[2,1-f][1,2,4]triazina

Siguiendo un procedimiento similar al de la síntesis del Compuesto B del Ejemplo 36, el 4-(2-fluoro-4-nitrofenoxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-6-ol (50 mg, 0.16 mmol, Compuesto A del Ejemplo 36) se convirtió al compuesto del

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título (32 mg, 46%). EM(ESI$^+$) m/z 432.2 (M + H)$^+$.



B) 3-Fluoro-4-(5-metil-6-(3-morfolinopropoxi)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)bencenamina

Siguiendo un procedimiento similar al de la síntesis del Compuesto C del Ejemplo 36, la 4-(2-fluoro-4-nitrofenoxi)-5-metil-6-(3-morfolinopropoxi)pirrolo[2,1-f][1,2,4]triazina (31 mg, 0.072 mmol) se convirtió al compuesto del título (28 mg, 95%). EM(ESI$^+$) m/z 402.3 (M + H)$^+$.

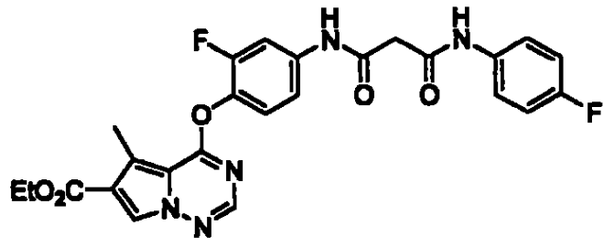
C) 1-(3-Fluoro-4-(5-metil-6-(3-morfolinopropoxi)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)tiourea, sal de clorohidrato

Siguiendo un procedimiento similar al Compuesto D del Ejemplo 36, la 3-fluoro-4-(5-metil-6-(3-morfolinopropoxi)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)bencenamina (28 mg, 0.07 mmol) se convirtió al compuesto del título (30 mg, 68%) como la sal HCl. ^{1}H RMN (DMSO-d_6) 12.45 (s, 1H), 11.80 (s, 1H), 11.65 (br s, 1H),

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8.00 (s, 2H), 7.90 (d, 1H), 7.50 (m, 2H), 7.40 (m, 2H), 7.25 (m, 2H), 3.10-4.10 (m, 16H), 2.40 (s, 3H); EM(ESI$^+$) m/z 597.2 $(M + H)^+$.

EJEMPLO 40

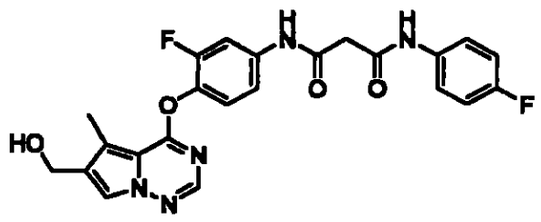


4-(2-fluoro-4-(3-(4-fluorofenilamino)-3-oxopropanamido)fenoxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-6-carboxilato de etilo

Siguiendo un procedimiento similar al de la síntesis del Compuesto D del Ejemplo 36, el 4-(4-amino-2-fluorofenoxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-6-carboxilato de etilo (70 mg, 0.21 mmol, Compuesto B del Ejemplo 6) se convirtió al compuesto del título (50 mg, 47%). ^{1}H RMN (DMSO-d_6) δ 10.50 (s, 1H), 10.30 (s, 1H), 8.45 (s, 1H), 8.16 (s, 1H), 7.90 (d, 1H), 7.67 (m, 2H), 7.51 (t, 1H), 7.40 (t, 1H), 7.20 (m, 2H), 4.33 (q, 2H), 3.52 (s, 2H), 2.77 (s, 3H), 1.35 (t, 3H); EM(ESI$^+$) EM(ESI$^+$) m/z 510.1$(M + H)^+$.

427 430

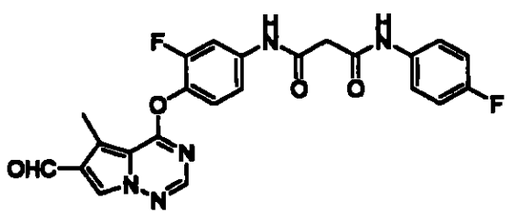
EJEMPLO 41



N^1-(3-Fluoro-4-(6-(hidroximetil)-5-metilpirrolo[2,1-f][1,2,4]triaizin-4-iloxi)fenil)-N^3-(4-fluorofenil)malonamida

A una solución del 4-(2-fluoro-4-(3-(4-fluorofenilamino)-3-oxopropanamido)fenoxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-6-carboxilato de etilo (66 mg, 0.13 mmol, Ejemplo 40) en 20 mL de THF a -78°C se le agregó DIBAL-H (1 M, 1.65 mL). La mezcla de reacción se permitió agitar a -78°C durante 1 horas y luego a temperatura ambiente durante 2 horas. En este momento, el análisis CLAR indicó el final de la reacción. La reacción se apagó con 4 mL de MeOH, seguido por la adición de 4 mL de H_2O. La mezcla se permitió agitar durante 0.5 hora, y luego el Na_2SO_4 se le agregó. La agitación continuó durante 1 hora. La filtración y concentración dio al compuesto del título (50 mg, 82%). ^1H RMN (CD_3OD) δ 7.70 (m, 3H), 7.50 (m, 2H), 7.25 (m, 2H), 7.00 (m, 2H), 4.60 (s, 2H), 3.45 (s, 2H), 2.50 (s, 3H); EM(ESI$^+$) m/z 468.2 $(M + H)^+$.

EJEMPLO 42

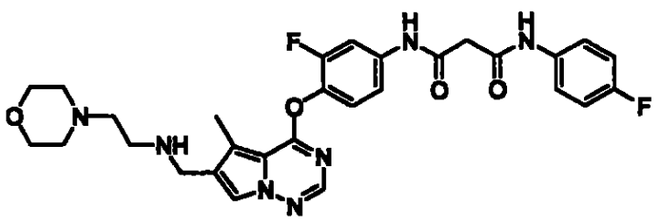


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N^1-(3-Fluoro-4-(6-formil-5-metilpirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)N^3-fluorofenil)malonamida

A una solución de N'-(3-fluoro-4-(6-(hidroximetil)-5-metilpirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-N^3-(4-fluorofenil)malonamida (12 mg, 0.026 mmol, Ejemplo 41) en 1 mL de THF se le agregó peryodinano Dess-Martin (48 mg, 0.11 mmol, Aldrich) a temperatura ambiente. La mezcla se permitió agitar durante 2 horas y el análisis CLAR indica el consumo total de la materia prima. La mezcla se filtró a través de un tapón de SiO_2, se lavó con EtOAc. El solvente orgánico luego se retiró a presión reducida y el residuo se purificó en CLAR preparativa para proporcionar el compuesto del título (10 mg, 83%). EM(ESI$^+$) m/z 466.2 $(M + H)^+$.

EJEMPLO 43

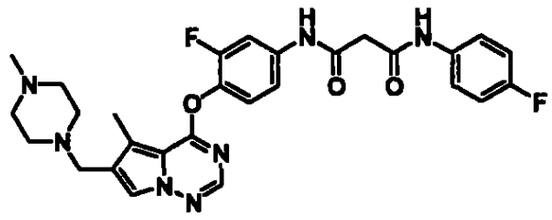


N^1-(3-Fluoro-4-(5-metil-6-((2-morfolinoetilamino)metil)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-N^3-(4-fluorofenil)malonamida, sal del ácido bis-trifluoroacético

A una solución de N^1-(3-fluoro-4-(6-formil-5-metilpirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-N^3-(4-

fluorofenil)malonamida (15 mg, 0.032 mmol, Ejemplo 42) en 1 mL de DMF, se agregaron 2-morfolinoetanamina (21 mg, 0.16 mmol), DIEA (0.04 mL) y $NaBH(OAc)_3$ (52 mg, 0.2 mmol). La mezcla se permitió agitar a temperatura ambiente durante 4 días. El análisis CLAR y el análisis CL-EM indicaron la formación del producto. La solución luego se disolvió en MeOH y se purificó por CLAR preparativa para dar el compuesto del título (4 mg, 21%) como la sal 2·TFA. ^1H RMN (CD_3OD) δ 7.92 (s, 1H), 7.82 (s, 1H), 7.70 (d, 1H), 7.50 (m, 2H), 7.28 (m, 2H), 6.98 (m, 2H), 4.31 (s, 2H), 3.68 (s, 4H), 3.20 (m, 4H), 2.82 (m, 2H), 2.65 (s, 4H), 2.56 (s, 3H); EM(ESI^+) m/z 580.2 $(M + H)^+$.

EJEMPLO 44



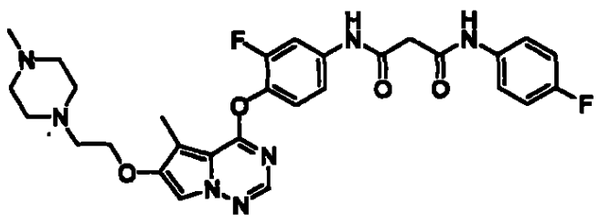
N^1-(3-Fluoro-4-(5-metil-6-((4-metilpiperazin-1-il)metil)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-N^3-(4-fluorofenil)malonamida, sal del ácido bis-trifluoroacético

Siguiendo un procedimiento similar al de la síntesis del Ejemplo 43, la N^1-(3-fluoro-4-(6-formil-5-metilpirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-N^3-(4-fluorofenil)malonamida (15 mg, 0.032 mmol, Ejemplo 42) se convirtió al compuesto del

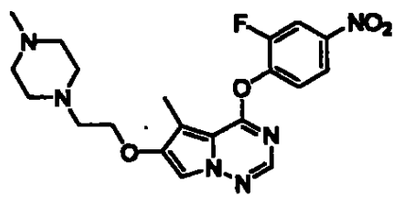
433

título (4 mg, 23%) como la sal 2·TFA. EM(ESI$^+$) m/z 550.2 (M + H)$^+$.

EJEMPLO 45

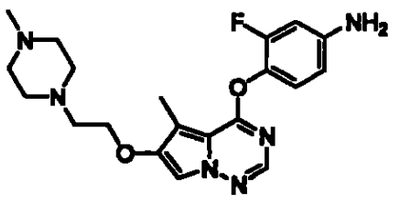


N^1-(3-Fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-N^3-(4-fluorofenil)malonamida, sal de bis clorohidrato



A) 4-(2-Fluoro-4-nitrofenoxi)-5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-f][1,2,4]triazina

Siguiendo un procedimiento similar al de la síntesis del Compuesto B del Ejemplo 36, el 4-(2-fluoro-4-nitrofenoxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-6-ol (55 mg, 0.18 mmol, Compuesto A del Ejemplo 36), 2-morfolinetanol (304 mg, 1.0 mmol) se convirtió al compuesto del título (352 mg, 82%). EM(ESI$^+$) m/z 431.2 (M + H)$^+$.



B) 3-Fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)bencenamina

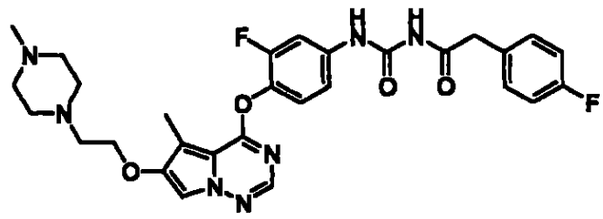
Siguiendo un procedimiento similar al de la síntesis del Compuesto C del Ejemplo 36, la 4-(2-fluoro-4-nitrofenoxi)-5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-f][1,2,4]triazina (2.90 g, 6.74 mmol) se convirtió al compuesto del título (1.38 g, 51%). EM(ESI$^+$) m/z 401.3 $(M + H)^+$.

C) N^1-(3-Fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-N^3-(4-fluorofenil)malonamida, sal de bis-clorohidrato

Siguiendo un procedimiento similar al de la síntesis del Compuesto D del Ejemplo 36, la 3-fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)bencenamina (60 mg, 0.15 mmol) se convirtió al compuesto del título (30 mg, 46%) como la sal 2·HCl. ^{1}H RMN (DMSO-d_6) δ 10.63 (s, 1H), 10.37 (s, 1H), 8.04 (s, 1H), 7.99 (s, 1H), 7.80 (d, 1H), 7.61 (m, 2H), 7.40 (m, 2H), 7.16 (m, 2H), 4.42 (br s, 2H), 3.38-3.60 (m, 10H), 2.81 (s, 3H), 2.40 (s, 3H);). EM(ESI$^+$) m/z 580.3 $(M + H)^+$.

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EJEMPLO 46

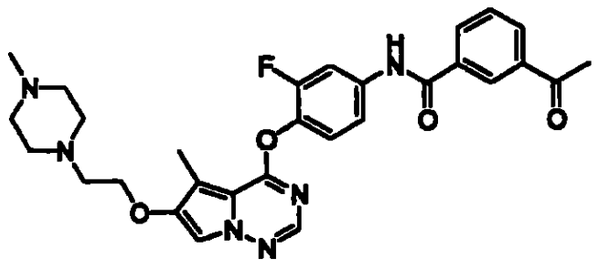


1-(3-Fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)urea, sal de bis-clorohidrato

A una solución de 3-fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)bencenamina (20 mg, 0.05 mmol, Compuesto B del Ejemplo 45) en 1 mL de THF a temperatura ambiente, se le agregó una solución de isocianato de 2-(4-fluorofenil)acetilo en tolueno (0.36 M, 0.18 mL, Compuesto C del Ejemplo 4) y la solución se permitió agitar durante la noche. El análisis CLAR y el análisis CL-EM indican el final de la reacción y el solvente orgánico se retiró de esta manera a presión reducida. El residuo se purificó en CLAR preparativa. El compuesto del título (15 mg, 46%) se obtiene finalmente como la sal 2·HCl después de un trabajo similar al que se describe por el Compuesto D del Ejemplo 36. ^{1}H RMN (DMSO-d_6) δ 11.02 (s, 1H), 10.58 (s, 1H), 8.04 (s, 1H), 7.99 (s, 1H), 7.70 (d, 1H), 7.35 (m, 4H), 7.16 (m, 2H), 4.44 (br.s, 2H), 3.40-3.70 (m, 12H), 2.81 (s, 3H), 2.39 (s, 3H); EM(ESI$^+$) m/z 580.1 $(M + H)^+$.

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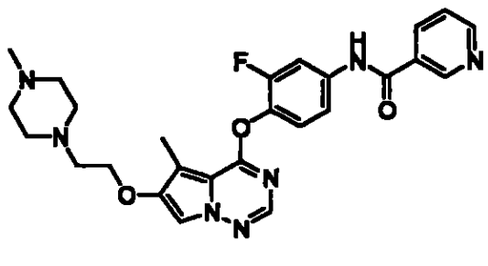
EJEMPLO 47



3-Acetil-N-(3-fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)benzamida, sal de bis-clorohidrato

Siguiendo un procedimiento similar al de la síntesis del Compuesto D del Ejemplo 36, la 3-fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)bencenamina (20 mg, 0.05 mmol, Compuesto B del Ejemplo 45) se convirtió al compuesto del título (11 mg, 35%) como la sal 2·HCl. ^{1}H RMN (CD_3OD) δ 8.20 (m, 1H), 7.90 (m, 2H), 7.84 (s, 1H), 7.80 (s, 1H), 7.70 (m, 1H), 7.50 (m, 2H), 7.32 (m, 1H), 4.54 (m, 2H), 3.60-4.10 (m, 10H), 3.08 (s, 3H), 2.50 (s, 3H); EM(ESI$^+$) m/z 547.2 $(M + H)^+$.

EJEMPLO 48

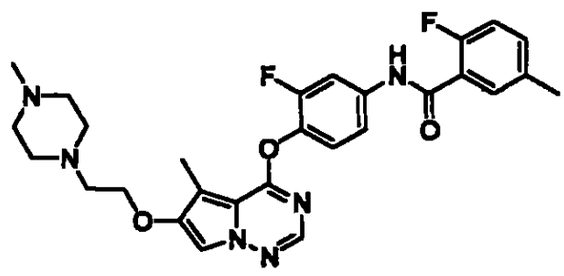


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N-(3-Fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)nicotinamida, sal de tris clorohidrato

Siguiendo un procedimiento similar al de la síntesis del Compuesto D del Ejemplo 36, la 3-fluoro-4-(5-metil-6-(2-(4-metilpiperazm-1-il)etoxi)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)bencenamina (20 mg, 0.05 mmol, Compuesto B del Ejemplo 45) se convirtió al compuesto del título (10 mg, 32%) como la sal 3·HCl. ^{1}H RMN (CD_3OD) δ 9.46 (s, 1H), 9.20 (d, 1H), 9.08 (d, 1H), 8.29 (m, 1H), 7.92 (d, 1H), 7.81 (s, 1H), 7.82 (s, 1H), 7.61 (m, 1H), 7.42 (m, 1H), 4.54 (m, 2H), 3.82-4.05 (m, 10H), 3.05 (s, 3H), 2.51 (s, 3H); EM(ESI$^+$) m/z 506.2 $(M + H)^+$.

EJEMPLO 49



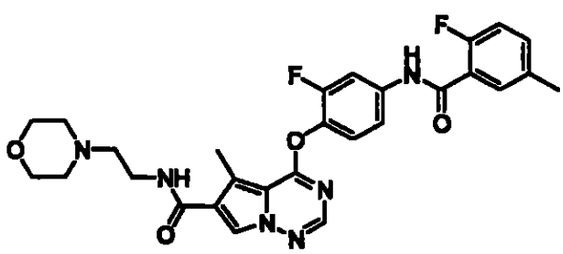
2-Fluoro-N-(3-fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-5-metilbenzamida, sal de bis-clorohidrato

Siguiendo un procedimiento similar al de la síntesis del Compuesto D del Ejemplo 36, la 3-fluoro-4-(5-metil-6-(2-(4-

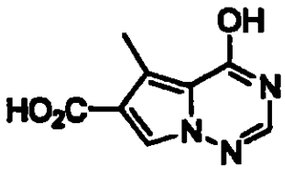
438

metilpiperazin-1-il)etoxi)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)bencenamina (20 mg, 0.05 mmol, Compuesto B del Ejemplo 45) se convirtió al compuesto del título (8 mg, 26% de rendimiento) como la 2·HCl. ^{1}H RMN (CD_3OD) δ 7.85 (d, 1H), 7.85 (s, 1H), 7.80 (s, 1H), 7.55 (m, 1H), 7.50 (m, 1H), 7.33 (m, 2H), 7.13 (t, 1H), 4.54 (m, 2H), 3.70-4.10 (m, 10H), 3.04 (s, 3H), 2.50 (s, 3H), 2.37 (s, 3H); EM(ESI$^+$) m/z 537.2 $(M + H)^+$.

EJEMPLO 50



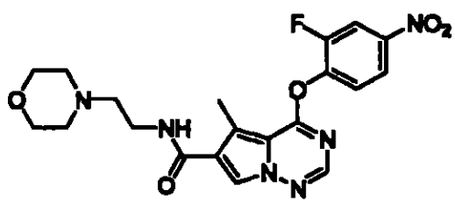
4-(2-Fluoro-4-(2-fluoro-5-metilbenzamido)fenoxi)-5-metil-N-(2-morfolinoetil)pirrolo[2,1-f][1,2,4]triazin-6-carboxamida, sal de clorohidrato



A) ácido 4-hidroxi-5-metilpirrolo[2,1-f][1,2,4]triazin-6-carboxílico

A una solución del 4-hidroxi-5-metilpirrolo[2,1-f][1,2,4]triazin-6-carboxilato de etilo (442 mg, 2.0 mmol)

(ver ejemplo 6 de la Sol. de Patente E.U.A. 2003/0186982, la descripción de la cual se incorpora en la presente para referencia) en 10 mL de THF, se le agregó una solución de NaOH (1 N, 6.0 mL). La mezcla se calentó a 60°C durante la noche y el análisis CLAR indica el final de la reacción. Después de enfriar, la solución se neutralizó con 6.0 mL de HCl 1 N. El solvente orgánico luego se retiró y el sólido se colectó después de la filtración al compuesto del título (350 mg, 91%). EM(ESI$^+$) m/z 194.2 $(M + H)^+$.



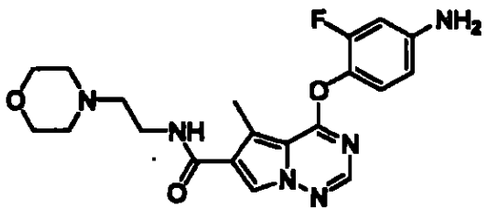
B) 4-(2-Fluoro-4-nitrofenoxi)-5-metil-N-(2-morfolinoetil)pirrolo[2,1-f][1,2,4]triazin-6-carboxamida

Una suspensión de ácido 4-hidroxi-5-metilpirrolo[2,1-f][1,2,4]triazin-6-carboxílico (100 mg, 0.52 mmol) en 2 mL de $POCl_3$, se calentó a 110°C durante 4 horas. La suspensión se volvió una solución clara y el exceso de $POCl_3$ se retiró con tolueno. El residuo luego se disolvió en 5 mL de acetonitrilo a 0°C. A esta solución se le agregaron Et_3N (0.72 mL, 5.2 mmol) y 2-morfolinoetanamina (0.13 mL, 1.04 mmol). La mezcla se agitó durante 0.5 hora y el análisis CLAR indica la formación del producto. La solución luego se diluyó con EtOAc y se lavó con H_2O y salmuera. La capa orgánica se secó sobre

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$MgSO_4$. Después de la filtración y concentración, el material crudo se llevó a la siguiente reacción.

El material crudo se disolvió en 2 mL de acetonitrilo y a este se le agregaron 2-fluoro-4-nitrofenol (94 mg, 0.60 mmol) y DABCO (78 mg, 0.70 mmol). La reacción se permitió agitar durante 1 hora y el análisis CLAR indica el final de la reacción. Después de la concentración, el residuo se purificó en CLAR preparativa para dar el compuesto del título (75 mg, 33%). EM(ESI$^+$) m/z 445.2 $(M + H)^+$.



C) 4-(4-Amino-2-fluorofenoxi)-5-metil-N(2-morfolinoetil)pirrolo[2,1-f][1,2,4]triazin-6-carboxamida

Siguiendo un procedimiento similar al de la síntesis del Compuesto C del Ejemplo 36, la 4-(2-fluoro-4-nitrofenoxi)-5-metil-N-(2-morfolinoetil)pirrolo[2,1-f][1,2,4]triazin-6-carboxamida (75 mg, 0.17 mmol) se convirtió al compuesto del título (65 mg, 92%). CLEM(ESI$^+$) m/z 415.3 $(M + H)^+$.

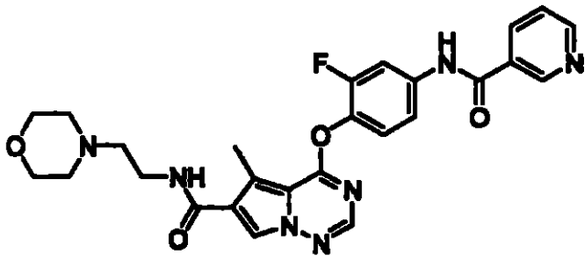
D) 4-(2-Fluoro-4-(2-fluoro-5-metilbenzamido)fenoxi)-5-metil-N-(2-morfolinoetil)pirrolo[2,1-f][1,2,4]triazin-6-carboxamida, sal de clorohidrato

A una solución de 4-(4-amino-2-fluorofenoxi)-5-metil-N-

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(2-morfolinoetil)pirrolo[2,1-f][1,2,4]triazin-6-carboxamida (25 mg, 0.06 mmol) en 1 mL de THF se agregaron Et_3N (0.2 mL) y una solución de cloruro de 2-fluoro-5-metilbenzoilo (20 mg, 0.11 mmol) en 1 mL de THF a temperatura ambiente. La mezcla se permitió agitar durante 1 hora y el análisis CLAR indica el consumo de la materia prima. La reacción se apagó con MeOH. La solución luego se concentró in vacuo y el residuo se purificó por CLAR preparativa para dar el compuesto del título (8.0 mg, 23%) como la sal HCl. ^1H RMN (CD_3OD) δ 8.48 (d, 1H), 7.83 (m, 3H), 7.28 (m, 3H), 7.00 (m, 1H), 2.90-4.00 (m, 12H), 2.76 (s, 3H), 2.33 (s, 3H); EM(ESI+) m/z 551.2 $(M + H)^+$.

EJEMPLO 51



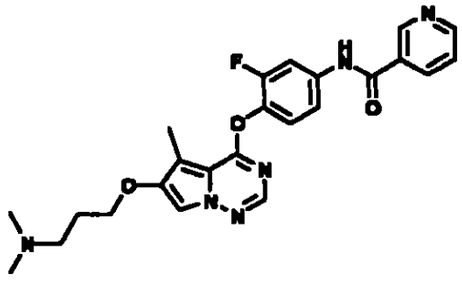
4-(2-Fluoro-4-(nicotinamido)fenoxi)-5-metil-N-(2-morfolinoetil)pirrolo[2,1-f][1,2,4]triazin-6-carboxamida, sal de bis-clorohidrato

Siguiendo un procedimiento similar al de la síntesis del Compuesto D del Ejemplo 50, la 4-(4-amino-2-fluorofenoxi)-5-metil-N-(2-morfolinoetil)pirrolo[2,1-f][1,2,4]triazin-6-carboxamida (30 mg, 0.07 mmol, Compuesto C del Ejemplo 50) se

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convirtió al compuesto del título (16 mg, 39%) como la sal de 2·HCl. ^{1}H RMN (CD_3OD) δ 9.08 (s, 1H), 8.70 (s, 1H), 8.44 (s, 1H), 8.17 (s, 1H), 7.87 (m, 2H), 7.38 (m, 2H), 7.22 (m, 2H), 3.82 (s, 4H), 3.61 (m, 2H), 2.75 (m, 9H); EM(ESI$^+$) m/z 520.2 $(M + H)^+$.

EJEMPLO 52

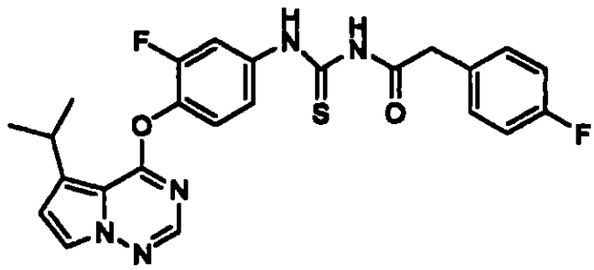


N-(4-(6-(3-(Dimetilamino)propoxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-4-iloxi)-3-fluorofenil)nicotinamida, sal de diclorohidrato

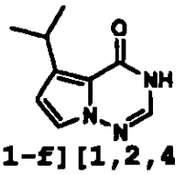
La 4-(6-(3-(Dimetilamino)propoxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-4-iloxi)-3-fluorobencenamina (54 mg, 0.15 mmol, Compuesto B del Ejemplo 32) se convierte al compuesto del título (8.7 mg, 11%) en una manera similar a la preparación del Compuesto D del Ejemplo 36. ^{1}H RMN (CD_3OD) δ 9.47 (s, 1H), 9.20-9.19 (m, 1H), 9.08-9.07 (m, 1H), 8.30-8.27 (m, 1H), 7.97-7.93 (m, 1H), 7.82 (s, 1H), 7.72 (s, 1H), 7.64-7.61 (m, 1H), 7.43-7.39 (m, 1H), 4.26-4.11 (m, 2H), 3.43-3.39 (m, 2H), 2.98 (s, 6H), 2.46 (s, 3H), 2.34-2.30 (m, 2H); EMAR(ESI), 463.1894 (M-H)$^-$ calculado, 463.1905 (M-H)$^-$ encontrado.

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EJEMPLO 53



1-(3-Fluoro-4-(5-isopropil-3,4-dihidropirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)tiourea

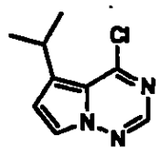


A) 5-Isopropilpirrolo[2,1-f][1,2,4]triazin-4(3H)-ona

El ácido 5-isopropil-4-oxo-3,4-dihidropirrolo[2,1-f][1,2,4]triazin-6-carboxílico (0.025 g, 1.13 mmol, 1.0 equiv, preparado en una manera similar al que se describe en solicitud de patente: US 2004/063708, incorporada en la presente para referencia en su totalidad) se le agregó al ácido fosfórico (5.0 g) y la mezcla de reacción se calentó hasta 160°C durante 1 hora. La reacción se enfrió hasta temperatura ambiente y se apagó con agua (50 ml). La solución se extrajo con acetato de etilo (3 x 50 ml), las fracciones orgánicas combinadas se lavó con $NaHCO_3$ saturado (1 x 100 mi), se secó (Na_2SO_4), se filtró y se concentró in vacuo. La purificación por (Merck KGaA, 230-400 tamaño de partícula de malla) cromatografía instantánea en gel de sílice, eluyendo con 3/1 acetato de etilo/hexano, proporciona el compuesto del

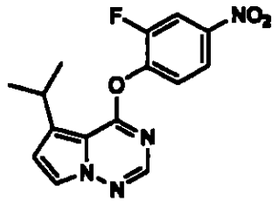
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título (0.060 g, 30%). EM(ESI$^-$) m/z 176 $(M-H)^-$; EMAR(ESI), 176.0824 $(M-H)^-$ calculado, 176.0818 $(M-H)^-$ encontrado.



B) 4-Cloro-5-isopropilpirrolo[2,1-f][1,2,4]triazina

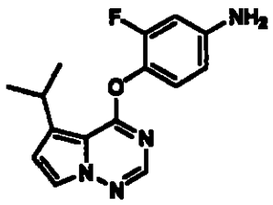
La 5-isopropilpirrolo[2,1-f][1,2,4]triazin-4(3H)-ona (0.035 g, 0.198 mmol, 1.0 equiv) se le agregó al oxicloruro de fósforo (2.0 ml, 21.5 mmol, 109 equiv) bajo una atmósfera de nitrógeno. La mezcla de reacción se calentó hasta reflujo durante 1.5 hora. La mezcla se enfrió hasta temperatura ambiente luego se concentró in vacuo. El residuo se dividió entre acetato de etilo y bicarbonato de sodio acuoso saturado. La capa acuosa se extrajo dos veces con acetato de etilo. Los lavados orgánicos combinados se secaron sobre sulfato de magnesio anhidro y se concentró in vacuo para proporcionar un sólido color marrón el cual se usó en la siguiente etapa sin purificación adicional. EM(ESI$^+$) m/z 196 $(M + H)^+$.



C) 4-(2-Fluoro-4-nitrofenoxi)-5-isopropil-3,4-dihidropirrolo[2,1-f][1,2,4]triazina

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A una mezcla de 4-cloro-5-isopropilpirrolo[2,1-f][1,2,4]triazina (0.038g, 0.194 mmol, 1.0 equiv) y 2-fluoro-4-nitrofenol (0.062 g, 0.388 mmol, 2.0 equiv) en CH_3CN anhidro (2mL), agitada durante cinco minutos bajo una atmósfera de nitrógeno, luego se le agregó DABCO (0.044 g, 0.388 mmol, 2.0 equiv) y la mezcla de reacción se calentó a 50°C durante 2 horas. La mezcla se enfrió hasta temperatura ambiente y se apagó con HCl 1 N. La solución se extrajo con CH_2Cl_2 (3 x 30 ml), los extractos orgánicos combinados se secaron sobre sulfato de magnesio anhidro, se filtraron y se concentraron in vacuo. El residuo se purificó por (Merck KGaA, 230-400 tamaño de partícula de malla) cromatografía instantánea en gel de sílice, eluyendo con 2/1 hexano/acetato de etilo, proporciona el compuesto del título (0.048g, 79%). ^1H RMN ($CDCl_3$) δ 8.07-8.13 (m, 2H), 7.77 (s, 1H), 7.68-7.69 (m, 1H), 7.46-7.50 (m, 1H), 6.71-6.72 (m, 1H), 3.53-3.56 (m, 1H), 1.29-1.31 (m, 6H); EMAR(ESI), calculado, 317.1050 $(M + H)^+$ encontrado, 317.1039.



D) 3-Fluoro-4-(5-isopropil-3,4-dihidropirrolo[2,1-f][1,2,4]triazin-4-iloxi)bencenamina

A una mezcla heterogénea de 4-(2-fluoro-4-nitrofenoxi)-5-isopropil-3,4-dihidropirrolo[2,1-f][1,2,4]triazina (0.044 g, 1.39

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mmol, 10 equiv) en 1/1 metanol anhidro/tetrahidrofurano (2 mL), a temperatura ambiente bajo atmósfera de nitrógeno, se le agregó polvo de zinc (0.090 g, 0.139 mmol, 1.0 equiv) y cloruro de amonio (0.075 g, 1.39 mmol, 10 equiv). La mezcla se agitó durante 4 horas antes de que el catalizador se filtró completamente y el filtrado se concentró in vacuo para proporcionar el compuesto del título (0.040g, 100%) como un sólido, el cual se usó sin purificación adicional. EMAR(ESI), 287.1308 $(M + H)^+$ calculado, 287.1300 $(M + H)^+$ encontrado.

E) 1-(3-Fluoro-4-(5-isopropil-3,4-dihidropirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)tiourea

A una solución homogénea de tiocianato de sodio (0.037 g, 0.46 mmol, 3.3 equiv) en acetato de etilo (1 mL), a temperatura ambiente bajo una atmósfera de nitrógeno, se le agregó cloruro de 4-fluorofenil-acetilo (0.048 ml, 0.35mmol, 2.5 equiv). La mezcla se agitó durante 2 horas antes de agregarse directamente a una solución homogénea de 3-fluoro-4-(5-isopropil-3,4-dihidropirrolo[2,1-f][1,2,4]triazin-4-iloxi)bencenamina (0.040g, 0.139 mmol, 1.0 equiv) en 1/1 THF/diclorometano anhidro (3 mL), bajo una atmósfera de nitrógeno. La mezcla de reacción se agitó a temperatura ambiente durante 16 horas antes de comenzar a apagar con HCl 1 N. La solución se extrajo con CH_2Cl_2 (3 x 50 ml), las fracciones orgánicas combinadas se lavaron con NaOH 1 N (50 ml),

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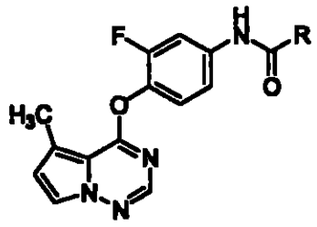
se secaron (Na_2SO_4), se filtraron y se concentraron in vacuo. La purificación por (Merck KGaA, 230-400 tamaño de partícula de malla) cromatografía instantánea en gel de sílice, eluyendo con 4/1 hexano/acetato de etilo, proporciona el compuesto del título (0.050 g, 75%). ^1H RMN ($CDCl_3$) δ 12.34 (s, 1H), 8.47 (m, 1H), 7.65-7.78 (m, 2H), 7.63-7.64 (m, 1H), 7.19-7.32 (m, 4H), 7.03-7.08 (m, 2H), 6.66-6.67 (m, 1H), 3.65 (s, 2H), 3.40-3.50 (m, 1H), 1.28-1.30 (m, 6H); EMAR(ESI) 482.1462, calculado, $(M+H)^+$ 482.1461 encontrado. Análisis elemental: $C_{24}H_{21}N_5O_2SF_2$. 0.23 H_2O. calculado: C; 59.35, H; 4.45, N; 14.42, encontrado: C; 59.36, H; 4.44, N; 14.03.

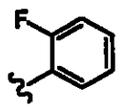
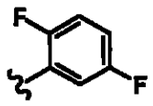
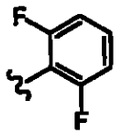
EJEMPLOS 54 HASTA 85

Los Ejemplos 54 hasta 85 ilustrados en la Tabla 1 abajo se sintetizan a partir de 3-fluoro-4-(5-metilpirrolo[2,1-f][1,2,4]triazin-4-iloxi)bencenamina (Compuesto B del Ejemplo 28) usando un equivalente del correspondiente ácido carboxílico (1 eq), PyBrOP (1 eq), DIEA (1 eq) en DMF. La mezcla de reacción se calentó hasta 70°C y los productos crudos se purificaron por CLAR preparativa (H_2O/MeOH/TFA al 0.1%, gradiente 35-90% MeOH sobre 10 minutos, 20 x 100 mm 5 µm columna YMC ODS-A) utilizando fraccionamiento dirigido a la masa. La muestra purificada se reconstituyó en 1:1/MeOH:DCE, se transfirió a un microtubo de plástico de 2.5 mL tarado, se secó por medio de evaporación centrífuga, se pesó y se analizó por CLEM (H_2O/MeOH/TFA al 0.1%).

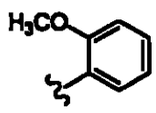
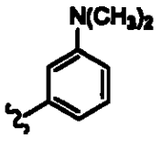
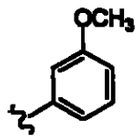
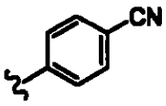
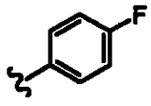
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TABLA 1

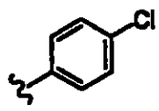
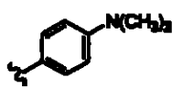
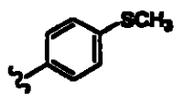
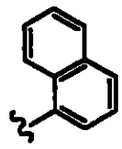


Ejemplo #	R	Nombre del compuesto	CL/EM $(M+H)^+$
54	Ph	N-(3-Fluoro-4-(5-metilpirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)benzamida	363.4
55		2-Fluoro-N-(3-fluoro-4-(5-metilpirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)benzamida	381.4
56		2,5-Difluoro-N-(3-Fluoro-4-(5-metilpirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)benzamida	399.3
57		2,6-Difluoro-N-(3-Fluoro-4-(5-metilpirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)benzamida	399.3

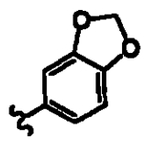
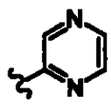
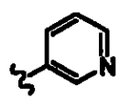
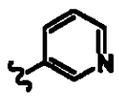
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Ejemplo #	R	Nombre del compuesto	CL/EM $(M+H)^+$
58		N-(3-Fluoro-4-(5-metilpirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)-2-metoxibenzamida	393.4
59		3-(Dimetilamino)-N-(3-Fluoro-4-(5-metilpirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)benzamida	406.4
60		N-(3-Fluoro-4-(5-metilpirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)-3-metoxibenzamida	393.4
61		4-Ciano-N-(3-Fluoro-4-(5-metilpirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)benzamida	388.4
62		4-Fluoro-N-(3-fluoro-4-(5-metilpirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)benzamida	381.4

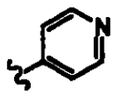
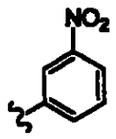
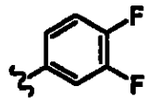
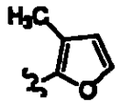
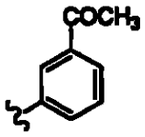
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Ejemplo #	R	Nombre del compuesto	CL/EM $(M+H)^+$
63		4-Cloro-N-(3-fluoro-4-(5-metilpirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)benzamida	397.8
64		4-(Dimetilamino)-N-(3-fluoro-4-(5-metilpirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)benzamida	406.4
65		N-(3-Fluoro-4-(5-metilpirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)-4-(metiltio)benzamida	409.5
66		N-(3-Fluoro-4-(5-metilpirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)furan-2-carboxamida	353.3
67		N-(3-Fluoro-4-(5-metilpirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)-1-naftamida	413.4

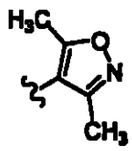
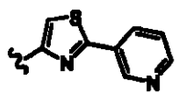
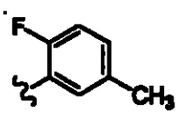
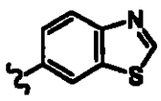
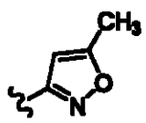
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Ejemplo #	R	Nombre del compuesto	CL/EM(M+H)+
68		N-(3-Fluoro-4-(5-metilpirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)tiofeno-3-carboxamida	369.4
69		N-(3-Fluoro-4-(5-metilpirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)benzo[d][1,3]dioxil-5-carboxamida	407.4
70		N-(3-Fluoro-4-(5-metilpirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)pirazina-2-carboxamida	365.3
71		N-(3-Fluoro-4-(5-metilpirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)picolinamida	364.4
72		N-(3-Fluoro-4-(5-metilpirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)nicotinamida	364.4

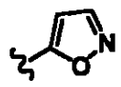
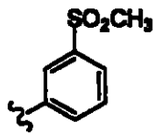
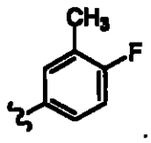
452

Ejemplo #	R	Nombre del compuesto	CL/EM $(M+H)^+$
73		N-(3-Fluoro-4-(5-metilpirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)isonicotinamida	364.4
74		N-(3-Fluoro-4-(5-metilpirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)-3-nitrobenzamida	408.4
75		3,4-Difluoro-N-(3-Fluoro-4-(5-metilpirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)benzamida	399.3
76		N-(3-Fluoro-4-(5-metilpirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)-3-metilfuran-2-carboxamida	367.4
77		3-Acetil-N-(3-fluoro-4-(5-metilpirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)benzamida	405.4

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Ejemplo #	R	Nombre del compuesto	CL/EM (M+H)+
78		N-(3-Fluoro-4-(5-metilpirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)-3,5-dimetilisoxazol-4-carboxamida	382.4
79		N-(3-Fluoro-4-(5-metilpirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)-2-(piridin-3-il)tiazol-4-carboxamida	447.5
80		2-Fluoro-N-(3-fluoro-4-(5-metilpirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)-5-metilbenzamida	395.4
81		N-(3-Fluoro-4-(5-metilpirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)benzo[d]tiazol-6-carboxamida	420.4
82		N-(3-Fluoro-4-(5-metilpirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)-5-metilisoxazol-3-carboxamida	368.3

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Ejemplo #	R	Nombre del compuesto	CL/EM(M+H)+
83		N-(3-Fluoro-4-(5-metilpirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)isoxazol-5-carboxamida	354.3
84		N-(3-Fluoro-4-(5-metilpirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)-3-(metilsulfonil)benzamida	441.5
85		4-Fluoro-N-(3-fluoro-4-(5-metilpirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)-3-metilbenzamida	395.4

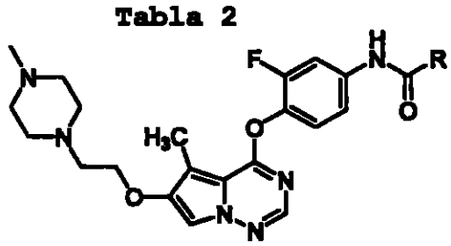
EJEMPLOS 86 HASTA 130

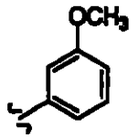
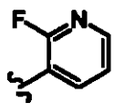
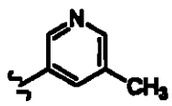
Los Ejemplos 86 hasta 130 ilustrados en la Tabla 2 abajo, se sintetizaron a partir de 3-fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)bencenamina (Compuesto B del Ejemplo 45). A un pozo individual de un reactor de 48 posiciones MiniBlock® XT se le agregó 375 µL de una solución 0.2 M del cloruro ácido en 1,2-dicloroetano (DCE) (0.075 mmol, 2.5 eq); 50 µL de piridina (0.62 mmol, 20 eq); y 150 µL de una solución 0.2 M de la amina en DCE (0.03 mmol, 1 eq). El reactor se agitó por medio de agitación orbital durante 14 horas. El producto crudo en DCE se diluyó hasta un volumen de 1 mL con metanol, luego se purificó por CLAR preparativa estándar

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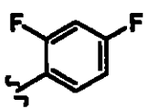
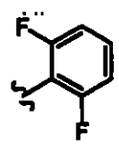
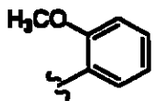
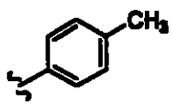
(H_2O/MeOH/TFA al 0.1%, gradiente 35-90% MeOH durante 10 minutos, 20x 100 mm 5µm columna YMC ODS-A) utilizando fraccionamiento dirigido a la masa. La muestra purificada se reconstituyó en 1:1/MeOH:DCE, se transfirió a un microtubo de plástico de 2.5 mL tarado, se secó por medio de evaporación centrífuga, se pesó y se analizó por CLEM (H_2O/MeOH/TFA al 0.1%).

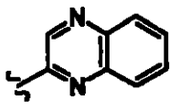
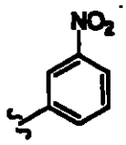
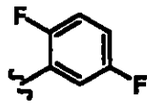
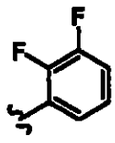
Tabla 2



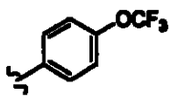
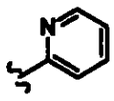
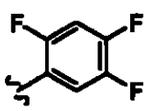
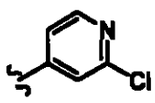
Ejemplo #	R	Nombre del compuesto	CL/EM $(M+H)^+$
86		N-(3-Fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)-3-metoxibenzamida	535.6
87		2-Fluoro-N-(3-Fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)nicotinamida	524.6
88		N-(3-Fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)-5-metilnicotinamida	520.6

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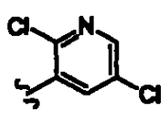
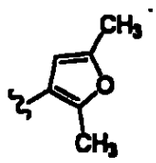
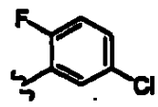
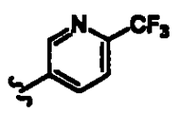
Ejemplo #	R	Nombre del compuesto	CL/EM(M+H)+
89		2,4-Difluoro-N-(3-Fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)benzamida	541.6
90		2,6-Difluoro-N-(3-Fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)benzamida	541.6
91		N-(3-Fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)-2-metoxibenzamida	535.6
92		N-(3-Fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)-4-metilbenzamida	519.6

Ejemplo #	R	Nombre del compuesto	CL/EM(M+H)+
93		N-(3-Fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)quinoxalina-2-carboxamida	557.6
94		N-(3-Fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)-3-nitrobenzamida	550.6
95		2,5-Difluoro-N-(3-Fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)benzamida	541.6
96		2,3-Difluoro-N-(3-Fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)benzamida	541.6

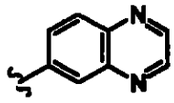
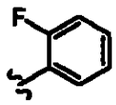
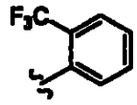
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Ejemplo #	R	Nombre del compuesto	CL/EM $(M+H)^+$
97		N-(3-Fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)-4-(trifluorometoxi)benzamida	589.6
98		N-(3-Fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)picolinamida	506.6
99		2,4,5-Trifluoro-N-(3-Fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)benzamida	559.5
100		2-Cloro-N-(3-Fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)isonicotinamida	541.0

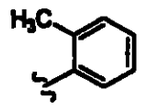
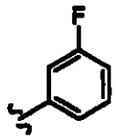
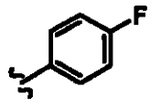
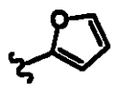
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Ejemplo #	R	Nombre del compuesto	CL/EM(M+H)+
101		2,5-Dicloro-N-(3-Fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)nicotinamida	575.4
102		N-(3-Fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)-2,5-dimetilfuran-3-carboxamida	523.6
103		5-Cloro-2-fluoro-N-(3-Fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)benzamida	558.0
104		N-(3-Fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)-6-(trifluorometil)nicotinamida	574.6

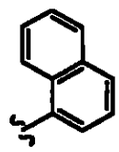
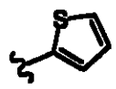
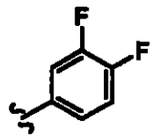
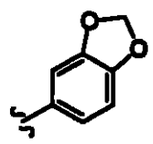
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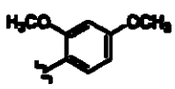
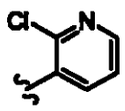
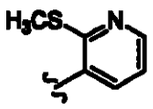
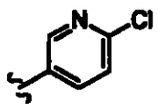
Ejemplo #	R	Nombre del compuesto	CL/EM(M+H)+
105		N-(3-Fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)furan-3-carboxamida	495.5
106		N-(3-Fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)quinoxalina-6-carboxamida	557.6
107		2-Fluoro-N-(3-Fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)benzamida	523.6
108		N-(3-Fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)-2-(trifluorometil)benzamida	573.6

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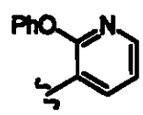
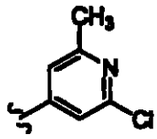
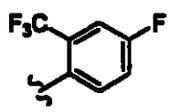
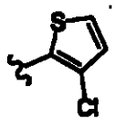
Ejemplo #	R	Nombre del compuesto	CL/EM $(M+H)^+$
109		N-(3-Fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)-2-metilbenzamida	519.6
110		3-Fluoro-N-(3-Fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)benzamida	523.6
111		4-Fluoro-N-(3-Fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)benzamida	523.6
112		N-(3-Fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)furan-2-carboxamida	495.5

462

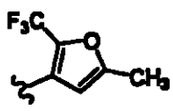
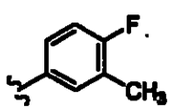
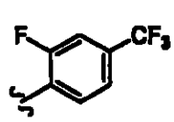
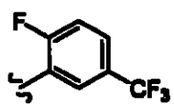
Ejemplo #	R	Nombre del compuesto	CL/EM(M+H)+
113		N-(3-Fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)-1-naftamida	555.6
114		N-(3-Fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)tiofen-2-carboxamida	511.6
115		3,4-Difluoro-N-(3-Fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)benzamida	541.6
116		N-(3-Fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)benzo[d][1,3]dioxol-5-carboxamida	549.6

Ejemplo #	R	Nombre del compuesto	CL/EM $(M+H)^+$
117		N-(3-Fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)-2,4-dimetoxibenzamida	565.6
118		2-Cloro-N-(3-Fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)nicotinamida	541.0
119		N-(3-Fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)-2-(metiltio)nicotinamida	552.7
120		6-Cloro-N-(3-fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)nicotinamida	541.0

464

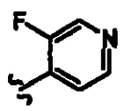
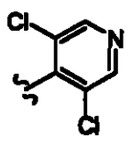
Ejemplo #	R	Nombre del compuesto	CL/EM(M+H)+
121		N-(3-Fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)-2-fenoxinicotinamida	598.7
122		2-Cloro-N-(3-Fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)-6-metilisonicotinamida	555.0
123		4-Fluoro-N-(3-Fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)-2-(trifluorometil)benzamida	591.6
124		3-Cloro-N-(3-Fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)tiofen-2-carboxamida	546.0

465

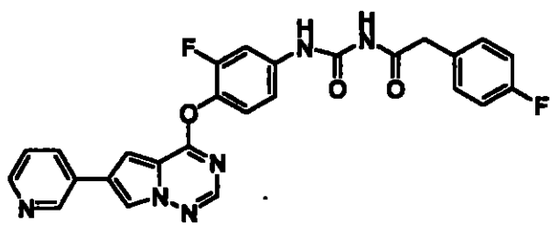
Ejemplo #	R	Nombre del compuesto	CL/EM $(M+H)^+$
125		N-(3-Fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)-5-metil-2-(trifluorometil)furan-3-carboxamida	577.6
126		4-Fluoro-N-(3-Fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)-3-metilbenzamida	537.6
127		2-Fluoro-N-(3-Fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)-4-(trifluorometil)benzamida	591.6
128		2-Fluoro-N-(3-Fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)	591.6

404

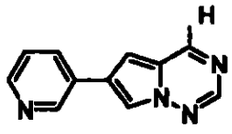
466

		fenil)-5-(trifluorometil)benzamida	
129		3-Fluoro-N-(3-fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)isonicotinamida	524.6
130		3,5-Dicloro-N-(3-Fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-*f*][1,2,4]triazin-4-iloxi)fenil)isonicotinamida	575.5

EJEMPLO 131

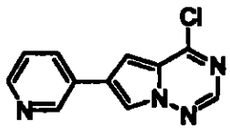


1-(3-Fluoro-4-(6-piridin-3-il)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-3-(2(4-fluorofenil)acetil)urea, sal del ácido trifluoroacético



A) 6-(Piridin-3-il)pirrolo[2,1-f](1,2,4]triazin-4-ol

Una solución de 6-bromopirrolo[2,1-f][1,2,4]triazin-4-ol (100 mg, 0.47 mmol, se preparó del 4-bromo-1H-pirrol-2-carboxilato de metilo: ver, generalmente, Kitamura, C. y Yamashita, Y. J. Chem. Soc. Perkin Trans. 1, 1997, 1443, la descripción de la cual se incorpora en la presente como referencia, usando un procedimiento similar resumido en la solicitud PCT WO 00/71129) y ácido piridin-3-ilborónico (172 mg, 1.40 mmol) en 2 mL de DMF y 2 mL de K_2CO_3 acuoso saturado se desgasificó y luego $Pd(PPh_3)_4$ (57 mg, 0.05 mmol) se le agregó. La mezcla se calentó luego a 120°C durante 3 horas. Análisis CL-EM indicó la desaparición de la materia prima. La mezcla se enfrió y la solución se filtró. El filtrado se purificó en CLAR preparativa para proporcionar el compuesto del título (100 mg, 65%) como una sal TFA. EM (ESI^+) m/z 213.2 $(M + H)^+$.

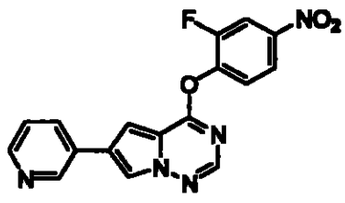


B) 4-Cloro-6-(piridin-3-il)pirrolo[2,1-f][1,2,4]triazina

A una suspensión de 6-(piridin-3-il)pirrolo[2,1-f][1,2,4]triazin-4-ol (100 mg, 0.30 mmol) en 10 mL de tolueno

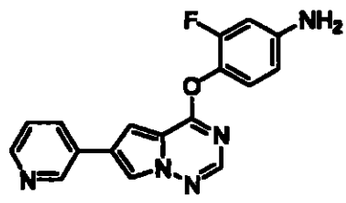
468

se agregaron $POCl_3$ (0.18 mL, 1.88 mmol) y DIEA (0.09 mL, 0.5 mmol). La suspensión se calentó a 100°C durante 7 horas. Después de enfriar, el exceso de $POCl_3$ se retiró a presión reducida. El residuo se suspendió en EtOAc, y luego se neutralizó con $NaHCO_3$ saturado. La capa orgánica se lavó luego con salmuera y se secó sobre $MgSO_4$. Después de la filtración y concentración, el residuo se purificó por cromatografía de columna instantánea para proporcionar el compuesto del título (23 mg, 33%). EM (ESI^+) m/z 231.2/233.2 $(M + H)^+$.



C) 4-(2-Fluoro-4-nitrofenoxi)-6-(piridin-3-il)pirrolo[2,1-f][1,2,4]triazina

Siguiendo un procedimiento similar al de la síntesis del Compuesto B del Ejemplo 2, 4-cloro-6-(piridin-3-il)pirrolo[2,1-f][1,2,4]triazina (23 mg, 0.1 mmol) se convirtió al compuesto del título (35 mg, 95%). EM (ESI^+) m/z 352.3 $(M + H)^+$.



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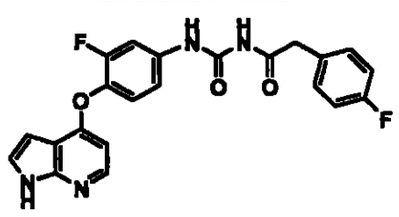
D) 3-Fluoro-4-(6-(piridin-3-il)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)bencenamina

Siguiendo un procedimiento similar al de la síntesis del Compuesto C del Ejemplo 36, 4-(2-fluoro-4-nitrofenoxi)-6-(piridin-3-il)pirrolo[2,1-f][1,2,4]triazina (35 mg, 0.10 mmol) se convirtió al compuesto del título (15 mg, 46%). EM(ESI$^+$) m/z 322.3 $(M + H)^+$.

E) 1-(3-Fluoro-4-(6-(piridin-3-il)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-3(2-(4-fluorofenil)acetil)urea, sal del ácido trifluoroacético

El compuesto del título se preparó usando siguiendo un procedimiento similar al de la síntesis del Ejemplo 46, 3-fluoro-4-(6-(piridin-3-il)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)bencenamina (15 mg, 0.046 mmol) se convirtió al compuesto del título (5.0 mg, 18%) como una sal TFA. ^{1}H RMN (DMSO-d_6) δ 10.99 (s, 1H), 10.53 (s, 1H), 9.12 (s, 1H), 8.75 (s, 1H), 8.50 (m, 1H), 8.30 (m, 1H), 8.12 (s, 1H), 7.67 (m, 2H), 7.30-7.50 (m, 5H), 7.12 (m, 2H), 3.69 (s, 2H); EM (ESI$^+$) m/z 501.2 $(M + H)^+$.

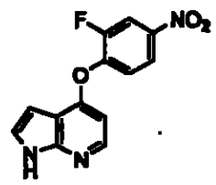
EJEMPLO 132



1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-3-(2-

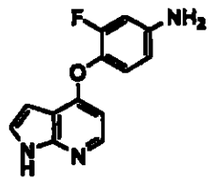
~~467~~ 470

(4-fluorofenil)acetil)urea, sal de clorohidrato



A) 4-(2-Fluoro-4-nitrofenoxi)-1H-pirrolo[2,3-b]piridina

Una mezcla de 4-cloro-1H-pirrolo[2,3-b]piridina (457 mg, 3.0 mmol, se preparó de conformidad con Thibault, C. et al. Org. Lett. 2003, 5, 5023) y 2-fluoro-4-nitrofenol (706 mg, 4.5 mmol), y N,N-diisopropiletilamina (580 mg, 4.5 mmol) en 1-metil-2-prolidinona (NMP) (3 mL) se calentó a 200°C bajo irradiación de microondas durante 1.0 hora. La mezcla se diluyó con acetato de etilo (150 mL), se lavó con solución KH_2PO_4 acuosa saturada, y Na_2CO_3 (1 M acuoso), se secó sobre Na_2SO_4. El producto se purificó por cromatografía de columna instantánea (gel de sílice, eluyendo con CH_2Cl_2 a 30% EtOAc/CH_2Cl_2) para proporcionar un sólido café (350 mg, 43%). EM(ESI$^+$) m/z 274 $(M + H)^+$.



B) 4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorobencenamina

A una suspensión de 4-(2-fluoro-4-nitrofenoxi)-1H-pirrolo[2,3-b]piridina (300 mg, 1.1 mmol) en tetrahidrofurano

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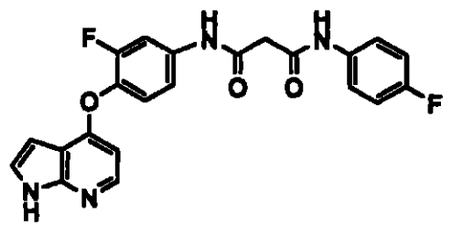
(5 mL) y metanol (10 mL), se agregaron polvo de zinc (350 mg, 5.5 mmol) y cloruro de amonio (294 mg, 5.5 mmol). La mezcla se agitó a temperatura ambiente durante la noche. La mezcla se filtró a través de una almohadilla de Celite®, se enjuagó con metanol. El filtrado se concentró. El producto se purificó por cromatografía de columna instantánea (gel de sílice, 1-5% MeOH en CH_2Cl_2) para proporcionar el producto deseado (205 mg, 77%) como un sólido blanco apagado. EM(ESI$^+$) m/z 244 $(M + H)^+$.

C) 1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea, sal de clorohidrato

Una mezcla de 4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorobencenamina (30 mg, 0.12 mmol) e isocianato de 2-(4-fluorofenil)acetilo, (Compuesto C, Ejemplo 4) (0.25 M en tolueno, 0.18 mmol) en THF (0.5 mL) se agitó a temperatura ambiente durante 1 hora. La mezcla se concentró in vacuo, se purificó por CLAR preparativa. Las fracciones deseadas se liofilizaron para dar una sal TFA blanca, la cual se disolvió en una cantidad pequeña de MeOH/H_2O con HCl 1 N (0.2 mL). Esta solución se liofilizó luego para proporcionar el compuesto del título (15 mg, 27%) como un sólido blanco. ^{1}H RMN ($CDCl_3$) δ 11.74 (s, 1H), 8.12 (d, 1H, J= 6.4 Hz), 7.73 (dd, 1H, J= 2.4, 13.0 Hz), 7.39 (d, 1H, J= 3.6 Hz), 6.90-7.3 (m, 6H), 6.65 (d, 1H, J= 6.4 Hz), 6.50 (d, 1H, J= 3.2 Hz), 3.68 (s, 2H); EM(ESI$^+$) m/z 423 $(M + H)^+$.

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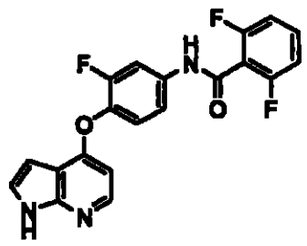
EJEMPLO 133



N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-(4--fluorofenil)malonamida, sal del ácido trifluoroacético

A una solución de 4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorobencenamina (Compuesto B, Ejemplo 132; 25 mg, 0.10 mmol) y ácido 3-(4-fluorofenilamino)-3-oxopropanoico, Compuesto A, Ejemplo 25 (25 mg, 1.27 mmol) en DMF (0.5 mL), se le agregó TBTU (48 mg, 0.15 mmol), seguido por DIPEA (0.1 mL). La mezcla resultante se agitó a temperatura ambiente durante 2 horas. El producto se purificó por CLAR preparativa para proporcionar el compuesto del título (sal TFA, 26 mg, 62%) como un sólido blanco. ^{1}H RMN ($CDCl_3$) δ 7.94 (d, 1H, J= 6.4 Hz), 7.66 (dd, 1H, J= 2.4, 13.0 Hz), 7.54 (m, 2H), 6.90-7.25 (m, 5H), 6.31 (d, 2H, J= 2.8 Hz), 3.37 (s, 2H); EM(ESI$^+$) m/z 423 $(M + H)^+$.

EJEMPLO 134

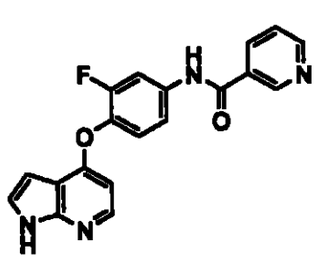


473

N-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-2,6-difluorobenzamida

A una solución de 4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorobencenamina (Compuesto B, Ejemplo 132; 20 mg, 0.08 mmol) en DMF (0.5 mL), se le agregó cloruro de 2,6-difluorobenzoilo (20 mg, 0.11 mmol), seguido por DIPEA (0.1 mL). La mezcla se agitó a temperatura ambiente durante 2 horas y el producto se purificó por CLAR preparativa. Las fracciones deseadas se liofilizaron para dar una sal TFA blanca, la cual se neutralizó con solución de bicarbonato de sodio acuoso saturado. La mezcla se extrajo con EtOAc (3x5 mL). Las capas orgánicas se secaron y concentraron in vacuo para proporcionar el compuesto del título (14 mg, 37%) como un sólido blanco. ^{1}H RMN (CD_3OD) δ 8.15 (d, 1H, J = 6.4 Hz), 7.87 (d, 1H, J= 2.4, 12.8 Hz), 7.40 (m, 4H), 7.04 (m, 2H), 6.69 (d, 2H, J=7.6 Hz), 6.52 (m, 1H); EM (ESI^+) m/z 384 $(M + H)^+$.

EJEMPLO 135



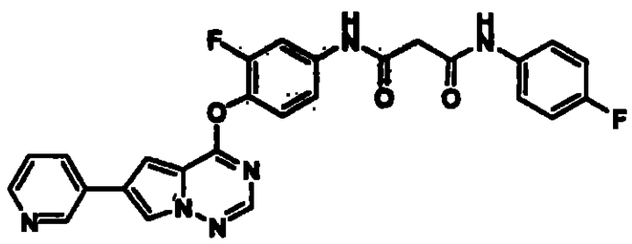
N-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-

474

fluorofenil)nicotinamida

En una forma similar como se describe para la preparación del Ejemplo 134, el compuesto del título se aisló como una sal TFA y se preparó usando cloruro de nicotinilo comercialmente disponible y 4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorobencenamina (Compuesto B, Ejemplo 132). Rendimiento: 55%. ^{1}H RMN (CD_3OD) δ 9.09 (s, 1H), 8.73 (d, 1H, J= 4.4 Hz), 8.44 (d, 1H, J= 8.0 Hz), 8.22 (d, 1H, J= 6.8 Hz), 8.22 (dd, 1H, J= 2.4, 12.4 Hz), 7.40-7.80 (m, 4H), 6.79 (d, 1H, J= 6.8 Hz), 6.59 (d, 1H, J= 3.6 Hz); EM (ESI$^+$) m/z 349 (M + H)$^+$.

EJEMPLO 136



N^1-(3-Fluoro-4-(6-(piridin-3-il)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-N^3-(4-fluorofenil)malonamida, sal del ácido trifluoroacético

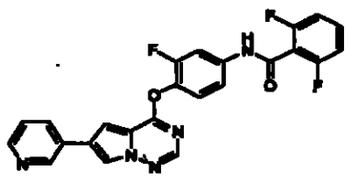
A una solución homogénea de 3-fluoro-4-(6-(piridin-3-il)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)bencenamina (32 mg, 0.10 mmol, Compuesto D del Ejemplo 131) y ácido 3-(4-fluorofenilamino)-3-oxopropanoico (20 mg, 0.10 mmol, Compuesto A del Ejemplo 25) en DMF anhidro (3 mL), a

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temperatura ambiente bajo atmósfera de nitrógeno, se le agregó diisopropiletilamina (26 µL, 0.15 mmol). La mezcla se agitó durante nueve minutos después de tetrafluoroborato de o-benzotriazol-1-il-N,N,N',N'-tetrametiluronio (48 mg, 0.15 mmol) se le agregó en una porción. La mezcla se agitó durante sesenta y tres horas después de dividirse entre cloroformo y salmuera. La capa acuosa se extrajo tres veces con cloroformo, y las capas orgánicas combinadas se secaron sobre sulfato de magnesio anhidro, se filtraron y concentraron in vacuo hasta retirar volátiles. El residuo resultante se purificó por CLAR preparativa (YMC S10 ODS, 30 x 500mm, 30 minutos gradiente del 58% hasta 90% metanol acuoso con 0.1% TFA). Las fracciones apropiadas se combinaron y liofilizaron para proporcionar el compuesto del título (18 mg, 30%) como un sólido blanco apagado. ^{1}H RMN ($CDCl_3$) δ 10.35 (br s, 1H), 9.49 (s, 1H), 9.18 (s, 1H), 8.80-8.65 (m, 2H), 8.36-8.29 (m, 1H), 8.17 (s, 1H), 8.04 (s, 1H), 7.83-7.68 (m, 2H), 7.55-7.49 (m, 2H), 7.35-7.23 (m, 2H), 7.10-7.00 (m, 2H), 3.58 (s, 2H); EMAR(ESI), 501.1487 $(M + H)^+$ calculado, 501.1491 $(M + H)^+$ encontrado.

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EJEMPLO 137

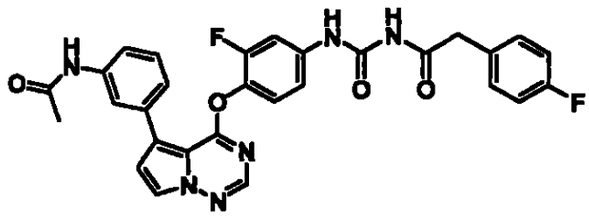


2,6-Difluoro-N-(3-fluoro-4-(6-(piridin-3-il)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)benzamida, sal del ácido trifluoroacético

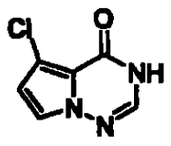
A una solución homogénea de 3-fluoro-4-(6-(piridin-3-il)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)bencenamina (64 mg, 0.20 mmol, Compuesto D del Ejemplo 131) en cloroformo anhidro (5 mL), a temperatura ambiente bajo atmósfera de nitrógeno, se le agregó diisopropiletilamina (49 uL, 0.28 mmol). La mezcla se agitó durante cinco minutos antes de que el cloruro de 2,6-difluorobenzoilo (33 µL, 0.26 mmol, Aldrich) se agregara. La mezcla se agitó durante ochenta y siete horas después de dividirse entre cloroformo y bicarbonato de sodio acuoso saturado. La capa orgánica se lavó una vez con bicarbonato de sodio acuoso saturado y una vez con salmuera, antes de que las capas orgánicas combinadas se secaran sobre sulfato de magnesio anhidro, se filtraron y concentraron in vacuo hasta retirar volátiles. El residuo resultante se purificó por CLAR preparativa (YMC S10 ODS, 30 x 500mm, 30 minutos gradiente del 58% hasta 90% metanol acuoso con 0.1% TFA). Las fracciones apropiadas se combinaron y liofilizaron para

proporcionar el compuesto del título (24 mg, 21%) como un sólido blanco. ^{1}H RMN (CD_3OD) δ 9.20 (s, 1H), 8.85-8.78 (m, 1H), 8.65-8.60 (m, 1H), 8.51 (d, 1H, J= 1.6 Hz), 8.00 (s, 1H), 7.98-7.90 (m, 1H), 7.81-7.74 (m, 1H), 7.58 (d, 1H, J= 1.8 Hz), 7.51-7.27 (m, 3H), 7.00-7.10 (m, 2H); EMAR(ESI), 462.1178 $(M + H)^+$ calculado, 462.1168 $(M + H)^+$ encontrado.

EJEMPLO 138



1-(4-(5-(3-Acetamidofenil)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea



A) 5-Cloropirrolo[2,1-f][1,2,4]triazin-4(3H)-ona

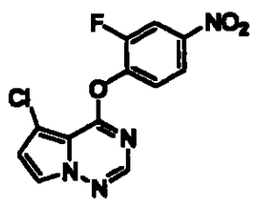
Una solución de 1-amino-3-cloro-1H-pirrol-2-carboxilato de metilo (10.0 g, 57.3 mmol, WO 03/099286: Compuesto A del Ejemplo 9) en formamida (40 mL) se calentó a 170°C durante 1 hora y luego a 190°C durante 1 hora. Sobre el enfriamiento a temperatura ambiente, la mezcla se solidificó. El producto se purificó por re-cristalización del acetato de etilo para dar el compuesto del título (6.53 g, 67%) como un sólido blanco.

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^{1}H RMN ($CDCl_3$) δ 10.24 (br s, 1H), 7.48 (d, 1H, J= 3.6 Hz), 7.29 (d, 1H, J= 2.8 Hz), 6.47 (d, 1H, J= 2.8 Hz); EM(ESI^+) m/z 170.1 $(M + H)^+$.

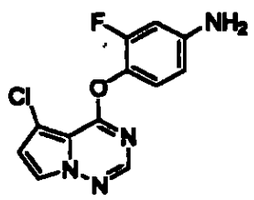
B) 4,5-Dicloropirrolo[2,1-f][1,2,4]triazina

A una solución de 5-cloropirrolo[2,1-f][1,2,4]triazin-4(3H)-ona (5.00 g, 29.5 mmol) en tolueno (100 mL) a temperatura ambiente bajo nitrógeno se le agregó diisopropiletilamina (5.14 mL, 29.5 mmol) seguido por oxicloruro de fósforo(III) (8.25 mL, 88.5 mmol). La mezcla se calentó a 100°C durante 20 horas y se enfrió luego hasta temperatura ambiente. La reacción se agregó lentamente a solución de bicarbonato de sodio acuoso saturado (500 mL) a 0°C. Después de que la adición se completó, la mezcla se agitó a temperatura ambiente durante 30 minutos. La fase acuosa se extrajo con acetato de etilo (3 x 500 mL), se secó sobre $MgSO_4$ anhidro, y se concentró in vacuo para dar el producto crudo (3.73 g, 67%) como un sólido amarillo el cual se usó sin purificación adicional. ^{1}H RMN ($CDCl_3$) δ 8.03 (s, 1H), 7.70 (d, 1H, J= 2.8 Hz), 6.84 (d, 1H, J=2.8 Hz); EM(ESI^+) m/z 188.1 $(M + H)^+$.



C) 5-Cloro-4-(2-fluoro-4-nitrofenoxi)pirrolo[2,1-f][1,2,4]triazina

Una mezcla de 4,5-dicloropirrolo[2,1-f][1,2,4]triazina (3.73 g, 19.8 mmol), 2-fluoro-4-nitrofenol (3.43 g, 21.8 mmol) y carbonato de potasio (5.47 g, 39.6 mmol) en DMF (100 mL) se agitó a 60°C durante 1 hora. Después de enfriar a temperatura ambiente, la reacción se filtró a través de un tapon corto de gel de sílice con acetato de etilo y luego se concentró in vacuo. El producto crudo se purificó por recristalización del acetato de etilo/hexanos (1:1) para dar el compuesto del título (4.37 g, 71%) como un sólido blanco. ^{1}H RMN ($CDCl_3$) δ 8.22-8.17 (m, 2H), 7.92 (s, 1H), 7.77 (d, 1H, J=2.8 Hz), 7.58 (t, 1H, J= 7.2 Hz); 6.87 (d, 1H, J= 3.2 Hz); EM(ESI$^+$) m/z 309.3 $(M + H)^+$.

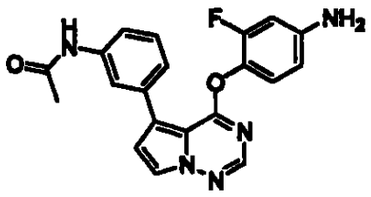


D) 4-(5-Cloropirrolo(2,1-f][1,2,4]triazin-4-iloxi)-3-fluorobencenamina

A una solución de 5-cloro-4-(2-fluoro-4-nitrofenoxi)pirrolo[2,1-f][1,2,4]triazina (2.00 g, 6.48 mmol) en THF (50 mL)/MeOH (80 mL) se le agregó polvo de zinc (2.12 g, 32.4 mmol) seguido por cloruro de amonio (1.73 g, 32.4 mmol). Después de agitar a temperatura ambiente durante 8

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horas, la mezcla de reacción se filtró a través de Celite® con MeOH y luego se concentró in vacuo. El residuo se tomó en acetato de etilo (200 mL) y se lavó con agua (2 x 100 mL) luego salmuera (1 x 100 mL). La fase orgánica se secó sobre Na_2SO_4 anhidro y se concentró in vacuo. El producto crudo se purificó por cromatografía instantánea en gel de sílice (50% EtOAc/hexanos) para dar el compuesto del título (1.51 g, 84%) como un sólido amarillo pálido. ^1H RMN ($CDCl_3$) δ 7.95 (s, 1H), 7.69 (d, 1H, J= 2.8 Hz), 7.09 (t, 1H, J= 8.4 Hz), 6.79 (d, 1H, J= 2.8 Hz), 6.58 (dd, 1H, J=11.6, 2.6 Hz), 6.51 (d, 1H, J= 8.7 Hz), 3.92 (br s, 2H); EM(ESI$^+$) m/z 279.2 $(M + H)^+$.



E) N-(3-(4-(4-Amino-2-fluorofenoxi)pirrolo[2,1-f][1,2,4]triazin-5-il)fenil)acetamida

Un matraz se cargó con acetato de paladio (4.5 mg, 0.02 mmol), Ligando X-Phos (24 mg, 0.05 mmol, Strem), 4-(5-cloropirrolo[2,1-f][1,2,4]triazin-4-iloxi)-3-fluorobencenamina (56 mg, 0.20 mmol), ácido 3-acetamidobencen borónico (72 mg, 0.40 mmol, Lancaster), y fosfato de potasio (127 mg, 0.60 mmol) en tal orden. El matraz se limpió con nitrógeno y luego t-BuOH se le agregó (0.40 mL). La mezcla se calentó a 80 °C por 8 h. Se agregaron partes adicionales de acetato de paladio (4.5 mg, 0.02

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mmol), Ligando X-Phos (24 mg, 0.05 mmol), y ácido 3-acetamidobencen borónico (72 mg, 0.40 mmol) y la reacción se agitó por 9 h adicionales a 80 °C. Después de enfriamiento a temperatura ambiente, la reacción se filtró usando MeOH para eliminar el fosfato de potasio y luego se concentró in vacuo. El producto crudo se purificó por CLAR preparativa de fase inversa y las fracciones apropiadas se concentraron in vacuo para eliminar MeOH. La capa acuosa resultante se hizo básica con solución saturada de bicarbonato de sodio y se extrajo con acetato de etilo. Los extractos orgánicos combinados se secaron sobre sulfato de sodio anhidro y concentraron in vacuo para dar el compuesto del título (20 mg, 26%) como un sólido blanco. ^{1}H RMN (CD_3OD) δ 7.84-7.94 (m, 2H), 7.44-7.41 (m, 1H), 7.34-7.19 (m, 3H), 6.92 (t, 1H, J=8.8 Hz), 6.87 (d, 1H, J=2.8 Hz), 6.50 (dd, 1H, J=12.4, 2.4 Hz), 6.46-6.43 (m, 1H), 2.04 (s, 3H); EM(ESI$^+$) m/z 378.3 $(M + H)^+$.

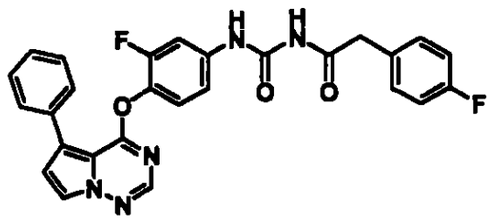
F) 1-(4-(5-(3-Acetamidofenil)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea

A una solución de N-(3-(4-(4-amino-2-fluorofenoxi)pirrolo[2,1-f][1,2,4]triazin-5-il)fenil)acetamida (20 mg, 0.053 mmol) en diclorometano (0.5 mL) a temperatura ambiente bajo nitrógeno se le agregó isocianato de 2-(4-fluorofenil)acetilo (250 µL, 0.064 mmol, 0.25 M en tolueno, Compuesto C del Ejemplo 4). La reacción se agitó a temperatura

ambiente durante 1 hora y luego se concentró in vacuo. El residuo se suspendió en metanol y filtró para recolectar 14 mg (47%) del compuesto del título como un sólido blanco. ^{1}H RMN (DMSO-d_6) δ 11.09 (s, 1H), 10.63 (s, 1H), 10.04 (s, 1H), 8.25-8.21 (m, 2H), 8.05 (s, 1H), 7.78 (d, 1H, J= 13.2 Hz), 7.51-7.38 (m, 7H), 7.23 (t, 2H, J=8.4 Hz), 7.13 (s, 1H), 3.81 (s, 2H), 2.10 (s, 3H); EM(ESI$^+$) m/z 557.4 $(M + H)^+$.

Los Ejemplos 139-144 se prepararon de una forma similar al Ejemplo 138.

EJEMPLO 139

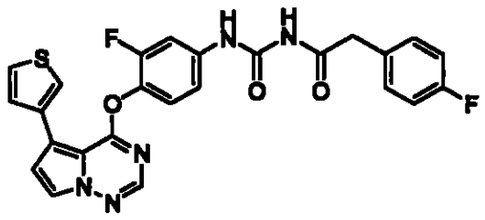


1-(3-Fluoro-4-(5-fenilpirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)urea

^{1}H RMN (DMSO-d_6) δ 10.56 (s, 1H), 8.55 (s, 1H), 7.89 (s, 1H), 7.77 (d, 1H, J=2.8 Hz), 7.62-7.57 (m, 3H), 7.33 (t, 2H, J=7.7 Hz), 7.26-7.19 (m, 4H), 7.10 (m, 1H), 7.02 (t, 2H, J=8.6 Hz), 6.88 (d, 1H, J=2.7 Hz), 3.65 (s, 2H); EM(ESI$^+$) m/z 500.3 $(M + H)^+$.

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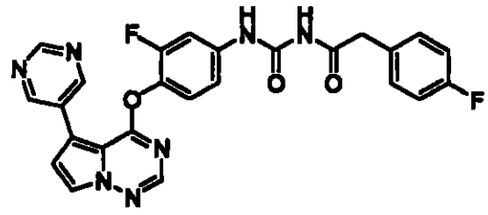
EJEMPLO 140



1-(3-Fluoro-4-(5-(tiofen-3-il)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)urea

^{1}H RMN (DMSO-d_6) δ 11.05 (s, 1H), 10.59 (s, 1H), 8.16 (d, 1H, J=2.8 Hz), 8.12 (s, 1H), 7.81 (d, 1H, J=1.6 Hz), 7.75 (dd, 1H, J=12.4, 2 Hz), 7.62-7.49 (m, 3H), 7.39-7.36 (m, 3H), 7.21-7.16 (m, 3H), 3.76 (s, 2H); EM(ESI$^+$) m/z 506.3 (M + H)$^+$.

EJEMPLO 141

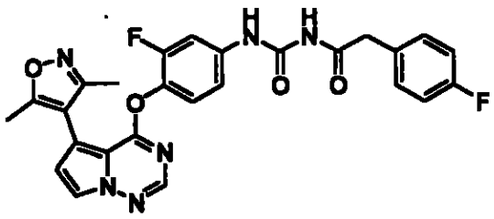


1-(3-Fluoro-4-(5-(pirimidin-5-il)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)urea

^{1}H RMN (DMSO-d_6) δ 11.10 (s, 1H), 10.65 (s, 1H), 9.21 (s, 2H), 9.18 (s, 1H), 8.37 (d, 1H, J=2.4 Hz), 8.31 (s, 1H), 7.80 (dd, 1H, J=12.4, 2 Hz), 7.58 (t, 1H, J=8.8 Hz), 7.44-7.40 (m, 4H), 7.23 (t, 2H, J=8.4 Hz), 3.80 (s, 2H); EM(ESI$^+$) m/z 502.3 (M + H)$^+$.

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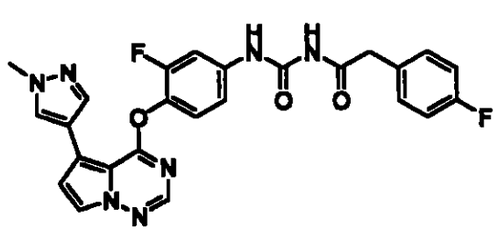
EJEMPLO 142



1-(4-(5-(3,5-Dimetilisoxazol-4-il)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea

^{1}H RMN (DMSO-d_6) δ 11.04 (s, 1H), 10.58 (s, 1H), 8.24 (d, 1H, J=2.4 Hz), 8.17 (s, 1H), 7.42 (dd, 1H, J=13.2, 2 Hz), 7.38-7.35 (m, 4H), 7.18 (t, 2H, J= 7.6 Hz), 7.06 (d, 1H, J=2.8 Hz), 3.75 (s, 2H), 2.37 (s, 3H), 2.20 (s, 3H); EM(ESI$^+$) m/z 519.3$(M+H)^+$.

EJEMPLO 143



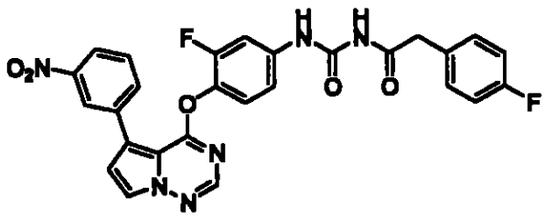
1-(3-Fluoro-4-(5-(1-metil-1H-pirazol-4-il)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)urea

^{1}H RMN(DMSO-d_6) δ 11.04(s, 1H), 10.59 (s, 1H), 8.11 (d, 1H, J=

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2.8 Hz), 8.05 (d, 2H, J= 2.4 Hz), 7.85 (s, 1H), 7.76 (dd, 1H, J= 12.4, 2 Hz), 7.52 (t, 1H, J= 8.4 Hz), 7.39-7.36 (m, 3H), 7.18 (t, 2H, J= 8.8 Hz), 7.12 (d, 1H, J= 2.8 Hz), 3.86 (s, 3H), 3.76 (s, 2H); EM (ESI^+) m/z 504.3 $(M + H)^+$.

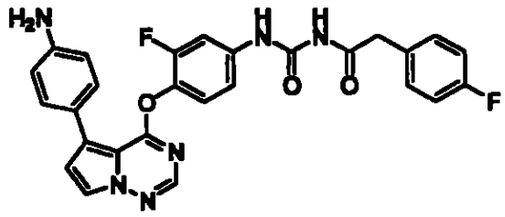
EJEMPLO 144



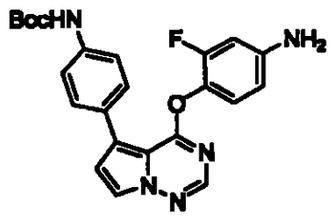
1-(3-Fluoro-4-(5-(3-nitrofenil)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)urea

^1H RMN (DMSO-d_6) δ 11.03 (s, 1H), 10.57 (s, 1H), 8.62 (s, 1H), 8.27 (d, 1H, J= 2.4 Hz), 8.23 (s, 1H), 8.20-8.16 (m, 2H), 7.76-7.72 (m, 2H), 7.49 (t, 1H, J = 8.8 Hz), 7.39-7.34 (m, 4H), 7.18 (t, 2H, J= 9.2 Hz), 3.75 (s, 2H); EM(ESI^+) m/z 545.2 $(M + H)^+$.

EJEMPLO 145



1-(4-(5-(4-Aminofenil)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea



A) 4-(4-(4-amino-2-fluorofenoxi)pirrolo[2,1-f][1,2,4]triazin-5-il)fenilcarbamato de tert-Butilo

Se preparó en una forma similar como en la Etapa E del Ejemplo 138 para dar el compuesto del título (46%) como un aceite amarillo. ^{1}H RMN ($CDCl_3$) δ 7.88 (s, 1H), 7.73 (d, 1H, J= 4 Hz), 7.54 (d, 2H, J= 8 Hz), 7.33-7.30 (m, 2H), 6.93 (t, 1H, J= 7.6 Hz), 6.82 (d, 1H, J = 4 Hz), 6.60-6.47 (m, 2H), 1.44 (s, 9H); EM(ESI$^+$) m/z 436.4 $(M + H)^+$.

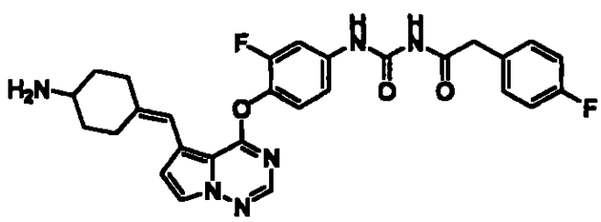
B) 1-(4-(5-(4-Aminofenil)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea

Preparado en una forma similar como en la Etapa F del Ejemplo 138 para dar el material protegido Boc (51%). El material protegido Boc se suspendió en éter (2 mL), se enfrió a 0°C, y se cargó con TFA (0.5 mL). Después de agitar a temperatura ambiente durante 1 hora, la reacción se concentró in vacuo. El residuo se suspendió en acetato de etilo (10 mL), se lavó con solución de bicarbonato de sodio acuoso saturado (5 mL), se secó sobre sulfato de sodio anhidro, y se concentró. El producto crudo se purificó por cromatografía instantánea en gel de sílice (60% EtOAc/hexanos). La liofilización del acetonitrilo (1

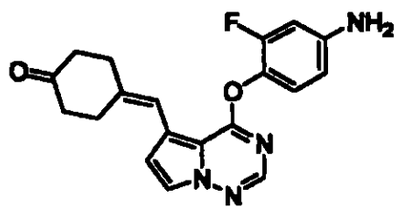
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mL)/agua (3 mL) dio el compuesto del título (38%) como un sólido café claro. ^{1}H RMN (DMSO-d_6) δ 10.95 (s, 1H), 10.50 (s, 1H), 8.02 (d, 1H, J= 2.8 Hz), 7.98 (s, 1H), 7.67 (dd, 1H, J= 12.4, 2 Hz), 7.36 (t, 1H, J= 8.8 Hz), 7.31-7.28 (m, 5H), 7.10 (t, 2H, J= 8.8 Hz), 6.89 (d, 1H, J= 2.8 Hz), 6.51 (d, 2H, J= 8.8 Hz), 5.08 (s, 2H), 3.68 (s, 2H); EM (ESI$^+$) m/z 515.3 $(M + H)^+$.

EJEMPLO 146



1-(4-(5-((4-Aminociclohexilideno)metil)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea

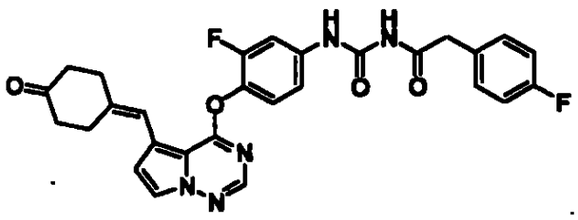


A) 4-((4-(4-Amino-2-fluorofenoxi)pirrolo[2,1-f][1,2,4]triazin-5-il)metileno)ciclohexanona

Preparado en una forma similar como en la Etapa E del Ejemplo 138 usando 4-((4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)metileno)ciclohexanona (se preparó de conformidad con el

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procedimiento de Morrill, C. y Grubbs, R. H. J. Org. Chem. 2003, 68, 6031-6034). para dar el compuesto del título (11%) como un aceite amarillo. ^{1}H RMN (CD_3OD) δ 7.76 (s, 1H), 7.73 (d, 1H, J= 2.8 Hz), 7.54-7.51 (m, 1H), 7.33 (d, 1H, J= 2.8 Hz), 6.92 (t, 1H, J= 7.6 Hz), 6.84 (d, 1H, J = 2.8 Hz), 6.46-6.41 (m, 1H), 2.83 (t, 2H, J= 6.8 Hz), 2.65 (t, 2H, J= 6.8 Hz), 2.45-2.38 (m, 4H); EM(ESI$^+$) m/z 353.2 $(M + H)^+$.



B) 1-(4-(5-(4-Aminofenil)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea

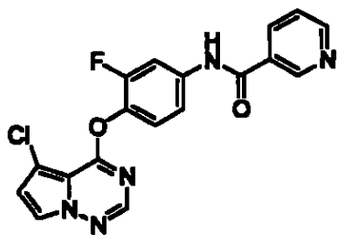
Preparado en una forma similar como en la Etapa F del Ejemplo 138 para dar el compuesto del título (38%) como un sólido amarillo. ^{1}H RMN (acetona-d_6) δ 10.62 (s, 1H), 9.87 (s, 1H), 7.80 (s, 1H), 7.79 (d, 1H, J= 2.8 Hz), 7.70 (dd, 1H, J= 12.8, 2.4 Hz), 7.33-7.19 (m, 4H), 6.96-6.93 (m, 3H), 6.16 (m, 1H), 3.75 (s, 2H), 2.82 (t, 2H, J= 6.8 Hz), 2.62 (t, 2H, J= 6.8 Hz), 2.37 (t, 2H, J= 6.8 Hz), 2.30 (t, 2H, J= 6.8 Hz); EM(ESI$^+$) m/z 532.2 $(M + H)^+$.

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C) 1-(4-(5-((4-Aminociclohexilideno)metil)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea

Una solución de 1-(4-(5-(4-aminofenil)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea (21 mg, 0.040 mmol) en metanol (0.5 mL) y THF (0.5 mL) a 0°C se cargó con acetato de amonio (30 mg, 0.40 mmol) seguido por cianoborohidruro de sodio (2.5 mg, 0.040 mmol). Después de agitar a 0°C durante 1 hora, la reacción se concentró in vacuo. El producto crudo se purificó por CLAR preparativa de fase inversa y las fracciones apropiadas se concentraron in vacuo. Tolueno se agregó (2 x 5 mL) y concentró para eliminar el exceso de TFA. La liofilización del acetonitrilo (1 mL) / agua (3 mL) dio la sal TFA del compuesto del título (19%) como un sólido blanco. ^{1}H RMN (CD_3OD) δ 7.77 (s, 1H), 7.76 (d, 1H, J= 2.8 Hz), 7.63 (dd, 1H, J= 12.8, 2.4 Hz), 7.29-7.14 (m, 4H), 7.03-6.93 (m, 2H), 6.91 (d, 1H, J= 2.8 Hz), 6.67 (s, 1H), 3.62 (s, 2H), 3.15-3.08 (m, 1H), 2.50-2.30 (m, 2H), 2.21-2.05 (m, 2H), 1.46-1.30 (m, 4H); EM(ESI$^+$) m/z 533.2 $(M + H)^+$.

EJEMPLO 147

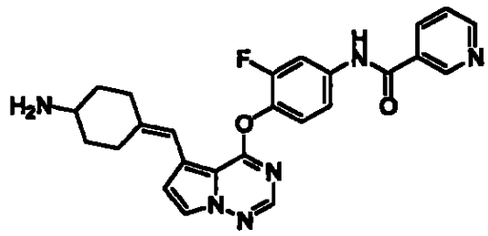


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N-(4-(5-Cloropirrolo[2,1-f][1,2,4]triazin-4-iloxi)-3-fluorofenil)nicotinamida

A 4-(5-cloropirrolo[2,1-f][1,2,4]triazin-4-iloxi)-3-fluorobencenamina (100 mg, 0.359 mmol, Compuesto D del Ejemplo 138) en DMF (2 mL) se le agregó ácido nicotínico (53 mg, 0.431 mmol, Aldrich), DIPEA (300 µL, 1.80 mmol), seguido por TBTU (173 mg, 0.539 mmol, Fluka). Después de agitar a temperatura ambiente durante la noche, la reacción se diluyó con 20 mL de EtOAc, se lavó con solución de cloruro de litio acuosa al 10% (2x10 mL) seguido por salmuera (1 x 10 mL), se secó sobre sulfato de sodio anhidro, y se concentró in vacuo. El producto crudo se purificó por cromatografía instantánea en gel de sílice (10% MeOH / EtOAc) para dar el compuesto del título (125 mg, 91%) como un sólido blanco. ^{1}H RMN (DMSO-d_6) δ 10.75 (s, 1H), 9.14 (d, 1H, J= 2 Hz), 8.80 (dd, 1H, J= 4.8, 1.2 Hz), 8.34-8.31 (m, 1H), 8.18 (d, 1H, J= 2.8 Hz), 8.17 (s, 1H), 7.96 (dd, 1H, J = 12.8, 2 Hz), 7.66-7.60 (m, 2H), 7.54 (t, 1H, J= 8.8 Hz), 7.10 (d, 1H, J=2.8 Hz); EM(ESI$^+$) m/z 383.9 $(M + H)^+$.

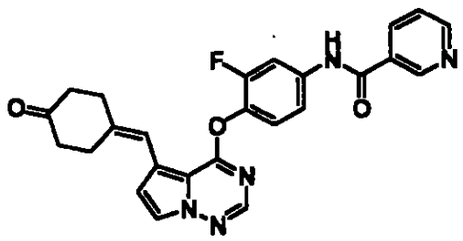
EJEMPLO 148



N-(4-(5-((4-Aminociclohexilideno)metil)pirrolo[2,1-

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f][1,2,4]triazin-4-iloxi)-3-fluorofenil)nicotinamida



A) N-(3-Fluoro-4-(5-((4-oxociclohexilideno)metil)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)nicotinamida

Preparado en una forma similar como en la Etapa E del Ejemplo 138 para dar el compuesto del título (66%) como un sólido amarillo. ^{1}H RMN (DMSO-d_6) δ 10.75 (s, 1H), 9.14 (d, 1H, J= 2 Hz), 8.82 (dd, 1H, J=4.8, 1.2 Hz), 8.36-8.33 (m, 1H), 8.13 (d, 1H, J= 2.8 Hz), 8.10 (s, 1H), 7.99-7.93 (m, 1H), 7.68-7.63 (m, 1H), 7.54 (t, 1H, J= 8.8 Hz), 7.07 (d, 1H, J= 2.8 Hz), 6.92 (s, 1H), 2.90 (t, 2H, J= 6.8 Hz), 2.74 (t, 2H, J= 6.8 Hz), 2.51 (t, 2H, J= 6.8 Hz), 2.42 (t, 2H, J= 6.8 Hz); EM(ESI$^+$) m/z 458.2 $(M + H)^+$.

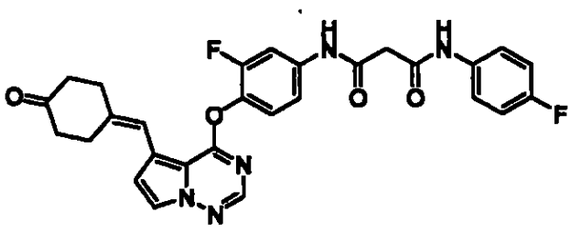
B) N-(4-(5-((4-Aminociclohexilideno)metil)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)-3-fluorofenil)nicotinamida

Preparado en una forma similar como la Etapa C del Ejemplo 146 para dar la sal de TFA del compuesto del título (6%) como un sólido amarillo pálido. ^{1}H RMN

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(CD_3OD) δ 9.15 (s, 1H), 8.80 (s, 1H), 8.59 (d, 1H, J= 8 Hz), 7.84-7.76 (m, 4H), 7.48 (d, 1H, J= 8 Hz), 7.29 (t, 1H, J= 8 Hz), 6.80 (d, 1H, J= 4 Hz), 6.67 (s, 1H), 3.62 (s, 2H), 3.10-3.08 (m, 1H), 2.48-2.05 (m, 4H), 1.47-1.20 (m, 4H); EM(ESI^+) m/z 459.2 $(M + H)^+$.

EJEMPLO 149

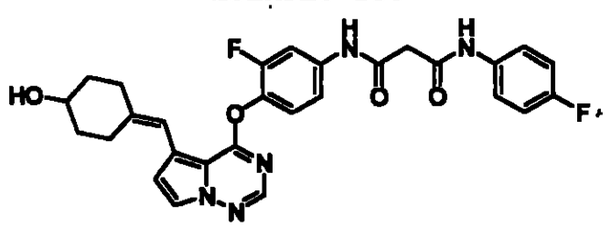


N^1-(3-Fluoro-4-(5-((4-oxociclohexilideno)metil)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-N^3-(4-fluorofenil)malonamida

Acoplamiento Suzuki en una forma similar como en la Etapa E del Ejemplo 138 seguido por la formación de malonamida como en la Etapa A del Ejemplo 133 dio el compuesto del título (39%) como un sólido amarillo. ^1H RMN (DMSO-d_6) δ 10.55 (s, 1H), 10.31 (s, 1H), 8.15 (d, 1H, J= 2.4 Hz), 8.11 (s, 1H), 7.86 (dd, 1H, J= 12.4, 2.8 Hz), 7.52 (t, 1H, J= 8.8 Hz), 7.44-7.42 (m, 1H), 7.25-7.19 (m, 2H), 7.09 (d, 1H, J= 2.8 Hz), 6.93 (s, 1H), 3.54 (s, 2H), 2.91 (t, 2H, J= 6.8 Hz), 2.73 (t, 2H, J= 6.4 Hz), 2.53 (t, 2H, J= 6.8 Hz), 2.45 (t, 2H, J= 6.8 Hz); MS(ESI^+) m/z 532.3 $(M + H)^+$.

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EJEMPLO 150



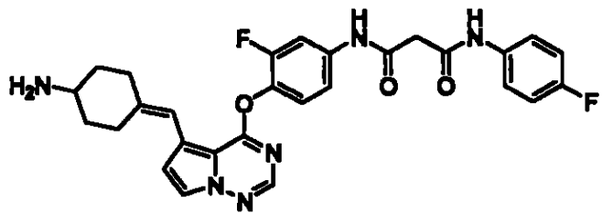
N^1-(3-Fluoro-4-(5-((4-hidroxiciclohexilideno)metil)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-N^3-(4-fluorofenil)malonamida

A N^1-(3-fluoro-4-(5-((4-oxociclohexilideno)metil)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-N^3-(4-fluorofenil)malonamida (80 mg, 0.15 mmol, Ejemplo 149) en metanol (2 mL) a 0°C se agregó una punta de espátula de borohidruro de sodio. La reacción se agitó a 0°C durante 30 minutos y se apagó luego con solución de cloruro de amonio acuosa saturada (10 mL) y se agitó a 0°C durante 5 minutos. La mezcla se extrajo con acetato de etilo (3 x 10 mL) y los extractos orgánicos combinados se secaron sobre sulfato de sodio anhidro y se concentraron in vacuo. El producto crudo se purificó por cromatografía instantánea en gel de sílice (10% MeOH / EtOAc) para dar el compuesto del título (30 mg, 37%) como un sólido blanco apagado. ^{1}H RMN (DMSO-d_6) δ 10.57 (s, 1H), 10.34 (s, 1H), 8.11 (d, 1H, J= 2.8 Hz), 8.10 (s, 1H), 7.86 (dd, 1H, J= 12.8, 2.4 Hz), 7.71-7.68 (m, 2H), 7.53 (t, 1H, J= 8.4 Hz), 7.46-7.43 (m, 1H), 7.25-7.21 (m, 2H), 6.99 (d, 1H, J= 2.8 Hz), 6.64 (s, 1H), 4.65 (br s, 1H), 3.76-3.75 (m, 1H), 3.56 (s, 2H), 2.90-

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2.85 (m, 1H), 2.51-2.45 (m, 1H), 2.27-2.24 (m, 2H), 1.92-1.85 (m, 2H), 1.46-1.41 (m, 2H); EM(ESI$^+$) m/z 534.3 $(M + H)^+$.

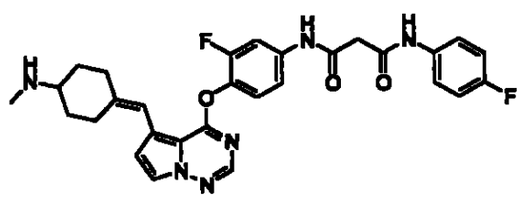
EJEMPLO 151



N^1-(4-(5-((4-Aminociclohexilideno)metil)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)-3-fluorofenil)-N^3-(4-fluorofenil)malonamida

Preparado en una forma similar como en la Etapa C del Ejemplo 146 para dar la sal TFA del compuesto del título (12%) como un sólido blanco. ^{1}H RMN (DMSO-d_6) δ 10.51 (s, 1H), 10.26 (s, 1H), 8.02 (d, 1H, J= 2.4 Hz), 7.99 (s, 1H), 7.74 (dd, 1H, J= 12.8, 2 Hz), 7.59-7.55 (m, 2H), 7.38 (t, 1H, J= 8.4 Hz), 7.32-7.35 (m, 1H), 7.13-7.08 (m, 2H), 6.90 (d, 1H, J= 2.8 Hz), 6.59 (s, 1H), 3.44 (s, 2H), 2.95-3.00 (m, 1H), 2.20-2.41 (m, 2H), 1.96-2.11 (m, 2H), 1.32-1.39 (m, 2H), 1.17-1.13 (m, 2H); EM(ESI$^+$) m/z 533.3 $(M + H)^+$.

EJEMPLO 152



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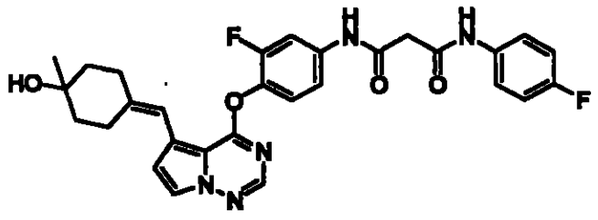
N^1-(3-Fluoro-4-(5-((4-(metilamino)ciclohexilideno)metil)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-N^3-(4-fluorofenil)malonamida, sal del ácido trifluoroacético

A N^1-(3-fluoro-4-(5-((4-oxociclohexilideno)metil)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-N^3-(4-fluorofenil)malonamida (20 mg, 0.038 mmol, Ejemplo 149) en dicloroetano (1 mL) se le agregó metilamina (23 µL, 0.045 mmol, 2 M THF), ácido acético (2.6 µL, 0.045 mmol), seguido por triacetoxiborohidruro de sodio (13 mg, 0.056 mmol). Después de agitar a temperatura ambiente durante 2 horas, la reacción se apagó con solución de bicarbonato de sodio acuoso al 5% (1 mL). Las capas se separaron y la capa orgánica se lavó con salmuera, se secó sobre sulfato de sodio anhidro, y se concentró in vacuo. El producto crudo se purificó por CLAR preparativa de fase inversa y las fracciones apropiadas se concentraron in vacuo. Tolueno se le agregó (2x4 mL) y concentró para eliminar el exceso de TFA. La liofilización del acetonitrilo (1 mL) / agua (3 mL) dio la sal TFA del compuesto del título (11 mg, 44%) como un sólido blanco. ^{1}H RMN (DMSO-d_6) δ δ 10.51 (s, 1H), 10.26 (s, 1H), 8.02 (d, 1H, J= 2.8 Hz), 8.00 (s, 1H), 7.74 (dd, 1H, J= 12.8, 2 Hz),

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7.59-7.55 (m, 2H), 7.40 (t, 1H, J= 8.4 Hz), 7.35-7.32 (m, 1H), 7.13-7.06 (m, 2H), 6.90 (d, 1H, 7= 2.8 Hz), 6.60 (s, 1H), 3.44 (s, 2H), 3.10-3.13 (m, 1H), 3.02-2.98 (m, 1H), 2.52-2.39 (m, 4H), 2.23-2.21 (m, 1H), 2.08-2.02 (m, 3H), 1.36-1.31 (m, 2H); EM(ESI$^+$) m/z 547.1 $(M + H)^+$.

EJEMPLO 153

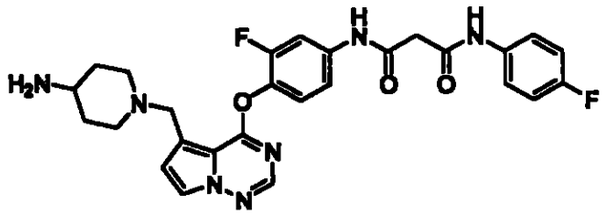


N^1-(3-Fluoro-4-(5-((4-hidroxi-4-metilciclohexilideno)metil)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-N^3-(4-fluorofenil)malonamida, sal del ácido trifluoroacético

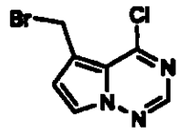
A N^1-(3-fluoro-4-(5-((4-oxociclohexilideno)metil)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-N^3-(4-fluorofenil)malonamida (10 mg, 0.019 mmol, Ejemplo 149) en THF (1 mL) a 0°C se le agregó metillitio (76 µL, 0.076 mmol, THF 1 M). Después de agitar a temperatura ambiente durante la noche, la reacción se apagó con salmuera (1 mL). Las capas se separaron y la capa orgánica se secó sobre sulfato de sodio anhidro y se concentró in vacuo. El producto crudo se purificó por CLAR preparativa de fase inversa y las fracciones apropiadas se concentraron in vacuo.

Tolueno se le agregó (2 x 2 mL) y se concentró para eliminar el exceso de TFA. La liofilización del acetonitrilo (1 mL) / agua (3 mL) dio la sal de TFA del compuesto del título (3 mg, 21%) como un sólido amarillo pálido. ^{1}H RMN (DMSO-d_6) δ 10.45 (s, 1H), 10.21 (s, 1H), 7.98 (d, 1H, J= 2.8 Hz), 7.96 (s, 1H), 7.74 (dd, 1H, J= 12.8, 2 Hz), 7.58-7.55 (m, 2H), 7.40 (t, 1H, J= 8 Hz), 7.33-7.31 (m, 1H), 7.13-7.08 (m, 2H), 6.87 (d, 1H, J=2.8 Hz), 6.51 (s, 1H), 4.20 (br s, 1H), 3.43 (s, 2H), 2.60-2.45 (m, 3H), 2.09-2.06 (m, 1H), 1.56-1.52 (m, 2H), 1.41-1.36 (m, 2H), 1.07 (s, 3H); EM(ESI$^+$) m/z 548.3 $(M + H)^+$.

EJEMPLO 154



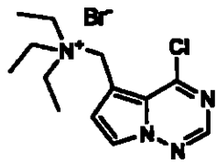
N^1-(4-(5-((4-Aminopiperidin-1-il)metil)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)-3-fluorofenil)-N^3-(4-fluorofenil)malonamida, sal del ácido trifluoroacético



A) 5-Bromometil-4-cloro-pirrolo[2,1-f][1,2,4]triazina

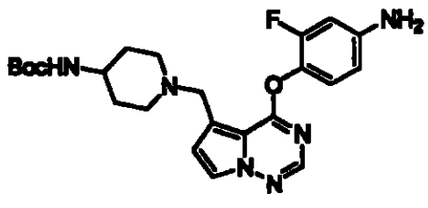
Una mezcla de 4-cloro-5-metil-pirrolo[2,1-f][1,2,4]triazina (2.0 g, 11.93 mmol, WO 03/042172) y AIBN

(195 mg, 1.19 mmol) en CCl_4 (80 mL) bajo N_2 se calentó a 100°C durante 5 minutos, NBS (2.55 g, 14.3 mmol) se agregó. La mezcla de reacción se agitó durante 10 minutos, luego se enfrió hasta temperatura ambiente, se filtró. La capa de CCl_4 se lavó con solución acuosa $NaHCO_3$ diluida, se secó ($MgSO_4$), filtró y concentró para dar el producto deseado (2.70 g, 92%).



B) Bromuro de (4-cloro-pirrolo[2,1-f][1,2,4]triazin-5-ilmetil)-trietilamonio

Una mezcla de 5-bromometil-4-cloro-pirrolo[2,1-f][1,2,4]triazina (2.7 g, 11 mmol), Et_3N (5 mL, 36 mmol) en THF (20 mL) se agitó a temperatura ambiente durante 12 horas. El sólido se filtró y se enjuagó con THF y Et_2O, se secó para dar el producto deseado (3.38 g, 89%). Tiempo de retención CLAR analítico = 0.776 minutos. (Chromolith SpeedROD 4.6 x 50 mm, 10-90% metanol acuoso durante 4 minutos que contiene 0.1% TFA, 4 mL/min, monitoreando a 220 nm); EM(ESI^+) m/z 267 $(M + H)^+$.



499

C) 1-((4-(4-amino-2-fluorofenoxi)pirrolo[2,1-f][1,2,4]triazin-5-il)metil)piperidin-4-ilcarbamato de tert-Butilo

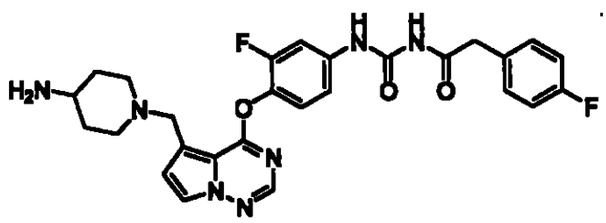
A 4-amino-2-fluorofenol (82 mg, 0.646 mmol) en THF (5 mL) a -78°C bajo nitrógeno se le agregó NaHMDS (650 µL, 0.650 mmol, hexanos 1 M). Después de agitar a -78°C durante 20 minutos, el matraz se transfirió a un baño a 0°C y bromuro de N-((4-cloropirrolo[2,1-f][1,2,4]triazin-5-il)metil)-trietilamonio sólido (200 mg, 0.807 mmol) se agregó inmediatamente. La reacción se permitió hasta entibiar a temperatura ambiente y se agitó durante 2 horas. DIPEA (280 µL, 1.6 mmol), piperidin-4-ilcarbamato de tert-butilo (129 mg, 0.646 mmol, Aldrich), y DMF (2 mL) se le agregó. La reacción se calentó a 120°C durante 4 horas. Después de enfriar a temperatura ambiente, la reacción se concentró in vacuo y el producto crudo se purificó por CLAR preparativa de fase inversa. Las fracciones apropiadas se concentraron in vacuo. Tolueno se le agregó (2x2 mL) y se concentró para dar la sal TFA del compuesto del título (100 mg, 27%) como un sólido amarillo. ^{1}H RMN (CD_3OD) δ 8.09 (s, 1H), 8.03 (d, 1H, J= 2.4 Hz), 7.23-7.13 (m, 2H), 6.83-6.61 (m, 2H), 4.73 (s, 2H), 3.67-3.64 (m, 1H), 3.30-3.19 (m, 2H), 2.31-2.24 (m, 2H), 1.76-1.63 (m, 2H), 1.49-1.45 (m, 2H), 1.45 (s, 9H); EM(ESI$^+$) m/z 457.5 $(M + H)^+$.

600

D) N^1-(4-(5-((4-Aminopiperidin-1-il)metil)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)-3-fluorofenil)-N^3-fluorofenil)malonamida, sal del ácido trifluoroacético

Preparado de una forma similar como en la Etapa A del Ejemplo 133. El material protegido Boc resultante se disolvió en éter (1 mL) a 0°C y se cargó con HCl 4 N en dioxano (3 mL). Después de agitar a 0°C durante 3 horas, la reacción se concentró in vacuo. El producto crudo se purificó por CLAR preparativa de fase inversa y las fracciones apropiadas se concentraron in vacuo. Tolueno se le agregó (2 x 2 mL) y se concentró para dar la sal TFA del compuesto del título (4 mg, 12%) como un sólido blanco. ^{1}H RMN (DMSO-d_6) δ 10.49 (s, 1H), 10.22 (s, 1H), 8.18 (s, 1H), 7.90 (d, 1H, J= 2.8 Hz), 7.76 (dd, 1H, J= 12.8, 2.4 Hz), 7.57-7.56 (m, 2H), 7.43-7.36 (m, 2H), 7.13-7.09 (m, 3H), 4.57 (s, 2H), 3.51-3.48 (m, 1H), 3.44 (s, 2H), 3.09-3.06 (m, 2H), 2.53-2.50 (m, 2H), 2.00-1.97 (m, 2H), 1.72-1.67 (m, 2H); EM(ESI$^+$) m/z 536.5 $(M + H)^+$.

EJEMPLO 155



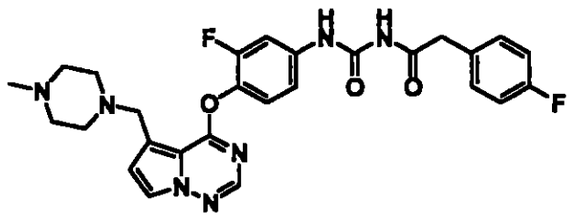
1-(4-(5-((4-Aminopiperidin-1-il)metil)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)-3-fluorofenil)-3-(2-(4-

501

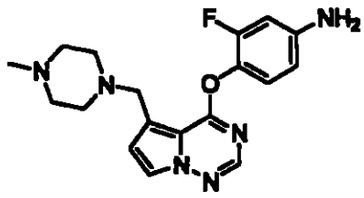
fluorofenil)acetil)urea, sal del ácido trifluoroacético

A 1-((4-(4-amino-2-fluorofenoxi)pirrolo[2,1-f][1,2,4]triazin-5-il)metil)piperidin-4-ilcarbamato de tert-butilo (50 mg, 0.088 mmol, Compuesto C del Ejemplo 154) en diclorometano (1 mL) a 0°C se le agregó isocianato de 2-(4-fluorofenil)acetilo (290 uL, 0.088 mmol, 0.3 M en tolueno, Compuesto C del Ejemplo 4). La reacción se agitó a 0°C durante 0.5 horas y se purificó directamente por cromatografía instantánea en gel de sílice (10% MeOH/EtOAc) para dar el material protegido Boc (33 mg, 59%) como un aceite incoloro. El material protegido Boc se suspendió en éter (2 mL) a 0°C y se cargó con HCl 4 N ein dioxano (5 mL). Después de agitar a 0°C durante 1.5 horas, la reacción se concentró in vacuo. El producto crudo se purificó por CLAR preparativa de fase inversa y las fracciones apropiadas se concentraron in vacuo. Tolueno se le agregó (2 x 2 mL) y concentró para dar la sal TFA del compuesto del título (3 mg, 8%) como un sólido blanco. ^{1}H RMN (DMSO-d_6) δ 11.01 (s, 1H), 10.57 (s, 1H), 8.21-8.18 (m, 2H), 7.73 (dd, 1H, J= 12.8, 2.4 Hz), 7.48-7.33 (m, 4H), 7.18-7.11 (m, 3H), 4.57 (m, 1H), 3.69 (s, 2H), 3.44 (s, 2H), 3.59-3.48 (m, 2H), 3.13-3.06 (m, 2H), 2.05-1.98 (m, 2H), 1.71-1.55 (m, 2H); EM(ESI$^+$) m/z 535.3 $(M + H)^+$.

EJEMPLO 156



1-(3-Fluoro-4-(5-((4-metilpiperazin-1-il)metil)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)urea



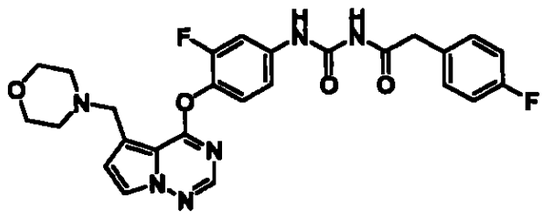
A) 1-(3-Fluoro-4-(5-((4-metilpiperazin-1-il)metil)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)urea

Preparado en una forma similar como en la Etapa C del Ejemplo 154 para dar la sal de TFA del compuesto del título (9%) como un sólido café. ^{1}H RMN (CD_3OD) δ 7.90 (s, 1H), 7.85 (d, 1H, J= 2.8 Hz), 7.17 (t, 1H, J= 8.8 Hz), 6.94 (d, 1H, J=2.8 Hz), 6.75 (dd, 1H, J= 11.6, 2.4 Hz), 6.72-6.69 (m, 1H), 4.39 (s, 2H), 3.40-3.31 (m, 8H), 2.79 (s, 3H); EM(ESI$^+$) m/z 357.3 $(M + H)^+$.

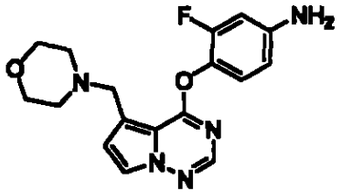
B) 1-(3-Fluoro-4-(5-((4-metilpiperazin-1-il)metil)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)urea

Preparado en una forma similar como en el Ejemplo 155 para dar el compuesto del título (83%) como un sólido blanco. ^{1}H RMN (CD_3OD) δ 7.80 (s, 1H), 7.77 (d, 1H, J= 2 Hz), 7.62 (dd, 1H, J= 12.4, 2.4 Hz), 7.27-7.17 (m, 4H), 6.99-6.95 (m, 2H), 6.84 (d, 1H, J= 2.4 Hz), 3.94 (s, 2H), 3.62 (s, 2H), 2.70-2.45 (m, 8H), 2.26 (s, 3H); EM(ESI$^+$) m/z 536.2 $(M + H)^+$.

EJEMPLO 157



1-(3-Fluoro-4-(5-(morfolinometil)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)urea



A) 3-Fluoro-4-(5-(morfolinometil)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)bencenamina

Preparado en una forma similar como en la Etapa C del

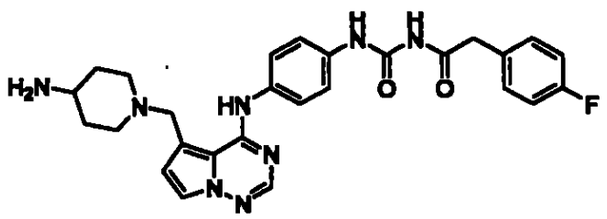
504

Ejemplo 154 para dar la sal TFA del compuesto del título (10%) como un sólido café claro. ^{1}H RMN (CD_3OD) δ 7.98 (s, 1H), 7.91 (d, 1H, J= 2.8Hz), 7.11 (t, 1H, J= 8.4 Hz), 7.02 (d, 1H, J= 2.8 Hz), 6.62 (dd, 1H, J= 12.4, 2.8 Hz), 6.60-6.57 (m, 1H), 4.67 (s, 2H), 4.00-3.94 (m, 2H), 3.68-3.61 (m, 2H), 3.43-3.40 (m, 2H), 3.22-3.20 (m, 2H); EM(ESI$^+$) m/z 344.3 $(M + H)^+$.

B) 1-(3-Fluoro-4-(5-(morfolinometil)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)urea

Preparado en una forma similar como en el Ejemplo 155 para dar el compuesto del título (83%) como un sólido blanco. ^{1}H RMN (CD_3OD) δ 7.89 (s, 1H), 7.85 (d, 1H, J= 2.8 Hz), 7.67 (dd, 1H, J= 12.4, 2.4 Hz), 7.30-7.19 (m, 4H), 7.01-6.94 (m, 3H), 4.28 (s, 2H), 3.70-3.76 (m, 4H), 3.62 (s, 2H), 2.88-2.80 (m, 2H); EM(ESI$^+$) m/z 523.2 $(M + H)^+$.

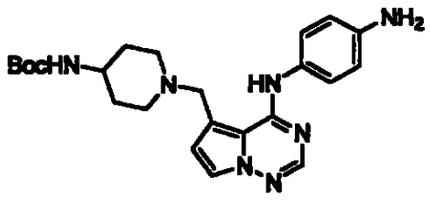
EJEMPLO 158



1-(4-(5-((4-Aminopiperidin-1-il)metil)pirrolo[2,1-f][1,2,4]triazin-4-ilamino)fenil)-3-(2-(4-

505

fluorofenil)acetil)urea



A) 1-((4-(4-Aminofenilamino)pirrolo[2,1-f][1,2,4]triazin-5-il)metil)piperidin-4-ilcarbamato de tert-butilo

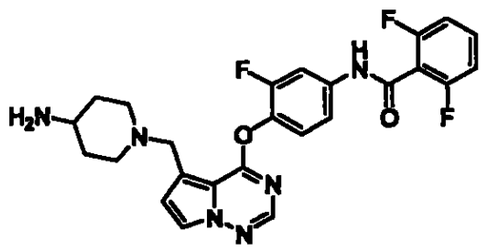
Preparado en una forma similar como en la Etapa C del Ejemplo 154 para dar la sal de TFA del compuesto del título (38%) como un aceite amarillo. ^{1}H RMN (CD_3OD) δ 7.57 (s, 1H), 7.33 (d, 1H, J= 2.4 Hz), 7.24-7.21 (m, 2H), 6.71-6.68 (m, 2H), 6.45 (d, 1H, J= 2.8 Hz), 3.67 (s, 2H), 3.34-3.28 (m, 1H), 2.95-2.90 (m, 2H), 1.80-1.77 (m, 2H), 1.41-1.33 (m, 2H), 1.32 (s, 9H); EM(ESI$^+$) m/z 438.3 $(M + H)^+$.

B) 1-(4-(5-((4-Aminopiperidin-1-il)metil)pirrolo[2,1-f][1,2,4]triazin-4-ilamino)fenil)-3-(2-(4-fluorofenil)acetil)urea

Preparado en una forma similar como en el Ejemplo 155 para dar el compuesto del título (47%) como un sólido blanco apagado. ^{1}H RMN (DMSO-d_6) δ 11.01 (s, 1H), 10.53 (s, 1H), 8.00-7.89 (m, 2H), 7.61-7.59 (m, 3H), 7.45-7.41 (m, 2H), 7.26-7.22 (m, 4H), 3.77 (s, 2H), 3.63 (s, 2H), 3.35-3.32 (m, 1H), 3.20-3.14 (m, 2H), 2.19-1.90 (m, 6H); EM(ESI$^+$) m/z 517.3 $(M+H)^+$.

506

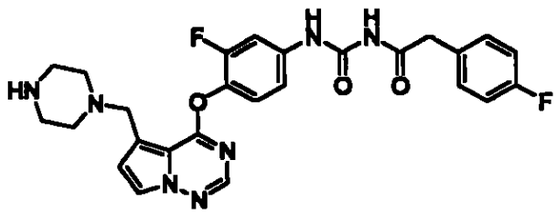
EJEMPLO 159



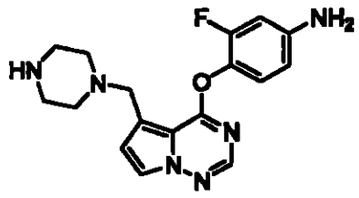
N-(4-(5-((4-Aminopiperidin-1-il)metil)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)-3-fluorofenil)-2,6-difluorobenzamida

Preparado en una forma similar como en el Ejemplo 147 para dar la sal TFA del compuesto del título (5%) como un sólido blanco. ^{1}H RMN (DMSO-d_6) δ 11.10 (s, 1H), 8.19-8.17 (m, 2H), 7.82 (dd, 1H, J= 12.8, 2.4 Hz), 7.49 (t, 1H, 7= 8.8 Hz), 7.49-7.47 (m, 2H), 7.25-7.21 (m, 2H), 7.14-7.09 (m, 1H), 4.59 (s, 2H), 3.54-3.48 (m, 3H), 3.15-3.08 (m, 2H), 2.08-2.00 (m, 2H), 1.74-1.66 (m, 2H); EM(ESI$^+$) m/z 497.2 $(M + H)^+$.

EJEMPLO 160



1-(3-Fluoro-4-(5-(piperazin-1-ilmetil)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)urea



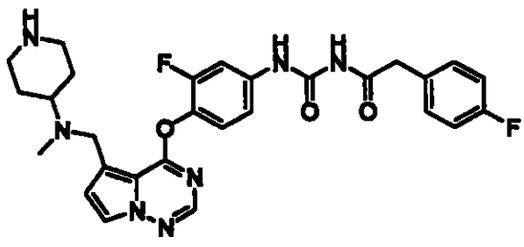
A) 3-Fluoro-4-(5-(piperazin-1-ilmetil)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)bencenamina

Preparado en una forma similar como en la Etapa C del Ejemplo 154 para dar el compuesto del título como un aceite amarillo. EM(ESI$^+$) m/z 443.3 $(M + H)^+$.

B) 1-(3-Fluoro-4-(5-(piperazin-1-ilmetil)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)urea

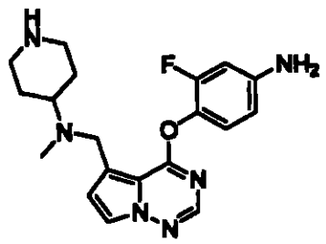
Preparado en una forma similar como en el Ejemplo 155 para dar el compuesto del título (6%) como un sólido blanco. ^{1}H RMN (DMSO-d_6) δ 11.00 (s, 1H), 10.55 (s, 1H), 8.12 (s, 1H), 8.11 (d, m, J= 2.8 Hz), 7.71 (dd, 1H, J= 12.8, 2.4 Hz), 7.42 (t, 1H, J= 8.8 Hz), 7.35-7.28 (m, 3H), 7.11 (t, 2H, J= 9.2 Hz), 7.03 (m, 1H), 4.58 (s, 2H), 3.69 (s, 2H), 3.66-3.59 (m, 4H), 3.32-3.05 (m, 4H); EM(ESI$^+$) m/z 522.3 $(M + H)^+$.

EJEMPLO 161



508

1-(3-Fluoro-4-(5-((metil(piperidin-4-il)amino)metil)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)urea



A) N-((4-(4-Amino-2-fluorofenoxi)pirrolo[2,1-f][1,2,4]triazin-5-il)metil)-N-metilpiperidin-4-amina

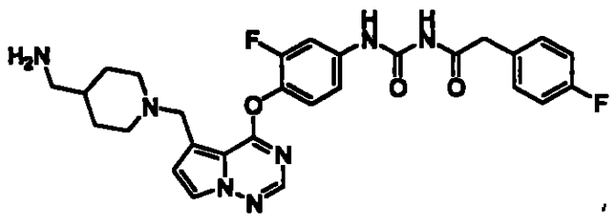
Preparado en una forma similar como en la Etapa C del Ejemplo 154 para dar el compuesto del título (38%) como un aceite amarillo. EM(ESI$^+$) m/z 471.3 $(M + H)^+$.

B) 1-(3-Fluoro-4-(5-((metil(piperidin-4-il)amino)metil)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)urea

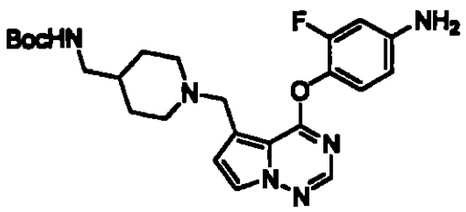
Preparado en una forma similar como en el Ejemplo 155 para dar el compuesto del título (32%) como un sólido blanco. ^{1}H RMN (DMSO-d_6) δ 11.00 (s, 1H), 10.55 (s, 1H), 8.19 (s, 1H), 8.16 (d, 1H, J= 2.4 Hz), 7.71 (dd, 1H, J= 12.4, 2 Hz), 7.42-7.34 (m, 2H), 7.32-7.28 (m, 2H), 7.16-7.06 (m, 3H), 4.44 (s, 2H), 3.69 (s, 2H), 3.64-3.59 (m, 4H), 2.87-2.84 (m, 1H), 2.72 (s, 3H), 2.19-2.15 (m, 2H), 1.87-1.82 (m, 2H); EM(ESI$^+$) m/z 550.3 $(M+H)^+$.

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EJEMPLO 162



1-(4-(5-((4-(Aminometil)piperidin-1-il)metil)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea



A) (1-((4-(4-Amino-2-fluorofenoxi)pirrolo[2,1-f][1,2,4]triazin-5-il)metil)piperidin-4-il)metilcarbamato de tert-butilo

Preparado en una forma similar como en la Etapa C del Ejemplo 154 para dar el compuesto del título (29%) como un aceite amarillo. EM(ESI$^+$) m/z 471.3 $(M + H)^+$.

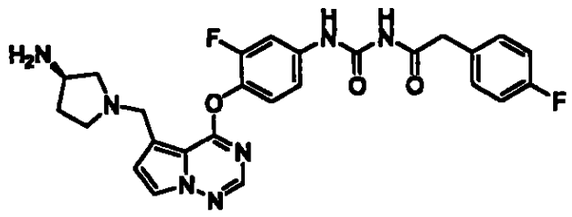
B) 1-(4-(5-((4-(Aminometil)piperidin-1-il)metil)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea

Preparado en una forma similar como en el Ejemplo 155 para dar el compuesto del título (26%) como un sólido blanco.

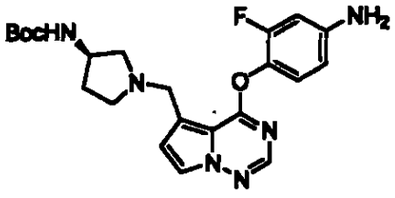
510

^{1}H RMN (DMSO-d_6) δ 11.01 (s, 1H), 10.53 (s, 1H), 7.99 (s, 1H), 7.97 (d, 1H, J= 2.4 Hz), 7.66 (dd, 1H, J= 13.2, 2.4 Hz), 7.36-7.28 (m, 4H), 7.09 (t, 2H, J= 8.8 Hz), 6.82 (d, 1H, J= 2.4 Hz), 3.77 (s, 2H), 3.68 (s, 2H), 3.84-3.82 (m, 2H), 2.38-2.36 (m, 1H), 1.88 (t, 2H, J= 10 Hz), 1.58-1.55 (m, 2H), 1.20-1.01 (m, 4H); EM(ESI$^+$) m/z 550.2 $(M + H)^+$.

EJEMPLO 163



(R)-1-(4-(5-((3-Aminopirrolidin-1-il)metil)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea



A) 1-((4-(4-Amino-2-fluorofenoxi)pirrolo[2,1-f][1,2,4]triazin-5-il)metil)pirrolidin-3-ilcarbamato de (R)-tert-Butilo

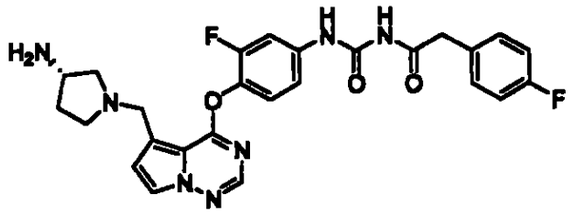
Preparado en una forma similar como en la Etapa C del Ejemplo 154 para dar el compuesto del título (30%) como un

aceite amarillo. EM(ESI$^+$) m/z 443.3 $(M + H)^+$.

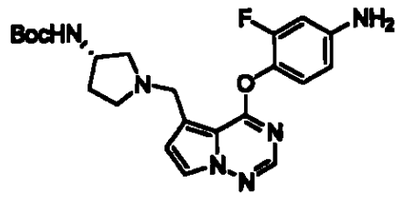
B) (R)-1-(4-(5-((3-Aminopirrolidin-1-il)metil)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea

Preparado en una forma similar como en el Ejemplo 155 para dar el compuesto del título (11%) como un sólido blanco. ^{1}H RMN (DMSO-d_6) δ 10.54 (s, 1H), 10.21 (s, 1H), 7.99 (s, 1H), 7.98 (d, 1H, J=2.4 Hz), 7.67 (dd, 1H, J= 12.4, 2 Hz), 7.40-7.26 (m, 3H), 7.13-7.07 (m, 3H), 6.84 (d, 1H, J= 2.8 Hz), 3.90 (s, 2H), 3.68 (s, 2H), 2.67-2.41 (m, 3H), 2.20-2.16 (m, 2H), 1.96-1.91 (m, 1H), 1.32-1.29 (m, 1H); EM(ESI$^+$) m/z 522.2 $(M + H)^+$.

EJEMPLO 164



(S)-1-(4-(5-((3-Aminopirrolidin-1-il)metil)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea



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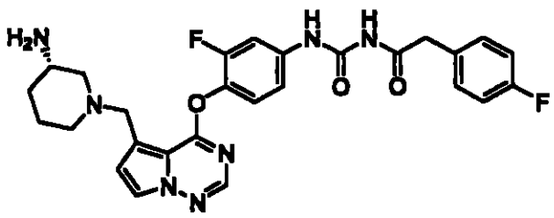
A) 1-((4-(4-Amino-2-fluorofenoxi)pirrolo[2,1-f][1,2,4]triazin-5-il)metil)pirrolidin-3-ilcarbamato de (S)-tert-Butilo

Preparado en una forma similar como en la Etapa C del Ejemplo 154 para dar el compuesto del título (30%) como un aceite amarillo. EM(ESI$^+$) m/z 443.3 $(M + H)^+$.

B) (S)-1-(4-(5-((3-Aminopirrolidin-1-il)metil)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea

Preparado en una forma similar como en el Ejemplo 155 para dar el compuesto del título (7%) como un sólido blanco. ^{1}H RMN (DMSO-d_6) δ 10.54 (s, 1H), 10.21 (s, 1H), 7.99 (s, 1H), 7.98 (d, 1H, J= 2.4 Hz), 7.67 (dd, 1H, J= 12.4, 2 Hz), 7.40-7.26 (m, 3H), 7.13-7.07 (m, 3H), 6.84 (d, 1H, J= 2.8 Hz), 3.90 (s, 2H), 3.68 (s, 2H), 2.67-2.41 (m, 3H), 2.20-2.16 (m, 2H), 1.96-1.91 (m, 1H), 1.32-1.29 (m, 1H); EM(ESI$^+$) m/z 522.2 $(M + H)^+$.

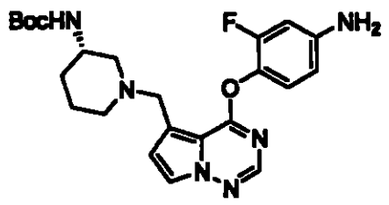
EJEMPLO 165



(S)-1-(4-(5-((3-Aminopiperidin-1-il)metil)pirrolo[2,1-

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f][1,2,4]triazin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea



A) 1-((4-(4-Amino-2-fluorofenoxi)pirrolo[2,1-f][1,2,4]triazin-5-il)metil)piperidin-3-ilcarbamato de (S)-tert-Butilo

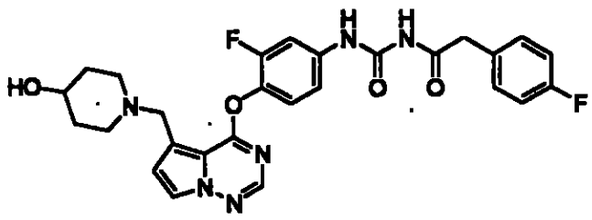
Preparado de forma similar como en la Etapa C del Ejemplo 154 para dar el compuesto del título (40%) como un aceite amarillo. EM(ESI$^+$) m/z 457.3 $(M + H)^+$.

B) (S)-1-(4-(5-((3-Aminopiperidin-1-il)metil)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea

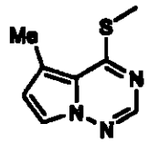
Preparado en una forma similar como en el Ejemplo 155 para dar la sal de TFA del compuesto del título (29%) como un sólido blanco. ^{1}H RMN (DMSO-d_6) δ 11.00 (s, 1H), 10.55 (s, 1H), 8.15 (m, 2H), 7.71 (dd, 1H, J= 12.4, 2 Hz), 7.41 (t, 1H, J= 8.4 Hz), 7.35-7.28 (m, 3H), 7.11 (t, 2H, J= 8.8 Hz), 7.05 (d, 1H, J= 2.8 Hz), 4.58 (s, 2H), 3.69 (s, 2H), 3.66-3.30 (m, 5H), 1.95-1.83 (m, 2H), 1.67-1.53 (m, 1H), 1.40-1.32 (m, 1H); EM(ESI$^+$) m/z 536.2 $(M + H)^+$.

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EJEMPLO 166

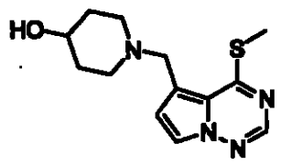


1-(3-Fluoro-4-(5-((4-hidroxipiperidin-1-il)metil)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)urea, sal del ácido trifluoroacético



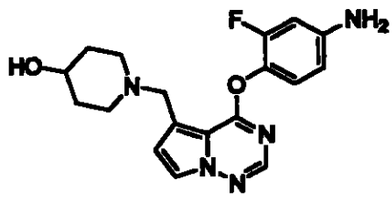
A) 5-Metil-4-metilsulfanil-pirrolo[2,1-f][1,2,4]triazina

A una solución de 4-cloro-5-metil-pirrolo[2,1-f][1,2,4]triazina (4.02 g, 24.0 mmol, WO 03/042172) en THF seco (200 mL) se burbujeó con N_2 a 0°C se le agregó NaSMe (1.85 g, 26.3 mmol). El burbujeado se continuó durante 5 minutos. La mezcla de reacción se agitó luego a temperatura ambiente durante la noche, se concentró in vacuo hasta aproximadamente 50 mL volumen, se diluyó con H_2O (280 mL) y se agitó a 0°C. El sólido se filtró, se lavó con agua fría, se secó para dar el producto deseado (3.91 g, 91%). Tiempo de retención CLAR analítico =3.38 minutos. (YMC S5 ODS columna 4.6 x 50 mm, 10-90% metanol acuoso durante 4 minutos que contiene ácido fosfórico 0.2% , 4 ml/min, monitoreado a 220 nm); EM(ESI$^+$) m/z 180 $(M + H)^+$.



B) 1-((4-(Metiltio)pirrolo[2,1-f][1,2,4]triazin-5-il)metil)piperidin-4-ol

Una solución de 5-metil-4-metilsulfanil-pirrolo[2,1-f][1,2,4]triazina (200 mg, 1.12 mmol), NBS (218 mg, 1.23 mmol), y AIBN (punta de espátula) en tetracloruro de carbono (4 mL) se calentó a 80°C durante 1 hora. Después de enfriar a temperatura ambiente, la solución se filtró para eliminar succinimida. Al filtrado se le agregó 4-hidroxipiperidina (126 mg, 1.34 mmol, Aldrich) y DIPEA (214 µL, 1.23 mmol). La reacción se agitó a temperatura ambiente durante la noche y se concentró luego in vacuo. El residuo se suspendió en metanol y se filtró. El filtrado se concentró y el producto crudo se purificó por cromatografía instantánea en gel de sílice (20% MeOH / EtOAc) para dar el compuesto del título (229 mg, 74%) como un sólido incoloro. ^{1}H RMN (DMSO-d_6) δ 8.25 (s, 1H), 7.88 (d, 1H, J= 2 Hz), 6.81 (d, 1H, J= 2 Hz), 4.54 (br s, 1H), 3.76 (s, 2H), 3.48-3.44 (m, 1H), 2.75-2.71 (m, 2H), 2.62 (s, 3H), 2.10-2.08 (m, 2H), 1.70-1.68 (m, 2H), 1.38-1.36 (m, 2H); EM(ESI$^+$) m/z 279.3 $(M + H)^+$.



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C) 1-((4-(4-Amino-2-fluorofenoxi)pirrolo[2,1-f][1,2,4]triazin-5-il)metil)piperidin-4-ol

A 1-((4-(metiltio)pirrolo[2,1-f][1,2,4]triazin-5-il)metil)piperidin-4-ol (188 mg, 0.675 mmol) en diclorometano (7 mL) a 0°C se le agregó TFA (78 µL, 1.01 mmol) seguido por m-CPBA (166 mg, 0.675 mmol, ~70% puro). Después de agitar a temperatura ambiente 0°C durante 1 hora, la mezcla se concentró in vacuo. Éter (20 mL) se le agregó y luego se decantó completamente para eliminar el ácido benzoico. El sulfóxido crudo resultante se secó bajo alto vacío. 4-Amino-2-fluorofenol (343 mg, 2.7 mmol) se disolvió en THF (10 mL), se enfrió a -78°C, y se cargó con NaHMDS (2.7 mL, 2.7 mmol, 1 M en THF). Después de agitar a 0°C durante 5 minutos, el sulfóxido crudo en THF (3 mL) se le agregó. La reacción se agitó a 0°C durante 30 minutos y se concentró luego in vacuo. El residuo se suspendió en EtOAc (20 mL), se lavó con agua (10 mL), se secó sobre sulfato de sodio anhidro, y se concentró in vacuo. El producto crudo se purificó por CLAR preparativa de fase inversa y las fracciones apropiadas se concentraron in vacuo para eliminar metanol. La solución acuosa resultante se hizó básica con solución de bicarbonato

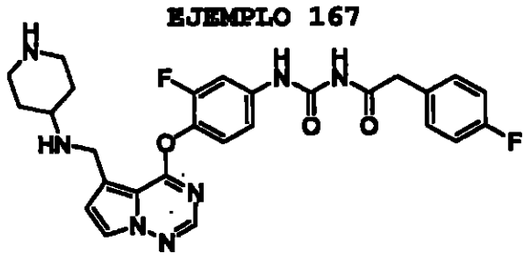
de sodio acuoso al 5% y se extrajo con EtOAc (3x10 mL). Los extractos combinados se secaron sobre sulfato de sodio anhidro y se concentraron in vacuo para dar 36 mg (15%) del compuesto del título como un sólido blanco. ^{1}H RMN (DMSO-d_6) δ 8.04 (s, 1H), 8.00 (d, 1H, J= 2.8 Hz), 7.02 (t, 1H, J= 8.8 Hz), 6.88 (d, 1H, J= 2.8 Hz), 6.51 (dd, 1H, J= 12.8, 2.8 Hz), 6.46-6.42 (m, 1H), 5.45 (br s, 2H), 3.83 (s, 2H), 3.18 (m, 1H), 2.76-2.71 (m, 2H), 2.12-2.06 (m, 2H), 1.72-1.67 (m, 2H), 1.41-1.38 (m, 2H); EM(ESI$^+$) m/z 358.4 $(M + H)^+$.

D) 1-(3-Fluoro-4-(5-((4-hidroxipiperidin-1-il)metil)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)urea, sal del ácido trifluoroacético

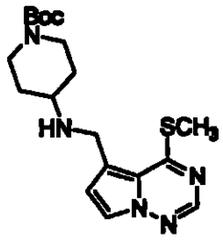
Preparado en una forma similar como en el Ejemplo 155 para dar la sal TFA del compuesto del título (12%) como un sólido blanco. ^{1}H RMN (DMSO-d_6) δ 11.00 (s, 1H), 10.55 (s, 1H), 8.18 (s, 1H), 8.16-8.14 (m, 1H), 7.71 (d, 1H, J= 12.4 Hz), 7.41-7.28 (m, 4H), 7.11-7.08 (m, 3H), 4.59-4.54 (m, 2H), 3.68 (s, 2H), 3.60-3.00 (m, 5H), 1.92-1.87 (m, 1H), 1.81-1.68 (m, 2H), 1.53-1.48 (m, 1H); EM(ESI$^+$) m/z 537.2 $(M + H)^+$.

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EJEMPLO 167

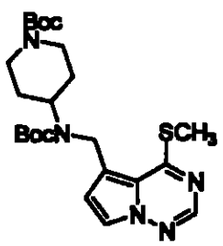


1-(3-Fluoro-4-(5-((piperidin-4-ilamino)metil)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)urea



A) 4-((4-(Metiltio)pirrolo[2,1-f][1,2,4]triazin-5-il)metilamino)piperidin-1-carboxilato de tert-Butilo

Preparado en una forma similar como en la Etapa A del Ejemplo 166 para dar el compuesto del título (50%) como un aceite incoloro. ^{1}H RMN (CD_3OD) δ 8.14 (s, 1H), 7.73 (d, 1H, J = 2.8 Hz), 6.91 (d, 1H, J= 2.8 Hz), 4.21 (s, 2H), 4.10-4.07 (m, 2H), 2.83-2.77 (m, 3H), 2.71 (s, 3H), 1.99-1.97 (m, 2H), 1.48 (s, 9H), 1.34-1.31 (m, 2H); EM(ESI$^+$) m/z 378.3 $(M+H)^+$.

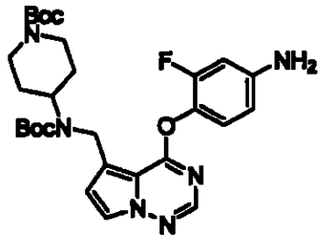


B) Éster de tert-butilo del ácido 4-[tert-Butoxicarbonil-

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(4-metilsulfanil-pirrolo[2,1-f][1,2,4]triazin-5-ilmetil)-amino]-piperidin-1-carboxílico

4-((4-(Metiltio)pirrolo[1,2-f][1,2,4]triazin-5-il)metilamino)piperidin-1-carboxilato de tert-butilo (210 mg, 0.556 mmol) se disolvió en diclorometano (5 mL) y se agregó trietilamina (120 µL, 0.834 mmol) seguido por dicarbonato de di-tert-butilo (134 mg, 0.612 mmol). Después de agitar a temperatura ambiente durante 8 horas, la reacción se diluyó con cloruro de metileno (20 mL), se lavó con solución de cloruro de amonio acuosa saturada (10 mL), se secó sobre sulfato de sodio anhidro, y se concentró in vacuo. El producto crudo se purificó por cromatografía instantánea en gel de sílice (20% EtOAc / hexanos) para dar el compuesto del título (207 mg, 78%) como un aceite incoloro. ^{1}H RMN ($CDCl_3$) δ 8.01 (s, 1H), 7.51 (d, 1H, J= 2.8 Hz), 6.57 (d, 1H, J = 2.8 Hz), 4.71 (s, 2H), 4.06-4.04 (m, 3H), 2.68-2.61 (m, 2H), 2.61 (s, 3H), 1.60-1.57 (m, 2H), 1.46-1.36 (m, 2H), 1.35 (s, 18H); EM(ESI$^+$) m/z 478.2 $(M + H)^+$.



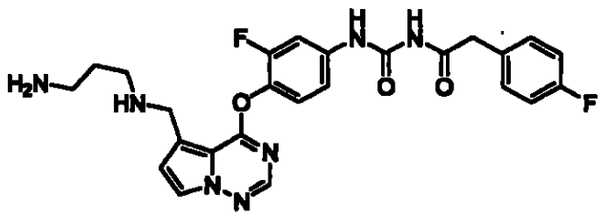
C) Éster de tert-butilo del ácido 4-{[4-(4-Amino-2-fluoro-fenoxi)-pirrolo[2,1-f][1,2,4]triazin-5-ilmetil]-tert-butoxicarbonil-amino}-piperidin-1-carboxílico

Preparado en una forma similar como en la Etapa C del Ejemplo 166 para dar el compuesto del título (43%) como un aceite incoloro. ^{1}H RMN ($CDCl_3$) δ 7.84 (s, 1H), 7.62 (d, 1H, J= 2.8 Hz), 6.98 (t, 1H, J= 8.8 Hz), 6.70 (d, 1H, J= 2.8 Hz), 6.47-6.41 (m, 2H), 4.72 (s, 2H), 4.10-4.04 (m, 2H), 3.77-3.75 (m, 1H), 2.62-2.60 (m, 2H), 1.71-1.38 (m, 4H), 1.35 (s, 18H); EM(ESI$^+$) m/z 557.2 $(M + H)^+$.

D) 1-(3-Fluoro-4-(5-((piperidin-4-ilamino)metil)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)urea

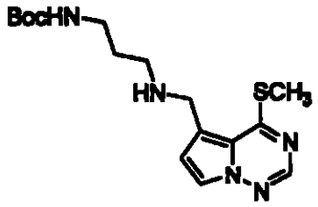
Preparado en una forma similar como en el Ejemplo 155 para dar el compuesto del título (34%)como un sólido blanco. ^{1}H RMN (DMSO-d_6) δ 11.01 (s, 1H), 10.55 (s, 1H), 8.16 (s, 1H), 8.12 (d, 1H, J= 2.4 Hz), 7.71 (dd, 1H, J= 12.4, 2 Hz), 7.42-7.28 (m, 4H), 7.18-7.08 (m, 3H), 4.51 (s, 2H), 3.69 (s, 2H), 3.50-3.29 (m, 3H), 2.88-2.85 (m, 2H), 2.23-2.18 (m, 2H), 1.72-1.64 (m, 2H); EM(ESI$^+$) m/z 536.2 $(M + H)^+$.

EJEMPLO 168



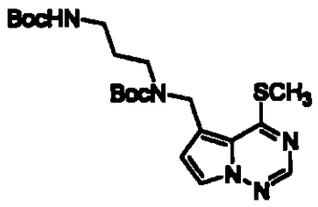
1-(4-(5-((3-Aminopropilamino)metil)pirrolo[2,1-

f][1,2,4]triazin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea



A) 3-((4-(metiltio)pirrolo[2,1-f][1,2,4]triazin-5-il)metilamino)propilcarbamato de tert-butilo

Preparado en una forma similar como en la Etapa B del Ejemplo 166 para dar el compuesto del título (51%) como un sólido amarillo. ^{1}H RMN (CD_3OD) δ 8.16 (s, 1H), 7.75 (d, 1H, J = 2.4 Hz), 6.94 (d, 1H, J= 2.8 Hz), 4.30 (s, 2H), 3.14 (t, 2H, J= 6.4 Hz), 2.83 (t, 2H, J= 7.2 Hz), 2.72 (s, 3H), 1.82-1.75 (m, 2H), 1.40 (s, 9H); EM(ESI$^+$) m/z 352.3 $(M + H)^+$.

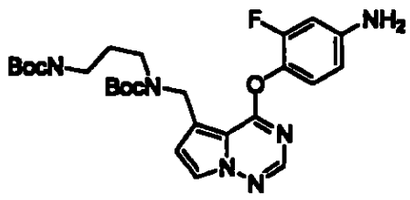


B) éster de tert-butilo del ácido {3-[tert-Butoxicarbonil-(4-metilsulfanil-pirrolo[2,1-f][1,2,4]triazin-5-ilmetil)-amino]-propil}-carbámico

Preparado en una forma similar a la Etapa B del Ejemplo 167 para dar el compuesto del título (77%) como un aceite amarillo pálido. ^{1}H RMN ($CDCl_3$) δ 8.14 (s, 1H), 7.73 (d, 1H, J = 2.4 Hz), 6.75 (d, 1H, J= 2 Hz), 4.88 (s,

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2H), 3.29-3.25 (m, 2H), 3.04-3.02 (m, 2H), 2.71 (s, 3H), 1.72-1.68 (m, 2H), 1.54 (s, 9H), 1.42 (s, 9H); EM(ESI$^+$) m/z 452.2 $(M + H)^+$.



C) Éster de tert-butilo del ácido (3-{[4-(4-amino-2-fluoro-fenoxi)-pirrolo[2,1-f][1,2,4]triazin-5-ilmetil]-tert-butoxicarbonil-amino}-propil)-carbámico

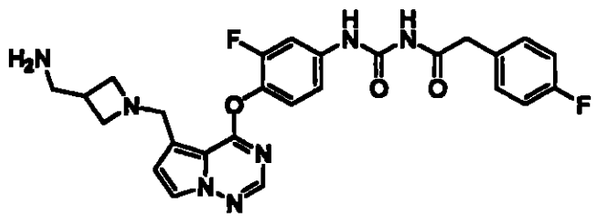
Preparado en una forma similar como en la Etapa C del Ejemplo 166 para dar el compuesto del título (29%) como un aceite incoloro. ^{1}H RMN ($CDCl_3$) δ 7.85 (s, 1H), 7.64 (d, 1H, J= 2.8 Hz), 7.00 (t, 1H, J= 8.8 Hz), 6.82-6.78 (m, 1H), 6.62 (dd, 1H, J= 12.8, 2.4 Hz), 6.54-6.51 (m, 1H), 4.72 (m, 2H), 3.28-3.23 (m, 2H), 3.02-3.00 (m, 2H), 1.58-1.55 (m, 2H), 1.43 (s, 9H), 1.35 (s, 9H); EM(ESI$^+$) m/z 531.2 $(M + H)^+$.

D) 1-(4-(5-((3-Aminopropilamino)metil)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea

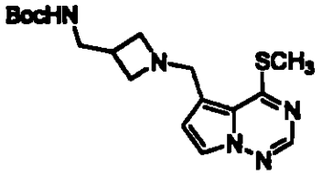
Preparado en una forma similar como en el Ejemplo 155 para dar el compuesto del título (17%) como un sólido blanco. ^{1}H RMN (DMSO-d_6) δ 11.01 (s, 1H), 10.52 (s, 1H),

8.00 (s, 1H), 7.98 (d, 1H, J= 2.8 Hz), 7.68 (dd, 1H, J= 12.8, 2.4 Hz), 7.34-7.28 (m, 4H), 7.13 (t, 2H, J= 9.2 Hz), 6.84 (d, 1H, J= 2.4 Hz), 3.68 (s, 2H), 3.52 (s, 2H), 2.90-2.85 (m, 2H), 2.28-2.20 (m, 2H), 1.35-1.30 (m, 2H); EM(ESI$^+$) m/z 510.2 $(M + H)^+$.

EJEMPLO 169



1-(4-(5-((3-(Aminometil)azetidin-1-il)metil)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea

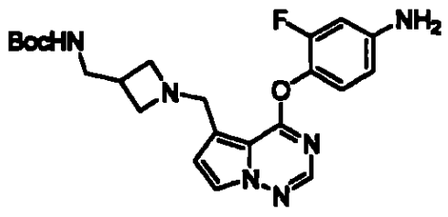


A) (1-((4-(Metiltio)pirrolo[2,1-f][1,2,4]triazin-5-il)metil)azetidin-3-il)metilcarbamato de tert-butilo

Preparado en una forma similar como en la Etapa B del Ejemplo 166 para dar el compuesto del título (31%) como un sólido blanco. ^{1}H RMN (CD_3OD) δ 8.12 (s, 1H), 7.72 (d, 1H, J= 2.4 Hz), 6.81 (d, 1H, J= 2.8 Hz), 4.07 (s, 2H), 3.46 (t, 2H, J= 8 Hz), 3.34-3.33 (m, 1H), 3.20-3.18 (m, 2H), 3.08 (t, 2H,

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J= 7.6 Hz), 2.65 (s, 3H), 1.44 (s, 9H); EM(ESI$^+$) m/z 364.3 (M + H)$^+$.



B) (1-((4-(4-amino-2-fluorofenoxi)pirrolo[2,1-f][1,2,4]triazin-5-il)metil)azetidin-3-il)metilcarbamato de tert-butilo

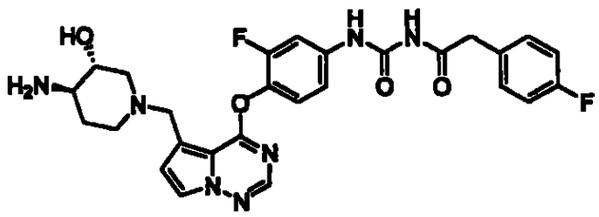
Preparado en una forma similar como en la Etapa C del Ejemplo 166 para dar el compuesto del título (33%) como un sólido café. EM(ESI$^+$) m/z 443.2 (M + H)$^+$.

C) 1-(4-(5-((3-(Aminometil)azetidin-1-il)metil)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea

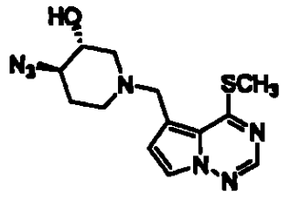
Preparado en una forma similar como en el Ejemplo 155 para dar el compuesto del título (4%) como un sólido blanco. ^{1}H RMN (DMSO-d_6) δ 11.02 (s, 1H), 10.56 (s, 1H), 8.18-8.15 (m, 2H), 7.68 (dd, 1H, J= 12.8, 2.4 Hz), 7.45-7.28 (m, 4H), 7.18-7.08 (m, 3H), 4.67 (s, 2H), 4.44-4.41 (m, 2H), 4.05-3.98 (m, 2H), 3.69 (s, 2H), 3.10-2.97 (m, 3H); EM(ESI$^+$) m/z 522.3 (M + H)$^+$.

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EJEMPLO 170

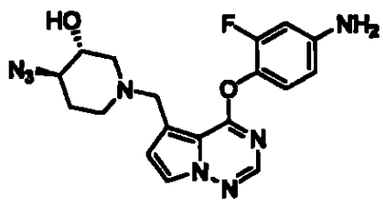


1-(4-(5-(((3R,4R)-4-Amino-3-hidroxipiperidin-1-il)metil)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea



A) (3R,4R)-4-Azido-1-((4-(metiltio)pirrolo[2,1-f][1,2,4]triazin-5-il)metil)piperidin-3-ol

Preparado en una forma similar como en la Etapa B del Ejemplo 166 para dar el compuesto del título (65%) como una espuma amarilla. ^{1}H RMN (CD_3OD) δ 8.36 (s, 1H), 7.99 (d, 1H, J = 2.4 Hz), 6.93 (d, 1H, J= 2.8 Hz), 3.92-3.88 (m, 2H), 3.35-3.30 (m, 1H), 3.08-2.90 (m, 2H), 2.72 (s, 3H), 2.14-2.10 (m, 2H), 2.00-1.91 (m, 2H), 1.47-1.44 (m, 1H); EM(ESI$^+$) m/z 320.2 $(M + H)^+$.



B) (3-R,4R)-1-((4-(4-Amino-2-fluorofenoxi)pirrolo[2,1-f][1,2,4]triazin-5-il)metil)-4-azidopiperidin-3-ol

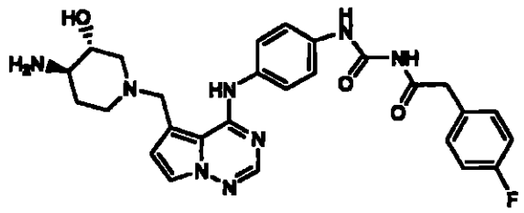
Preparado en una forma similar como en la Etapa C del Ejemplo 166 para dar el compuesto del título (24%) como un sólido café. EM(ESI$^+$) m/z 399.2 $(M + H)^+$.

C) 1-(4-(5-(((3R,4R)-4-Amino-3-hidroxipiperidin-1-il)metil)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea

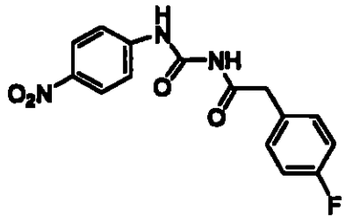
El acilurea se preparó en una forma similar como en el Ejemplo 155 para dar la azida correspondiente (48%). EM(ESI$^+$) m/z 578.16 $(M + H)^+$. La azida (35 mg, 0.06 mmol) se disolvió luego en acetato de etilo (1 mL) a 0°C y se cargó con trimetilfosfina (0.11 mL, 0.11 mmol) seguido por agua (1 gota). Después de agitar a temperatura ambiente durante 3 horas, la reacción se concentró in vacuo y se purificó por CLAR preparativa de fase inversa. Las fracciones apropiadas se concentraron in vacuo y se le agregó tolueno (2 x 2 mL) y se concentró para dar la sal TFA del compuesto del título (8 mg, 17%) como un sólido blanco. ^{1}H RMN (DMSO-d_6) δ 11.00 (s, 1H), 10.55 (s, 1H), 8.18-8.16 (m, 2H), 7.72 (dd, 1H, J= 12.8, 2.4 Hz), 7.36-7.28 (m, 4H), 7.14-7.09 (m, 3H), 4.62 (s, 2H), 3.69 (s, 2H), 3.22-2.85 (m, 6H), 2.03-1.98 (m, 1H), 1.68-1.65 (m, 1H); EM(ESI$^+$) m/z 510.2 $(M+H)^+$.

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EJEMPLO 171



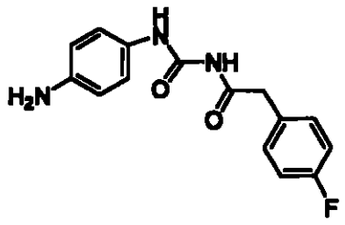
1-(4-(5-(((3R,4R)-4-Amino-3-hidroxipiperidin-1-il)metil)pirrolo[2,1-f][1,2,4]triazin-4-ilamino)fenil)-3-(2-(4-fluorofenil)acetil)urea



A) 1-(2-(4-Fluorofenil)acetil)-3-(4-nitrofenil)urea

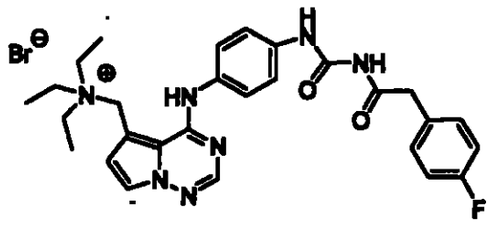
A una solución agitada de p-nitroanilina (200 mg, 1.45 mmol) en tetrahidrofurano (1 mL) a temperatura ambiente se agregó isocianato de 2-(4-fluorofenil)acetilo (2 mL, 0.32 M en tolueno, Compuesto C del Ejemplo 4). Después de 18 horas, la mezcla se concentró in vacuo y el residuo se disolvió en acetato de etilo (5 mL). La solución se concentró lentamente en rotoevaporador sin calentamiento. Cuando un precipitado comenzó a formarse, el matraz se retiró del rotoevaporador y se permitió agitar durante 2 horas. El sólido formado se filtró y se lavó con cantidad pequeña de acetato de etilo y se secó in vacuo para proporcionar un compuesto cristalino

amarillo brillante (200 mg, 44%). EM(ESI$^+$) m/z 318.3 (M + H)$^+$.



B) 1-(4-Aminofenil)-3-(2-(4-fluorofenil)acetil)urea

A una solución de 1-(2-(4-fluorofenil)acetil)-3-(4-nitrofenil)urea (200 mg, 0.63 mmol) en acetato de etilo (10 mL) se le agregó paladio sobre carbono 10% (15 mg) y el matraz se llenó con hidrógeno usando un globo. La mezcla se agitó durante 18 horas, se filtró y el catalizador se lavó con acetato de etilo. El filtrado se concentró in vacuo para dar un sólido el cual se trituró con una cantidad pequeña de éter y se secó in vacuo hasta obtener el compuesto deseado (180 mg) como un sólido amarillo pálido. EM(ESI$^+$) m/z 287.4 (M+H)$^+$.



C) Bromuro de N,N-dietil-N-((4-(4-(3-(2-(4-fluorofenil)acetil)ureido)fenilamino)pirrolo[2,1-f][1,2,4]triazin-5-il)metil)etanaminio

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A una solución de bromuro de (4-cloro-pirrolo[2,1-f][1,2,4]triazin-5-ilmetil)-trietilamonio (75 mg, 0.22 mmol, Compuesto B del Ejemplo 154) en cloroformo (1.5 mL) se le agregó 1-(4-aminofenil)-3-(2-(4-fluorofenil)acetil)urea (50 mg, 0.17 mmol) y la mezcla se calentó a reflujo durante 6 horas. La mezcla se enfrió a temperatura ambiente, se concentró in vacuo y el residuo se trituró con acetonitrilo. El sólido resultante se usó en la siguiente Etapa sin purificación.

D) 1-(4-(5-(((3R,4R)-4-Azido-3-hidroxipiperidin-1-il)metil)pirrolo[2,1-f][1,2,4]triazin-4-ilamino)fenil)-3-(2-(4-fluorofenil)acetil)urea

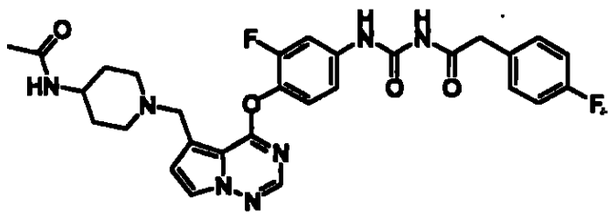
A una solución de bromuro de N,N-dietil-N-((4-(4-(3-(2-(4-fluorofenil)acetil)ureido)fenilamino)pirrolo[2,1-f][1,2,4]triazin-5-il)metil)etanaminio crudo en cloroformo (3 mL), se agregaron (3R,4R)-4-azidopiperidin-3-ol (0.28 mg, 0.2 mmol, WO 04/058144) y trietilamina (0.2 mL). La mezcla de reacción se agitó a 60°C durante 2 horas, se enfrió a temperatura ambiente y se lavó luego con agua. La capa acuosa se extrajo con cloroformo (3 x 8 mL). Los extractos orgánicos combinados se concentraron in vacuo para dar el producto crudo como un sólido amarillo.

El sólido crudo anterior se disolvió en tetrahidrofurano (3 mL), trifenilfosfina (80 mg) y agua (0.02 mL) se agregaron

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y la mezcla de reacción resultante se calentó a reflujo durante 2 horas. La mezcla de reacción se enfrió a temperatura ambiente, se concentró in vacuo y el producto crudo se purificó por CLAR de fase inversa preparativa. Las fracciones apropiadas se colectaron, concentraron y trataron con HCl 1 N (2 mL). La solución se concentró in vacuo, se disolvió en agua y liofilizó hasta obtener el compuesto del título (48 mg, 47% durante tres Etapas) como un sólido blanco. ^{1}H RMN (CD_3OD) δ 7.87 (s, 1H), 7.77 (s, 1H), 7.65 (d, 2H, J= 8.4 Hz), 7.46 (d, 2H, J= 8.3 Hz), 7.28 (dd, 2H, J= 5.4, 8.4 Hz), 7.06 (s, 1H), 6.98 (t, 2 H, J= 8.7 Hz), 4.7 (br s, 2H), 3.9 (br s, 2H), 3.63 (s, 2H), 3.56 (br s, 2H), 3.20-3.10 (br s, 2H), 2.99-2.87 (br s, 1H), 2.96 (br d, 1H, J= 10.8 Hz), 1.91 (br t, J= 10.8 Hz); EM(ESI$^+$) m/z 533.4 (M + H)$^+$.

EJEMPLO 172



1-(4-(5-((4-Acetamidopiperidin-1-il)metil)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea

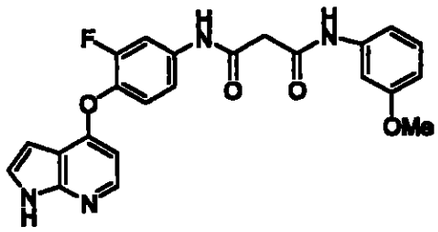
A 1-(4-(5-((4-aminopiperidin-1-il)metil)pirrolo[2,1-

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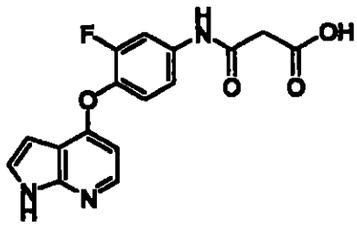
f][1,2,4]triazin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea (30 mg, 0.056 mmol, Ejemplo 155) en cloruro de metileno (1 mL) se le agregó piridina (6 µL, 0.067 mmol) seguido por cloruro de acetilo (5 µL, 0.067 mmol). DMF (0.5 mL) se le agregó para solubilizar la reacción. Después de agitar a temperatura ambiente durante 2 horas, una segunda porción de piridina (6 uL) y cloruro de acetilo (5 µL) se le agregó. Después de agitar a temperatura ambiente durante 1 hora, la reacción se diluyó con acetato de etilo (10 mL), se lavó con solución de cloruro de litio acuosa al 10% seguido por salmuera (1x5 mL cada uno), se secó sobre sulfato de sodio anhidro, y se concentró in vacuo. El producto crudo se purificó por CLAR preparativa de fase inversa. Las fracciones apropiadas se concentraron in vacuo y tolueno se le agregó (2 x 2 mL) y se concentró para dar la sal TFA del compuesto del título (15 mg, 39%) como un sólido blanco. ^{1}H RMN (DMSO-d_6) δ 11.00 (s, 1H), 10.55 (s, 1H), 8.19 (s, 1H), 8.14 (d, 1H, J= 2.8 Hz), 7.89 (d, 1H, J= 7.2 Hz), 7.71 (dd, 1H, J= 12.4, 2.4 Hz), 7.43-7.28 (m, 4H), 7.14-7.07 (m, 3H), 4.54 (s, 2H), 3.68 (s, 2H), 3.45-2.42 (m, 3H), 3.12-3.10 (m, 2H), 1.88-1.85 (m, 2H), 1.73 (s, 3H), 1.52-1.50 (m, 2H); EM(ESI$^+$) m/z 578.2 $(M + H)^+$.

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EJEMPLO 173



N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-(3-metoxifenil)malonamida, sal del ácido trifluoroacético



A) Ácido 3-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenilamino)-3-oxopropanoico

A una solución de 4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorobencenamina (900 mg, 3.7 mmol, Compuesto B del Ejemplo 132) en CH_2Cl_2 (30 mL) a -40°C, se le agregó 3-cloro-3-oxopropanoato de etilo (555 mg, 3.7 mmol, Aldrich), seguido por piridina (1 mL). La mezcla resultante se agitó a -40°C durante 1 hora. La mezcla se diluyó con CH_2Cl_2, se lavó con KH_2PO_4 saturado, y se secó sobre $MgSO_4$. La mezcla se filtró a través de una almohadilla corta de gel de sílice, eluyendo con 2% MeOH/EtOAc para dar un aceite café (1.1 g). El éster se saponificó en EtOH (15 mL) y NaOH (1 N en H_2O, 15 mL) a 0°C durante 1 hora, se neutralizó con HCl 1 N a un pH

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4. EtOH se retiró a partir de la mezcla de reacción a presión reducida y el sólido se colectó por filtración. El sólido se enjuagó luego con H_2O y se secó ($MgSO_4$) para proporcionar el compuesto del título (670 mg, 55%) como un sólido beige. CL/EM(ESI$^+$) m/z 330 $(M + H)^+$.

B) N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-(3-metoxifenil)malonamida, sal del ácido trifluoroacético

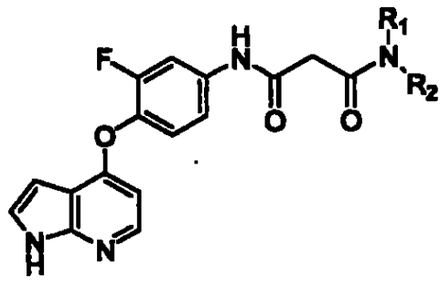
A una solución agitada de ácido 3-(4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenilamino)-3-oxopropanoico (16.5 mg, 0.05 mmol) en DMF (0.4 mL), se le agregó HATU (38 mg, 0.1 mmol), seguido por 3-metoxibencenamina (18 mg, 0.15 mmol) y DMAP (3 mg). La mezcla se calentó a 45°C durante 4 horas. El producto deseado se purificó por CLAR preparativa para dar el compuesto del título (17 mg, 62%) como un sólido blanco. ^{1}H RMN (CD_3OD) δ 8.15 (d, 1H, J= 6.6 Hz), 7.80 (dd, 1H, J= 11.8, 2.2 Hz), 7.41 (d, 1H, J= 3.9 Hz), 7.29-7.38 (m, 2H), 7.23 (m, 1H), 7.12 (t, 1H, J= 8.3 Hz), 7.00 (dd, 1H, J= 8.3, 1.1 Hz), 6.69 (d, 1H, J= 6.6 Hz), 6.60 (dd, m, J= 8.3, 2.2 Hz), 6.51 (d, 1H, J= 3.3 Hz), 3.90 (s, 3H); CLEM(ESI$^+$) m/z 435 $(M + H)^+$.

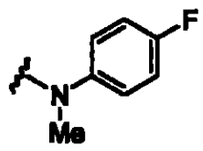
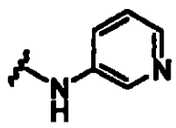
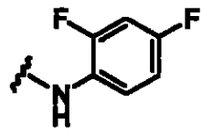
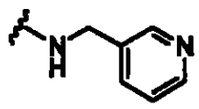
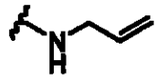
534

EJEMPLOS 174-236

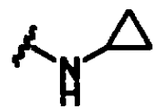
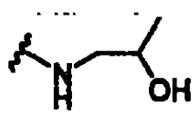
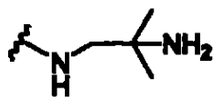
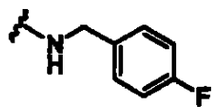
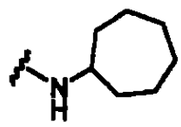
Los ejemplos 174-236 ilustrados en la Tabla 3 se prepararon a partir del ácido 3-(4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenilamino)-3-oxopropanoico (Compuesto A del Ejemplo 173) y las aminas correspondientes, en la presencia de HATU, DIPEA, y DMAP en DMF. Los productos crudos se purificaron por CLAR preparativa (H_2O/MeOH/0.1% TFA, gradiente 35-90% MeOH durante 10 minutos, 20 x 100 mm 5 µm columna YMC ODS-A). Las fracciones se evaporaron centrifugamente, se pesaron y analizaron por CLEM (H_2O/MeOH/0.1% TFA).

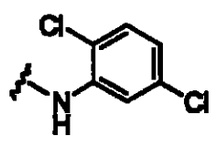
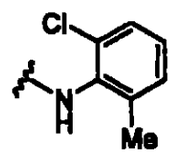
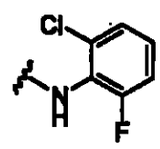
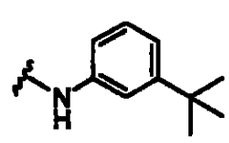
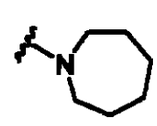
TABLA 3

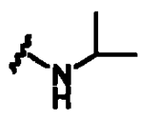
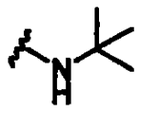
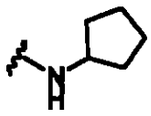
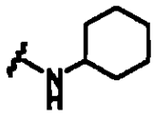
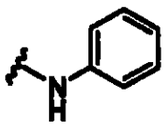


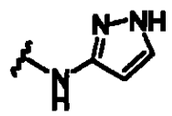
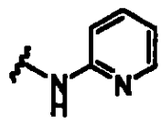
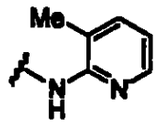
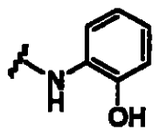
Ejemplo #	NR_1R_2	Nombre del compuesto	CL/EM $(M+H)^+$
174		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-(4-fluorofenil)-N^3-metilmalonamida	437
175		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-(piridin-3-il)malonamida	406
176		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-(2,4-difluorofenil)malonamida	441
177		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-(piridin-3-ilmetil)malonamida	420
178		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-alilmalonamida	369

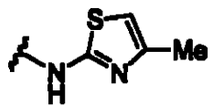
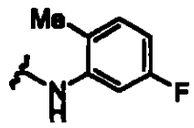
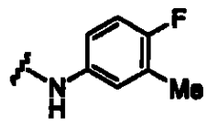
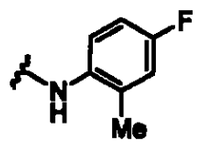
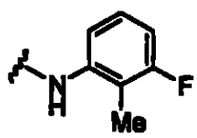
536

Ejemplo #	NR_1R_2	Nombre del compuesto	CL/EM $(M+H)^+$
179		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-ciclopropilmalonamida	369
180		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-(2-hidroxipropil)malonamida	387
181		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-(2-amino-2-metilpropil)malonamida	400
182		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-(4-fluorobencil)malonamida	437
183		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-cicloheptilmalonamida	425

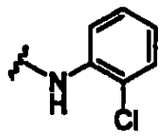
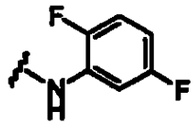
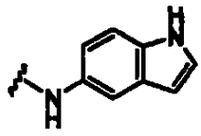
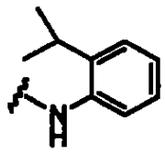
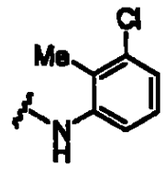
Ejemplo #	NR_1R_2	Nombre del compuesto	CL/EM $(M+H)^+$
184		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-(2,5-diclorofenil)malonamida	474
185		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-(2-cloro-6-metilfenil)malonamida	453
186		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-(2-cloro-6-fluorofenil)-malonamida	457
187		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-(3-tert-butilfenil)malonamida	461
188		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-3-(azepan-1-il)-3-oxopropanamida	411

Ejemplo #	NR_1R_2	Nombre del compuesto	CL/EM $(M+H)^+$
189		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-isopropilmalonamida	371
190		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-tert-butilmalonamida	385
191		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-ciclopentilmalonamida	397
192		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-ciclohexilmalonamida	411
193		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-fenilmalonamida	405

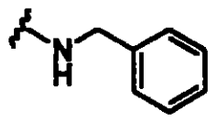
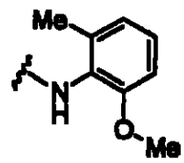
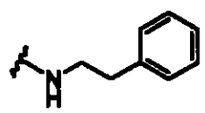
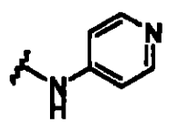
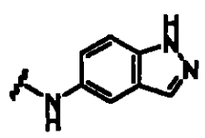
Ejemplo #	NR_1R_2	Nombre del compuesto	CL/EM $(M+H)^+$
194		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-(1H-pirazol-3-il)malonamida	395
195		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-(piridin-2-il)malonamida	406
196		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-(3-metilpiridin-2-il)malonamida	420
197		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-(3,3-dimetilbutil)malonamida	413
198		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-(2-hidroxifenil)malonamida	421

Ejemplo #	NR_1R_2	Nombre del compuesto	CL/EM $(M+H)^+$
199		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-(4-metiltiazol-2-il)malonamida	426
200		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-(5-fluoro-2-metilfenil)malonamida	437
201		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-(4-fluoro-3-metilfenil)-malonamida	437
202		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-(4-fluoro)-2-metilfenil)malonamida	437
203		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-(3-fluoro-2-metilfenil)-malonamida	437

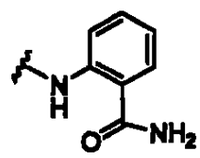
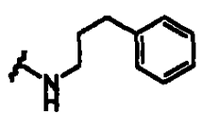
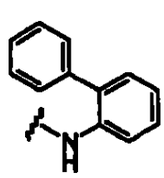
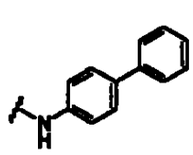
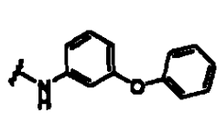
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Ejemplo #	NR_1R_2	Nombre del compuesto	CL/EM $(M+H)^+$
204		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-(2-clorofenil)-malonamida	439
205		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-(2,5-difluorofenil)-malonamida	441
206		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-(1H-indol-5-il)malonamida	444
207		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-(2-isopropilfenil)-malonamida	447
208		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-(3-cloro-2-metilfenil)malonamida	453

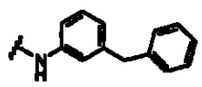
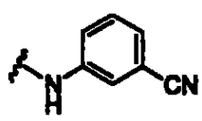
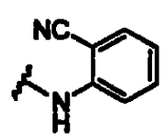
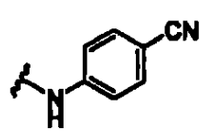
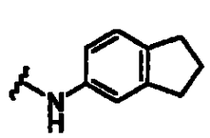
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542

Ejemplo #	NR_1R_2	Nombre del compuesto	CL/EM $(M+H)^+$
209		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-bencilmalonamida	419
210		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-(2-metoxi-6-metilfenil)-malonamida	449
211		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-fenetilmalonamida	433
212		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-(piridin-4-il)malonamida	406
213		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-(1H-indazol-5-il)malonamida	445

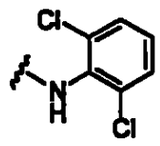
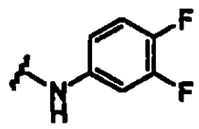
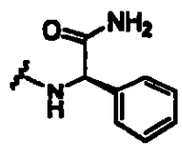
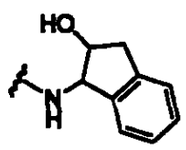
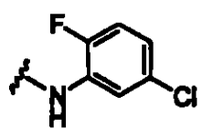
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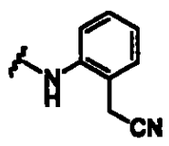
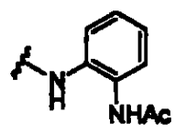
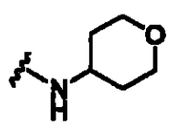
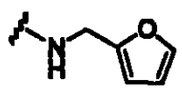
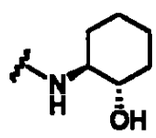
Ejemplo #	NR_1R_2	Nombre del compuesto	CL/EM $(M+H)^+$
214		2-(3-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenilamino)-3-oxopropanamido)benzamida	448
215		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-(3-fenilpropil)malonamida	447
216		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-(2-bifenil)malonamida	481
217		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-(4-bifenil)malonamida	481
218		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-(3-fenoxifenil)malonamida	497

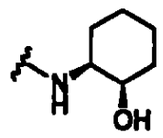
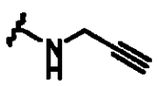
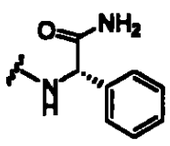
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Ejemplo #	NR_1R_2	Nombre del compuesto	CL/EM $(M+H)^+$
219		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-(3-bencilfenil)malonamida	495
220		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-(3-cianofenil)malonamida	430
221		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-(2-cianofenil)malonamida	430
222		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-(4-cianofenil)malonamida	430
223		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-(2,3-dihidro-1H-inden-5-il)malonamida	445

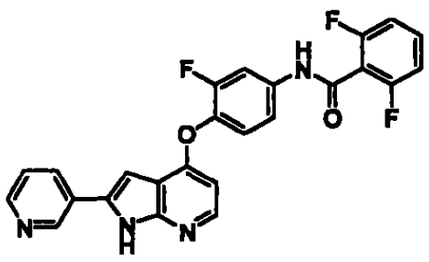
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Ejemplo #	NR_1R_2	Nombre del compuesto	CL/EM $(M+H)^+$
224		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-(2,6-diclorofenil)malonamida	474
225		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-(3,4-difluorofenil)malonamida	441
226		(R)-N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-(2-amino-2-oxo-1-feniletil)malonamida	462
227		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-(2-hidroxi-2,3-dihidro-1H-inden-1-il)malonamida	461
228		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-(5-cloro-2-fluorofenil)-malonamida	457

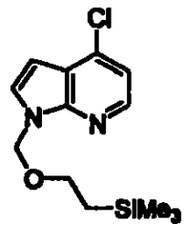
Ejemplo #	NR_1R_2	Nombre del compuesto	CL/EM $(M+H)^+$
229		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-(2-(cianometil)fenil)malonamida	444
230		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-(2-acetamidofenil)malonamida	462
231		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-(tetrahidro-2H-piran-4-il)malonamida	413
232		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-(furan-2-ilmetil)malonamida	409
233		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-(trans-2-hidroxiciclohexil)malonamida	427

Ejemplo #	NR_1R_2	Nombre del compuesto	CL/EM $(M+H)^+$
234		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-(cis-2-hidroxiciclohexil)malonamida	427
235		N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-(prop-2-inil)malonamida	367
236		(S)-N^1-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N^3-(2-amino-2-oxo-1-feniletil)malonamida	462

EJEMPLO 237

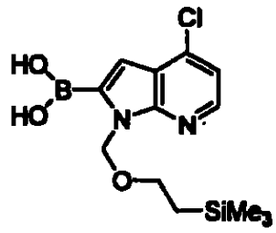


2,6-Difluoro-N-(3-fluoro-4-(2-(piridin-3-il)-1H-pirrolo[2,3-b]piridin-4-iloxi)fenil)benzamida, sal de clorohidrato



A) 4-Cloro-1-((2-(trimetilsilil)etoxi)metil)-1H-pirrolo[2,3-b]piridina

A una solución de 4-cloro-1H-pirrolo[2,3-b]piridina (3.05 g, 20 mmol, se preparó de conformidad con Thibault, C. et al. Org. Lett. 2003, 5, 5023) en DMF (50 mL) a -40°C bajo N_2, se le agregó NaH (60% en aceite mineral, 880 mg, 22 mmol). La mezcla se agitó a temperatura ambiente durante 15 minutos, luego se enfrió hasta -40°C. A esta solución se le agregó (2-(clorometoxi)etil)trimetilsilano (3.67 g, 22 mmol). La mezcla resultante se agitó a temperatura ambiente durante la noche. La mezcla se diluyó con EtOAc, se lavó dos veces con LiCl al 10%, y se secó sobre $MgSO_4$. El compuesto del título se purificó por cromatografía de columna instantánea (gel de sílice, eluyendo con hexano, seguido por Et_2O) para dar el producto deseado (5.6 g, rendimiento cuantitativo) como un aceite. CL/EM(ESI$^+$) m/z 283 $(M + H)^+$.

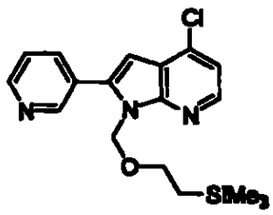


B) Ácido 4-cloro-1-((2-(trimetilsilil)etoxi)metil)-1H-

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pirrolo[2,3-b]piridin-2-ilborónico

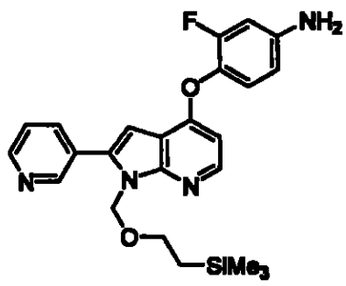
A una solución de 4-cloro-1-((2-(trimetilsilil)etoxi)metil)-1H-pirrolo[2,3-b]piridina (565 mg, 2 mmol) en THF (5 mL) a -40°C bajo N_2, se le agregó n-BuLi (2.0 M en ciclohexano, Aldrich, 2.4 mmol). La mezcla de reacción se agitó a -40°C durante 1 hora y luego se trató con triisopropilborato (489 mg, 2.6 mmol). La mezcla se entibió lentamente a temperatura ambiente y se agitó durante la noche. A esta solución se le agregó HCl 1 N en H_2O (20 mL), y la mezcla se agitó durante 20 minutos, se neutralizó con solución K_2HPO_4 acuosa saturada y se extrajo con éter. La capa orgánica se secó sobre Na_2SO_4. Después de la filtración y la concentración a presión reducida, el compuesto del título se obtuvo como un sólido beige ligero (640 mg, rendimiento cuantitativo). CL/EM(ESI$^+$) m/z 327 $(M+H)^+$.



C) 4-Cloro-2-(piridin-3-il)-1-((2-(trimetilsilil)etoxi)metil)-1H-pirrolo[2,3-b]piridina

El argón se burbujeó a través de una mezcla de ácido 4-cloro-1-((2-(trimetilsilil)etoxi)metil)-1H-pirrolo[2,3-b]piridin-2-ilborónico (5.55 g, 17 mmol), 3-yodopiridina (6.97 g, 34 mmol), $Pd(OAc)_2$, 2-diciclohexilfosfino-2',4',6'-

tri-i-propil-1,1'-bifenilo (405 mg, 0.85 mmol), y K_3PO_4 (2 M en H_2O, 34 mmol) en DME (50 mL) durante 10 minutos y luego se calentó a reflujo durante la noche. La mezcla de reacción se diluyó con EtOAc y se lavó con solución K_2HPO_4 acuosa saturada. El compuesto del título se purificó por cromatografía de columna instantánea (gel de sílice, 20% EtOAc/CH_2Cl_2) para proporcionar el producto deseado (3.2 g, 52% de rendimiento) como un aceite. CL/EM(ESI_+) m/z 361 $(M + H)^+$.

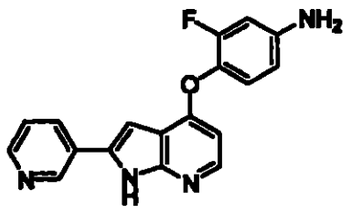


D) 3-Fluoro-4-(2-(piridin-3-il)-1-((2-(trimetilsilil)etoxi)metil)-1H-pirrolo[2,3-b]piridin-4-iloxi)bencenamina

Una mezcla de 4-cloro-2-(piridin-3-il)-1-((2-(trimetilsilil)etoxi)metil)-1H-pirrolo[2,3-b]piridina (3.2 g, 8.9 mmol), 2-fluoro-4-nitrofenol (2.79 g, 17.8 mmol), y DIPEA (3.5 mL, 20 mmol) en NMP (15 mL) se calentó en un tubo sellado a 185°C durante 3 días. La mezcla se diluyó con EtOAc y se filtró a través de una almohadilla corta de Celite® (EtOAc). El filtrado se lavó con solución Na_2CO_3 al 5% y se secó sobre $MgSO_4$. El compuesto del título se purificó por

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cromatografía de columna instantánea (gel de sílice, 100% CH_2Cl_2 a 50% EtOAc/CH_2Cl_2) para proporcionar el producto deseado (295 mg, 7.4%) como un sólido café claro. CL/EM(ESI^+) m/z 451 $(M + H)^+$.



E) 3-Fluoro-4-(2-(piridin-3-il)-1H-pirrolo[2,3-b]piridin-4-iloxi)bencenamina

Una mezcla de 3-fluoro-4-(2-(piridin-3-il)-1-((2-(trimetilsilil)etoxi)metil)-1H-pirrolo[2,3-b]piridin-4-iloxi)bencenamina (275 mg, 0.61 mmol), fluoruro de tetrabutilamonio (1 M en THF, 4 mL), y 1,2-diaminoetano (0.2 mL) en THF (4 mL) se calentó a 65°C durante 24 horas. El solvente se retiró in vacuo. El residuo se purificó por cromatografía de columna instantánea (gel de sílice, 5% MeOH/EtOAc) para proporcionar el producto deseado (180 mg, 92%) como un sólido amarillo. CL/EM(ESI^+) m/z 321 $(M + H)^+$.

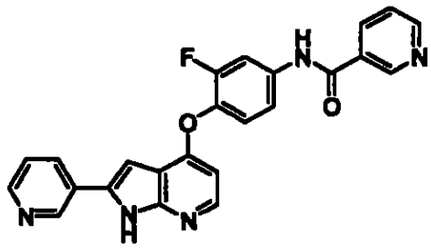
F) 2,6-Difluoro-N-(3-fluoro-4-(2-(piridin-3-il)-1H-pirrolo[2,3-b]piridin-4-iloxi)fenil)benzamida, sal de clorohidrato

A una solución de 3-fluoro-4-(2-(piridin-3-il)-1H-pirrolo[2,3-b]piridin-4-iloxi)bencenamina (15 mg, 0.047 mmol)

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y piridina (0.1 mmol) en THF a 0°C se le agregó cloruro de 2,6-difluorobenzoilo (10 mg, 0.056 mmol). La mezcla de reacción se agitó a 0°C durante 1 hora, se concentró in vacuo, y el residuo resultante se purificó por CLAR preparativa. Las fracciones deseadas se liofilizaron para dar una sal TFA blanca, la cual se disolvió en una cantidad pequeña de MeOH/H_2O con HCl 1 N (0.2 mL). Esta solución se liofilizó luego para proporcionar el compuesto del título (sal HCl, 12 mg, 48%) como un sólido amarillo. ^{1}H RMN (CD_3OD) δ 9.29 (s, 1H), 8.85 (d, 1H, J= 9.6 Hz), 8.74 (d, 1H, J= 5.2 Hz), 8.26 (d, 1H, J= 6.8 Hz), 8.01 (dd, 1H, J= 8.4, 5.6 Hz), 7.88 (dd, 1H, J = 12.4, 2.4 Hz), 7.50-7.35 (m, 4H), 7.10-7.00 (m, 2H), 6.73 (d, 1H, 7= 6.4 Hz); CL/EM(ESI$^+$) m/z 461 (M + H)$^+$.

EJEMPLO 238



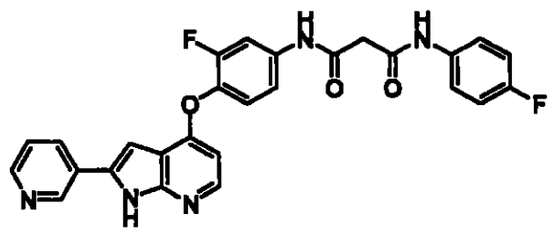
N-(3-Fluoro-4-(2-(piridin-3-il)-1H-pirrolo[2,3-b]piridin-4-iloxi)fenil)nicotinamida

Preparado en una forma similar como en el Ejemplo 237. ^{1}H RMN (CD_3OD) δ 9.36 (s, 1H), 9.33 (s, 1H), 9.00-8.90 (m,

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3H), 8.79 (d, m, J= 5.2 Hz), 8.31 (d, 1H, J= 6.8 Hz), 8.12-8.05 (m, 2H), 7.99 (dd, 1H, J= 12.8, 2.4 Hz), 7.63 (d, 1H, J= 8.8 Hz), 7.52 (s, 1H), 7.48-7.40 (m, 2H), 6.78 (d, 1H, J= 6.4 Hz); CL/EM(ESI$^+$) m/z 461 $(M + H)^+$.

EJEMPLO 239



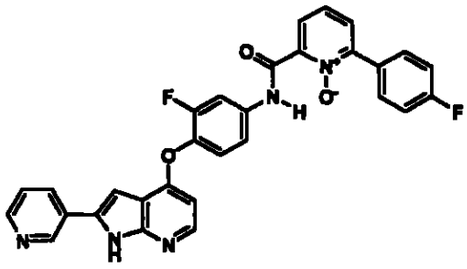
N^1-(3-Fluoro-4-(2-(piridin-3-il)-1H-pirrolo[2,3-b]piridin-4-iloxi)fenil)-N^3-(4-fluorofenil)malonamida, sal de clorohidrato

A una solución agitada de 3-fluoro-4-(2-(piridin-3-il)-1H-pirrolo[2,3-b]piridin-4-iloxi)bencenamina (16 mg, 0.05 mmol, Compuesto E del Ejemplo 237), ácido 3-(4-fluorofenilamino)-3-oxopropanóico (19.7 mg, 0.1 mmol, Compuesto A del Ejemplo 25), y HATU (38 mg, 0.1 mmol) en DMF (0.5 mL) se le agregó DIPEA (0.1 mL). La mezcla se agitó a temperatura ambiente durante 2 horas, se concentró in vacuo, y el residuo se purificó por CLAR preparativa. Las fracciones deseadas se liofilizaron para dar una sal TFA blanca, la cual se disolvió en una cantidad pequeña de MeOH/H_2O con HCl 1 N (0.2 mL) y se liofilizó para proporcionar el compuesto del título (sal HCl, 12 mg, 42%) como un sólido amarillo. ^{1}H RMN

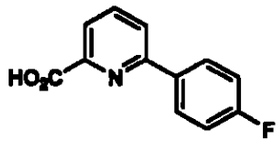
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(CD_3OD) δ 9.25 (s, 1H), 8.81 (d, 1H, J= 8.7 Hz), 8.72 (d, 1H, J= 5.4 Hz), 8.25 (d, 1H, J=6.7 Hz), 8.00 (dd, 1H, J=8.1, 6.1 Hz), 7.82 (dd, 1H, J= 12.1, 1.3 Hz), 7.53-7.48 (m, 2H), 7.40-7.32 (m, 3H), 7.00-6.95 (m, 2H), 6.71 (d, 1H, J= 6.72 Hz), 3.48 (s, 2H); CL/EM (ESI^+) m/z 500 $(M + H)^+$.

EJEMPLO 240



[3-Fluoro-4-(2-piridin-3-il-1H-pirrolo[2,3-b]piridin-4-iloxi)-fenil]-amida del ácido 6-(4-Fluoro-fenil)-1-oxi-piridin-2-carboxílico, sal del ácido trifluoroacético

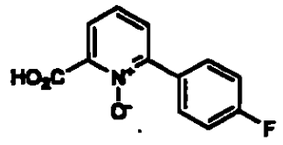


A) Ácido 6-(4-Fluorofenil)picolínico

Una solución de ácido 2-bromo-picolínico (2.02 g, 10 mmol, Aldrich) en DME que contiene 4 mL de Na_2CO_3 acuoso al 10% se purgó con gas de Ar, se trató con $Pd(PPh_3)_4$ seguido por 2-(4-fluorofenil)-5,5-dimetil-1,3,2-dioxaborinano (2.40 g, 11.5 mmol, Aldrich) y EtOH (20 mL). Esta mezcla se purgó también luego con gas de Ar. La mezcla de reacción se calentó

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a 100°C durante 2.5 horas en un tubo sellado. El ácido 2-bromo-picolínico adicional (900 mg) y $Pd(PPh_3)_4$ se le agregó, y después de purgar con gas de Ar esto se calentó a 100°C durante 4.5 horas. El ácido trifluoroacético (20 mL) se le agregó a la reacción y la mezcla se concentró in vacuo. El MeOH (150 mL) se le agregó al residuo y el material insoluble se filtró. El filtrado se concentró in vacuo, y el residuo resultante se purificó por cromatografía de columna instantánea sobre gel de sílice eluyendo con EtOAc/MeOH (9:1) seguido por EtOAc/MeOH/HOAc (14:30:1) para proporcionar el producto deseado (1.0 g, 40% basado en materia prima de borinano) como un sólido blanco. ^1H RMN (CD_3OD) δ 8.01 (d, 1H, J= 7.7 Hz), 7.94-7.87 (m, 3H), 7.73 (d, 1H, J= 7.7 Hz), 7:13 (t, 2H, J= 8.8 Hz); EM(ESI$^+$) m/z 234 $(M + H)^+$.



B) ácido N-óxido 6-(4-Fluorofenil)picolínico

Una mezcla del derivado de ácido picolínico anterior (1.0 g, 4.6 mmol), Na_2HPO_4 (1.2 g) y m-CPBA (1.1 g, ~70% de Aldrich) en CH_2ClCH_2Cl (30 mL) se agitó a temperatura ambiente durante 2 horas. El Na_2HPO_4 adicional (0.8 g) y m-CPBA (1.0 g) se agregaron a la mezcla de reacción y esto se agitó durante 3 horas a temperatura ambiente. El Na_2HPO_4 (0.5 g) y m-CPBA (0.5 g) se agregaron nuevamente

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a la mezcla de reacción y esto se agitó a temperatura ambiente durante la noche. El $CHCl_3$ (160 mL) y solución HCl acuosa 2 N (50 mL) se agregaron a la mezcla y la capa orgánica se separó, se secó sobre $MgSO_4$ y se concentró in vacuo. El residuo se purificó por cromatografía de columna instantánea en gel de sílice eluyendo con EtOAc/MeOH/HOAc (70:24:6) hasta obtener el producto deseado el cual se contaminó con m-CPBA. Este material impuro se purificó por CLAR preparativa para obtener el producto deseado (175 mg, 16%) como un sólido blanco. ^1H RMN (DMF d_6) δ 8.45 (dd, 1H, J = 8.3, 2.2 Hz), 8.15 (d, 1H, J= 2.2 Hz), 8.13-8.00 (m, 4H), 7.45 (t, 2H, J= 8.7 Hz).

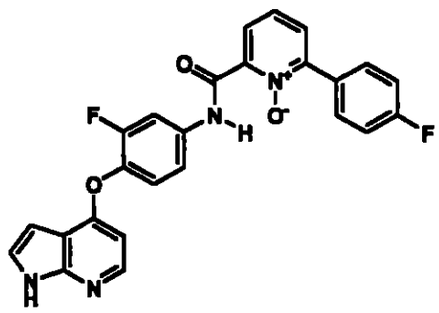
C) [3-Fluoro-4-(2-piridin-3-il-1H-pirrolo[2,3-b]piridin-4-iloxi)-fenil]-amida del ácido 6-(4-fluoro-fenil)-1-oxi-piridin-2-carboxílico, sal del ácido trifluoroacético

A una solución de N-óxido del ácido 6-(4-fluorofenil)picolínico (30 mg, 0.13 mmol), HOBT (16 mg), y EDCI.HCl (50 mg, 0.26 mmol) en DMF (4 mL) a temperatura ambiente se le agregó 3-fluoro-4-(2-(piridin-3-il)-1H-pirrolo[2,3-b]piridin-4-iloxi)bencenamina (40 mg, 0.12 mmol, Compuesto E del Ejemplo 237). La mezcla de reacción se agitó a temperatura ambiente durante la noche y se

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concentró a presión reducida. El residuo se purificó por CLAR preparativa para proporcionar el producto deseado (20 mg, 24%) como un sólido beige. ^{1}H RMN (DMF-d_6) δ 14.07 (br s, 1H), 12.64 (br s, 1H), 9.35 (s, 1H), 8.65 (d, 1H, J= 4.4 Hz), 8.53 (d, 1H, J= 7.7 Hz), 8.49 (dd, 1H, J= 8.2, 2.2 Hz), 8.23 (d, 1H, J= 5.5 Hz), 8.19 (dd, 1H, J= 13.2, 2.8 Hz), 8.02-7.62 (m, 6H), 7.55 (t, 1H, J= 8.8 Hz), 7.43 (t, 2H, J= 8.8 Hz), 7.22 (s, 1H), 6.55 (d, 1H, J= 5.5 Hz); EM(ESI$^+$) m/z 459.1 $(M + H)^+$.

EJEMPLO 241

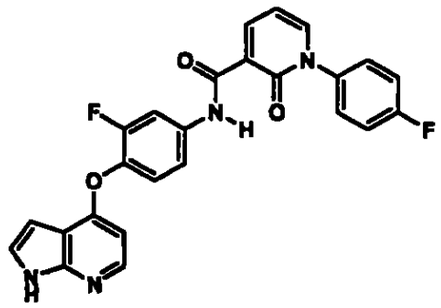


[3-Fluoro-4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-fenil]-amida del ácido 6-(4-Fluoro-fenil)-1-oxi-piridin-2-carboxílico, sal del ácido trifluoroacético

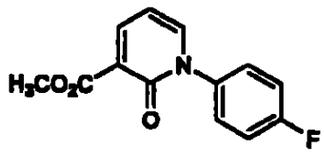
A una solución de N-óxido del ácido 6-(4-fluorofenil)picolínico (47 mg, 0.20 mmol, Compuesto B del Ejemplo 240), HOBT (20 mg), y EDCI.HCl (60 mg, 0.31 mmol) en DMF (4 mL) a temperatura ambiente se le agregó 4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorobencenamina (50 mg, 0.20 mmol, Compuesto B del Ejemplo 132). La mezcla se

agitó a temperatura ambiente durante la noche y se concentró a presión reducida. El residuo resultante se purificó por CLAR preparativa para proporcionar el producto deseado (68 mg, 12%) como un sólido blanco. ^{1}H RMN (DMF-d_6) δ 14.07 (br s, 1H), 12.14 (br s, 1H), 8.49 (dd, 1H, J= 7.7, 1.7 Hz), 8.26 (d, 1H, J= 6.1 Hz), 8.18 (dd, 1H, J= 12.7, 1.7 Hz), 8.02-7.96 (m, 3H), 7.84 (t, 1H, J= 8.3 Hz), 7.67 (d, 1H, J= 8.8 Hz), 7.57-7.52 (m, 2H), 7.43 (d, 2H, J= 8.8 Hz), 6.62 (d, 1H, J= 6.0 Hz), 6.46 (d, 1H, J= 2.8 Hz); EM(ESI$^+$) m/z 536.1 $(M + H)^+$.

EJEMPLO 242



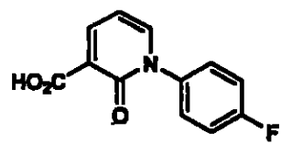
N-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridin-3-carboxamida, sal del ácido trifluoroacético



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A) 1-(4-Fluorofenil)-2-oxo-1,2-dihidropiridin-3-carboxilato de metilo

A una solución de 2-oxo-2H-piran-3-carboxilato de metilo (2.31 g, 15 mmol, Aldrich) en THF (40 mL) y DMF (10 mL) a temperatura ambiente se le agregó 4-fluoroanilina (1.67 g, 15 mmol), y la mezcla de reacción se agitó durante 2.5 horas. Al intermediario 4-fluoroanilina formado por medio de una adición Michael se le agregó EDCI.HCl (3.85 g, 20 mmol) y DMAP (120 mg) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante la noche. A la mezcla de reacción se agregaron HCl acuoso 1 N (50 mL) y EtOAc (150 mL). La capa EtOAc se separó, y la capa acuosa se lavó con EtOAc (150 mL). Las capas EtOAc combinadas se secaron sobre $MgSO_4$ y concentraron in vacuo hasta obtener un material semi-sólido (~4.4 g). El producto crudo se disolvió en éter (100 mL) y metanol (15 mL), y el sólido el cual se formó después de la agitación se filtró completamente. El filtrado se concentró in vacuo para proporcionar el producto deseado (2.95 g, 80%) como un semi-sólido, el cual fue suficientemente puro para usarse en la siguiente Etapa sin purificación adicional. ^1H RMN (DMSO-d_6) δ 8.23 (dd, 1H, J= 7.2, 2.2 Hz), 7.57 (dd, 1H, J= 6.6, 1.7 Hz), 7.32-7.34 (m, 2H), 7.17 (t, 2H, J= 8.8 Hz), 6.32 (t, 1H, J= 7.1 Hz), 3.89 (s, 3H); EM(ESI$^+$) m/z 248.2 $(M + H)^+$.



B) Ácido 1-(4-Fluorofenil)-2-oxo-1,2-dihidropiridin-3-carboxílico

Una mezcla de 1-(4-fluorofenil)-2-oxo-1,2-dihidropiridin-3-carboxilato de metilo (crudo 2.45 g, 12 mmol) y NaOH acuoso 6 N (2.5 mL) en metanol (60 mL) se agitó a temperatura ambiente durante 4 horas. A la mezcla de reacción se le agregó HCl concentrado (1 mL) lentamente con agitación a temperatura ambiente. El precipitado el cual se formó, se filtró, se lavó con una cantidad pequeña de agua y se secó hasta obtener el producto del ácido deseado (2.1 g) como un sólido amarillo. El filtrado se concentró in vacuo. El residuo se mezcló con agua (50 mL) y se lavó con EtOAc (2 x 130 mL). Las capas de EtOAc se secaron sobre $MgSO_4$ y se concentraron in vacuo. El residuo se trituró con una cantidad pequeña de éter hasta obtener un segundo cuerpo del producto (195 mg, total 2.30 g, 82%). ^1H RMN (DMSO-d_6) δ 8.47 (dd, 1H, J= 7.2, 2.2 Hz), 8.19 (dd, 1H, J= 6.6, 1.7 Hz), 7.62-7.60 (m, 2H), 7.42 (t, 2H, J= 8.8 Hz), 6.78 (t, 1H, J= 7.1 Hz); MS(ESI$^+$) m/z 234.2 $(M + H)^+$.

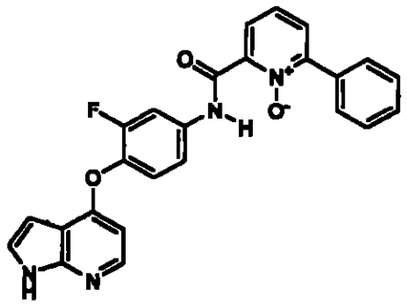
C) N-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridin-3-carboxamida, sal del ácido trifluoroacético

A una solución de ácido 1-(4-fluorofenil)-2-oxo-1,2-dihidropiridin-3-carboxílico (70 mg, 0.30 mmol), HOBT (30 mg), y EDCI.HCl (200 mg, 1.04 mmol) en DMF (8 mL) a temperatura ambiente se le

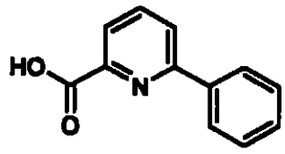
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agregó 4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorobencenamina (70 mg, 0.29 mmol, Compuesto B del Ejemplo 132). La mezcla se agitó a temperatura ambiente durante la noche y se concentró in vacuo. El residuo resultante se purificó por CLAR preparativa para proporcionar el producto deseado (71 mg, 43%) como un sólido beige. ^{1}H RMN (DMSO-d_6) δ 12.04 (br s, 1H), 11.96 (br s, 1H), 8.52 (dd, 1H, J= 7.2, 2.2 Hz), 8.08 (t, 2H, J= 5.5 Hz), 7.96 (dd, 1H, J= 12.7, 2.2 Hz), 7.55-7.53 (m, 2H), 7.84 (t, 1H, J= 8.3 Hz), 7.43 (dd, 1H, J= 8.8, 1.7Hz), 7.38-7.32 (m, 3H), 6.67 (t, 1H, J= 7.2 Hz), 6.43 (d, 1H, J= 6.1 Hz), 6.46 (dd, 1H, J= 3.3, 1.4 Hz); EM(ESI$^+$) m/z 459.1 $(M + H)^+$.

EJEMPLO 243



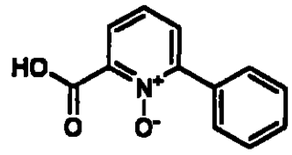
[3-fluoro-4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-fenil]-amida del ácido 1-oxi-6-fenil-piridina-2-carboxílico, sal del ácido trifluoroacético



A) ácido 6-Fenilpicolínico

Una mezcla de ácido 6-bromopicolínico (2.02 g, 10 mmol),

ácido feniborónico (1.22 g, 10 mmol), carbonato de cesio (5.00 g) y $PdCl_2[(t\text{-}Bu)_2P(OH)]_2$ (70 mg, CombiPhos Catalysts, me. Princeton, NJ) en DMF (20 mL) y agua (3 mL) se purgó con Ar-gas y se calentó a 110°C durante 24 h. La reacción fue incompleta y no progresó. A la mezcla de reacción se agregó EtOAc (200 mL) y HCl acuoso 1N (40 mL). La capa EtOAc se separó, y la capa acuosa se lavó con EtOAc (150 mL). Las capas EtOAc combinadas se secaron sobre Na_2SO_4 y se concentraron in vacuo. El residuo se purificó por CLAR preparativa para proporcionar el producto deseado (350 mg, 18%) como un sólido blanco. ^{1}HRMN ($CDCl_3$) δ 10.45 (s, 1H), 8.18-7.96 (m, 5H), 7.51-7.53 (m, 3H).



B) N-óxido del ácido 6-Fenilpicolínico

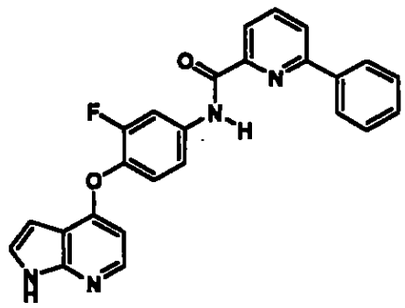
Una mezcla del ácido 6-fenilpicolínico (150 mg, 0.75 mmol), K_2HPO_4 (600 mg) m-CPBA (300 mg, max 70% de Aldrich) en dicloroetano (8.0 mL) se calentó a 60°C durante 1.5 h. Se agregó m-CPBA adicional (2 x 300 mg) y la mezcla se calentó a 60°C durante 40 minutos. La mezcla de reacción se purificó por CLAR preparativa para proporcionar el producto deseado (110 mg, 68 %) como un sólido blanco. ^{1}H RMN (DMF-d_7) δ 8.57 (s, 1H), 8.43 (d, 1H, J = 2.2 Hz), 8.10-7.88 (m, 5H), 7.59-7.57 (m, 3H).

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C) [3-fluoro-4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-fenil]-amida del ácido 1-Oxi-6-fenil-piridina-2-carboxílico, sal del ácido trifluoroacético

A una solución del N-óxido del ácido 6-fenilpicolínico (25 mg, 0.12 mmol), HOBT (20 mg), y EDCI.HCl (120 mg, 1.14 mmol) en DMF (3.5 mL) a temperatura ambiente se agregó 4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorobencenamina (40 mg, 0.16 mmol, el compuesto B del ejemplo 132). La mezcla de reacción se agitó a temperatura ambiente durante la noche y se concentró in vacuo. El residuo resultante se purificó por CLAR preparativa para proporcionar el producto deseado (36 mg, 54%) como un sólido blanco. ^{1}H RMN (DMF-d_7) δ 14.12 (br s, 1H), 12.10 (br s, 1H), 8.48 (dd, 1H, J= 7.9, 1.6 Hz), 8.24 (d, 1H, J= 5.5 Hz), 8.18 (dd, 1H, J= 14.8, 2.2 Hz), 7.95-7.89 (m, 3H), 7.83 (t, 1H, J= 7.7 Hz), 7.67 (dd, 1H, J= 8.6, 1.2 Hz), 7.61-7.51 (m, 5H), 6.60 (d, 1H, J= 5.5 Hz), 6.44 (d, 1H, J= 3.3 Hz); EM(ES$^+$) m/z 441.1 $(M + H)^+$.

EJEMPLO 244



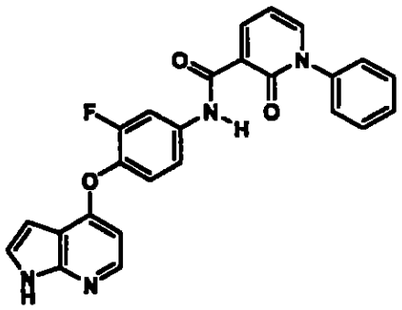
N-(4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-6-

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fenilpicolinamida, sal del ácido trifluoroacético

A una solución del ácido 6-fenilpicolínico (48 mg, 0.24 mmol, compuesto A del ejemplo 243), HOBT (25 mg), y EDCI.HCl (155 mg, 0.81 mmol) en DMF (3.5 mL) a temperatura ambiente se agregó 4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorobencenamina (65 mg, 0.26 mmol, Compuesto B del ejemplo 132). La mezcla se agitó a temperatura ambiente durante la noche y se concentró in vacuo. El residuo se purificó por CLAR preparativa para proporcionar el producto deseado (25 mg, 19%) como un sólido café ligero. ^{1}H RMN (DMF-d_7) δ 11.93 (br s, 1H), 11.01 (br s, 1H), 8.36 (dd, 2H,J= 7.2,1.6 Hz), 8.31-8.17 (m, 5H), 7.59-7.50 (m, 6H), 6.53 (d, 1H,J= 5.5 Hz); 6.41 (d, 1H, J= 2.8 Hz); EM(ESI$^+$) m/z 425.1 $(M + H)^+$.

EJEMPLO 245

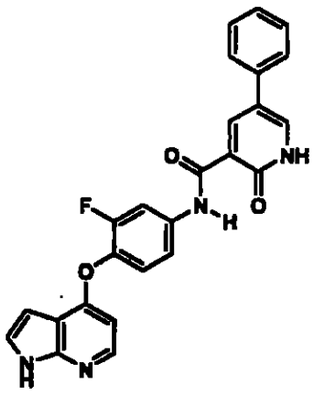


N-(4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-2-oxo-1-fenil-1,2-dihidropiridina-3-carboxamida, sal del ácido trifluoroacético

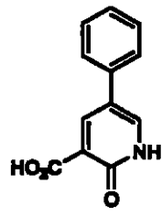
A una solución del ácido 2-oxo-1-fenil-1,2-dihidropiridina-3-carboxílico (30 mg, 0.14 mmol, se preparó en una manera similar como en las etapas A y B del ejemplo 242), HOBT (20 mg), y EDCI.HCl (80 mg, 0.42 mmol) en DMF (3.5 mL) a temperatura ambiente se agregó 4-(1H-

pirrolo[2,3-b]piridin-4-iloxi)-3-fluorobencenamina (31 mg, 0.13 mmol, Compuesto B del Ejemplo 132). La mezcla de reacción se agitó a temperatura ambiente durante la noche y se concentró in vacuo. El residuo se purificó por CLAR preparativa para proporcionar el producto deseado (10 mg, 14 %) como un sólido beige. ^{1}H RMN (acetona-d_6) δ 13.40 (br s, 1H), 12.32 (br s, 1H), 8.66 (dd, 1H, J= 7.1, 1.6 Hz), 8.43 (d, 1H, J= 6.6 Hz), 8.18 (dd, 1H, J= 13.2, 2.2 Hz), 8.03 (dd, 1H, J= 6.6, 2.2 Hz), 7.67-7.49 (m, 8H), 6.89 (d, 1H, J= 6.6 Hz), 6.75 (t, 1H, J= 6.3 Hz), 6.58 (d, 1H, J= 3.3 Hz); EM(ESI$^+$) m/z 441.1 $(M + H)^+$.

EJEMPLO 246



N-(4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-2-oxo-5-fenil-1,2-dihidropiridina-3-carboxamida, sal del ácido trifluoroacético



A) ácido 2-oxo-5-fenil-1,2-dihidropiridina-3-carboxílico

566

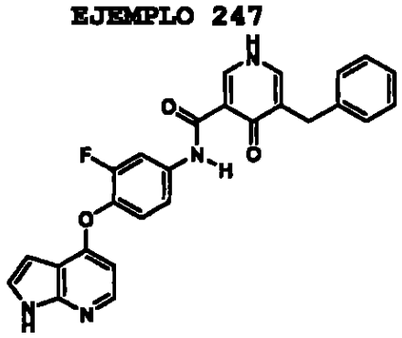
Una mezcla del ácido 5-bromo-2-hidroxinicotínico (436 mg, 2.00 mmol, Syn. Comm., 19 (3&4), 553-559 (1989)), ácido fenilborónico (248 mg, 2.03 mmol), Cs_2CO_3 (1.20 g) y $PdCl_2[(t\text{-}Bu)_2P(OH)]_2$ (170 mg, CombiPhos Catalysts, Inc. Princeton, NJ) en DMF (10 mL) y agua (1.0 mL) se purgó con Ar gas y se calentó a 110°C durante 6 h. Se agregó ácido fenilborónico adicional (75 mg) y la mezcla se calentó a 110°C durante 5 h. A la reacción se agregó TFA (3 mL), y la mezcla se concentró in vacuo a un volumen de ~12 mL. La mezcla se purificó por CLAR preparativa para proporcionar el producto deseado (78 mg, 18%). ^1H RMN (DMF-d_7) δ 14.8 (br s, 1H), 13.8 (br s, 1H), 8.73 (s, 1H), 8.46 (s, 1H), 7.74 (d, 1H, J= 7.2 Hz), 7.53-7.42 (m, 3H), 5.81 (s, 1H).

B) N-(4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-2-oxo-5-fenil-1,2-dihidropiridina-3-carboxamida

A una solución del ácido 2-oxo-5-fenil-1,2-dihidropiridina-3-carboxílico (35mg, 0.16 mmol), HOBT (25 mg), y EDCI.HCl (80 mg, 0.42 mmol) en DMF (3.0 mL) a temperatura ambiente se agregó 4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorobencenamina (30 mg, 0.12 mmol, Compuesto B del ejemplo 132). La mezcla se agitó a temperatura ambiente durante la noche y se concentró in vacuo. El residuo se purificó por CLAR preparativa para proporcionar el producto deseado (12 mg, 13 %) como un sólido café ligero. ^1H RMN

(CD$_3$OD) δ 8.81 (d, 1H, J= 2.8 Hz), 8.17 (d, 1H, J= 6.6 Hz), 8.00 (dd, 1H, J= 12.6, 2.2 Hz), 7.94 (d, 1H, J= 3.3 Hz), 7.52-7.27 (m, 7H), 6.80 (d, 1H, J= 9.3 Hz), 6.72 (d, 1H, J= 6.6 Hz), 6.54 (d, 1H, J= 3.8 Hz); EM(ESI$^+$) m/z 441.1 $(M + H)^+$.

EJEMPLO 247



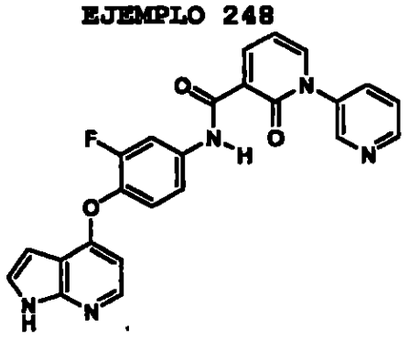
N-(4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-5-bencil-4-oxo-1,4-dihidropiridina-3-carboxamida, sal del ácido trifluoroacético

A una solución del ácido 5-bencil-4-oxo-1,4-dihidropiridina-3-carboxílico (35 mg, 0.15 mmol) y HOBt (30 mg) en DMF (2.5 mL) a temperatura ambiente se agregó EDCI.HCl (80 mg, 0.42 mmol) seguido por 4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorobencenamina (35 mg, 0.16 mmol, Compuesto B del ejemplo 132). La mezcla de reacción se agitó a temperatura ambiente durante 40 h y se concentró in vacuo. El residuo resultante se purificó por CLAR preparativa para proporcionar el producto deseado (38 mg, 45%) como un sólido blanco. ^{1}H RMN (DMSO-d$_6$) δ 13.21 (br s, 1H), 12.38 (s, 1H), 12.08 (br s, 1H), 8.59 (d, 1H, J= 4.4

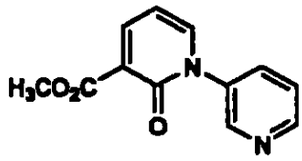
568

Hz), 8.17 (d, 1H, J= 5.5 Hz), 8.03 (dd, 1H, J= 13.2, 2.2 Hz), 7.80 (d, 1H, J= 3.9 Hz), 7.48-7.19 (m, 8H), 6.52 (d, 1H, J= 5.5 Hz), 6.34 (d, 1H, J= 1.6 Hz), 3.81 (s, 2H); EM (ESI^+) m/z 455.1 $(M + H)^+$.

EJEMPLO 248



N-(4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-2-oxo-1-(piridin-3-il)-1,2-dihidropiridina-3-carboxamida, sal del ácido trifluoroacético

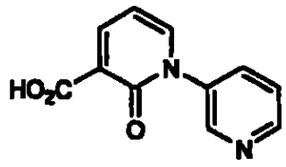


A) Metil 2-oxo-1-(piridin-3-il)-1,2-dihidropiridina-3-carboxilato

A una solución de metil 2-oxo-2H-piran-3-carboxilato (462 mg, 3 mmol, Aldrich) en DMF (6 mL) a temperatura ambiente se agregó 3-aminopiridina (282 mg, 3 mmol). La mezcla de reacción se agitó durante la noche a temperatura ambiente, se trató con EDCI.HCl (650 mg, 3.4 mmol) y DMAP (200 mg), se agitó durante 24 h adicionales, y se concentró

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in vacuo. El residuo se purificó por CLAR preparativa para proporcionar el producto deseado (980 mg, 95%) como un sólido beige. ^{1}H RMN ($CDCl_3$) δ 13.00 (br s, 1H), 8.83 (br s, 1H), 8.74 (br s, 1H), 8.29 (dd, 1H, J= 7.2, 1.7 Hz), 8.18 (d, 1H, J= 8.3 Hz), 7.73 (dd, 1H, J= 7.7, 5.0 Hz), 7.66 (dd, 1H, J= 6.6, 1.6 Hz), 6.42 (t, 1H, J= 7.1 Hz), 3.87 (s, 3H).



B) ácido 2-oxo-1-(piridin-3-il)-1,2-dihidropiridina-3-carboxílico

Una mezcla de metil 2-oxo-1-(piridin-3-il)-1,2-dihidropiridina-3-carboxilato (980 mg, 2.85 mmol) y NaOH 6N (1 mL) y metanol (20 mL) se agitó a temperatura ambiente durante la noche. A la mezcla de reacción se agregó HCl acuoso 1N (6 mL) y la mezcla se concentró in vacuo para obtener el ácido (1.0 g, 100 %) como un sólido amarillo ligero que contenía una pequeña cantidad de NaCl. Este material se usó directamente en la siguiente etapa sin purificación adicional. ^{1}H RMN (CD_3OD) δ 8.85 (d, 1H, J= 1.7 Hz), 8.77 (d, 1H, J= 4.9 Hz), 8.59 (dd, 1H, J= 7.1, 1.7 Hz), 8.21 (d, 1H, J= 8.2 Hz), 8.10 (dd, 1H, J= 6.6, 2.2 Hz), 7.79 (dd, 1H, J= 8.2, 5.0 Hz), 6.80 (t, 1H, J= 6.6 Hz); EM(ESI$^+$)

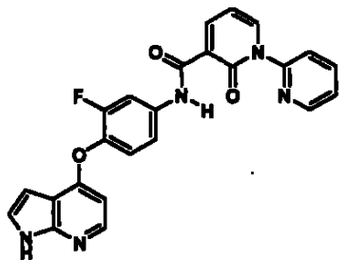
570

m/z 217.2 $(M + H)^+$.

C) N-(4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-2-oxo-1-(piridin-3-il)-1,2-dihidropiridina-3-carboxamida, sal del ácido trifluoroacético

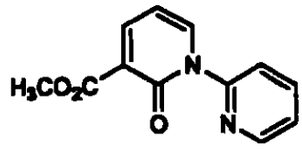
A una solución del ácido 2-oxo-1-(piridin-3-il)-1,2-dihidropiridina-3-carboxílico (22 mg, 0.10 mmol) y HOBt (5 mg) en DMF (3 mL) a temperatura ambiente se agregó EDCI.HCl (24.5 mg, 0.13 mmol seguido por 4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorobencenamina (24 mg, 0.10 mmol, Compuesto B del ejemplo 132). La mezcla de reacción se agitó a temperatura ambiente durante la noche y se concentró in vacuo. El residuo resultante se purificó por CLAR preparativa para proporcionar el producto deseado (25 mg, 45%) como un sólido beige. ^{1}H RMN (DMF-d_7) δ 12.26 (br s, 1H), 12.18 (s, 1H), 8.90 (d, 1H, J= 2.2 Hz), 8.78 (d, 1H, J= 3.9 Hz), 8.71 (dd, 1H, J= 7.1, 2.2 Hz), 8.28-8.15 (m, 4H), 7.72-7.48 (m, 4H), 6.87 (t, 1H, J= 7.2 Hz), 6.64 (d, 1H, J= 5.5 Hz), 6.47 (br s, 1H); EM (ESI^+) m/z 442.2 $(M + H)^+$.

EJEMPLO 249



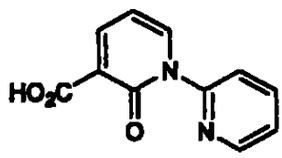
N-(4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-2-oxo-

1-(piridin-2-il)-1,2-dihidropiridina-3-carboxamida, sal del ácido trifluoroacético



A) Metil 2-oxo-1-(piridin-2-il)-1,2-dihidropiridina-3-carboxilato

A una solución de metil 2-oxo-2H-piran-3-carboxilato (462 mg, 3 mmol, Aldrich) en DMF (6 mL) a temperatura ambiente se agregó 3-aminopiridina (282 mg, 3 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 12 h y se trató con EDCI.HCl (650 mg, 3.4 mmol) y DMAP (200 mg). La mezcla de reacción se agitó durante 2.5 días a temperatura ambiente, y más del DMF se retiró in vacuo. El residuo se purificó por CLAR preparativa para proporcionar el producto deseado (500 mg, 72%) como un material cristalino. ^{1}H RMN ($CDCl_3$) δ 8.53 (d, 1H, J= 5.0 Hz), 8.20 (dd, 1H, J= 9.2, 2.2 Hz), 8.06 (dd, 1H, J= 6.0,1.1 Hz), 7.89-7.82 (m, 2H), 7.32 (dd, 1H, J= 6.6, 5.0 Hz), 6.36 (t, 1H, J= 6.6 Hz), 3.86 (s, 3H); EM(ESI$^+$) m/z 231.2 $(M + H)^+$.



B) ácido 2-oxo-1-(piridin-2-il)-1,2-dihidropiridina-3-carboxílico

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Una mezcla de metil 2-oxo-1-(piridin-2-il)-1,2-dihidropiridina-3-carboxilato (500 mg, 2.17 mmol) y NaOH 3N (1 mL) y metanol (10 mL) se agitó a temperatura ambiente durante la noche. A la reacción se agregó TFA (0.5 mL) y la mezcla se concentró in vacuo. El residuo se disolvió en agua (3 mL) y i-PrOH (10 mL). El sólido el cual se formó se filtró, se lavó con una pequeña porción de agua y i-PrOH, y se secó para obtener el ácido (260 mg, 55 %) como un sólido blanco. ^{1}H RMN (DMF-d_7) δ 14.14 (br s, 1H), 8.72 (d, 1H, J= 4.9 Hz), 8.62 (dd, 1H, J= 7.7, 2.2 Hz), 8.47 (dd, 1H, J= 6.6,2.2 Hz), 8.18-7.98 (m, 2H), 7.67 (dd, 1H, J= 7.2,5.3 Hz), 6.97 (t, 1H, J= 6.6 Hz); EM(ESI$^+$) m/z 217.2 $(M + H)^+$.

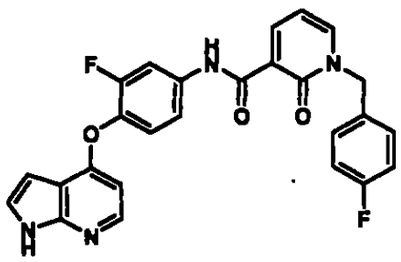
C) N-(4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-2-oxo-1-(piridin-2-il)-1,2-dihidropiridina-3-carboxamida, sal del ácido trifluoroacético

A una solución del ácido 2-oxo-1-(piridin-2-il)-1,2-dihidropiridina-3-carboxílico (200 mg, 0.93 mmol) y HOBt (100 mg) en DMF (5 mL) a temperatura ambiente se agregó EDCI.HCl (250 mg, 1.30 mmol) seguido por 4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorobencenamina (226 mg, 0.93 mmol, Compuesto B del ejemplo 132) en DMF (4 mL). La mezcla de reacción se agitó a temperatura ambiente durante la noche y se concentró in vacuo. El residuo se purificó por CLAR preparativa para proporcionar el producto deseado (290 mg, 56%) como un sólido

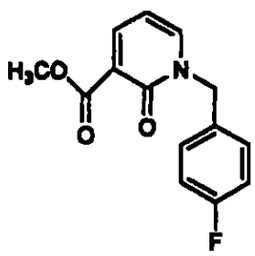
573

blanco. ^{1}H RMN (DMF-d_7) δ 12.16 (br s, 1H), 12.15 (br s, 1H), 11.99 (br s, 1H), 8.77-8.55 (m, 2H), 8.39-8.35 (m, 1H), 8.22-8.15 (m, 4H), 7.72-7.47 (m, 3H), 6.87 (t, 1H, J= 7.2 Hz), 6.55 (t, 1H, J= 5.5 Hz), 6.42 (d, 1H, J= 2.3 Hz); EM(ESI$^+$) m/z 442.1 $(M + H)^+$.

EJEMPLO 250



N-(4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-1-(4-fluorobencil)-2-oxo-1,2-dihidropiridina-3-carboxamida, sal de clorohidrato

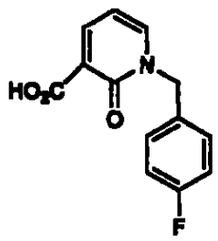


A) Metil 1-(4-fluorobencil)-2-oxo-1,2-dihidropiridina-3-carboxilato

Una mezcla heterogénea de metil 2-oxo-2H-piran-3-carboxilato (2.0 g, 13 mmol, 1.0 eq, Aldrich) y 4-fluorobencilamina (1.5 mL, 13 mmol, 1.0 eq) en DMF (10 mL) se agitó a temperatura ambiente durante 3 h. La mezcla de

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reacción se trató con EDCI (3.4 g, 18 mmol, 1.4 eq) y DMAP (0.11 g, 9.91 mmol, 0.07 eq) a temperatura ambiente y la solución resultante se agitó durante 12 h. La mezcla de reacción se apagó con HCl acuoso 1N y la solución se extrajo con acetato de etilo (4 x 50 mL). Los extractos orgánicos combinados se lavaron con LiCl acuoso al 10% (3 x 70 mL), se secaron (Na_2SO_4), se filtraron y el filtrado se concentró in vacuo para proporcionar el producto (2.5 g, 73%) como un sólido, el cual se usó sin purificación adicional. ^1H RMN (DMSO-d_6) δ 8.17-8.20 (m, 1H), 8.03-8.05 (m, 1H), 7.38-7.46 (m, 2H), 7.16-7.22 (m, 2H), 6.37 (dd, 1H, J= 6.94 Hz), 5.13 (s, 2H), 3.73 (s, 3H); EMAR(ESI): calculado: 262.0879, encontrado: 262.0885.



B) ácido 1-(4-Fluorobencil)-2-oxo-1,2-dihidropiridina-3-carboxílico

Una solución de metil 1-(4-fluorobencil)-2-oxo-1,2-dihidropiridina-3-carboxilato (2.4 g, 9.2 mmol, 1.0 eq) en MeOH (25 ml) se trató con hidróxido de sodio acuoso 5N (4.6 mL, 24 mmol, 2.6 eq) a temperatura ambiente y la mezcla de reacción se agitó durante 15 h. La mezcla de reacción se

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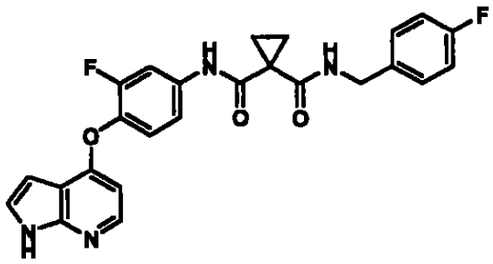
concentró in vacuo, se diluyó con agua y la solución se extrajo con acetato de etilo (descartando la fracción orgánica). La fracción acuosa se enfrió a 0°C y se acidificó con HCl concentrado. El sólido resultante se filtró, se lavó con agua y el sólido se secó in vacuo para proporcionar el producto (1.6 g, 70%) el cual fue suficientemente puro para el uso en la etapa subsecuente sin purificación adicional. ^{1}H RMN (DMSO-d_6) δ 8.44-8.39 (m, 2H), 7.46-7.42 (m, 2H), 7.24-7.18 (m, 2H), 6.78 (d, 1H, J= 6.98 Hz), 5.31 (s, 2H); EMAR(ESI), calculado: 248.0723, encontrado: 248.0718.

C) N-(4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-1-(4-fluorobencil)-2-oxo-1,2-dihidropiridina-3-carboxamida, sal de clorohidrato

Una solución homogénea del ácido 1-(4-fluorobencil)-2-oxo-1,2-dihidropiridina-3-carboxílico (0.051 g, 0.21 mmol, 1.0 eq), 4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorobencenamina (0.50 g, 0.21 mmol, 1.0 eq, Compuesto B del ejemplo 132) y TBTU (0.086 g, 0.23 mmol, 1.1 eq) en DMF (1 mL) se trató con DIPEA (0.11 mL, 0.62 mmol, 3.0 eq) a temperatura ambiente. La mezcla de reacción se agitó durante 12 h y se apagó con LiCl acuoso al 10% (15 mL). La solución resultante se extrajo con acetato de etilo (4 x 40 mL). Los extractos orgánicos combinados se

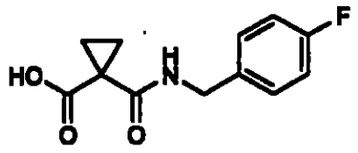
lavaron con LiCl acuoso al 10% (4 x 50 mL), se secaron (Na_2SO_4), se filtraron y el filtrado se concentró in vacuo. El residuo se purificó por cromatografía instantánea (SiO_2, se eluyó 0-2.5% MeOH en $CHCl_3$) y las fracciones apropiadas se aislaron y se concentraron in vacuo. La base libre se disolvió en THF, se enfrió a 0°C y la solución homogénea se trató con HCl 4N anhidro en dioxano. La mezcla de reacción se calentó a temperatura ambiente, se concentró in vacuo y el residuo se trituró con dietil éter. El sólido se secó in vacuo para proporcionar el compuesto del título (0.062 g, 59%) como una sal HCl. ^{1}H RMN (DMSO-d_6) δ 12.43 (s, 1H), 12.27 (s, 1H), 8.50-8.52 (m, 1H), 8.35-8.37 (m, 1H), 8.25-8.27 (m, 1H), 8.05-8.08 (m, 1H), 7.43-7.55 (m, 5H), 7.20-7.24 (m, 2H), 6.71 (t, 1H, J= 6.89 Hz), 6.65 (d, 1H, J= 6.03 Hz), 6.43 (s, 1H), 5.32 (s, 2H); EMAR (ESI$^+$): calculado: 473.1425, encontrado: 473.1427.

EJEMPLO 251



N-(4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N-(4-

fluorobencil)ciclopropano-1,1-dicarboxamida, sal del ácido trifluoroacético



A) ácido 1-((4-Fluorobencil)carbamoil)ciclopropanocarboxílico

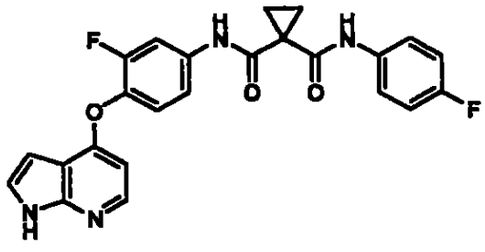
A una solución del ácido 1,1-ciclopropanocarboxílico (390 mg, 3.0 mmol, Aldrich) en THF (5 mL) a 0°C se agregó trietilamina (0.418 mL, 3.0 mmol). La mezcla de reacción se agitó a 0°C durante 30 minutos y se trató con cloruro de tionilo (0.219 mL, 3.0 mmol, Aldrich). La mezcla de reacción luego se agitó a 0°C durante otros 30 minutos y una solución de 4-fluorobencilamina (375 mg, 3.0 mmol, Aldrich) en 2 mL de THF se agregó. La mezcla de reacción se agitó a 0°C durante 2 h, se diluyó con 100 mL del acetato de etilo y se extrajo con NaOH 1N (10 mL). La fase acuosa se acidificó con HCl 1N a un pH 1-2. El sólido que se formó se colectó por filtración (343 mg, 48%). EM(ESI$^+$) m/z 238.2 $(M + H)^+$.

B) N-(4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N-(4-fluorobencil)ciclopropano-1,1-dicarboxamida, sal del ácido trifluoroacético

A una solución de 4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorobencenamina (45 mg, 0.1 mmol, Compuesto B

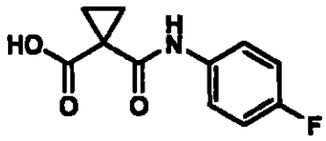
del ejemplo 132) y ácido 1-((4-fluorobencil)carbamoil)ciclopropanocarboxílico (24 mg, 0.1 mml) en DMF (0.5 mL) a temperatura ambiente se agregó HATU (57 mg., 0.15 mmol, Perseptive Biosystem) y DIEA (0.05 mL, 0.3 mmol, Aldrich). La mezcla de reacción se agitó a temperatura ambiente durante 2 h, y luego se apagó por la adición de 2 mL de metanol. La mezcla de reacción se purificó por CLAR preparativa. Las fracciones deseadas se combinaron, se concentraron a presión reducida, y se liofilizaron hasta secarse para proporcionar el producto deseado (39 mg, 67%) como un sólido blanco. ^{1}H RMN (DMSO-d_6) δ 11.99 (br s, 1H), 10.81 (s, 1H), 8.46 (t, 1H, J= 5.8 Hz), 8.13 (d, 1H, J= 6.1 Hz), 7.86 (dd, 1H, J = 13.2, 2.2 Hz), 7.41-7.46 (m, 2H), 7.37(t, 1H, J=9.1 Hz), 7.28-7.32 (m, 2H), 7.13 (t, 3H, J= 9.1 Hz), 6.44 (d, 1H, J= 6.1 Hz), 6.30 (s, 1H), 4.30 (d, 2H, J= 5.5 Hz), 1.39 (d, 4H, J= 2.2 Hz); EM(ESI$^+$) m/z 463.1 $(M + H)^+$.

EJEMPLO 252



579

N-(4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N-(4-fluorofenil)ciclopropano-1,1-dicarboxamida



A) ácido 1-((4-Fluorofenil)carbamoil)ciclopropanocarboxílico

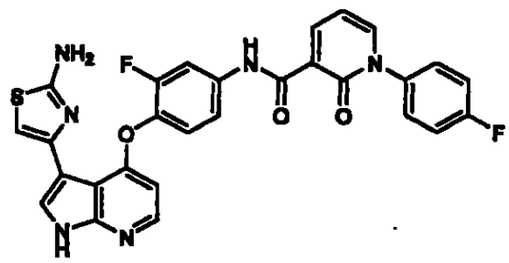
A una solución del ácido 1,1-ciclopropanocarboxílico (390 mg, 3.0 mmol, Aldrich) en THF (5 mL) a 0°C se agregó trietilamina (0.418 mL, 3.0 mmol). La mezcla de reacción se agitó a 0°C durante 30 minutos y se trató con cloruro de tionilo (0.219 mL, 3.0 mmol, Aldrich). La mezcla de reacción se agitó a 0°C durante 30 minutos adicionales, y se trató con una solución de 4-fluoroanilina (333 mg, 3.0 mmol, Aldrich) en 2 mL de THF. La mezcla de reacción se agitó a 0°C durante 2 h, luego se diluyó con 100 mL del acetato de etilo y se extrajo con NaOH 1N (10 mL). La fase acuosa se acidificó con HCl 1N a un pH 1-2. El sólido que se formó se colectó por filtración (508 mg, 76%). EM(ESI$^+$) m/z 224.2 $(M + H)^+$.

B) N-(4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-N-(4-fluorofenil)ciclopropano-1,1-dicarboxamida

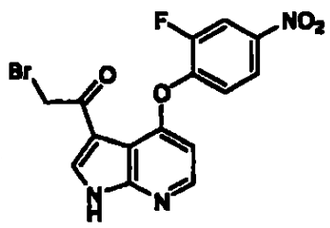
Se preparó en una manera similar como en la etapa B del ejemplo 251 (41 mg, 73%). ^{1}H RMN (DMSO-d_6) δ 11.97 (br s, 1H),

10.35 (s, 1H), 9.99 (s, 1H), 8.12 (d, 1H, J= 5.5 Hz), 7.85 (d, 1H, J= 13.2 Hz), 7.62 (m, 2H), 7.43 (m, 2H), 7.36 (t, 1H, J= 9.4 Hz), 7.14 (t, 2H, J= 9.1 Hz), 6.43 (d, 1H, J= 5.5 Hz), 6.29 (s, 1H), 1.46 (d, 4H, J= 2.8 Hz); EM(ESI$^+$) m/z 449.1 (M + H)$^+$.

EJEMPLO 253



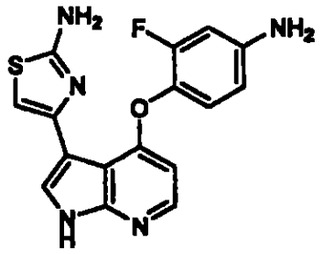
N-(4-(3-(2-Aminotiazol-4-il)-1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridina-3-carboxamida



A) 2-Bromo-1-(4-(2-fluoro-4-nitrofenoxi)-1H-pirrolo[2,3-b]piridin-3-il)etanona

A una solución de 4-(2-fluoro-4-nitrofenoxi)-1H-pirrolo[2,3-b]piridina (1.00 g, 3.66 mmol, Compuesto A del ejemplo 132) en DCE (100 mL) a temperatura ambiente se agregó cloruro de aluminio (2.43, g, 18.3 mmol, Alfa

Aesar). La mezcla de reacción se agitó a temperatura ambiente durante 1 h y luego se trató con cloruro de bromoacetilo (7.32 mmol, Aldrich). La mezcla de reacción luego se agitó a temperatura ambiente durante 2 h y se apagó por la adición de 100 mL del EtOAc, 30 mL de MeOH, y 30 mL de K_2HPO_4 acuoso saturado. Esta mezcla se filtró a través de una almohadilla de Celite®. La capa orgánica se lavó con salmuera, se secó ($MgSO_4$), y se concentró in vacuo. El residuo se purificó por cromatografía instantánea (SiO_2, se eluyó con 2-5% MeOH en diclorometano) para proporcionar el producto deseado (1.12 g, 78%) como un sólido amarillo ligero. EM(ESI$^+$) m/z 393.9 $(M + H)^+$.



B) 4-(4-(4-Amino-2-fluorofenoxi)-1H-pirrolo[2,3-b]piridin-3-il)tiazol-2-amina

A una solución de 2-bromo-1-(4-(2-fluoro-4-nitrofenoxi)-1H-pirrolo[2,3-b]piridin-3-il)etanona (392 mg, 1.0 mmol) en ácido acético (10 mL) se agregó tiourea (228 mg, 3.0 mmol, Aldrich). La mezcla de reacción se agitó a temperatura ambiente durante 3 h, y luego se diluyó con 50 mL del EtOAc. La mezcla de reacción se lavó

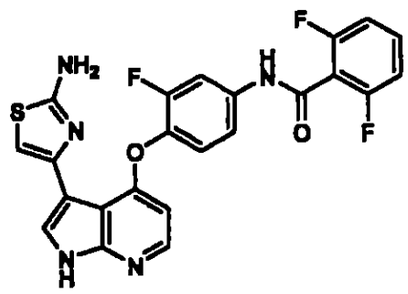
con una solución de $NaHCO_3$ acuoso saturado y salmuera. La capa orgánica se secó ($MgSO_4$) y se concentró in vacuo para dar un sólido amarillo ligero. El sólido se disolvió en un solvente mezclado (20 mL de THF y 40 mL de MeOH). Cloruro de amonio (267 mg, 5.0 mmol, EMD) y polvo de Zn (327 mg, 5.0 mmol, Aldrich). Luego se agregaron a la solución resultante. La mezcla de reacción se agitó a temperatura ambiente durante la noche, se diluyó con 100 mL del EtOAc y se filtró a través de una almohadilla de Celite®. El filtrado se concentró in vacuo y el residuo resultante se purificó por CLAR preparativa. Las fracciones deseadas se combinaron, se neutralizaron con la solución $NaHCO_3$ acuosa saturada, y se concentraron a presión reducida. El sólido que se formó se colectó por filtración (194 mg, 57% durante dos etapas). EM(ESI$^+$) m/z 342.2 $(M + H)^+$

D) N-(4-(3-(2-Aminotiazol-4-il)-1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridina-3-carboxamida

Se preparó en una manera similar como en la etapa C del ejemplo 242 (5.6 mg, 12%). ^1H RMN (CD_3OD) δ 8.60 (dd, 1H, J= 5.5, 1.7 Hz), 8.08 (d, 1H, J= 5.5 Hz), 7.90-7.88 (m, 2H), 7.67 (s, 1H), 7.45-7.42 (m, 2H), 7.29 (d, 1H, J= 5.5 Hz), 7.25-7.18 (m, 4H), 6.65 (t,

1H, J= 7.4 Hz), 6.43 (d, 1H, J= 6.1 Hz); EM(ESI$^+$) m/z 557.1 $(M + H)^+$.

EJEMPLO 254

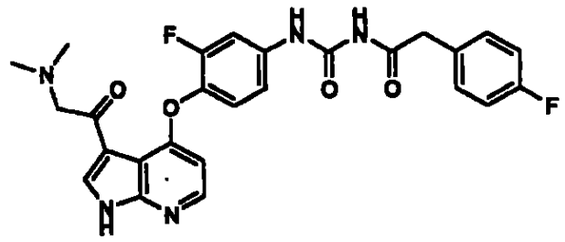


N-(4-(3-(2-Aminotiazol-4-il)-1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-2,6-difluorobenzamida, sal del ácido trifluoroacético

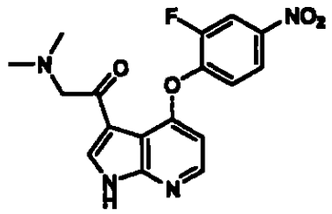
A una solución de 4-(4-(4-amino-2-fluorofenoxi)-1H-pirrolo[2,3-b]piridin-3-il)tiazol-2-amina (20 mg, 0.06 mmol, Compuesto B del ejemplo 253) en 0.5 mL de piridina a -20°C se agregó una solución de cloruro de 2,6-difluorobenzoilo (10.6 mg, 0.06 mmol, Aldrich) en 0.3 mL de diclorometano. La mezcla de reacción se agitó a -20°C durante 30 minutos y se apagó por la adición de MeOH (0.5 mL). La mezcla de reacción se concentró in vacuo y el residuo resultante se purificó por CLAR preparativa. Las fracciones deseadas se combinaron, se concentraron a presión reducida, y se liofilizaron para proporcionar el producto deseado (sal TFA, 9.2 mg, 22%) como un sólido blanco. ^{1}H RMN (CD_3OD) δ 8.10 (d, 1H, J= 6.1 Hz), 7.68 (s, 1H), 7.48-7.37 (m, 2H), 7.24 (t, 1H, J= 8.3 Hz), 7.05-7.01

(m, 3H), 6.86 (s, 1H), 6.46 (d, 1H, J= 5.5 Hz); EM(ESI$^+$) m/z 482.1 $(M + H)^+$.

EJEMPLO 255



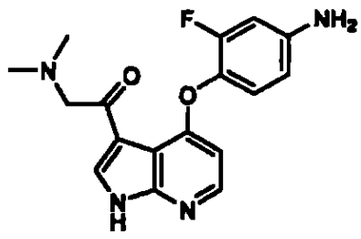
1-(4-(3-(2-(Dimetilamino)acetil)-1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea



B) 2-(Dimetilamino)-1-(4-(2-fluoro-4-nitrofenoxi)-1H-pirrolo[2,3-b]piridin-3-il)etanona

A una solución de 2-bromo-1-(4-(2-fluoro-4-nitrofenoxi)-1H-pirrolo[2,3-b]piridin-3-il)etanona (96 mg, 0.24 mmol, Compuesto A del ejemplo 253) en THF (5 mL) a 0°C se agregó dimetilamina (solución 1.0 M en THF, 0.72 mL, 0.72 mmol). La mezcla de reacción se agitó a 0°C durante 1 h y se concentró a presión reducida para dar el producto deseado (80 mg, 93%) como un sólido amarillo ligero, el cual se lavó con agua fría y se secó al aire. EM (ESI$^+$) m/z

359.2 $(M + H)^+$.



C) 1-(4-(4-Amino-2-fluorofenoxi)-1H-pirrolo[2,3-b]piridin-3-il)-2-(dimetilamino)etanona

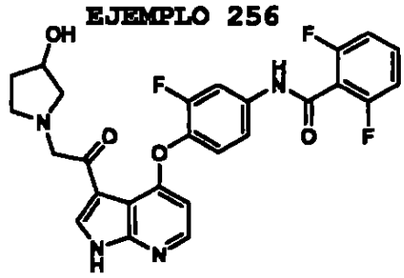
A una solución de 2-(dimetilamino)-1-(4-(2-fluoro-4-nitrofenoxi)-1H-pirrolo[2,3-b]piridin-3-il)etanona (80 mg, 0.22 mmol) en un solvente mezclado (5 mL de THF y 5 mL de MeOH) se agregaron cloruro de amonio (64.2 mg, 1.2 mmol, EMD) y polvo de Zn (78.4 mg, 1.2 mmol, Aldrich). La mezcla de reacción se agitó a temperatura ambiente durante la noche, se diluyó con 30 mL del EtOAc y se filtró a través de una almohadilla de Celite®. El filtrado se concentró in vacuo y el residuo resultante se purificó por CLAR preparativa. Las fracciones deseadas se combinaron, se neutralizaron con una solución de $NaHCO_3$ acuoso saturado, y se concentró in vacuo. El sólido que se formó se colectó por filtración (51 mg, 71 %). EM(ESI$^+$) m/z 328.1 $(M + H)^+$.

D) 1-(4-(3-(2-(Dimetilamino)acetil)-1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea

Se preparó en una manera similar como en la etapa C del

ejemplo 132 (5.7 mg, 11 %). ^{1}H RMN (CD_3OD) δ 10.67 (s, 1H), 8.27 (s, 1H), 8.08 (d, 1H, J= 6.1 Hz), 7.65 (d, 1H, J= 12.6 Hz), 7.24-7.16 (m, 4H), 6.96 (t, 2H, J= 8.8 Hz), 6.45 (d, 1H, J= 5.5 Hz), 4.74 (s, 2H), 3.60 (s, 2H), 2.86 (s, 6H); EM(ESI$^+$) m/z 508.2 $(M + H)^+$.

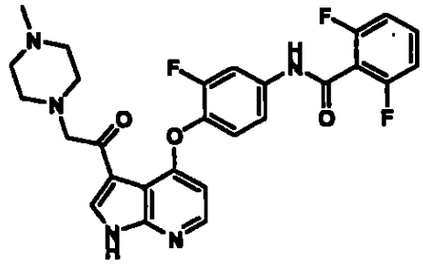
EJEMPLO 256



2,6-Difluoro-N-(3-fluoro-4-(3-(2-(3-hidroxipirrolidin-1-il)acetil)-1H-pirrolo[2,3-b]piridin-4-iloxi)fenil)benzamida

Se preparó en una manera similar como en el ejemplo 254. ^{1}H RMN (CD_3OD) δ 8.29 (d, 1H, J= 6.6 Hz), 8.13 (d, 1H, J= 5.5 Hz), 7.80 (dd, 1H, J= 12.7,2.2 Hz), 7.46-7.38 (m, 2H), 7.23 (t, 1H, J= 9.1 Hz), 7.03 (t, 2H, J= 8.3 Hz), 6.53 (d, 1H, J= 5.5 Hz), 5.01-4.86 (m, 2H), 4.49-4.46 (m, 1H), 3.77-3.64 (m, 2H), 3.35-3.06 (m, 2H), 2.25-1.98 (m, 2H); EM(ESI$^+$) m/z 511.2 $(M + H)^+$.

EJEMPLO 257

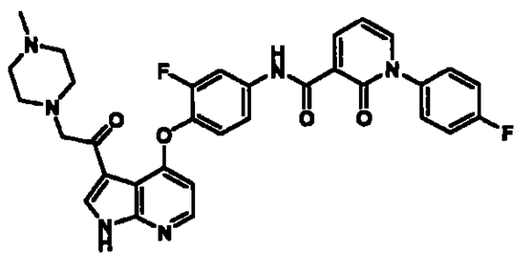


587

2,6-Difluoro-N-(3-fluoro-4-(3-(2-(4-metilpiperazin-1-il)acetil)-1H-pirrolo[2,3-b]piridin-4-iloxi)fenil)benzamida

Se preparó en una manera similar como en el ejemplo 254. ^{1}H RMN (CD_3OD) δ 8.23 (s, 1H), 8.11 (d, 1H, J= 5.5 Hz), 7.79 (dd, 1H, J= 12.1, 2.2 Hz), 7.46-7.34 (m, 2H), 7.16 (t, 1H, J= 8.8 Hz), 7.03 (t, 2H, J= 8.3 Hz), 6.53 (d, 1H, J= 6.1 Hz), 4.11 (s, 2H), 3.21-2.92 (m, 8H), 2.76 (s, 3H); EM(ESI$^+$) m/z 524.3 $(M + H)^+$.

EJEMPLO 258

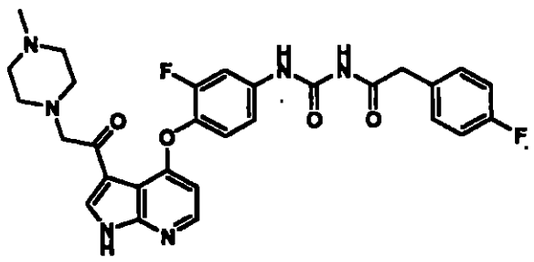


N-(3-Fluoro-4-(3-(2-(4-metilpiperazin-1-il)acetil)-1H-pirrolo[2,3-b]piridin-4-iloxi)fenil)-1-(4-fluorofenill)-2-oxo-1,2-dihidropiridina-3-carboxamida

Se preparó en una manera similar como en el ejemplo 253. ^{1}H RMN (CD_3OD) δ 8.59 (dd, 1H, J= 7.2, 2.2 Hz), 8.53 (s, 1H), 8.08 (d, 1H, J= 5.5 Hz), 7.89-7.85 (m, 2H), 7.44-7.41 (m, 2H), 7.28-7.18 (m, 3H), 7.15 (1, 1H, J= 8.8 Hz), 6.65 (1, 1H, J= 6.7 Hz), 6.48 (d, 1H, J= 5.5 Hz), 4.13 (s, 2H), 3.21-2.89 (bm, 8), 2.76 (s, 3H); EM(ESI$^+$) m/z 599.2 $(M + H)^+$.

588

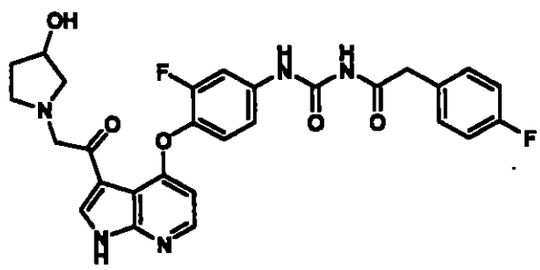
EJEMPLO 259



1-(3-Fluoro-4-(3-(2-(4-metilpiperazin-1-il)acetil)-1H-pirrolo[2,3-b]piridin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)urea

Se preparó en una manera similar como en el ejemplo 255. ^{1}H RMN (CD_3OD) δ 8.28 (s, 1H), 8.12 (d, 1H, J= 6.1 Hz), 7.66 (dd, 1H, J= 10.1, 2.8 Hz), 7.28-7.16 (m, 4H), 6.97-6.92 (m, 3H), 6.51 (d, 1H, J= 6.1 Hz), 4.43 (s, 2H), 3.88 (s, 2H), 3.49 (s, 2H), 3.37-3.20 (m, 4H), 2.82 (s, 3H); EM(ESI$^+$) m/z 563.2 $(M + H)^+$.

EJEMPLO 260

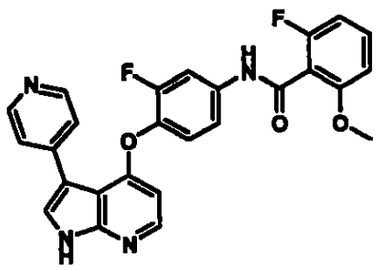


1-(3-Fluoro-4-(3-(2-(3-hidroxipirrolidin-1-il)acetil)-1H-pirrolo[2,3-b]piridin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)urea

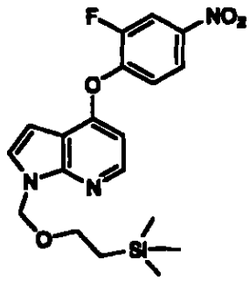
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Se preparó en una manera similar como en el ejemplo 255. ^{1}H RMN (CD_3OD) δ 10.69 (s, 1H), 8.27 (d, 1H, J= 8.8 Hz), 8.09 (d, 1H, J= 5.5 Hz), 7.66 (d, 1H, J= 12.7 Hz), 7.27-7.16 (m, 4H), 6.98 (t, 2H, J= 8.8 Hz), 6.47 (d, 1H, J= 5.5 Hz), 4.99 (m, 1H), 4.49-4.44 (m, 2H), 3.90-3.68 (m, 2H), 3.62 (s, 2H), 3.37-3.09 (m, 2H), 2.15-1.92 (m, 2H); EM(ESI$^+$) m/z 550.1 $(M + H)^+$.

EJEMPLO 261



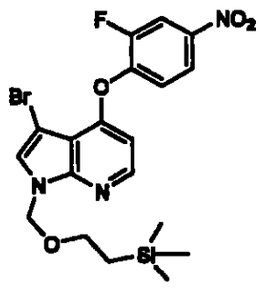
2-Fluoro-N-(3-fluoro-4-(3-(Piridin-4-il)-1H-pirrolo[2,3-b]piridin-4-iloxi)fenil)-6-metoxibenzamida



A) 4-(2-Fluoro-4-nitrofenoxi)-1-((2-(trimetilsilil)etoxi)metil)-1H-pirrolo[2,3-b]piridina

A una solución de 4-(2-fluoro-4-nitrofenoxi)-1H-pirrolo[2,3-b]piridina (1.68 g, 6.15 mmol, Compuesto A del

ejemplo 132) en 20 mL de DMF a -40°C se agregó hidruro de sodio (271 mg, 6.77 mmol, 60% en aceite mineral, Aldrich). La mezcla de reacción se agitó a 0°C durante 30 minutos, se enfrió a -40°C, y se trató con cloruro de 2-(trimetilsilil)etoximetilo (1.20 mL, 6.77 mmol, Aldrich). La mezcla de reacción se agitó a temperatura ambiente durante 1 h, se apagó por la adición de agua fría (40 mL) y se extrajo con EtOAc (3 x 100mL). Los extractos orgánicos combinados se secaron ($MgSO_4$) y se concentraron in vacuo para dar el producto deseado (2.40 g, 97%) como un sólido café. EM(ESI$^+$) m/z 404.2 $(M + H)^+$.

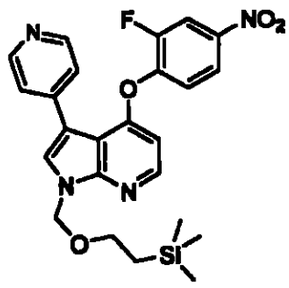


B) 3-Bromo-4-(2-fluoro-4-nitrofenoxi)-1-((2-(trimetilsilil)etoxi)metil)-1H-pirrolo[2,3-b]piridina

A una solución de 4-(2-fluoro-4-nitrofenoxi)-1-((2-(trimetilsilil)etoxi)metil)-1H-pirrolo[2,3-b]piridina (2.40 g, 5.96 mmol) en 20 mL de acetonitrilo a 0°C se agregó una solución de NBS (1.01 g, 5.69 mmol, Aldrich) en 10 mL de acetonitrilo. La mezcla de reacción se agitó a 0°C durante 30 minutos, se apagó por la adición de agua fría (50 mL), y se extrajo con EtOAc (3 x 120 mL). Los extractos orgánicos combinados se secaron ($MgSO_4$) y se

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concentraron in vacuo. El residuo se purificó por cromatografía instantánea (SiO_2, se eluyó con diclorometano) para proporcionar el producto deseado (2.70 g, 94%) como un aceite amarillo ligero. EM (ESI^+) m/z 482.9 $(M + H)^+$.

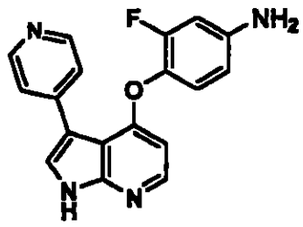


C) 4-(2-Fluoro-4-nitrofenoxi)-3-(piridin-4-il)-1-((2-(trimetilsilil)etoxi)metil)-1H-pirrolo[2,3-b]piridina

Un tubo sellado se cargó con una solución de 3-bromo-4-(2-fluoro-4-nitrofenoxi)-1-((2-(trimetilsilil)etoxi)metil)-1H-pirrolo[2,3-b]piridina (480 mg, 1.0 mmol) en tolueno (5 mL), ácido piridin-4-ilborónico (246 mg, 2.0 mmol, Lancaster), 0.5 mL del etanol, y fosfato de potasio (1.0 mL, solución 2M, 2.0 mmol). Se burbujeó el argón a través de una mezcla durante 15 minutos, y la mezcla de reacción se trató con tetraquis(trifenilfosfina)Pd(0) (58 mg, 0.05 mmol, Strem). El tubo se selló y la mezcla se calentó a 95°C durante 18 h con agitación vigorosa. La mezcla de reacción luego se enfrió a temperatura ambiente y se diluyó con EtOAc. La mezcla se lavó con una solución $NaHCO_3$ acuosa saturada y

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salmuera, se secó ($MgSO_4$), y se concentró in vacuo. El residuo se purificó por cromatografía instantánea (SiO_2, se eluyó con 2% de MeOH en diclorometano) para dar el producto deseado (237 mg, 49%) como un aceite café espeso. EM(ESI$^+$) m/z 481.1 $(M + H)^+$.



D) 3-Fluoro-4-(3-(piridin-4-il)-1H-pirrolo[2,3-b]piridin-4-iloxi)bencenamina

A una solución de 4-(2-fluoro-4-nitrofenoxi)-3-(piridin-4-il)-1-((2-(trimetilsilil)etoxi)metil)-1H-pirrolo[2,3-b]piridina (237 mg, 0.49 mmol) en un solvente mezclado (8 mL de MeOH y 4 mL de THF) se agregaron cloruro de amonio (131 mg, 2.49 mmol, EMC) y polvo de zinc (163 mg, 2.49 mmol, Aldrich). La mezcla de reacción se agitó a temperatura ambiente durante 3 h, se diluyó con EtOAc (40 mL), y se filtró a través de una almohadilla de Celite®. El filtrado se concentró in vacuo para dar un sólido. EM(ESI$^+$) m/z 451.3 $(M + H)^+$. El sólido se disolvió en 15 mL de THF y se trató con TBAF (4 mL, solución 1.0 M en THF, Aldrich) y etano-1,2-diamina (0.4 mL, Aldrich). La mezcla de reacción se pusó a reflujo durante 16 h, se enfrió a temperatura ambiente, se diluyó con EtOAc, se lavó con salmuera, se

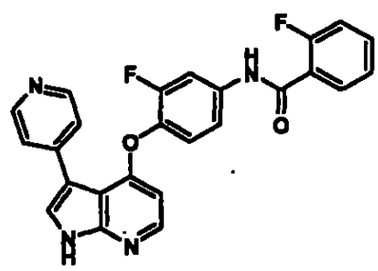
593

secó ($MgSO_4$), y se concentró in vacuo. El residuo se purificó por cromatografía instantánea (SiO_2, se eluyó con 2-5% MeOH en diclorometano) para proporcionar el producto deseado (127 mg, 81% durante dos etapas). EM (ESI^+) m/z 321.2 $(M + H)^+$.

E) 2-Fluoro-N-(3-fluoro-4-(3-(piridin-4-il)-1H-pirrolo[2,3-b]piridin-4-iloxi)fenil)-6-metoxibenzamida

Se preparó en una manera similar como en el ejemplo 254 (3.2 mg, 7%). ^1H RMN (DMSO-d_6) δ 12.92 (s, 1H), 10.80 (s, 1H), 8.72 (d, 2H, J= 7.2 Hz), 8.44 (s, 1H), 8.31 (d, 2H, J= 7.2 Hz), 8.16 (d, 2H, J= 5.5 Hz), 7.94-7.86 (m, 1H), 7.55-7.41 (m, 2H), 6.97-6.91 (m, 1H), 6.88 (t, 1H, J= 8.8 Hz), 6.45 (d, 1H, J= 5.5 Hz), 3.78 (s, 3H); EM(ESI^+) m/z 473.1 $(M + H)^+$.

EJEMPLO 262

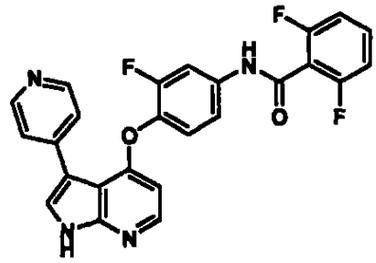


2-Fluoro-N-(3-fluoro-4-(3-(piridin-4-il)-1H-pirrolo[2,3-b]piridin-4-iloxi)fenil)benzamida

Se preparó en una manera similar como en el ejemplo 261.

^{1}H RMN (DMSO-d_6) δ 12.97 (s, 1H), 10.76 (s, 1H), 8.78 (d, 2H, J= 8.8 Hz), 8.50 (s, 1H), 8.36 (d, 2H, J= 6.1 Hz), 8.23 (d, 1H, J= 5.5 Hz), 7.96 (d, 1H, J= 8.8 Hz), 7.70-7.54 (m, 4H), 7.39-7.35 (m, 2H), 6.50 (d, 1H, J= 5.5 Hz); EM(ESI$^+$) m/z 443.1 $(M + H)^+$.

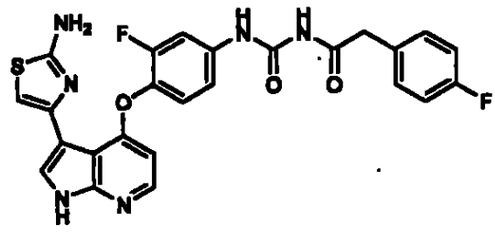
EJEMPLO 263



2,6-Difluoro-N-(3-fluoro-4-(3-(piridin-4-il)-1H-pirrolo[2,3-b]piridin-4-iloxi)fenil)benzamida

Se preparó en una manera similar como en el ejemplo 261. ^{1}H RMN (DMSO-d_6) δ 12.89 (s, 1H), 11.10 (s, 1H), 8.70 (d, 2H, J= 6.6 Hz), 8.42 (s, 1H), 8.27 (d, 2H, J= 6.6 Hz), 8.16 (d, 1H, J= 5.5 Hz), 7.86 (d, 1H, J= 11.6 Hz), 7.58-7.48 (m, 3H), 7.23 (t, 2H, J= 8.3 Hz), 6.45 (d, 1H, J= 5.5 Hz); EM (ESI$^+$) m/z 461.1 $(M + H)^+$.

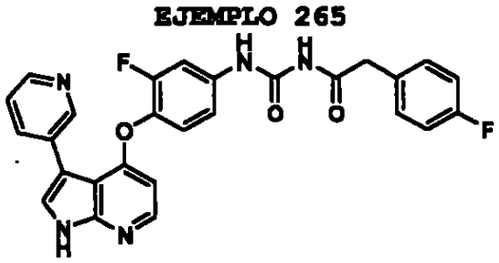
EJEMPLO 264



1-(4-(3-(2-Aminotiazol-4-il)-1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea, sal del ácido trifluoroacético

A una solución de 4-(4-(4-amino-2-fluorofenoxi)-1H-pirrolo[2,3-b]piridin-3-ill)tiazol-2-amina (34 mg, 0.1 mmol, Compuesto B del ejemplo 253) en un solvente mezclado (0.5 mL de DMF y 0.5 mL de THF) a temperatura ambiente se agregó una solución de 2-(4-fluorofenil)acetil isocianato en tolueno (0.4 M, 0.25 ml, 0.1 mmol, Compuesto C del Ejemplo 4). La mezcla de reacción se agitó a temperatura ambiente durante 1 h, se concentró in vacuo y el residuo resultante se purificó por CLAR preparativa. La fracciones deseadas se combinaron, se concentraron a presión reducida, y se liofilizaron para proporcionar el producto deseado (sal TFA, 21.2 mg, 28%) como un sólido blanco. ^{1}H RMN (CD_3OD) δ 10.69 (s, 1H), 8.08 (d, 1H, J= 5.5 Hz), 7.68 (s, 1H), 7.66 (d, 1H, J= 12.1 Hz), 7.26-7.18 (m, 4H), 6.98 (t, 2H, J= 8.8 Hz), 6.84 (s, 1H), 6.42 (d, 1H, J= 6.1 Hz), 3.62 (s, 2H); EM(ESI$^+$) m/z 521.1 (M + H)$^+$.

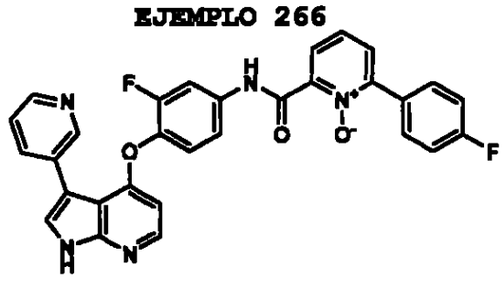
EJEMPLO 265



1-(3-Fluoro-4-(3-(piridin-3-il)-1H-pirrolo[2,3-b]piridin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)urea

Se preparó en una manera similar como en el ejemplo 264. ^{1}H RMN (DMSO-d_6) δ 12.71 (s, 1H), 11.04 (s, 1H), 10.61 (s, 1H), 9.18 (s, 1H), 8.84 (d, 1H, J= 8.3 Hz), 8.74 (d, 1H, J= 5.5 Hz), 8.20 (d, 1H, J= 5.5 Hz), 8.12 (s, 1H), 8.06 (dd, 1H, J= 8.3, 2.8 Hz), 7.78 (dd, 1H, J= 12.7,2.2 Hz), 7.47 (1, 1H, J= 8.8 Hz), 7.40-7.34 (m, 3H), 7.16 (t, 2H, J= 8.8 Hz), 6.41 (d, 1H, J= 5.5 Hz), 3.75 (s, 2R); EM(ESI$^+$) m/z 500.1 $(M + H)^+$.

EJEMPLO 266

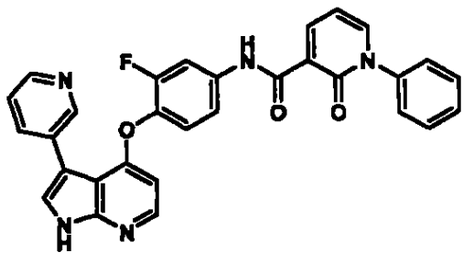


[3-fluoro-4-(3-piridin-3-il-1H-pirrolo[2,3-b]piridin-4-iloxi)-fenil]-amida del ácido 6-(4-Fluoro-fenil)-1-oxi-piridina-2-carboxílico

Se preparó en una manera similar como en el ejemplo 241. ^{1}H RMN (DMSO-d_6) 8 13.58 (s, 1H), 12.50 (s, 1H), 9.10 (s, 1H), 8.66 (d, 1H, J= 5.5 Hz), 8.32 (dd, 1H, J= 8.2, 2.2 Hz), 8.19 (d, 1H, J= 5.5 Hz), 8.05-8.02 (m, 2H), 7.89-7.85 (m, 5H), 7.73 (t, 1H, J= 7.7 Hz), 7.60 (d, 1H, J= 8.8 Hz), 7.50 (t, 1H, J= 8.8 Hz), 7.38 (t, 2H, J= 8.8 Hz), 6.41 (d, 1H, J= 6.5 Hz); EM (ESI$^+$) m/z 536.2 $(M + H)^+$.

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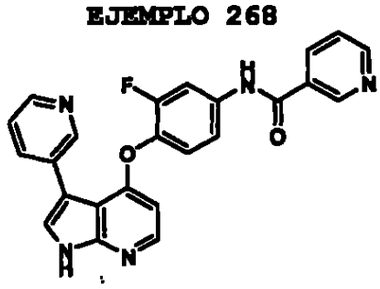
EJEMPLO 267



N-(3-Fluoro-4-(3-(piridin-3-il)-1H-pirrolo[2,3-b]piridin-4-iloxi)fenil)-2-oxo-1-fenil-1,2-dihidropiridina-3-carboxamida

Se preparó en una manera similar como en el ejemplo 245. ^{1}H RMN (DMSO-d_6) δ 12.48 (s, 1H), 12.15 (s, 1H), 9.09 (s, 1H), 8.65-8.59 (m, 3H), 8.18 (d, 1H, J= 5.5 Hz), 8.15 (dd, 1H, J= 6.6, 2.2 Hz), 8.04-7.99 (m, 2H), 7.88 (m, 1H), 7.59-7.46 (m, 7H), 6.74 (t, 1H, J= 7.2 Hz), 6.40 (d, 1H, J= 5.5 Hz); EM (ESI$^+$) m/z 518.1 (M + H)$^+$.

EJEMPLO 268

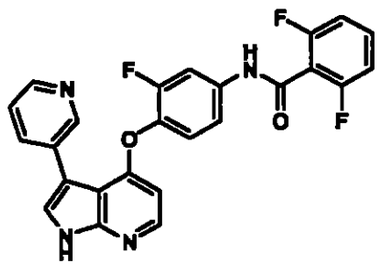


N-(3-Fluoro-4-(3-(piridin-3-il)-1H-pirrolo[2,3-b]piridin-4-iloxi)fenil)nicotinamida

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Se preparó en una manera similar como en el ejemplo 254. ^{1}H RMN (DMSO-d_6) δ 12.65 (s, 1H), 10.96 (s, 1H), 9.22 (s, 1H), 9.18 (s, 1H), 8.84 (t, 2H, J= 5.0 Hz), 8.74 (d, 1H, J= 5.5 Hz), 8.49 (d, 1H, J= 8.3 Hz), 8.21 (d, 1H, J= 5.5 Hz), 8.11 (d, 1H, J= 1.7 Hz), 8.08-8.01 (m, 2H), 7.73-7.69 (m, 2H), 7.54 (t, 1H, J= 8.8 Hz), 6.43 (d, 1H, J= 5.5 Hz); EM(ESI$^+$) m/z 426.2 $(M + H)^+$.

EJEMPLO 269

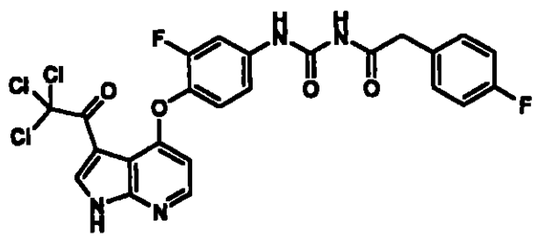


2,6-Difluoro-N-(3-fluoro-4-(3-(piridin-3-il)-1H-pirrolo[2,3-b]piridin-4-iloxi)fenil)benzamida

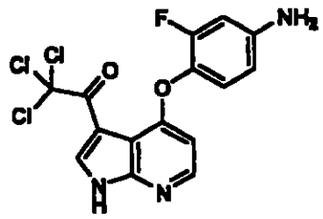
Se preparó en una manera similar como en el ejemplo 254. ^{1}H RMN (DMSO-d_6) δ 11.23 (s, 1H), 9.20 (d, 1H, J= 1.7 Hz), 8.87 (d, 1H, J= 8.3 Hz), 8.77 (d, 1H, J= 5.5 Hz), 8.23 (d, 1H, J= 5.5 Hz), 8.55 (s, 1H), 8.08 (dd, 1H, J= 8.2, 2.2 Hz), 7.90 (d, 1H, J= 13.7 Hz), 7.62-7.55 (m, 3H), 7.27 (t, 2H, J= 8.3 Hz), 6.50 (d, 1H, J= 5.5 Hz); EM(ESI$^+$) m/z 461.1 $(M + H)^+$.

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EJEMPLO 270



1-(3-Fluoro-4-(3-(2,2,2-tricloroacetil)-1H-pirrolo[2,3-b]piridin-4iloxi)fenil)-3-(2-(4-fluorofenil)acetil)urea



A) 1-(4-(4-Amino-2-fluorofenoxi)-1H-pirrolo[2,3-b]piridin-3-il)-2,2,2-tricloroetanona

A una solución de 4-(2-fluoro-4-nitrofenoxi)-1H-pirrolo[2,3-b]piridina (546 mg, 2.0 mmol, Compuesto A del ejemplo 132) en 100 mL de dicloroetano a temperatura ambiente se agregó cloruro de aluminio (1.33 g, 10 mmol, Alfa Aesar). La mezcla de reacción se agitó a temperatura ambiente durante 30 minutos, se trató con cloruro de tricloroacetilo (0.34 mL, 3.0 mmol), y luego se agitó a 45°C durante 5 h. Después de enfriarse a 0°C, Se agregó agua con hielo (30 mL) a la mezcla y se ajustó el pH hasta 7-8 con una solución K_2HPO_4 acuosa. La

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mezcla luego se filtró a través de una almohadilla de Celite®. La capa orgánica se secó ($MgSO_4$), se concentró in vacuo y el residuo resultante se purificó por cromatografía instantánea (SiO_2, se eluyó con MeOH al 2-7% en diclorometano) para proporcionar la 2,2,2-tricloro-1-(4-(2-fluoro-4-nitrofenoxi)-1H-pirrolo[2,3-b]piridin-3-il)etanona (498 mg, 60%). EM (ESI^+) m/z 417.9 $(M + H)^+$.

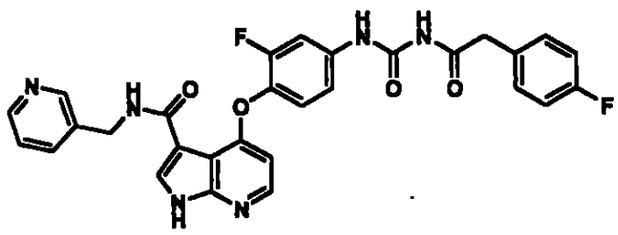
A una solución del intermediario de arriba (83 mg, 0.2 mmol) en un solvente mezclado (3 mL de MeOH y 2 mL de THF) se agregaron cloruro de amonio (53.5 mg, 1.0 mmol, EMC) y polvo de zinc (65.4 mg, 1.0 mmol, Aldrich). La mezcla de reacción se agitó a temperatura ambiente durante 3 h, se diluyó con EtOAc (10 mL), y se filtró a través de una almohadilla de Celite®. El filtrado se concentró in vacuo para dar el producto deseado (78 mg, 100%) como un sólido. EM(ESI^+) m/z 390.1, 392.1 $(M + H)^+$.

C) 1-(3-Fluoro-4-(3-(2,2,2-tricloroacetil)-1H-pirrolo[2,3-b]piridin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)urea

Se preparó en una manera similar como en el ejemplo 264 (33 mg, 37%). ^1H RMN (DMSO-d_6) δ 13.18 (s, 1H), 11.02 (s, 1H), 10.57 (s, 1H), 8.62 (s, 1H), 8.25 (d, 1H, J= 5.5 Hz), 7.78 (dd, 1H, J= 10.5, 2.2 Hz), 7.38-7.35 (m, 3R), 7.28 (t, 1H, J= 9.4 Hz), 7.18 (t, 2H, J= 8.8 Hz), 6.52 (d, 1H, J= 5.5 Hz), 3.75 (s, 2H); EM(ESI^+) m/z 567.05 $(M + H)^+$.

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EJEMPLO 271

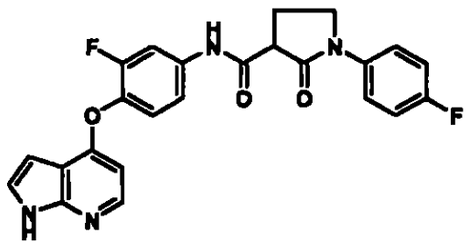


1-(4-(3-((piridin-3-ilmetil)carbamoil)-1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea

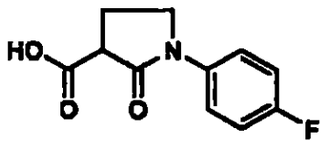
A una solución de 1-(3-fluoro-4-(3-(2,2,2-tricloroacetil)-1H-pirrolo[2,3-b]piridina 4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)urea (7.0 mg, 0.012 mmol, Ejemplo 270) en 0.5 mL de DMF se agregó 3-(aminometil)piridina (10 mg, 0.092 mmol, Aldrich). La mezcla de reacción se agitó a temperatura ambiente durante 1h, y se apagó por la adición de 1 mL de agua fría. El precipitado que se formó se colectó por filtración, se lavó con agua fría (1 mL) y acetonitrilo frío (1 mL) y se secó bajo vacío para proporcionar el producto deseado (4.3 mg, 64%) como un sólido blanco. ^{1}H RMN (DMSO-d_6) δ 12.38 (s, 1H), 11.03 (s, 1H), 10.57 (s, 1H),. 8.48 (s, 1H), 8.40 (t, 1H, J= 5.5 Hz), 8.34 (d, 1H, J= 3.3 Hz), 8.11 (d, 1H, J= 5.5 Hz), 8.00 (s, 1H), 7.73 (d, 1H, J = 13.2 Hz), 7.65 (d, 1H, J= 7.7 Hz), 7.37-7.29 (m, 4H), 7.16 (t, 3H, J= 8.8 Hz), 6.34 (d, IH, J= 5.5 Hz), 4.48 (d, 2H, J= 5.5 Hz), 3.74 (s, 2H); EM(ESI$^+$) m/z 567.1 $(M + H)^+$.

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EJEMPLO 272



N-(4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-1-(4-fluorofenil)-2-oxopirrolidina-3-carboxamida



A) ácido 1-(4-Fluorofenil)-2-oxopirrolidina-3-carboxílico

A una solución de 6,6-dimetil-5,7-dioxaspiro[2,5]-octano-4,8-diona (1.02 g, 6.0 mmol, Aldrich) en 3 mL de DMF se agregó 4-fluorobencenamina (666 mg, 6.0 mmol, Aldrich). La mezcla de reacción se agitó a temperatura ambiente durante la noche. La mezcla de reacción se vació en agua fría (10 mL). El precipitado que se formó se colectó por filtración, se lavó con agua, y se secó bajo vacío para proporcionar el producto deseado (980 mg, 73%) como un sólido color marrón. EM(ESI$^+$) m/z 224.3 $(M + H)^+$.

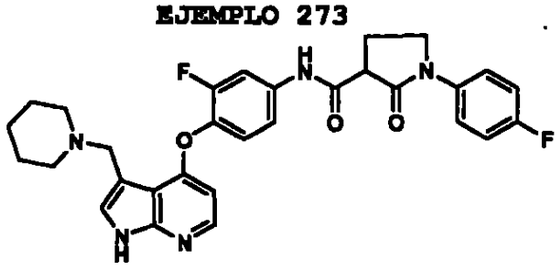
B) N-(4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-1-(4-fluorofenil)-2-oxopirrolidina-3-carboxamida

Se preparó en una manera similar como en la etapa B del

603

ejemplo 251 (98 mg, 49%). ^{1}H RMN (DMSO-d_6) δ 11.76 (s, 1H), 10.63 (s, 1H), 8.06 (d, 1H, J= 5.5 Hz), 7.86 (dd, 1H, J= 13.2, 2.2 Hz), 7.71-7.68 (m, 2H), 7.45-7.36 (m, 3H), 7.25 (t, 2H, J= 8.8 Hz), 6.38 (d, 1H, J= 6.5 Hz), 6.22 (dd, 1H, J= 3.3, 2.2 Hz), 3.94-3.89 (m, 2H), 3.77 (1, 1H, J= 8.5 Hz), 2.49-2.33 (m, 2H); EM(ESI$^+$) m/z 449.2 $(M + H)^+$.

EJEMPLO 273

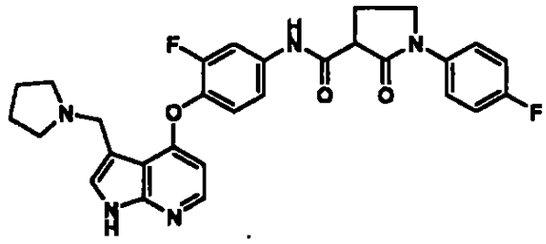


N-(3-Fluoro-4-(3-(piperidin-1-ilmetil)-1H-pirrolo[2,3-b]piridin-4-iloxi)fenil)-1-(4-fluorofenil)-2-oxopirrolidina-3-carboxamida, sal del ácido trifluoroacético

A una solución de N-(4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-1-(4-fluorofenil)-2-oxopirrolidina-3-carboxamida (22.4 mg, 0.05 mmol, Compuesto B del ejemplo 272) y paraformaldehido (2.4 mg, 0.08 mmol) en un solvente mezclado (1 mL de isopropanol y 0.2 mL de DMF) se agregó piperidina (8.5 mg, 0.1 mmol). La mezcla de reacción se calentó a 85°C durante 7 h, se concentró in vacuo, y el residuo resultante se purificó por CLAR preparativa. Las fracciones deseadas se liofilizaron para dar el producto deseado (sal TFA, 3.4 mg, 13%) como un sólido blanco. ^{1}H RMN (CD_3OD) δ 8.15 (d, 1H, J= 5.5 Hz), 7.91 (dd, 1H, J= 11.0, 2.2 Hz), 7.67-7.63 (m, 3H), 7.48-7.38 (m, 2H), 7.15 (t,

2H, J= 8.8 Hz), 6.45 (d, 1H, J= 5.5 Hz), 4.64 (s, 2H), 3.99-3.95 (m, 2H), 3.81 (t, 1H, J= 8.8 Hz), 3.61-3.59 (m, 2H), 3.10-3.06 (m, 2H), 2.61-2.47 (m, 2H), 1.97-1.93 (m,2H), 1.81-1.71 (m, 4H); EM(ESI+) m/z 546.2 $(M + H)^+$.

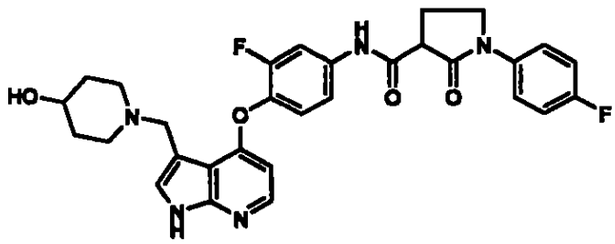
EJEMPLO 274



N-(3-Fluoro-4-(3-(pirrolidin-1-ilmetil)-1H-pirrolo[2,3-b]piridin-4-iloxi)fenil)-1-(4-fluorofenil)-2-oxopirrolidina-3-carboxamida

Se preparó en una manera similar como en el ejemplo 273. ^{1}H RMN (DMSO-d_6) δ 12.13 (s, 1H), 10.62 (s, 1H), 8.04 (d, 1H, J= 5.5 Hz), 7.84 (dd, 1H, J= 13.2, 2.2 Hz), 7.65-7.62 (m, 3H), 7.43-7.39 (m, 2H), 7.19 (1, 2H, J= 8.8 Hz), 6.25 (d, 1H, J= 6.5 Hz), 4.54 (d, 2H, J= 3.3 Hz), 3.91-3.85 (m, 2H), 3.72 (t, 1H, J= 8.5 Hz), 3.38-3.37 (m, 2H), 3.20-3.77 (m, 2H), 2.38-2.31 (m,2H), 1.95-1.91 (m, 2H), 1.81-1.76 (m, 2H); EM(ESI$^+$) m/z 532.2 $(M + H)^+$.

EJEMPLO 275

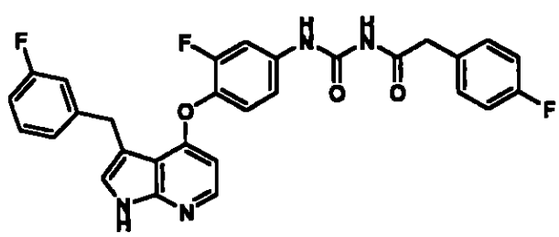


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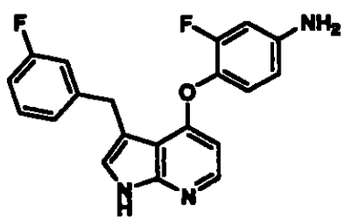
N-(3-Fluoro-4-(3-((4-hidroxipiperidin-1-il)metil)-1H-pirrolo[2,3-b]piridin-4-iloxi)fenil)-1-(4-fluorofenil)-2-oxopirrolidina-3-carboxamida

Se preparó en una manera similar como en el ejemplo 273. ^{1}H RMN (DMSO-d_6) δ 11.71 (s, 1H), 10.88 (s, 1H), 8.00 (d, 1H, J= 5.5 Hz), 7.79 (dd, 1H, J= 12.7, 2.2 Hz), 7.67-7.64 (m, 2H), 7.30-7.35 (m, 3H), 7.20 (t, 2H, J= 8.8Hz), 6.30 (d, 1H, J= 6.5 Hz), 6.16 (s, 1H), 4.51 (d, 1H, J= 4.4Hz), 3.83-3.79 (m, 2H), 3.38 (m, 1H), 3.70-2.69 (m, 5H), 2.28-2.19 (m, 3H), 1.65-1.62 (m, 2H), 1.37-1.26 (m, 2H); EM(ESI$^+$) m/z 562.2 (M + H)$^+$.

EJEMPLO 276



1-(4-(3-(3-Fluorobencil)-1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea



A) 4-(3-(3-Fluorobencil)-1H-pirrolo[2,3-b]piridin-4-iloxi)-3-

606

fluorobencenamina

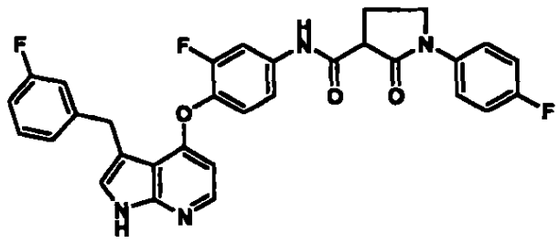
A una solución de 4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorobencenamina (49 mg, 0.2 mmol, Compuesto B del ejemplo 132) en 2 mL de metanol se agregaron hidróxido de sodio (40 mg, 1.0 mmol, EMD) y 3-fluorobenzaldehido (62 mg, 0.5 mmol, Aldrich). La mezcla de reacción se agitó a temperatura ambiente durante 16 h, se vació en agua fría (5 mL), y se extrajo con EtOAc (3 x 30 mL). Los extractos orgánicos se secaron ($MgSO_4$) y se concentraron in vacuo. El residuo se disolvió en 2 mL de diclorometano, y se trató con 1 mL de TFA y 0.2 mL de trietilsilana (Aldrich). La mezcla de reacción se agitó durante 1 h y se concentró a presión reducida. El residuo se purificó por CLAR preparativa y las fracciones deseadas se combinaron, se concentraron in vacuo, se neutralizaron con una solución $NaHCO_3$ acuosa saturada, y se extrajeron con diclorometano. Los extractos orgánicos se secaron ($MgSO_4$) y se concentraron in vacuo para dar el compuesto deseado (12.1 mg, 35% durante dos etapa). EM (ESI^+) m/z 351.4 $(M + H)^+$.

B) 1-(4-(3-(3-Fluorobencil)-1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea

Se preparó en una manera similar como en el ejemplo 264 (3.4 mg, 11 %). ^1H RMN (DMSO-d_6) δ 11.58 (s, 1H), 10.96 (s, 1H), 10.49 (s, 1H), 7.95 (d, 1H, J= 5.5 Hz), 7.67 (dd, 1H, J= 11.6, 2.1 Hz), 7.31-6.67 (m, 12H), 6.10 (d, 1H, J=

5.5 Hz), 4.09 (s, 2H), 3.68 (s, 2H); EM(ESI$^+$) m/z 531.2 (M + H)$^+$.

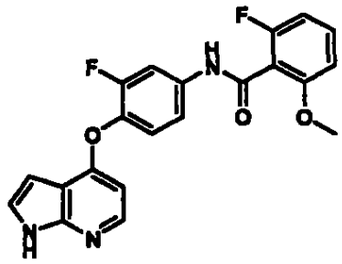
EJEMPLO 277



N-(4-(3-(3-Fluorobencil)-1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-1-(4-fluorofenil)-2-oxopirrolidino-3-carboxamida

Se preparó en una manera similar como en el ejemplo 273. ^{1}H RMN (DMSO-d_6) δ 11.74 (s, 1H), 10.62 (s, 1H), 8.03 (d, 1H, J= 5.5 Hz), 7.84 (dd, 1H, J= 12.7, 2.2 Hz), 7.71-7.68 (m, 2H), 7.41 (d, 1H, J= 8.8 Hz), 7.30 (d, 1H, J= 1.7 Hz), 7.26-7.22 (m, 3H), 7.16 (t, 1H, J= 8.5 Hz), 7.08 (d, 1H, J= 7.7 Hz), 7.01 (d, 1H, J= 10.4 Hz), 6.94 (t, 1H, J= 8.8 Hz), 6.22 (d, 1H, J= 5.5 Hz), 4.17 (s, 2H), 3.94-3.90 (m, 2H), 3.76 (t, 1H, J= 8.5 Hz), 2049-2.35 (m, 2H); EM(ESI$^+$) m/z 557.2 (M + H)$^+$.

EJEMPLO 278

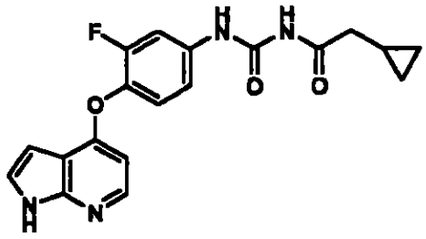


608

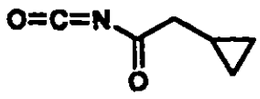
N-(4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-2-fluoro-6-metoxibenzamida

Se preparó en una manera similar como en el ejemplo 261 (12.1 mg, 31 %). ^{1}H RMN (DMSO-d_6) δ 11.97 (s, 1H), 10.86 (s, 1H), 8.14 (d, 1H, J= 5.5 Hz), 7.92 (dd, 1H, J= 13.2, 2.2 Hz), 7.54-7042 (m, 4H), 7.03 (d, 1H, J= 8.2 Hz), 6.95 (t, 1H, J= 8.8 Hz), 6048 (d, 1H, J= 6.1 Hz), 6.35 (d, 1H, J= 1.4 Hz); EM(ESI$^+$) m/z 396.2 $(M + H)^+$.

EJEMPLO 279



1-(4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-3-(2-ciclopropilacetil)urea



A) 2-Ciclopropilacetil isocianato

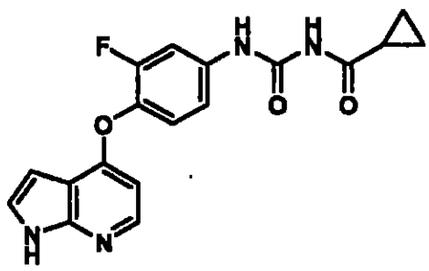
A una suspensión de cianato de plata (435 mg, 3.0 mmol, Aldrich) en 10 mL de tolueno se agregó cloruro de ciclopropilacetilo (313 mg, 3.0 mmol, Aldrich). La mezcla de reacción se puso a reflujo durante 2 h, se enfrió a temperatura ambiente y se filtró. El filtrado se usó como una

solución 0.3 M durante la siguiente reacción.

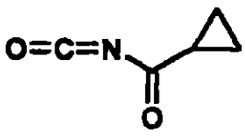
B) 1-(4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-3-(2-ciclopropilacetil)urea

Se preparó en una manera similar como en el ejemplo 264 (13.5 mg, 59%). ^{1}H RMN (CD_3OD) δ 8.03 (d, 1H, J= 5.5 Hz), 7.80-7.76 (m, 1H), 7.27-7.24 (m, 3H), 6.41 (d, 1H, J= 5.5 Hz), 6.38 (d, 1H, J= 3.9 Hz), 2.25 (d, 1H, J= 7.2 Hz), 0.64-0.59 (m, 2H), 0.28-0.23 (m, 2H); EM(ESI$^+$) m/z 369.2 (M + H)$^+$.

EJEMPLO 280



1-(4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-3-(ciclopropanocarbonil)urea



A) Ciclopropanocarbonil isocianato

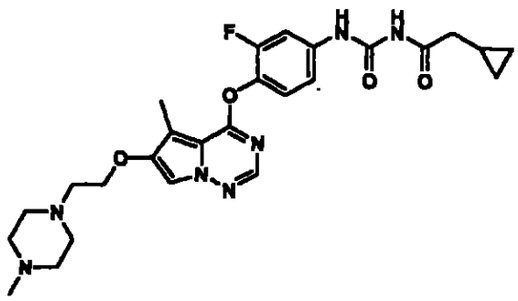
610

Se preparó en una manera similar como en la etapa A del ejemplo 279.

B) 1-(4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-3-(ciclopropanocarbonil)urea

Se preparó en una manera similar como en la etapa B del ejemplo 279 (17.2 mg, 60%). ^{1}H RMN (CD_3OD) δ 7.93 (d, 1H, J= 5.5 Hz), 7.57 (d, 1H, J= 13.8 Hz), 7.12-7.08 (m, 3H), 6.31 (m,2H), 1.02 (m, 2H), 0.90 (m, 2H); EM(ESI$^+$) m/z 355.19 (M + H)$^+$.

EJEMPLO 281

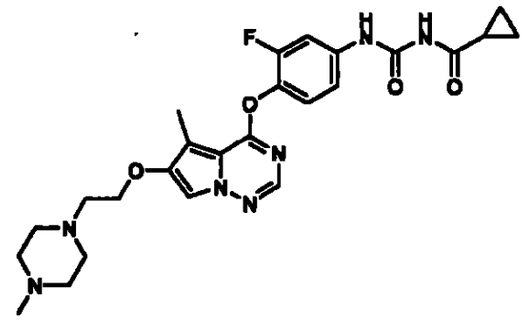


1-(2-Ciclopropilacetil)-3-(3-fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)urea

Se preparó en una manera similar como en el ejemplo 264 usando el compuesto B del ejemplo 45 y Compuesto A del ejemplo 279 (21.0 mg, 81%). ^{1}H RMN (CD_3OD) δ 7.81 (s, 1H), 7.74 (d, 1H, J= 5.5 Hz), 7.25 (m, 3H), 4.18 (t, 2H, J= 5.5 Hz), 3.35 (t, 2H, J= 1.7 Hz), 2.90 (t, 2H, J= 5.5 Hz), 2.74-2.54 (m, 4H), 2.45 (s, 3H), 2.33 (t, 4H, J= 2.8 Hz), 1.12 (m, 1H), 0.67-0.64 (m, 2H), 0.29-0.25 (m, 2H); EM(ESI$^+$) m/z 529.3 (M + H)$^+$.

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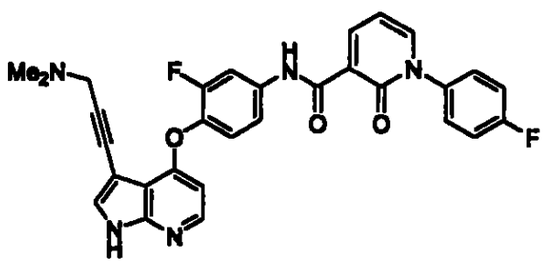
EJEMPLO 282



1-Ciclopropanocarbonil-3-(3-fluoro-4-(5-metil-6-(2-(4-metilpiperazin-1-il)etoxi)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)urea

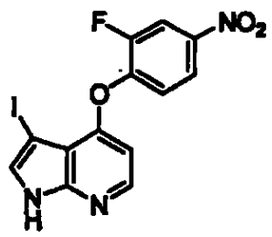
Se preparó en una manera similar como en el ejemplo 264 usando el compuesto B del ejemplo 45 y compuesto A del ejemplo 280 (20.3 mg, 64%). ^{1}H RMN (CD_3OD) δ 10.85 (s, 1H), 7.70 (s, IH), 7.76-7.72 (m, 2H), 7.22-7.14 (m, 2H), 4.14 (t, 2H, J= 5.5 Hz), 2.94 (t, 2H, J= 5.5 Hz), 2.89-2.60 (m, 4H), 2.78 (s, 3H), 2.34 (s, 4H), 1.70-1.67 (m, 1H), 0.99-0.95 (m, 2H), 0.91-0.86 (m, 2H); EM (ESI$^+$) m/z 512.3 $(M + H)^+$.

EJEMPLO 283



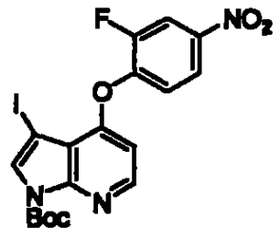
N-(4-(3-(3-(Dimetilamino)prop-1-inil)-1H-pirrolo[2,3-b]pir

idin-4-iloxi)-3-fluorofenil)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridina-3-carboxamida, sal del ácido trifluoroacético



A) 4-(2-Fluoro-4-nitrofenoxi)-3-yodo-1H-pirrolo[2,3-b]piridina

Una mezcla de 4-(2-fluoro-4-nitrofenoxi)-1H-pirrolo[2,3-b]piridina (550 mg, 2 mmol, Compuesto A del ejemplo 132) y N-yodosuccinimida (450 mg, 2 mmol) en CH_2Cl_2 (50 mL) se agitó a temperatura ambiente durante 1 h. La mezcla se lavó con salmuera, se secó sobre $MgSO_4$, y se pasó a través de una almohadilla corta de gel de sílice, se eluyó con EtOAc. El filtrado se concentró in vacuo para dar el producto deseado (rendimiento cuantitativo) como un sólido amarillo. CL/EM(ESI^+) m/z 400 $(M + H)^+$.

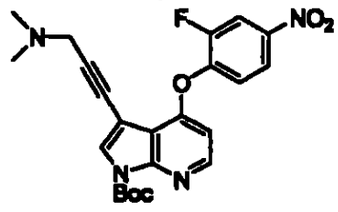


B) tert-Butil 4-(2-fluoro-4-nitrofenoxi)-3-yodo-1H-

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pirrolo[2,3-b]piridina-1-carboxilato

A una solución de 4-(2-fluoro-4-nitrofenoxi)-3-yodo-1H-pirrolo[2,3-b]piridina (400 mg, 1 mmol) en DMF (10 mL) a -40°C bajo N_2 se agregó NaH (60% en aceite mineral, 1.2 mmol). La mezcla se agitó a 0°C durante 20 min., y se enfrió a -40°C. A esta mezcla, se agregó Boc_2O (330 mg, 1.5 mmol). La mezcla se agitó a -40°C durante 1 h, se diluyó con una solución de citrato de sodio acuoso al 5%, se extrajo con EtOAc. La capa orgánica se secó sobre $MgSO_4$ y se concentró in vacuo. El compuesto crudo se purificó por cromatografía de columna instantánea (gel de sílice, 20% EtOAc/ CH_2Cl_2) para dar el compuesto deseado (460 mg, 92%) como un sólido amarillo. CL/EM(ESI$^+$) m/z 500 $(M + H)^+$.

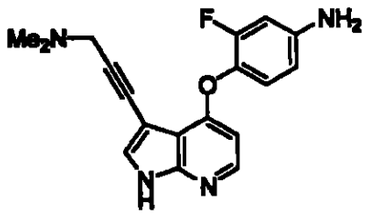


C) tert-Butil 3-(3-(dimetilamino)prop-1-inil)-4-(2-fluoro-4-nitrofenoxi)-1H-pirrolo[2,3-b]piridina-1-carboxilato

Una corriente de argón se burbujeó a través de una mezcla de tert-butil 4-(2-fluoro-4-nitrofenoxi)-3-yodo-1H-pirrolo[2,3-b]piridina-1-carboxilato (200 mg, 0.4 mmol), N,N-dimetilprop-2-in-1-amina (66 mg, 0.8 mmol), $Pd(dppf)_2Cl_2$:CH_2Cl_2 (33 mg, 0.04 mmol), y CuI (20 mg) en trietilamina (0.4 mL) y THF (3 mL) durante 5 minutos. La

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mezcla de reacción se calentó en un tubo sellado a 70°C durante 2 h y el solvente se retiró in vacuo. El compuesto crudo se purificó por cromatografía de columna instantánea (gel de sílice, 5% de MeOH/EtOAc) para proporcionar el producto deseado (170 mg, 95%) como un aceite amarillo. CL/EM(ESI$^+$) m/z 455 $(M + H)^+$.



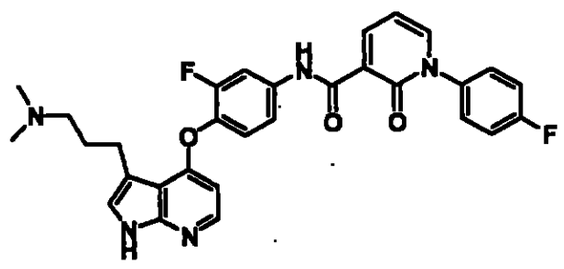
D) 4-(3-(3-(Dimetilamino)prop-1-inil)-1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorobencenamina

A una mezcla de tert-butil 3-(3-(dimetilamino)prop-1-inil)-4-(2-fluoro-4-nitrofenoxi)-1H-pirrolo[2,3-b]piridina-1-carboxilato (170 mg, 0.374 mmol) en THF (10 mL) y MeOH (10 mL), se agregó polvo de zinc (<10 micrones, 500 mg) y NH_4Cl (500 mg). La mezcla de reacción se agitó a temperatura ambiente durante 2 h, se diluyó con EtOAc, y se filtró a través de una almohadilla de Celite®. El filtrado se lavó con una solución de KH_2PO_4 acuoso saturado, se secó sobre $MgSO_4$, se filtró, y se concentró in vacuo para proporcionar el producto deseado (110 mg, 90%) como un sólido amarillo. CL/EM (ESI$^+$) m/z 325 $(M + H)^+$.

E) N-(4-(3-(3-(Dimetilamino)prop-1-inil)-1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridina-3-carboxamida, sal del ácido trifluoroacético

A una mezcla de 4-(3-(3-(dimetilamino)prop-1-inil)-1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorobencenamina (33 mg, 0.1 mmol), ácido 1-(4-fluorofenil)-2-oxo-1,2-dihidropiridina-3-carboxílico (46 mg, 0.2 mmol, Compuesto B del ejemplo 242), y HATU (Perseptive BiosysteEM, 76 mg, 0.2 mmol) en DMF (1 mL), se agregó DIPEA (0.1 mL). La mezcla de reacción se agitó a temperatura ambiente durante la noche y se concentró in vacuo. El compuesto crudo se purificó por CLAR preparativa, y las fracciones apropiadas se liofilizaron para proporcionar el compuesto del título (15 mg, sal TFA, 23%) como un sólido amarillo. ^{1}H RMN (CD_3OD) δ 8.73 (dd, 1H, J= 7.6, 2.4 Hz), 8.14 (d, 1H, J= 5.6 Hz), 8.00-8.16 (m, 2H), 7.74 (s, IH), 7.54-7.60 (m, 2H), 7.30-7.47 (m, 4H), 6.78 (dd, 1H, J= 6.8, 6.8 Hz), 6.47 (d, 1H, J= 5.6 Hz), 4.30 (s, 2H), 2.99 (s, 6H); CL/EM (ESI$^+$) m/z 540 $(M + H)^+$.

EJEMPLO 284



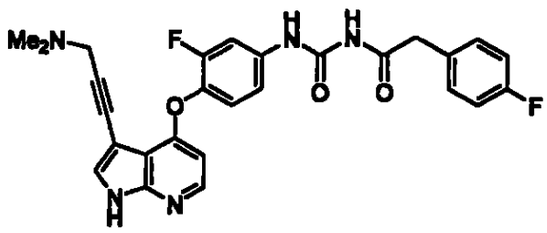
616

N-(4-(3-(3-(Dimetilamino)propil)-1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridina-3-carboxamida, sal del ácido trifluoroacético

Una mezcla de N-(4-(3-(3-(dimetilamino)prop-1-inil)-1-(1-(4-fluorofenil)-2-oxo-1,2-dihidropiridina-3-carbonil)-1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridina-3-carboxamida (32 mg, sal TFA, 0.037 mmol, se obtuvo como un subproducto en la etapa E del ejemplo 283), y Pd/C (10%, 100 mg) en MeOH (5 mL) se hidrogenó bajo 1 atm durante 1 h. La mezcla se burbujeó a través de una corriente de N_2 durante 5 minutos, se filtró a través de una almohadilla de Celite®. El filtrado se purificó por CLAR preparativa para proporcionar el compuesto del título como un sólido blanco (10 mg, sal TFA, 39% rendimiento). ^{1}H RMN (CD_3OD) δ 8.62 (dd, 1H, J= 7.2, 2.0 Hz), 8.04 (d, 1H, J= 6.4 Hz), 7.95 (dd, 1H, J= 12.8, 1.2 Hz), 7.90 (dd, 1H, J= 6.8, 2.4 Hz), 7.20-7.50 (m, 6H), 6.66 (t, 1H, J= 7.20 Hz), 6.43 (d, 1H, J= 6.4Hz), 3.11 (t, 2H, J= 8.0 Hz), 2.96 (t, 2H, J= 7.2 Hz), 2.77 (s, 6H), 2.11 (m, 2H); CL/EM (ESI$^+$) m/z 544 $(M + H)^+$.

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EJEMPLO 285

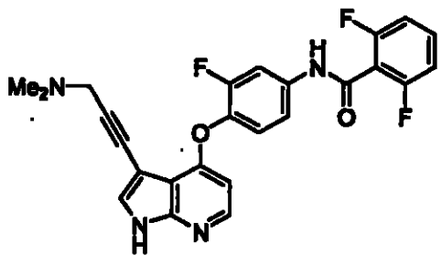


1-(4-(3-(3-(Dimetilamino)prop-1-inil)-1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea, sal del ácido trifluoroacético

A una solución de 4-(3-(3-(dimetilamino)prop-1-inil)-1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorobencenamina (15 mg, 0.046 mmol, Compuesto D del ejemplo 283) en THF (1.5 mL) se agregó 2-(4-fluorofenil)acetilisocianato (0.05 mmol, Compuesto C del ejemplo 4) a temperatura ambiente. La mezcla se agitó durante 1 h y se concentró in vacuo. El compuesto crudo se purificó por CLAR preparativa para dar el producto deseado (sal TFA, 12 mg, 42% rendimiento) como un sólido blanco. ^{1}H RMN (DMSO-d_6) δ 12.30 (s, 1H), 10.98 (s, 1H), 10.52 (s, 1H), 10.00 (s, 1H), 8.07 (d, 1H, J= 5.6Hz), 7.74(d, 1H, J= 2.4Hz), 7.73 (dd, 1H, J= 12.4, 2.4Hz), 7.25-7.40 (m, 4H), 7.10 (m, 2H), 6.26 (d, 1H, J= 5.2 Hz), 4.21 (s, 2H), 3.68 (s, 2H), 2.43 (s, 6R); CL/EM(ESI$^+$) m/z 504 $(M + H)^+$.

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EJEMPLO 286

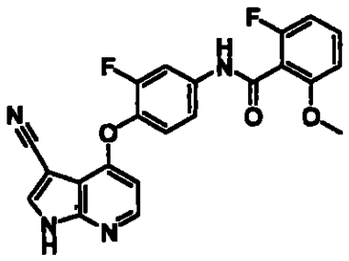


N-(4-(3-(3-(Dimetilamino)prop-1-inil)-1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-2,6-difluorobenzamida, sal del ácido trifluoroacético

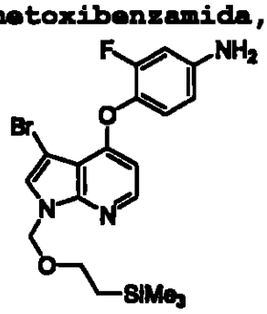
A una solución de 4-(3-(3-(dimetilamino)prop-1-inil)-1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorobencenamina (15 mg, 0.046 mmol, Compuesto D del ejemplo 283) y piridina (0.05 mL) en CH_2Cl_2 (1.0 mL) a 0°C, se agregó cloruro de 2,6-difluorobenzoilo (9 mg, 0.05 mmol). La mezcla se agitó a 0°C durante 30 minutos y se concentró in vacuo. El compuesto crudo se purificó por CLAR preparativa para dar el producto deseado (sal TFA, 11 mg, 41 %) como un sólido blanco. ^{1}H RMN (CD_3OD) δ 8.05 (d, 1H, J= 5.6 Hz), 7.82 (dd, 1H, J= 12.4, 2.4 Hz), 7.63 (s, 1H), 7.35-7.50 (m, 2H), 7.25 (t, 1H, J= 8.8 Hz), 7.00-7.06 (m, 2H), 6.38 (d, 1H, J= 5.6 Hz), 4.19 (s, 2H), 2.87 (s, 6H); CL/EM(ESI) m/z 465 $(M + H)^+$.

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EJEMPLO 287



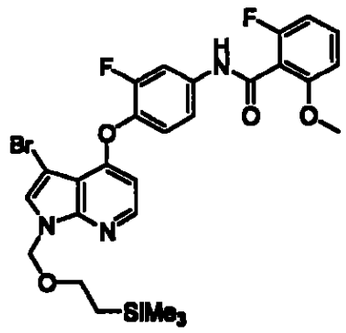
N-(4-(3-Ciano-1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-2-fluoro-6-metoxibenzamida, sal de clorohidrato



A) 4-(3-Bromo-1-((2-(trimetilsilil)etoxi)metil)-1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorobencenamina

Una mezcla de 3-bromo-4-(2-fluoro-4-nitrofenoxi)-1-((2-(trimetilsilil)etoxi)metil)-1H-pirrolo[2,3-b]piridina (626 mg, 1.3 mmol, Compuesto B del ejemplo 261), polvo de zinc (1.0 g), y cloruro de amonio (1.0 g) en THF (25 mL) y MeOH (25 mL) se agitó a temperatura ambiente durante la noche. La mezcla se diluyó con CH_2Cl_2 y se filtró a través de una almohadilla corta de Celite®. La solución resultante luego se concentró a presión reducida, y el residuo se purificó por cromatografía de columna instantánea (gel de sílice, se eluyó con 30% EtOAc/CH_2Cl_2) para dar el producto deseado (420 mg, 71

%) como un aceite claro. CL/EM(ESI$^+$) m/z 453 $(M + H)^+$.



B) N-(4-(3-Bromo-1-((2-(trimetilsilil)etoxi)metil)-1H-pirrolo[2,3-5b]piridin-4-iloxi)-3-fluorofenil)-2-fluoro-6-metoxibenzamida

A una solución agitada de 4-(3-bromo-1-((2-(trimetilsilil)etoxi)metil)-1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorobencenamina (400 mg, 0.85 mmol), ácido 2-fluoro-6-metoxibenzoico (226 mg, 1.33 mmol), y HATU (641 mg, 1.33 mmol) en DMF (6 mL) se agregó DIPEA (387 mg, 3 mmol), seguido por DMAP (50 mg). La mezcla resultante se agitó a temperatura ambiente durante la noche, se diluyó con EtOAc, y se lavó con una solución saturada de K_2HPO_4 acuoso saturado y salmuera. La capa orgánica se secó sobre $MgSO_4$ y se concentró in vacuo. El residuo se purificó por cromatografía de columna instantánea (gel de sílice, se eluyó con 30% de EtOAc/CH_2Cl_2) para dar el producto deseado (370 mg, 72%) como un sólido blanco. CL/EM(ESI) m/z 605 $(M + H)^+$.

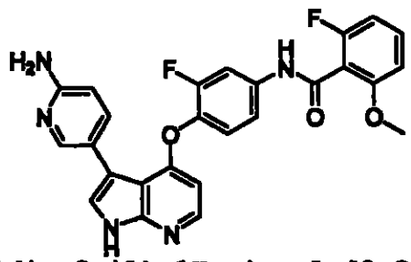
621

C) N-(4-(3-Ciano-1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-2-fluoro-6-metoxibenzamida, sal de clorohidrato

Una mezcla de N-(4-(3-bromo-1-((2-(trimetilsilil)etoxi)metil)-1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-2-fluoro-6-metoxibenzamida (30 mg, 0.05 mmol), $Zn(CN)_2$ (17 mg, 0.15 mmol), $Pd(dppf)_2Cl_2:CH_2Cl_2$ (5 mg, Aldrich), $-Zn(OAc)_2$ (1 mg) y polvo de zinc (1 mg) en DMF (0.6 mL) se calentó en un tubo sellado a 120°C durante 15 h. La mezcla se diluyó con CH_2Cl_2, se filtró a través de una almohadilla de Celite@ (CH_2Cl_2). El filtrado se lavó con salmuera, se secó sobre $MgSO_4$, se filtró, y se concentró a presión reducida. El residuo resultante se trató con TBAF (1 M en THF, 1.0 mmol) y etano-1,2-diamina (30 µL) en THF (3 mL). La mezcla se puso a reflujo durante 15 h y se concentró in vacuo. El residuo se purificó por CLAR preparativa. Las fracciones deseadas se liofilizaron para dar una sal TFA blanca, la cual se disolvió en una pequeña cantidad de $MeOH/H_2O$ con HCl 1N (0.1 mL). esta solución luego se liofilizó para proporcionar el compuesto del título (sal HCl, 12 mg, 53%) como un sólido blanco. ^1H RMN (DMSO-d_6) δ 10.80 (s, 1H), 8.36 (d, 1H, J= 2.8 Hz), 8.14 (d, 1H, J= 5.6 Hz), 7.87 (dd, 1H, J= 12.8,2.0 Hz), 7.37 (m, 3H), 6.95 (d, 1H, J= 8.4 Hz), 6.88 (t, 1H, J= 8.8 Hz), 6.41 (d, 1H, J= 5.2 Hz), 3.79 (s, 3H); CL/EM(ESI$^+$) m/z 421 $(M + H)^+$.

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EJEMPLO 288

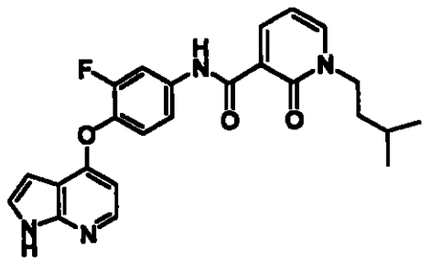


N-(4-(3-(6-Aminopiridin-3-il)-1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-2-fluoro-6-metoxibenzamida

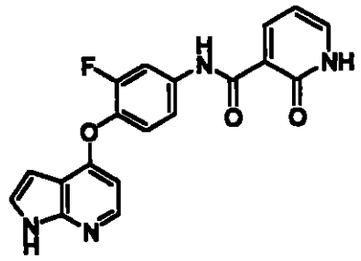
Una mezcla de N-(4-(3-bromo-1-((2-(trimetilsilil)etoxi)metil)-1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-2-fluoro-6-metoxibenzamida (50 mg, 0.08 mmol, Compuesto B del ejemplo 287), 5-(4,4,5,5-tetrametil-1,3-dioxolan-2-il)piridin-2-amina (36 mg, 0.16 mmol, Oakwood), $Pd(PPh_3)_4$ (10 mg), y K_3PO_4 (2 M en H_2O, 0.32 mmol) en tolueno (1 mL), EtOH (0.2 mL), y DME (0.4 mL) se purgó con Ar durante 10 minutos. La mezcla de reacción se calentó a 95°C durante 2 h, se diluyó con EtOAc, y se lavó con salmuera. La capa orgánica se secó sobre $MgSO_4$, se filtró, y se concentró in vacuo para dar un residuo, el cual se trató con TBAF (1 M en THF, 1 mL), etano-1,2-diamina (50 µL) en THF (3 mL) se puso a reflujo durante 24 h. La mezcla se diluyó con EtOAc, se lavó con salmuera, se secó con $MgSO_4$, y se concentró in vacuo. El residuo se purificó por cromatografía de columna instantánea (gel de sílice, 5% de NH_3 2M en $MeOH/CH_2Cl_2$) para dar el producto deseado, el cual se convirtió a la sal HCl por liofilización con HCl 1N en H_2O (sólido blanco, 10 mg, 26% rendimiento). ^1H RMN (CD_3OD) δ 8.32

(dd, 1H, J= 9.2, 2.0 Hz), 8.21 (d, 1H, J= 6.1 Hz), 8.15 (d, 1H, J= 2.0 Hz), 7.94 (dd, 1H, J= 12.7, 2.5 Hz), 7.70 (s, 1H), 7.44-7.50 (m, 2H), 7.36 (1, 1H, J= 8.7 Hz), 7.08 (d, 1H, J= 9.2 Hz), 6.98 (d, 1H, J= 8.7 Hz), 6.85 (t, 1H, J= 8.7 Hz), 6.56 (d, 1H, J= 5.6 Hz), 3.92 (s, 3H); CL/EM(ESI$^+$) m/z 488 $(M + H)^+$.

EJEMPLO 289



N-(4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-1-isopentil-2-oxo-1,2-dihidropiridina-3-carboxamida, sal del ácido trifluoroacético



A) N-(4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-2-oxo-1,2-dihidropiridina-3-carboxamida

A una solución agitada de 4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorobencenamina (24 mg, 0.1 mmol, Compuesto B

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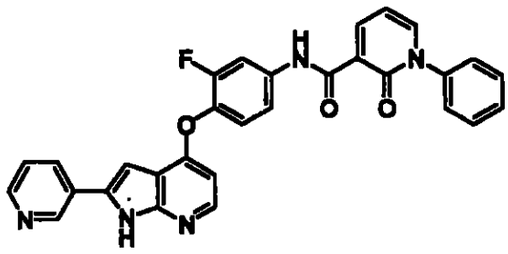
del ejemplo 132), ácido 2-hidroxinicotínico (27 mg, 0.2 mmol), y HATU (76 mg, 0.2 mmol) en DMF (1 mL) se agregó DIPEA (0.1 mL) y DMAP (5 mg). La mezcla resultante se agitó a temperatura ambiente durante 2 h y se concentró in vacuo. El residuo se purificó por CLAR preparativa para dar el producto deseado (8 mg, 22%) como un sólido blanco. CL/EM(ESI$^+$) m/z 365 $(M + H)^+$.

B) N-(4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-1-isopentil-2-oxo-1,2-dihidropiridina-3-carboxamida, sal del ácido trifluoroacético

Una mezcla de N-(4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-2-oxo-1,2-dihidropiridina-3-carboxamida (8 mg, 0.02 mmol), Na_2CO_3 (50 mg), y 1-yodo-3-metilbutano (50 mg) en DMF (1 mL) se agitó a temperatura ambiente durante la noche. La mezcla de reacción se concentró in vacuo y el residuo se purificó por CLAR preparativa para dar el producto deseado (sal TFA, 5 mg, 42%) como un sólido blanco. ^{1}H RMN (CD_3OD) δ 12.50 (s, 1H), 8.46 (dd, 1H, J= 7.1, 2.0 Hz), 8.16 (d, 1H, J= 6.1 Hz), 7.90-8.00 (m, 2H), 7.38-7.44 (m, 2H), 7.33 (1, 1H, J= 8.7 Hz), 6.70 (d, 1H, J= 6.6 Hz), 6.51-6.57 (m, 2H), 4.08 (t, 2H, J= 7.6 Hz), 1.51-1.53 (m, 3H), 0.92 (d, 6H, J= 6.1 Hz); CL/EM(ESI$^+$) m/z 435 $(M + H)^+$.

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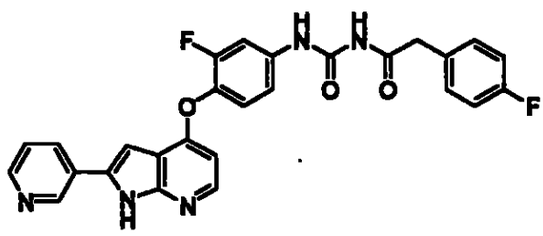
EJEMPLO 290



N-(3-Fluoro-4-(2-(piridin-3-il)-1H-pirrolo[2,3-b]piridin-4-iloxi)fenil)-2-oxo-1-fenil-1,2-dihidropiridina-3-carboxamida

Se preparó en una manera similar como en el ejemplo 239 usando 3-fluoro-4-(2-(piridin-3-il)-1H-pirrolo[2,3-b]piridin-4-iloxi)bencenamina (Compuesto E del ejemplo 237) y 2-oxo-1-fenil-1,2-dihidropiridina-3-carboxílico. ^{1}H RMN (DMSO-d_6) δ 12.87 (s, 1H), 12.18 (s, 1H), 9.39 (s, 1H), 8.70-8.85 (m, 2H), 8.60 (d, 1H, J= 7.1 Hz), 8.00-8.25 (m, 3H), 7.94 (s, 1H), 7.30-7.75 (m, 8H), 6.77 (t, 1H, J= 6.6 Hz), 6.45 (d, 1H, J= 4.6 Hz), 4.21 (s, 2H), 3.68 (s, 2H), 2.43 (s, 6H); CL/EM (ESI$^+$) m/z 518 $(M + H)^+$.

EJEMPLO 291

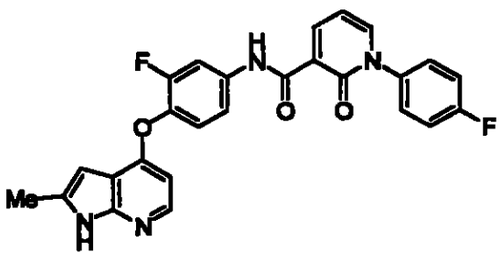


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1-(3-Fluoro-4-(2-(piridin-3-il)-1H-pirrolo[2,3-b]piridin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)urea, sal de clorohidrato

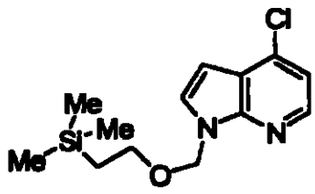
Una mezcla de 3-fluoro-4-(2-(piridin-3-il)-1H-pirrolo[2,3-b]piridin-4-iloxi)bencenamina (25 mg, 0.078 mmol, Compuesto E del ejemplo 237) y 2-(4-fluorofenil)acetil isocianato (0.09 mmol en tolueno, Compuesto C del ejemplo 4) en THF se agitó a temperatura ambiente durante 1 h. El solvente se retiró in vacuo y el residuo se purificó por CLAR preparativa para proporcionar el producto deseado (sal HCl, 18 mg, 40%) como un sólido amarillo. ^{1}H RMN (CD_3OD) δ 10.76 (s, 1H), 9.19 (s, 1H), 8.70 (d, 1H, J= 8.0 Hz), 8.66 (d, 1H, J= 5.2 Hz), 8.18 (d, 1H, J= 6.4 Hz), 8.00 (dd, 1H, J= 8.4, 5.6 Hz), 7.75 (dd, 1H, J= 13.2, 2.4 Hz), 7.10-7.35 (m, 4H), 6.90-7.03-7.40 (m, 3H), 6.63 (d, 1H, J= 6.4 Hz); CL/EM (ESI) m/z 500 $(M + H)^+$.

EJEMPLO 292



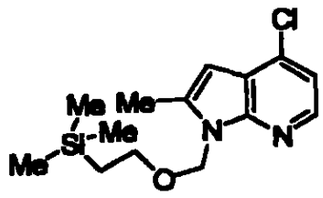
N-(3-Fluoro-4-(2-metil-1H-pirrolo[2,3-b]piridin-4-iloxi)fenil)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridina-3-carboxamida

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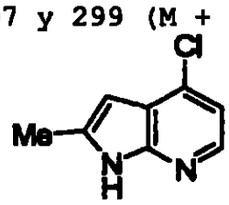
A) 4-Cloro-1-((2-(trimetilsilil)etoxi)metil)-1H-pirrolo[2,3-b]piridina

A una suspensión de NaH (88 mg, 60% en aceite mineral, 2.2 mmol) en DMF (1 mL) se agregó 4-cloro-1H-pirrolo[2,3-b]piridina (305 mg, 2 mmol, se preparó de conformidad a Thibault, C. et al. Org. Lett. 2003,5,5023) a temperatura ambiente con agitación. La mezcla se agitó durante 5 min. y se agregó éter clorometil trimetilsililetilo (350 mg, 2.1 mmol, Aldrich). La mezcla se agitó a temperatura ambiente durante 1 h, se vació en hielo y se extrajo con acetato de etilo (3 x 10 mL). Los extractos combinados se lavaron con salmuera, se secaron ($MgSO_4$) y se concentraron a presión reducida para dar el producto crudo, el cual se purificó por cromatografía instantánea (5% de acetato de etilo en hexanos) para proporcionar el compuesto del título (300 mg, 1.06 mmol, 53%) como un líquido. ^1H RMN ($CDCl_3$) δ 8.28 (d, 1H, J= 5.5 Hz), 7.45 (d, 1H, J= 3.6 Hz), 7.18 (d, 1H, J= 5.5 Hz), 6.69 (d, 1H, J= 3.6 Hz), 5.74 (s, 2H), 3.60 (t, 2H, J= 6.8 Hz), 0.96 (t, 2H, J= 6.8 Hz), 0.07 (s, 9H); EM(ESI$^+$) m/z 283 y 285 $(M + H, 1\ Cl)^+$.



B) 4-Cloro-2-metil-1-((2-(trimetilsilil)etoxi)metil)-1H-pirrolo[2,3-b]piridina

A una solución de 4-cloro-1-((2-(trimetilsilil)etoxi)metil)-1H-pirrolo[2,3-b]piridina (150 mg, 0.53 mmol) en THF (1 mL) a -78°C bajo argón se agregó butilitio (0.4 mL, 1.6 M en hexanos, 6.4 mmol) gota a gota. La mezcla se agitó a la misma temperatura durante 5 minutos y se trató con yodometano (0.1 mL). La mezcla se calentó a temperatura ambiente, se apagó por la adición de una solución de cloruro de amonio saturado y se extrajo con acetato de etilo (3 x 10 mL). Los extractos combinados se lavaron con salmuera, se secaron ($MgSO_4$) y se concentraron in vacuo para dar el producto crudo (150 mg, 95%), el cual se uso para la siguiente reacción. ^1H RMN ($CDCl_3$) δ 8.19 (d, 1H, J= 5.5 Hz), 7.14 (d, 1H, J= 5.5 Hz), 6.42 (s, 1H), 5.74 (s, 2H), 3.60 (t, 2H, J= 6.8 Hz), 2.61 (s, 3H), 0.96 (t, 2H, J= 6.8 Hz), 0.07 (s, 9H); EM(ESI$^+$) m/z 297 y 299 (M + H, 1 Cl)$^+$.



C) 4-Cloro-2-metil-1H-pirrolo[2,3-b]piridina

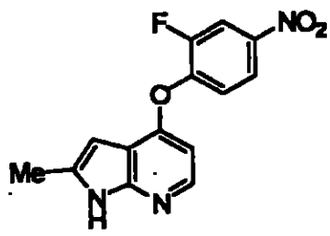
Una mezcla de 4-cloro-2-metil-1-((2-

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(trimetilsilil)etoxi)metil)-1H-pirrolo[2,3-b]piridina (296.5 mg, 1 mmol) y TBAF (5 mL, 1 M en THF, Aldrich) se puso a reflujo durante la noche. El THF se retiró a presión reducida y el residuo se diluyó con agua (5 mL). El precipitado que se formó se colectó, se lavó con agua y se secó ($MgSO_4$) para proporcionar el compuesto del título (101 mg,60%). ^1H RMN (CD_3OD) δ 7.99 (d, 1H, J= 5.5 Hz), 7.06 (d, 1H, J= 5.5 Hz), 6.23 (s, 1H), 2.46 (s, 3H); EM(ESI$^+$) m/z 167 y 169 (M + H, 1 Cl)$^+$.

D) 2-Metil-1H-pirrolo[2,3-b]piridin-4-ol

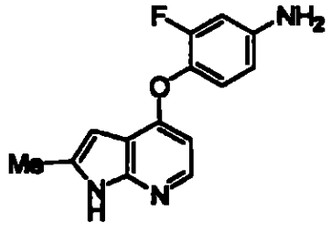
Una mezcla de 4-cloro-2-metil-1H-pirrolo[2,3-b]piridina (120 mg, 0.72 mmol) y acetato de sodio (150 mg, 1.83 mmol) en ácido acético (1.5 mL) se procesó en microondas 200°C durante 40 minutos. La mezcla se purificó por CLAR preparativa y las fracciones apropiadas se concentraron in vacuo y se liofilizaron para proporcionar el compuesto del título (90 mg, 47%). ^1H RMN (CD_3OD) δ 8.09 (d, 1H, J= 5.5 Hz), 6.80 (d, 1H,J= 5.5 Hz), 6.49 (s, 1H), 2.46 (s, 3H); EM(ESI$^+$) m/z 149 (M + H)$^+$.



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D) 4-(2-Fluoro-4-nitrofenoxi)-2-metil-1H-pirrolo[2,3-b]piridina

Una mezcla de 2-metil-1H-pirrolo[2,3-b]piridin-4-ol (90 mg, sal TFA, 0.34 mmol), 3,4-difluoronitrobenceno (0.05 mL) y carbonato de potasio (100 mg, 0.72 mmol) en DMF (1 mL) se agitó a 50°C durante 2 h. La mezcla se diluyó con agua y se extrajo con acetato de etilo (3 x 5 mL). Los extractos combinados se lavaron con agua, se secaron ($MgSO_4$) y se concentraron in vacuo para proporcionar el producto crudo, el cual se purificó por CLAR preparativa para dar el compuesto del título (45 mg, 46%). ^1H RMN (CD_3OD) δ 8.25 (dd, 2H, J= 10.4, 2.6 Hz), 8.12 (m, 1H), 8.04 (d, 1H, J= 5.5 Hz), 7.30 (t, 1H, J= 8.3 Hz), 6.67 (d, 1H, J= 5.5 Hz), 5.95 (s, 1H), 2.41 (s, 3H); EM(ESI$^+$) m/z 288 $(M + H)^+$.



E) 3-Fluoro-4-(2-metil-1H-pirrolo[2,3-b]piridin-4-iloxi)bencenamina

Una mezcla de 4-(2-fluoro-4-nitrofenoxi)-2-metil-1H-pirrolo[2,3-b]piridina (43 mg, 0.15 mmol), polvo de zinc (50 mg, 0.75 mmol) y cloruro de amonio (50 mg) en THF/Metanol (1/2, 0.6 mL) se agitó a temperatura ambiente durante 1h, se filtró y se concentró in vacuo para proporcionar el producto

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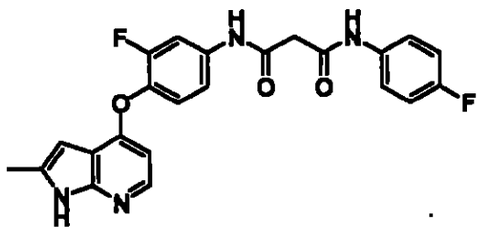
deseado (35 mg, 90%), el cual fue suficientemente puro para usarse en la reacción subsecuente. ^{1}H RMN (DMSO-d_6) δ 11.71 (s, 1H), 8.04 (d, 1H, J= 5.5 Hz), 7.10 (t, 1H, J= 8.4 Hz), 6.64 (dd, 1H, J= 10.4, 2.6 Hz), 6.51 (m, 1H), 6.35 (d, 1H, J= 5.5 Hz), 5.95 (s, 1H), 5.50 (s 2H), 2.41 (s,3H); EM(ESI$^+$) m/z 258 $(M + H)^+$.

F) N-(3-Fluoro-4-(2-metil-1H-pirrolo[2,3-b]piridin-4-iloxi)fenil)-1-(4-fluorofenil)-2-oxo-1,2-dibidropiridina-3-carboxamida

Una mezcla de 3-fluoro-4-(2-metil-1H-pirrolo[2,3-b]piridin-4-iloxi)bencenamina (17 mg, 0.066 mmol), ácido 1-(4-fluorofenil)-2-oxo-1,2-dihidropiridina-3-carboxílico (20 mg, 0.086 mmol) en DMF (0.5 mL) se agitó con un reactivo BOP (50 mg, 0.11 mmol) y trietilamina (0.01 mL) a 50°C durante 1 h. La mezcla de reacción se enfrió a temperatura ambiente y se diluyó con agua. El precipitado se colectó y se lavó con agua. El producto crudo se purificó por CLAR preparativa y las fracciones apropiadas se colectaron, se neutralizaron y se concentraron in vacuo para dar el compuesto del título (7.85 mg, 25%) como un sólido. ^{1}H RMN (DMSO-d_6) δ 12.07 (s, 1H), 11.56 (s, 1H), 8.49 (d, 1H, J= 6.2 Hz), 8.12 (d, 1H, J= 6.2 Hz), 7.98 (dd, 1H, J= 10.4, 2.6 Hz), 7.95 (d, 1H, J= 5.5 Hz), 7.61 (m, 2H), 7.43 (m, 3H), 7.29 (t, 1H, J= 8.40 Hz), 6.72 (t, 1H, J= 6.2 Hz), 6.36 (d, 1H, J= 5.5 Hz), 5.88 (s,

1H), 2.32 (s, 3H); EM (ESI^+) m/z 473 $(M + H)^+$.

EJEMPLO 293

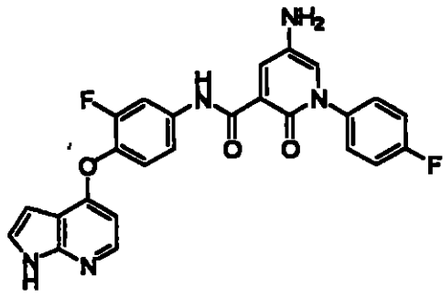


N^1-(3-Fluoro-4-(2-metil-1H-pirrolo[2,3-b]piridin-4-iloxi)fenil)-N^3-(4-fluorofenil)malonamida, sal de clorohidrato

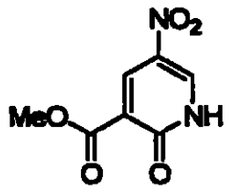
A una mezcla de 3-fluoro-4-(2-metil-1H-pirrolo[2,3-b]piridin-4-iloxi)bencenamina (20 mg, 0.078 mmol, Compuesto E del ejemplo 292), ácido 3-(4-fluorofenilamino)-3-oxopropanoico (20 mg, 1 mmol, Compuesto A del ejemplo 25), y HATU (44 mg, 0.12 mmol) en DMF (0.5 mL) se agregó DIPEA (0.1 mL). La mezcla de reacción se agitó a temperatura ambiente durante 2 h y se concentró in vacuo. El residuo se purificó por CLAR preparativa para dar el producto deseado (sal HCl, 12.5 mg, 34%) como un sólido blanco. ^1H RMN (CD_3OD) δ 8.05 (d, 1H, J= 7.2 Hz), 7.79 (dd, 1H, J= 12.7, 2.8 Hz), 7.50-7.53 (m, 2H), 7.27-7.36 (m, 2H), 6.97 (m, 2H), 6.70 (d, 1H, J= 6.6 Hz), 6.20 (s, 1H), 3.47 (s, 2H), 2.40 (s, 3H); CL/EM(ESI^+) m/z 437 $(M + H)^+$.

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EJEMPLO 294



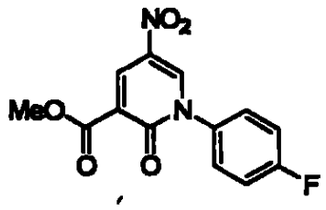
N-(4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-5-amino-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridina-3-carboxamida, sal de clorohidrato



A) Metil 5-nitro-2-oxo-1,2-dihidropiridina-3-carboxilato

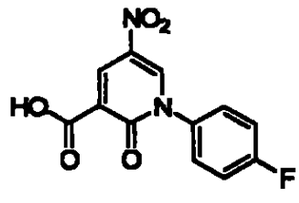
A una solución del ácido 2-hidroxi-5-nitronicotínico (0.80 g, 4.35 mmol, Combi-Blocks) en metanol (10 mL) a 0°C se agregó cloruro de tionilo (1 mL) gota a gota. La mezcla se agitó a 0°C durante 1 h, luego a 60°C durante 2 h. El exceso de metanol se retiró a presión reducida y el residuo se neutralizó con una solución de bicarbonato de sodio acuoso. El sólido se colectó, se lavó con agua y se secó para proporcionar el compuesto del título (0.85 g, 99%). ^{1}H RMN (DMSO-d_6) δ 8.44 (s, 1H), 8.34 (s, 1H), 3.67 (s, 3H); EM

(ESI$^+$) m/z 199 $(M + H)^+$.



B) Metil 1-(4-fluorofenil)-5-nitro-2-oxo-1,2-dihidropiridina-3-carboxilato

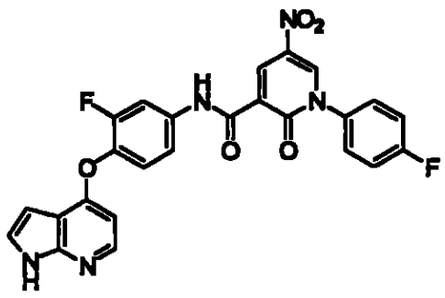
Una mezcla de metil 5-nitro-2-oxo-1,2-dihidropiridina-3-carboxilato (850 mg, 4.29 mmol), ácido 4-fluorofenilborónico (1.40 g, 10 mmol, Combi-Blocks) y acetato de cobre (200 mg, 1.1 mmol) en piridina (1 mL) y dioxano (20 mL) se agitó a 80°C durante 4 h. La mezcla de reacción se enfrió a temperatura ambiente y se diluyó con una solución de amonio. El sólido se colectó, se lavó con agua y se secó para proporcionar el compuesto del título (656 mg, 52%). ^{1}H RMN (DMSO-d_6) δ 8.95 (d, 1H, J= 3.2 Hz), 8.80 (d, 1H, J= 3.2 Hz), 7.40 (m, 2H), 7.25 (m, 2H), 3.95 (s, 3H); EM(ESI$^+$) m/z 293 $(M + H)^+$.



C) ácido 1-(4-Fluorofenil)-5-nitro-2-oxo-1,2-dihidropiridina-3-carboxílico

Una mezcla de metil 1-(4-fluorofenil)-5-nitro-2-

oxo-1,2-dihidropiridina-3-carboxilato (75 mg, 0.245 mmol) y una solución de NaOH 2N (1 mL) se agitó a 80°C durante 2 h. La mezcla de reacción se enfrió a temperatura ambiente y se acidificó con una solución HCl 1N. El sólido que se formó se colectó, se lavó con agua y se secó para proporcionar el compuesto del título (45 mg, 66%), el cual se usó directamente en la siguiente reacción. ^{1}H RMN (DMSO-d_6) δ 13.41 (s, 1H), 9.28 (d, 1H, J= 3.2 Hz), 8.70 (d, 1H, J= 3.2 Hz), 7.60 (m, 2H), 7.41 (m, 2H); EM(ESI$^+$) m/z 279 (M + H)$^+$.



D) N-(4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-1-(4-fluorofenil)-5-nitro-2-oxo-1,2-dihidropiridina-3-carboxamida

Una mezcla del ácido 1-(4-fluorofenil)-5-nitro-2-oxo-1,2-dihidropiridina-3-carboxílico (40 mg, 0.14 mmol) y 4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorobencenamina (35 mg, 0.14 mmol, Compuesto B del ejemplo 132) en DMF (1 mL) se agitó con un reactivo BOP (100 mg, 0.23 mmol) y trietilamina (0.1 mL) a 50°C durante 1 h. La mezcla de reacción se enfrió a temperatura ambiente y se diluyó con agua. El sólido que se formó se colectó,

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se lavó con una solución de bicarbonato de sodio acuoso, una solución HCl 1N, y agua para proporcionar el compuesto del título (54 mg, 76%). ^{1} RMN (DMSO-d_6) δ 12.19 (s, 1H), 11.04 (s, 1H), 9.37 (d, 1H, J= 2.6 Hz), 9.03 (d, 1H, J= 2.6 Hz), 8.18 (d, 1H, J= 5.5 Hz), 8.01 (dd, 1H, J= 10.2, 2.6 Hz), 7.71 (m,2H), 7.61 (m, 1 H), 7.46 (m, 4H), 6.55 (d, 1H, J= 5.5 Hz), 6.36 (s, 1Hz); EM (ESI^+) m/z 504 $(M + H)^+$.

E) N-(4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-5-amino-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridina-3-carboxamida, sal de clorohidrato

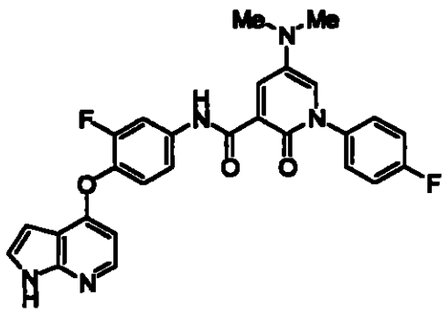
Una solución de N-(4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-1-(4-fluorofenil)-5-nitro-2-oxo-1,2-dihidropiridina-3-carboxamida (51 mg, 0.1 mmol) en DMF (1 mL) y etanol (5 mL) se hidrogenó en la presencia de Pd/C (10%, 10 mg) bajo una atmósfera de hidrógeno durante 4 h a temperatura ambiente. La mezcla de reacción se filtró y se concentró in vacuo. El residuo se purificó por CLAR preparativa y la fracción que contenía el compuesto deseado se colectó y se concentró in vacuo. El producto se convirtió a la sal HCl por la adición de una solución HCl 1N y se liofilizó para proporcionar el compuesto del título (7.6 mg, 15%) como un sólido amarillo ligero. ^{1}H RMN (CD_3OD) δ 8.56 (d, 1H, J= 3.2 Hz), 8.31 (d, 1H, J= 5.5 Hz), 8.08 (dd, 1H, J= 10.4, 2.6 Hz), 7.78 (m, 1H), 7.56 (m, 5H), 7.48 (m, 2H), 7.35 (t, 1H, J= 8.7 Hz), 6.90 (d, 1H, J=

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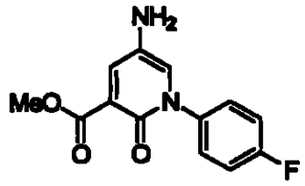
637

5.5 Hz), 6.69 (s, IH); EM(ESI$^+$) m/z 474 $(M + H)^+$.

EJEMPLO 295



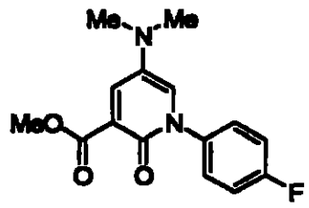
N-(4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-5-(dimetilamino)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridina-3-carboxamida



A) Metil 5-amino-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridina-3-carboxilato

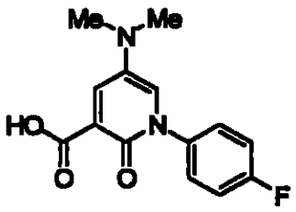
Una mezcla de metil 1-(4-fluorofenil)-5-nitro-2-oxo-1,2-dihidropiridina-3-carboxilato (1.46 g, 5 mmol, Compuesto B del ejemplo 294), polvo de zinc (1.63 g, 25 mmol) y cloruro de amonio (1.5 g, 28 mmol) en metanol/THF (1: 1,20 mL) se agitó a temperatura ambiente durante 2 h. La mezcla de reacción se filtró y se concentró in vacuo para proporcionar el producto deseado (1.30 g, 99%), el cual se usó directamente en la siguiente reacción sin purificación. ^{1}H

RMN (CD_3OD) δ 8.08 (s, 1H), 7.41 (m, 2H), 7.29 (m, 3H), 3.84 (s, 3H); EM(ESI) m/z 263 $(M + H)^+$.



B) Metil 5-(dimetilamino)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridina-3-carboxilato

A una solución de metil 5-amino-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridina-3-carboxilato (30 mg, 0.11 mmol) y formalina (37%,0.1 mL) en ácido acético (1 mL) se agregó triacetoxiborohidruro de sodio (50 mg, 0.23 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 1 h y se purificó por CLAR preparativa. Las fracciones que contenían el producto deseado se colectaron, se neutralizaron y se concentraron in vacuo para proporcionar el sólido. El sólido se colectó, se lavó con agua y se secó para dar el compuesto del título (25 mg, 77%). ^1H RMN (CD_3OD) δ 8.31 (d, 1H, J= 2.6 Hz), 7.41 (m, 2H), 7.26 (m, 3H), 3.89 (s, 3H), 2.79 (s, 6H); EM(ESI^+) m/z 291 $(M + H)^+$.



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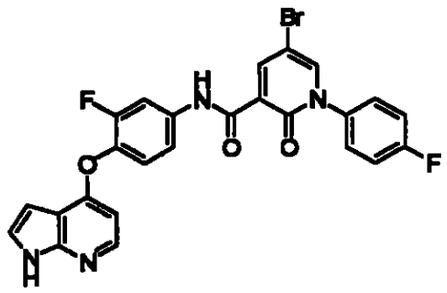
C) ácido 5-(Dimetilamino)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridina-3-carboxílico

El compuesto del título se preparó de metil 5-(dimetilamino)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridina-3-carboxilato (25 mg, 0.086 mmol) utilizando el procedimiento descrito en la etapa C del ejemplo 294 (20 mg, 84%). ^{1}H RMN (CD_3OD) 88.31 (d, 1H, J= 2.6 Hz), 7.41 (m, 2H), 7.26 (m, 3H), 2.70 (s, 6H); EM(ESI$^+$) m/z 277 $(M + H)^+$.

D) N-(4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-5-(dimetilamino)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridina-3-carboxamida

El compuesto del título se preparó del ácido 5-(dimetilamino)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridina-3-carboxílico (20 mg, 0.072 mmol) utilizando el procedimiento descrito en la etapa D del ejemplo 294 (13.5 mg, 37%). ^{1}H RMN (DMSO-d_6) δ 12.54 (s, 1H), 11.79 (s, 1H), 8.45 (d, 1H, J= 3.2 Hz), 8.10 (d, 1H, J= 5.5 Hz), 8.01 (dd, 1H, J= 10.4, 2.6 Hz), 7.62 (m, 1H), 7.44 (m, 6H), 6.40 (d, 1H, J= 5.5 Hz), 6.24 (s, 1Hz), 2.82 (s, 6H); EM(ESI$^+$) m/z 502 $(M + H)^+$.

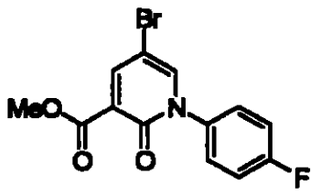
EJEMPLO 296



N-(4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fiuorofenil)-5-

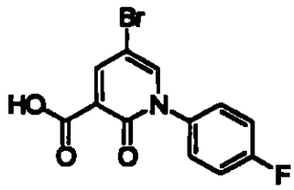
640

bromo-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridina-3-carboxamida



A) Metil 5-bromo-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridina-3-carboxilato

El compuesto del título se preparó del ácido 5-bromo-2-hidroxinicotínico (Combi-Blocks) utilizando el procedimiento descrito en las etapas A y B del ejemplo 294 en 69% de rendimiento. ^{1}H RMN (DMSO-d_6) δ 8.29 (d, 1H, J= 3.2 Hz), 8.14 (d, 1H, J= 3.2 Hz), 7.50 (m, 2H), 7.37 (m, 2H), 3.75 (s, 3H); EM(ESI) m/z 326 y 328 $(M + H, 1\ Br)^+$.



B) ácido 5-Bromo-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridina-3-carboxílico

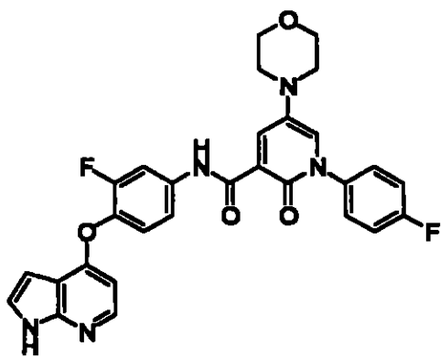
El compuesto del título se preparó del metil 5-bromo-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridina-3-carboxilato (65 mg, 0.2 mmol) utilizando el procedimiento descrito en la etapa del ejemplo 294 (55 mg, 88%). ^{1}H RMN (DMSO-d_6) δ 8.58 (d, 1H, J= 2.6 Hz), 8.44 (d, 1H, J= 2.6 Hz), 7.69 (m, 2H),

7.43 (t, 2H, J= 8.8 Hz); EM(ESI$^+$) m/z 312 y 314 (M + H, 1Br)$^+$.

C) N-(4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-5-bromo-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridina-3-carboxamida

El compuesto del título se preparó del ácido 5-bromo-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridina-3-carboxílico (31.2 mg, 0.1 mmol) utilizando el procedimiento descrito en la etapa D del ejemplo 294 (28 mg, 52%). ^{1}H RMN (DMSO-d_6) δ 11.93 (s, 1H), 11.80 (s, 1H), 8.53 (m, 2H), 8.01 (dd, 1H, J= 10.4, 2.6 Hz), 7.64 (m, 2H), 7.41 (m, 6H), 6.41 (br.s, 1H), 6.27 (s, 1H); EM(ESI$^+$) m/z 537 y 539 (M + H, 1 Br)$^+$.

EJEMPLO 297



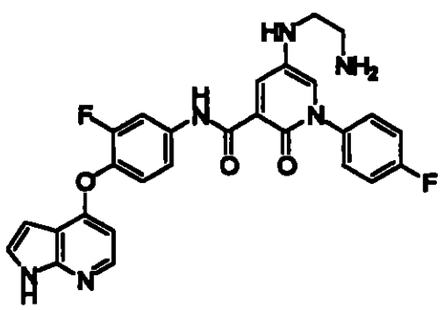
N-(4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-1-(4-fluorofenil)-5-morfolino-2-oxo-1,2-dihidropiridina-3-carboxamida

Una mezcla de N-(4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-5-bromo-1-(4-fluorofenil)-2-oxo-1,2-

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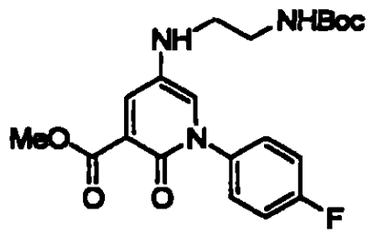
dihidropiridina-3-carboxamida (40 mg, 0.074 mmol, Ejemplo 296) y morfolina (0.1 mL) en dimetilacetamida (1 mL) se procesó en microondas 160°C durante 30 minutos. La mezcla de reacción se enfrió a temperatura ambiente y se purificó por CLAR preparativa. Las fracciones que contienen el producto deseado se colectaron, se neutralizaron y se concentraron in vacuo para proporcionar un sólido. El sólido se colectó, se lavó con agua y se secó para dar el compuesto del título (7.5 mg, 18%). ^{1}H RMN (DMSO-d_6) δ 12.38 (s, 1H), 11.75 (s, 1H), 8.50 (d, 1H, J=2.6 Hz), 8.06 (d, 1H, J= 5.5 Hz), 8.01 (dd, 1H, J= 10.4, 2.6 Hz), 7.60 (m, 2H), 7.41 (m, 6H), 6.41 (d, 1H, J= 5.5 Hz), 6.21 (s, 1H), 3.72 (m, 4H), 3.00 (m, 4H); EM(ESI$^+$) m/z 544 $(M + H)^+$.

EJEMPLO 298



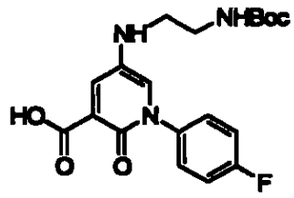
N-(4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-5-(2-aminoetilamino)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridina-3-carboxamida

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A) Metil 5-(2-(tert-butoxicarbonil)etilamino)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridina-3-carboxilato

A una solución de metil 5-bromo-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridina-3-carboxilato (131 mg, 0.5 mmol, Compuesto A del ejemplo 296) y tert-butil 2-oxoetilcarbamato (159 mg, 1 mmol, Aldrich) en ácido acético (1 mL) se agregó triacetoxiborohidruro de sodio (212 mg, 1 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 1 h, se apagó por adición de agua, y se extrajo con acetato de etilo (3 x 10 mL). Los extractos orgánicos combinados se lavaron con salmuera, una solución de bicarbonato de sodio acuoso y se secaron. La solución se concentró in vacuo y el residuo se purificó por cromatografía de columna instantánea (SiO_2, 10% de acetato de etilo en hexanos) para proporcionar el compuesto del título (60 mg, 30%) como un gel. ^1H RMN ($CDCl_3$) δ 7.90(d, 1H, J=2.6Hz), 7.37 (m, 2H), 7.13 (m, 2H),6.81 (d, 1H, J= 2.6 Hz), 3.88 (s, 3H), 3.30 (m, 2H), 3.10 (m, 2H), 1.46 (s, 9H); EM(ESI$^+$) m/z 406 $(M + H)^+$.



B) ácido 5-(2-(tert-Butoxicarbonil)etilamino)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridina-3-carboxílico

El compuesto del título se preparó de metil 5-(2-(tert-butoxicarbonil)etilamino)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridina-3-carboxilato (60 mg, 0.15 mmol) utilizando el procedimiento descrito en la etapa C del ejemplo 294 (50 mg, 85%), el cual se usó directamente en la siguiente reacción sin purificación adicional. ^{1}H RMN ($CDCl_3$) δ 8.26 (d, 1H, J= 2.6 Hz), 7.50 (m, 2H), 7.25 (m, 2H), 6.91 (d, 1H, J= 2.6 Hz), 3.30 (m, 2H), 3.10 (m, 2H), 1.46 (s, 9H); EM(ESI$^+$) m/z 392 $(M + H)^+$.

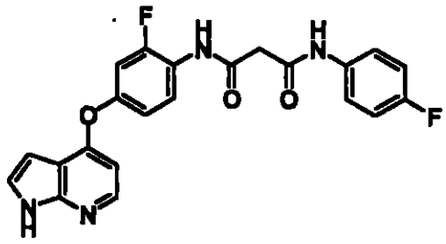
C) N-(4-(1H-pirrolo[2,3-b]piridina-4-iloxi)-3-fluorofenil)-5-(2-aminoetilamino)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridina-3-carboxamida

Una mezcla del ácido 5-(2-(tert-butoxicarbonil)etilamino)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridina-3-carboxílico (50 mg, 0.13 mmol) y 4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorobencenamina (40 mg, 0.16 mmol, Compuesto B del ejemplo 132), reactivo BOP (100 mg, 0.23 mmol) en DMF (1 mL) se agitó a 50°C con trietilamina

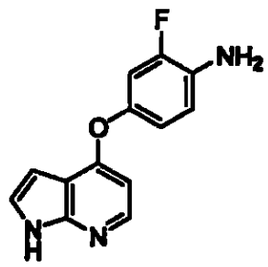
645

(0.1 mL) durante 1 h. La mezcla de reacción se enfrió a temperatura ambiente, se diluyó con agua, y se extrajo con cloruro de metileno (3 x 10 mL). Los extractos orgánicos combinados se lavaron con agua, se secaron y se concentraron in vacuo. El residuo se agitó con TFA (1 mL) a temperatura ambiente durante 30 minutos. El TFA se retiró y el residuo se purificó por CLAR preparativa. La fracción que contenía el producto deseado se colectó y se concentró in vacuo. El residuo se convirtió a la sal HCl por la adición de una solución HCl 1N y se liofilizó para dar el compuesto del título (20 mg, 27%). ^{1}H RMN (CD_3OD) δ 8.35 (d, 1H, J= 2.6 Hz), 8.26 (d, 1H, J= 5.5 Hz), 8.01 (dd, 1H, J= 10.4,2.6 Hz), 7.48 (m, 2H), 7.41 (m, 6H), 6.81 (d, 1H, J= 5.5 Hz), 6.60 (s, 1H), 3.26 (t, 2H, J= 6.1 Hz), 3.07 (t, 2H, J= 6.1 Hz); EM(ESI$^+$) m/z 517 $(M + H)^+$.

EJEMPLO 299



N^1-(4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-2-fluorofenil)-N^3-(4-fluorofenil)malonamida, sal del ácido trifluoroacético



A) 4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-2-fluorobencenamina

A una solución de 4-cloro-1H-pirrolo[2,3-b]piridina (50 mg, 0.33 mmol, se preparó de conformidad a Thibault, C. et al. Org. Lett. 2003,5,5023) en NMP (0.5 mL) se agregó 4-amino-3-fluorofenol (51 mg, 0.40 mmol) y DIEA (0.1 mL, 0.57 mmol). La mezcla se calentó a 250°C en un horno de microondas durante 1 h y luego se enfrió a temperatura ambiente. A la mezcla se agregó NaH (10 mg, 0.4 mmol) y la mezcla se volvió a calentar a 250°C durante 3 h. Después de enfriarse, la mezcla se diluyó con H_2O y se extrajo con EtOAc. La capa orgánica se lavó con H_2O, salmuera, y se secó sobre $MgSO_4$. Después de la filtración y concentración in vacuo, El residuo se purificó por cromatografía de columna instantánea (ISCO RediSep® cartucho de gel de sílice) para dar el compuesto del título (15 mg, 19%). EM (ESI) m/z 244.1 $(M+H)^+$.

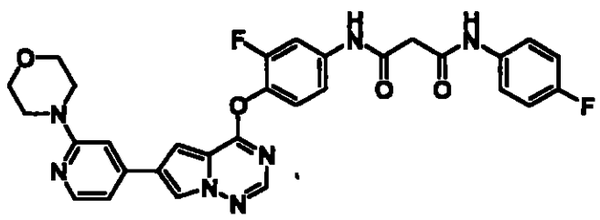
B) N^1-(4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-2-fluorofenil)-N^3-(4-fluorofenil)malonamida, ácido trifluoroacético

A una solución de 4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-2-fluorobencenamina (14 mg, 0.058 mmol) y ácido 3-(4-fluorofenilamino)-3-oxopropanoico (12 mg, 0.06 mmol, Compuesto A del ejemplo 25) en DMF (1 mL) se agregaron DIEA (0.04 mL, 0.23 mmol) y TBTU (22 mg, 0.07 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 2 d y se

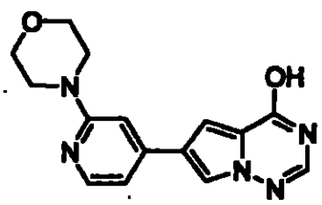
647

concentró in vacuo. El residuo se purificó por CLAR preparativa para dar el compuesto del título (18 mg, 74%). ^{1}H RMN (CD_3OD) δ 8.25 (d, 1H, J= 7.5 Hz), 8.19 (t, 1H, J= 7.5 Hz), 7.55 (m, 2H), 7.49 (d, 1H, J= 3.5 Hz), 7.25 (d, 1H, J= 8.0 Hz), 7.13 (d, 1H, J= 7.0 Hz), 7.01 (m, 2H), 6.84 (d, 1H, J= 7.0 Hz), 6.60 (d, 1H, J= 3.5 Hz), 3.60 (s, 2H); EM(ESI) m/z 423.1 $(M+H)^+$.

EJEMPLO 300



N^1-(3-Fluoro-4-(6-(2-morfolinopiridin-4-il)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-N^3-(4-fluorofenil)malonamida

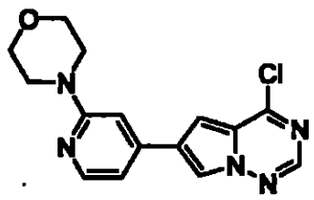


A) 6-(2-Morfolinopiridin-4-il)pirrolo[2,1-f][1,2,4]triazin-4-ol

A una solución de 6-bromopirrolo[2,1-f][1,2,4]triazin-4-ol (100 mg, 0.47 mmol, se preparó del metil 4-bromo-1H-pirrol-2-carboxilato: Ver, generalmente, Kitamura, C. y Yamashita, Y. J Chem. Soc. Perkin Trans. 1,1997, 1443, descrito en el cual se incorpora en la presente como referencia, usando un procedimiento similar resumido en la Sol. PCT WO 00/71129) y 4-(4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-

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il)piridin-2-il)morfolina (290 mg, 1.0 mmol) en DMF (2 mL) se agregaron una solución K_2CO_3 acuosa saturada (2.0 mL) y $Pd(PPh_3)_4$ (60 mg, 0.05 mmol). La mezcla de reacción se purgó con N_2 durante 10 minutos y luego se calentó a 80°C durante 5 h y 100°C durante 12 h. Después de enfriarse, la mezcla se diluyó con H_2O y se filtró para proporcionar el producto crudo, el cual se trituró con DCM para proporcionar el compuesto del título (114 mg, 82% rendimiento). EM(ESI) m/z 298.2 $(M+H)^+$.

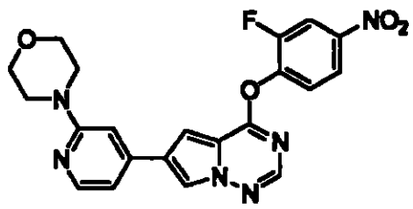


B) 4-Cloro-6-(2-morfolinopiridin-4-il)pirrolo[2,1-f][1,2,4]triazina

A una suspensión de 6-(2-morfolinopiridin-4-il)pirrolo[2,1-f][1,2,4]triazin-4-ol (110 mg, 0.37 mmol) en tolueno (100 mL) se agregó una gota de DMF y $POCl_3$ (30 mL). El matraz se selló y se calentó a 100°C durante 3 d. La mezcla de reacción se enfrió a temperatura ambiente y se concentró in vacuo. El residuo luego se disolvió en DCM, se neutralizó con una solución $NaHCO_3$ acuosa saturada y la capa orgánica se separó. La capa acuosa se extrajo con DCM (2 x 50 mL). Las capas orgánicas combinadas se secaron sobre $MgSO_4$, se filtraron y se concentraron in vacuo para proporcionar el producto deseado, el cual se usó directamente en la siguiente etapa. EM(ESI) m/z 316.2/318.2

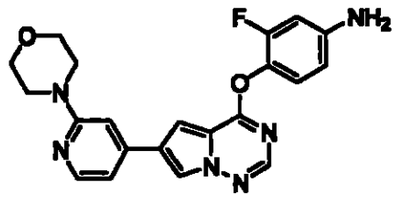
649

$(M + H)^+$.



C) 4-(2-Fluoro-4-nitrofenoxi)-6-(2-morfolinopiridin-4-il)pirrolo[2,1-f][1,2,4]triazina

A una suspensión de 4-cloro-6-(2-morfolinopiridin-4-il)pirrolo[2,1-f][1,2,4]triazina cruda en MeCN (5 mL) se agregaron 2-fluoro-4-nitrofenol (59 mg, 0.37 mmol) y DABCO (45 mg, 0.4 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 2 h. El solvente se retiró in vacuo y el residuo se purificó por cromatografía de columna instantánea (ISCO RediSep® cartucho de gel de sílice) para dar el compuesto deseado (54 mg, 33% rendimeinto en dos etapas). EM(ESI) m/z 437.2 $(M + H)^+$.



D) 3-Fluoro-4-(6-(2-morfolinopiridin-4-il)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)bencenamina

A una solución de 4-(2-fluoro-4-nitrofenoxi)-6-(2-morfolinopiridin-4-il)pirrolo[2,1-f][1,2,4]triazina (54 mg, 0.12 mmol) en una mezcla de THF (2.0 mL) y MeOH (2.0 mL) se agregaron NH_4Cl (127 mg, 2.4 mmol) y polvo de Zn (78 mg, 1.2

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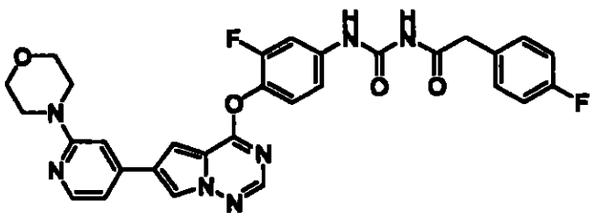
mmol). La mezcla de reacción se agitó a temperatura ambiente durante 3 h, se filtró y se concentró in vacuo. El residuo se purificó por CLAR preparativa para proporcionar el producto deseado (40 mg, 82% rendimiento). EM(ESI) m/z 407.19 $(M+H)^+$.

E) N^1-(3-Fluoro-4-(6-(2-morfolinopiridin-4-il)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-N^3-(4-fluorofenil)malonamida

A una solución de 3-fluoro-4-(6-(2-morfolinopiridin-4-il)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)bencenamina (15 mg, 0.037 mmol) y ácido 3-(4-fluorofenilamino)-3-oxopropanoico (8 mg, 0.04 mmol, compuesto A del ejemplo 25) en DMF (1 mL) se agregaron DIEA (0.1 mL, 0.57 mmol) y TBTU (13 mg, 0.04 mmol). La mezcla de reacción se agitó a temperatura ambiente durante la noche y luego se purificó usando CLAR preparativa. La fracción que contiene el producto deseado se colectó y se concentró in vacuo. El residuo se neutralizó con NH_4OH 1N y se concentró nuevamente. El sólido que se formó se filtró, se lavó con NH_4OH 1N, se disolvió en $MeOH/H_2O$, y se liofilizó para dar el compuesto del título (8 mg, 37%). ^1H RMN (DMSO-d_6) δ 10.49 (s, 1H), 10.23 (s, 1H), 8.63 (s, 1H), 8.55 (s, 1H), 8.06 (s, 1H), 8.00 (d, 1H, J= 7.5 Hz), 7.70 (m, 1H), 7.50 (m, 2H), 7.30-7.45 (m, 3H), 7.04-7.17 (m, 3H), 6.85-6.92 (m, 2H), 3.36 (s, 4H), 3.44 (s, 6H); EM(ESI) m/z 586.2 $(M + H)^+$.

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EJEMPLO 301

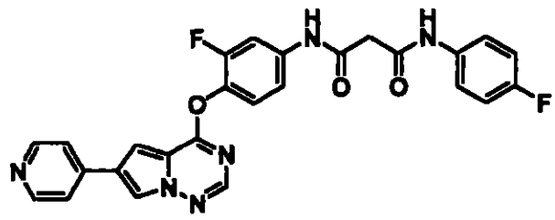


1-(3-Fluoro-4-(6-(2-morfolinopiridin-4-il)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)urea

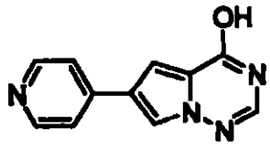
A una solución de 3-fluoro-4-(6-(2-morfolinopiridin-4-il)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)bencenamina (15 mg, 0.037 mmol, Compuesto D del ejemplo 300) en THF (1 mL) se agregaron DIEA (0.1 mL, 0.57 mmol) y 2-(4-fluorofenil)acetil isocianato (0.347 M, 0.21 mL, 0.074 mmol, Compuesto C del ejemplo 4). La mezcla de reacción se agitó a temperatura ambiente durante 1 h y el precipitado se colectó en un embudo Buchner y se lavó con tolueno para dar el compuesto del título (10 mg, 46%). ^{1}H RMN (DMSO-d_6) δ 11.05 (s, 1H), 10.60 (s, 1H), 8.71 (s, 1H), 8.62 (s, 1H), 8.13 (s, 1H), 8.09 (d, 1H, J= 7.5 Hz), 7.80 (d, 1H, J= 8.0 Hz), 7.35-7.54 (m, 5H), 7.18 (t, 2H, J= 7.5 Hz), 6.91 (d, 1H, J= 8.0Hz), 3.71-3.76 (m, 6H), 3.48-3.51 (m, 4H); EM (ESI) m/z 586.2 $(M + H)^+$.

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EJEMPLO 302

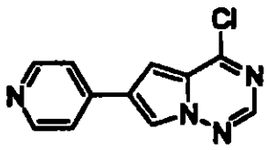


N^1-(3-Fluoro-4-(6-(piridin-4-il)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-N^3-(4-fluorofenil)malonamida, sal del ácido trifluoroacético



A) 6-(Piridin-4-il)pirrolo[2,1-f][1,2,4]triazin-4-ol

Siguiendo un procedimiento similar como se describe en la etapa A del ejemplo 300, 6-(piridin-4-il)pirrolo[2,1-f][1,2,4]triazin-4-ol (100 mg, 0.47 mmol) se acopló con ácido piridin-4-ilborónico (172 mg, 1.40 mmol) para proporcionar el compuesto del título (72 mg, 72%). EM(ESI) m/z 213.2 $(M + H)^+$.



B) 4-Cloro-6-(piridin-4-il)pirrolo[2,1-f][1,2,4]triazina

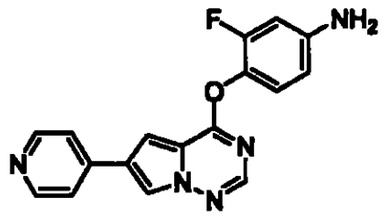
Siguiendo un procedimiento similar como se describe en la etapa B del ejemplo 300, 6-(piridin-4-il)pirrolo[2,1-

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f][1,2,4]triazin-4-ol (62 mg, 0.29 mmol) se convirtió al compuesto del título (30 mg, 45%). EM(ESI) m/z 231.1/233.1 (M + H)$^+$.

C) 4-(2-Fluoro-4-nitrofenoxi)-6-(piridin-4-il)pirrolo[2,1-f][1,2,4]triazina

Siguiendo un procedimiento similar como se describe en la etapa C del ejemplo 300, 4-cloro-6-(piridin-4-il)pirrolo[2,1-f][1,2,4]triazina (37 mg, 0.16 mmol) se convirtió al compuesto deseado (50 mg, 89%). EM(ESI) m/z 352.2 (M + H)$^+$.



D) 3-Fluoro-4-(6-(piridin-4-il)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)bencenamina

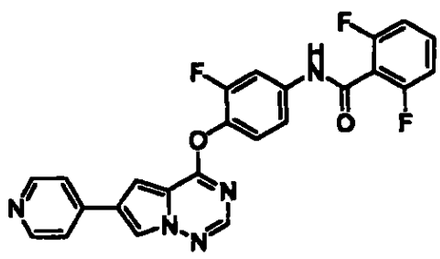
Siguiendo un procedimiento similar como se describe en la etapa D del ejemplo 300, 4-(2-fluoro-4-nitrofenoxi)-6-(piridin-4-il)pirrolo[2,1-f][1,2,4]triazina (50 mg, 0.14 mmol) se convirtió al compuesto deseado (50 mg, rendimiento cuantitativo). EM(ESI) m/z 322.3 (M+H)$^+$.

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E) N^1-(3-Fluoro-4-(6-(piridin-4-il)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-N^3-(4-fluorofenil)malonamida, sal del ácido trifluoroacético

Siguiendo un procedimiento similar como se describe en la etapa E del ejemplo 300, 3-fluoro-4-(6-(piridin-4-il)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)bencenamina (20 mg, 0.06 mmol) se convirtió al compuesto del título (8.5 mg, 28%). ^{1}H RMN (DMSO-d_6) δ 10.53 (s, 1H), 10.27 (s, 1H), 9.06 (s, 1H), 8.80 (d, 2R, J= 7.0 Hz), 8.30 (d, 2R, J = 6.0 Hz), 8.24 (s, 1H), 7.98 (s, 1H), 7.80 (d, 1H, J= 8.0 Hz), 7.60 (m, 2H), 7.35-7.45 (m, 2R), 7.16 (t, 2H, J= 8.0 Rz), 3.49 (s, 2R); EM(ESI) m/z 501.2 $(M + H)^+$.

EJEMPLO 303



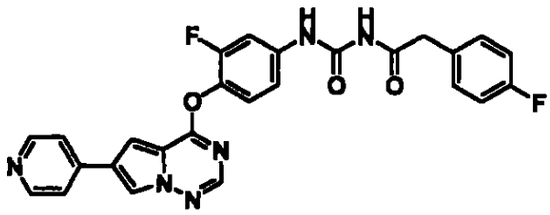
2,6-Difluoro-N-(3-fluoro-4-(6-(piridin-4-il)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)benzamida, sal del ácido trifluoroacético

A una solución de 3-fluoro-4-(6-(Piridin-4-il)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)bencenamina (20

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mg, 0.06 mmol, Compuesto D del ejemplo 302) en DCM (1 mL) se agregaron DIEA (0.1 mL, 0.57 mmol) y una solución de cloruro de 2,6-difluorobenzoilo en DCM (0.5 M, 0.14 mL, 0.07 mmol) a temperatura ambiente. La mezcla de reacción se agitó durante 0.5 h y se apagó con NH_4OH 1N. La solución luego se concentró in vacuo y el residuo se purificó por CLAR preparativa para dar el compuesto del título (15 mg, 54%). ^1H RMN (DMSO-d_6) δ 11.09 (s, 1H), 8.96 (s, 1H), 8.70 (m, 2H), 8.18 (s, 1H), 8.10 (br. s, 2R), 7.90 (s, 1H), 7.80 (d, 1H, J= 8.0 Hz), 7.45-7.55 (m, 3H), 7.23 (t, 2H, J= 8.0 Hz); EM(ESI) m/z 462.2 $(M + H)^+$.

EJEMPLO 304



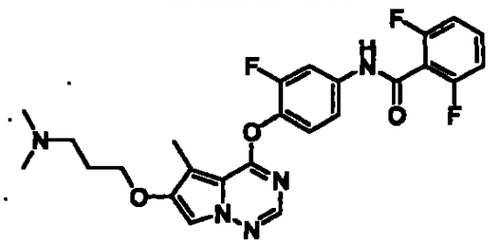
1-(3-Fluoro-4-(6-(piridin-4-il)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)urea, sal del ácido trifluoroacético

Siguiendo un procedimiento similar como se describe en el ejemplo 301, 3-fluoro-4-(6-(Piridin-4-il)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)bencenamina (16 mg, 0.05 mmol, Compuesto D del ejemplo 302) se convirtió al compuesto del

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título (6.5 mg, 26%). ^{1}H RMN (DMSO-d_6) δ 10.99 (s, 1H), 10.55 (s, 1H), 9.04 (s, 1H), 8.78 (d, 2H, J= 6.4 Hz), 8.31 (d, 2H, J= 6.4 Hz), 8.20 (s, 1H), 7.96 (s, 1H), 7.72 (m, 1H), 7.09-7.44 (m, 6H), 3.69 (s, 2H); EM(ESI) m/z 501.2 $(M + H)^+$.

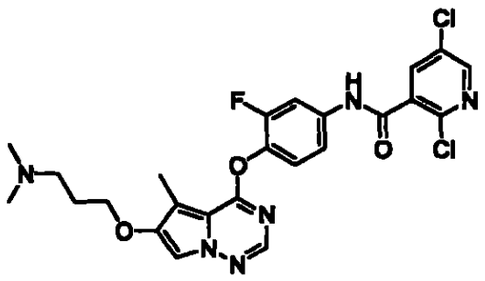
EJEMPLO 305



N-(4-(6-(3-(Dimetilamino)propoxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-4-iloxi)-3-fluorofenil)-2,6-difluorobenzamida, sal de clorohidrato

Siguiendo un procedimiento similar como se describe en el ejemplo 134, 4-(6-(3-(dimetilamino)propoxi)-5-metilpirrolo[2,11][1,2,4]triazin-4-iloxi)-3-fluorobencenamina (36 mg, 0.1 mmol, Compuesto B del ejemplo 32) se convirtió al compuesto del título (20 mg, 40%). ^{1}H RMN (DMSO-d_6) δ 11.17 (s, 1H), 10.40 (s, 1H), 8.00 (d, 2H, J= 4.0 Hz), 7.86 (d, 1H, J= 12.0 Hz), 7.65 (m, 1H), 7.51 (d, 2H, J= 5.0 Hz), 7.29 (t, 2H, J= 8.0 Hz), 4.15 (m, 2H), 3.24 (m, 2H), 2.80 (s, 6H), 2.40 (s, 3H), 2.18 (m, 2H); EM(ESI) m/z 500.3 $(M + H)^+$.

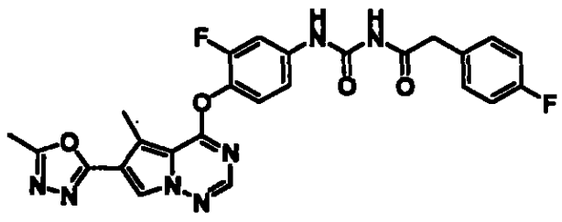
EJEMPLO 306



2,5-Dicloro-N-(4-(6-(3-(dimetilamino)propoxi)-5-metilpirrolo[2,1-J][1,2,4]triazin-4-iloxi)-3-fluorofenil)nicotinamida, sal de clorohidrato

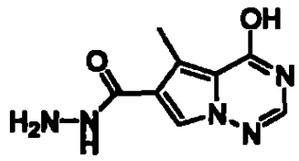
Siguiendo un procedimiento similar como se describe en el ejemplo 134, 4-(6-(3-(dimetilamino)propoxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-4-iloxi)-3-fluorobencenamina (36 mg, 0.1 mmol, Compuesto B del ejemplo 32) se convirtió al compuesto del título (10mg, 18%). ^{1}H RMN (DMSO-d_6) δ 11.12(s, 1H), 10.50 (s, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 8.00 (s, 1H), 7.86 (d, 1H, J= 12 Hz), 7.52 (s, 1H), 7.38 (s, 1H), 7.25 (s, 1H), 7.12 (s, 1H), 4.12 (m, 2H), 3.26 (m, 2H), 2.78 (s, 6H), 2.41 (s, 3H), 2.20 (m, 2H); EM(ESI) m/z 533.2 $(M + H)^+$.

EJEMPLO 307



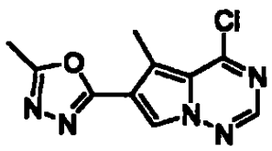
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1-(3-Fluoro-4-(5-metil-6-(5-metil-1,3,4-oxadiazol-2-il)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)urea



A) 4-Hidroxi-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carbohidrazida

El etil 4-hidroxi-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxilato (467 mg, 2.11 mmol, preparación: Ver patente E.U.A. No. 6,670,357) se disolvió en $N_2H_4H_2O$/EtOH (4:1,5 mL). La solución se calentó a 88°C durante 4 h, se enfrió a temperatura ambiente y se concentró in vacuo para dar el compuesto del título (450 mg, >95%). EM(ESI) m/z 208.1 $(M + H)^+$.

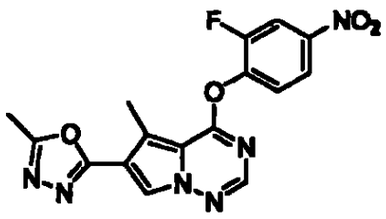


B) 4-Cloro-5-metil-6-(8-metil-1,3,4-oxadiazol-2-il)pirrolo[2,1-f][1,2,4]triazina

A una suspensión de 4-hidroxi-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carbohidrazida (100 mg, 0.48 mmol) en $POChl_3$ (5 mL) se agregó AcOH (50 mg, 0.83 mmol). La mezcla de reacción se calentó a 80°C durante 3 días, se enfrió a

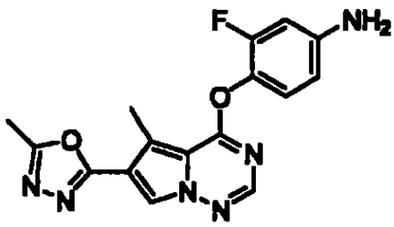
659

temperatura ambiente y se concentró in vacuo. El residuo resultante se disolvió en EtOAc y se trató con una solución de $NaHCO_3$ acuoso saturado, salmuera, y se secó over $MgSO_4$. La filtración, seguida por la concentración, proporciono el compuesto del título, el cual se uso directamente en la siguiente etapa. EM (ESI) m/z 250.1/252.1 $(M + H)^+$.



C) 4-(2-Fluoro-4-nitrofenoxi)-5-metil-6-(5-metil-1,3,4-oxadiazol-2-il)pirrolo[2,1-f][1,2,4]triazina

Siguiendo un procedimiento similar como se describe en la etapa C del ejemplo 300, 4-cloro-5-metil-6-(5-metil-1,3,4-oxadiazol-2-il)pirrolo[2,1-f][1,2,4]triazina se convirtió al compuesto del título (50 mg, 28% en dos etapas). EM(ESI) m/z 371.2 $(M + H)^+$.



D) 3-Fluoro-4-(5-metil-6-(5-metil-1,3,4-oxadiazol-2-il)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)bencenamina

Siguiendo un procedimiento similar como se describe en la etapa D del ejemplo 300, 4-(2-fluoro-4-nitrofenoxi)-5-metil-6-(5-metil-1,3,4-

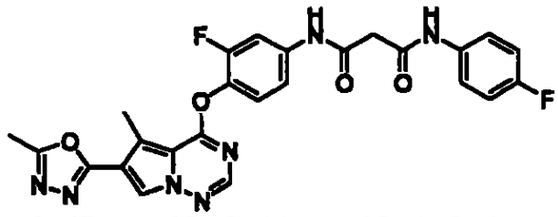
660

oxadiazol-2-il)pirrolo[2,1-f][1,2,4]triazina (50 mg, 0.13 mmol) se convirtió al compuesto del título (45 mg, >95%). EM(ESI) m/z 341.2 $(M + H)^+$.

E) 1-(3-Fluoro-4-(5-metil-6-(5-metil-1,3,4-oxadiazol-2-il)pirrolo [2,1-f][1,2,4]triazin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)urea

Siguiendo un procedimiento similar como se describe por el ejemplo 301, 3-fluoro-4-(5-metil-6-(5-metil-1,3,4-oxadiazol-2-il)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)bencenamina (20 mg, 0.06 mmol) se convirtió al compuesto del título (11 mg, 35%). ^1H RMN ($CDCl_3$) δ 10.80 (s, 1H), 8.69 (s, 1H), 8.18 (s, 1H), 7.96 (s, 1H), 7.70 (m, 1H), 7.10-7.30 (m, 6H), 3.75 (s, 2H), 2.92 (s, 3H), 2.64 (s, 3H); EM(ESI) m/z 520.2 $(M + H)^+$.

EJEMPLO 308



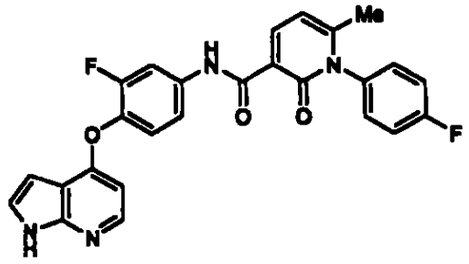
N^1-(3-Fluoro-4-(5-metil-6-(5-metil-1,3,4-oxadiazo]-2-il)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)fenil)-N^3-(4-fluorofenil)malonamida

Siguiendo un procedimiento similar como se describe en la etapa E del ejemplo 300, 3-fluoro-4-(5-metil-6-(5-metil-1,3,4-oxadiazol-2-il)pirrolo[2,1-f][1,2,4]triazin-4-iloxi)bencenamina (20 mg, 0.06 mmol)

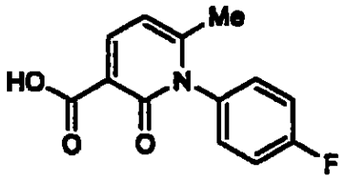
661

se convirtió al compuesto del título (8 mg, 26%). ^{1}H RMN ($CDCl_3$) δ 9.26 (s, 1H), 8.47 (s, 1H), 8.21 (s, 1H), 7.96 (s, 1H), 7.80 (m, 1H), 7.50 (m, 2H), 7.10-7.30 (m, 4H), 3.60 (s, 2H), 2.93 (s, 3H), 2.69 (s, 3H); EM (ESI) m/z 520.1 $(M + H)^+$.

EJEMPLO 309



N-(4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-1-(4-fluorofenil)-6-metil-2-oxo-1,2-dibidropiridina-3-carboxamida



A) ácido 1-(4-Fluorofenil)-6-metil]-2-oxo-1,2-dihidropiridina-3-carboxílico

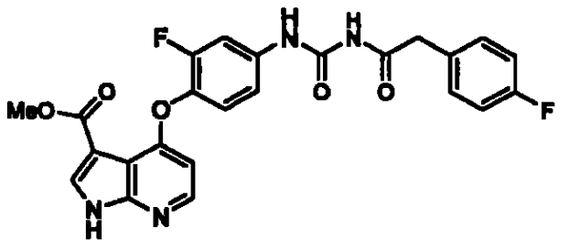
Se preparó en una manera similar como en las etapas B y C del ejemplo 294 usando el ácido 2-hidroxi-6-metilnicotínico (Aldrich). ^{1}H RMN ($DMSO-d_6$) δ 8.41 (d, 1H, J= 6.5 Hz), 8.08 (s, 1H), 7.51-7.48 (m, 4H), 6.81 (d, 1H, J= 6.5 Hz), 2.10 (s, 3R); EM(ESI^+) m/z 248 $(M + H)^+$.

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B) N-(4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-1-(4-fluorofenil)-6-metil-2-oxo-1,2-dihidropiridina-3-carboxamida

Se preparó en una manera similar como en la etapa D del ejemplo 294 (21 % rendimiento). ^{1}H RMN (DMSO-d_6) δ 12.11 (s, 1H), 11.83 (s, 1H), 8.56 (d, 1H, J= 6.5 Hz), 8.13 (d, 1H, J= 5.5 Hz), 8.01 (dd, 1H, J= 10.4, 2.6 Hz), 7.56-7.50 (m, 7H), 6.78 (d, 1H, J= 6.5 Hz), 6.44 (d, 1H, J= 5.5 Hz), 6.30 (s, 1H), 2.14 (s, 3H); EM(ESI$^+$) m/z 473 $(M + H)^+$.

EJEMPLO 310



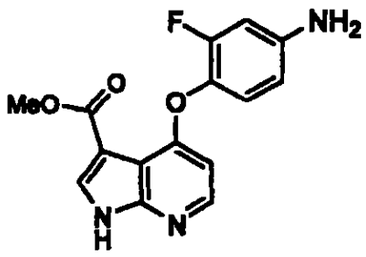
Metil 4-(2-fluoro-4-(3-(2-(4-fluorofenil)acetil)ureido)fenoxi)-1H-pirrolo[2,3-b]piridin-3-3-carboxilato

A) Metil 4-(2-fluoro-4-nitrofenoxi)-1H-pirrolo[2,3-b]piridina-3-carboxilato

A una solución de 2,2,2-tricloro-1-(4-(2-fluoro-4-nitrofenoxi)-1H-pirrolo[2,3-b]piridin-3-il)etanona (490 mg, 1.17 mmol, Ver: Etapa A del ejemplo 270) en un solvente mezclado (10 mL de MeOH y 10 mL de THF) se agregó NaOH 1N (10

663

mL, 10 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 3 h, y se diluyó con EtOAc (30 mL). La capa orgánica se lavó con $NaHCO_3$ acuosa saturada, se secó y se concentró in vacuo para dar el producto deseado (235 mg, 61 %) como un sólido café ligero. EM(ESI$^+$) m/z 332.2 $(M + H)^+$.



B) Metil 4-(4-amino-2-fluorofenoxi)-1H-pirrolo[2,3-b]piridina-3-carboxilato

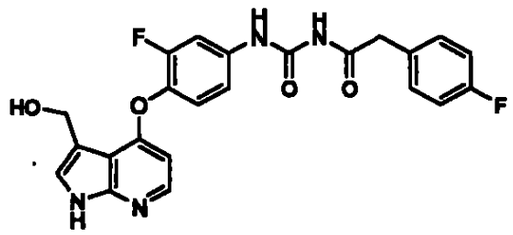
A una solución de metil 4-(2-fluoro-4-nitrofenoxi)-1H-pirrolo[2,3-b]piridina-3-carboxilato (230 mg, 0.69 mmol) en un solvente mezclado (10 mL de MeOH y 10 mL de THF) se agregaron cloruro de amonio (185 mg, 3.45 mmol) y polvo de zinc (226 mg, 3.45 mmol). La mezcla de reacción se agitó a temperatura ambiente durante la noche, se diluyó con EtOAc (50 ml), y se filtró a través de una almohadilla de Celite®. El filtrado se concentró in vacuo para dar el producto deseado (207 mg, 100%) como un sólido amarillo. EM(ESI$^+$) m/z 302.2 $(M + H)^+$.

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C) Metil 4-(2-fluoro-4-(3-(2-(4-fluorofenil)acetil)ureido)fenoxi)-1H-pirrolo[2,3-b]piridina-3-carboxilato

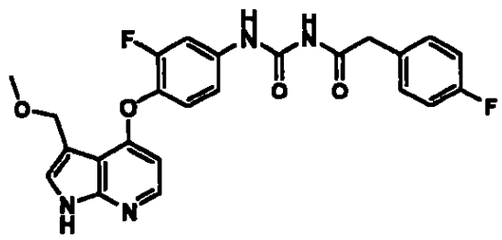
Se preparó en una manera similar como en la etapa C del ejemplo 132 (61 mg, 36%). ^{1}H RMN (DMSO-d_6) δ 11.01 (s, 1H), 10.54 (s, 1H), 8.15 (s, 1H), 8.14 (d, 1H, J= 5.5 Hz), 7.74 (dd, 1H, J= 12.5, 2.2 Hz), 7.31-7.36 (m, 3H), 7.14-7.19 (m, 3H), 6.45 (d, 1H, J= 5.5 Hz), 3.73 (s, 2H), 3.69 (s, 3H). EM(ESI$^+$) m/z 481.1 (M + H)$^+$.

EJEMPLO 311



1-(3-Fluoro-4-(3-(hidroximetil)-1H-pirrolo[2,3-b]piridin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)urea

EJEMPLO 312



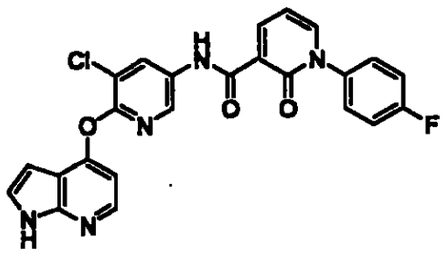
665

1-(3-Fluoro-4-(3-(metoximetil)-1H-pirrolo[2,3-b]piridin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)urea

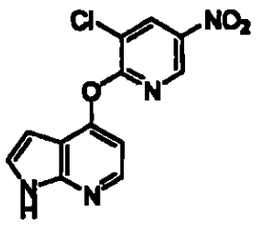
A una solución de metil 4-(2-fluoro-4-(3-(2-(4-fluorofenil)acetil)ureido)fenoxi)-1H-pirrolo[2,3-b]piridina-3-carboxilato (19.2 mg, 0.04 mmol, Compuesto C del ejemplo 310) en THF (1 mL) a 0°C se agregó DIBAL-H (1.5 M soln en tolueno, 133 µL, 0.2 mmol, Aldrich). La mezcla de reacción se agitó a 0°C durante 2 h, y se apagó por la adición de 2 mL de metanol. La mezcla de reacción se concentró in vacuo y se purificó por CLAR preparativa. Las fracciones deseadas se combinaron, se concentraron in vacuo y se liofilizaron para dar un sólido blanco. El CL/EM indicó que el sólido contenía dos compuestos. El sólido se purificó nuevamente por cromatografía de columna instantánea (ISCO RediSep® cartucho de gel de sílice, se eluyó con 1-10% MeOH en diclorometano) para proporcionar los ejemplos 311 y 312. Para 1-(3-fluoro-4-(3-(hidroximetil)-1H-pirrolo[2,3-b]piridin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)urea (Ejemplo 311, 7.47 mg, 42%): ^{1}H RMN (DMSO-d_6) δ 11.47 (s, 1H), 10.94 (s, 1H), 10.49 (s, 1H), 7.92 (d, 1H, J= 5.5 Hz), 7.68 (dd, 1H, J= 13.2, 2.2 Hz), 7.31-7.19 (m, 5H), 7.09 (t, 2H, J= 8.8 Hz), 6.10 (d, 1H, J= 5.5 Hz), 4.68 (q, 1H, J= 5.5 Hz), 4.65 (d, 1H, J= 5.5 Hz), 3.67 (s, 2H); EM(ESI) m/z 453.3 $(M + H)^+$. Para 1-(3-Fluoro-4-(3-

(metoximetil)-1H-pirrolo[2,3-b]piridin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)urea (Ejemplo 312): ^{1}H RMN (DMSO-d_6) δ 11.67 (s, 1H), 10.97 (s, 1H), 10.64 (s, 1H), 7.96 (d, 1H, J= 5.5 Hz), 7.68 (d, 1H, J= 12.5),7.34-7.28 (m, 5H), 7.23 (t, 1H, J= 8.8 Hz), 7.01 (t, 2H, J= 8.8 Hz), 6.16 (d, 1H, J= 5.5 Hz), 4.54 (s, 2H), 3.70 (s, 2H), 3.18 (s, 3H); EM(ESI$^+$) m/z 467.2 $(M + H)^+$.

EJEMPLO 313



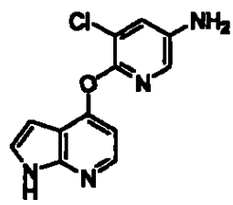
N-(6-(1H-pirrolo[2,3-b]piridin-4-iloxi)-5-cloropiridin-3-il)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridina-3-carboxamida, sal del ácido trifluoroacético



A) 4-(3-Cloro-5-nitropiridin-2-iloxi)-1H-pirrolo[2,3-b]piridina

A una solución de 1H-pirrolo[2,3-b]piridin-4-ol (210

mg, 1.56 mmol, Ver: Thibault, C. et al. Org. Lett. 2003,5,5023) en 3 mL de MeCN se agregó K_2CO_3 (240 mg, 1.74 mmol). La suspensión se agitó durante 10 minutos y se trató con 2,3-dicloro-5-nitropiridina (270 mg, 1.40 mmol, Ver: Koch, V. and Schnatterer, S. Synthesis, 1990, 499). La mezcla de reacción se agitó durante 12 h y se apagó con 20 mL de H_2O. La solución se extrajo con EtOAc y la capa orgánica se lavó con salmuera, y se secó sobre $MgSO_4$. Después de la filtración y concentración in vacuo, el residuo se purificó por cromatografía de columna instantánea (ISCO RediSep® cartucho de gel de sílice) para dar el compuesto del título (220 mg, 54%). EM (ESI) m/z 291.1 $(M + H)^+$.



B) 6-(1H-pirrolo[2,3-b]piridin-4-iloxi)-5-cloropiridin-3-amina

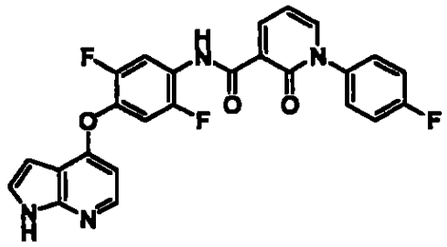
Siguiendo un procedimiento similar como se describe en la etapa B del ejemplo 132, 4-(3-cloro-5-nitropiridin-2-iloxi)-1H-pirrolo[2,3-b]piridina (140 mg, 0.48 mmol) se reduce para el compuesto de título (90 mg, 72%). EM(ESI) m/z 261.1 $(M + H)^+$.

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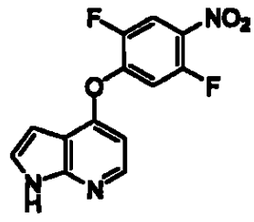
C) N-(6-(1H-pirrolo[2,3-b]piridin-4-iloxi)-5-cloropiridin-3-il)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridina-3-carboxamida, sal del ácido trifluoroacético

Siguiendo un procedimiento similar como se describe en la etapa C del ejemplo 242, 6-(1H-pirrolo[2,3-b]piridin-4-iloxi)-5-cloropiridin-3-amina, dihidrocloruro (14 mg, 0.042 mmol) se convirtió al compuesto del título (5.0 mg, 20%). ^{1}H RMN (DMSO-d_6) δ 12.08 (s, 1H), 11.86 (s, 1H), 8.67 (d, 1H, J= 2.0 Hz), 8.57 (dd, 1H, J= 7.0, 2.0 Hz), 8.41 (d, 1H, J= 2.0 Hz), 8.18 (d, 1H, J= 5.5 Hz), 8.14 (dd, 1H, J= 6.5, 2.0 Hz), 7.60 (dd, 2H, J= 9.0,5.0 Hz), 7.38-7.43 (m, 3H), 6.76 (d, 1H, J= 5.5 Hz), 6.73 (t, 1H, J= 7.0 Hz), 6.08 (m, 1H); EM(ESI) m/z 476.2 $(M + H)^+$.

EJEMPLO 314



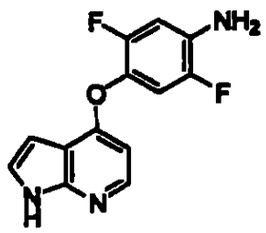
N-(4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-2,5-difluorofenil)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridina-3-carboxamida, sal del ácido trifluoroacético



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A) 4-(2,5-Difluoro-4-nitrofenoxi)-1H-pirrolo[2,3-b]piridina

Siguiendo un procedimiento similar como se describe en la etapa A del ejemplo 313 y usando 1,2,4-trifluoro-5-nitrobenceno, 1H-pirrolo[2,3-b]piridin-4-ol (268 mg, 2.0 mmol) se convirtió al compuesto del título (230 mg, 40%). EM(ESI) m/z 292.2 $(M + H)^+$.



B) 4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-2,5-difluorobencenamina

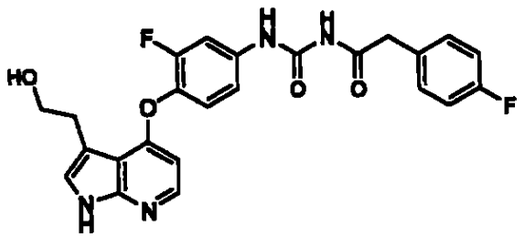
Siguiendo un procedimiento similar como se describe en la etapa B del ejemplo 132, 4-(2,5-difluoro-4-nitrofenoxi)-1H-pirrolo[2,3-b]piridina (230 mg, 0.79 mmol) se convirtió al compuesto del título (34 mg, 17%). EM(ESI) m/z 262.2 $(M + H)^+$.

C) N-(4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-2,5-difluorofenil)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridina-3-carboxamida, ácido trifluoroacético

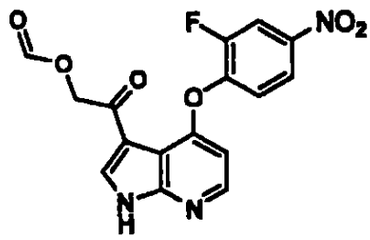
Siguiendo un procedimiento similar como se describe en la etapa C del ejemplo 242, 4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-2,5-difluorobencenamina, diclorohidrato (14 mg, 0.042 mmol) se convirtió al compuesto del título (4.5 mg, 18%). ^1H

RMN (DMSO-d_6) δ 12.42 (s, 1H), 11.86 (s, 1H), 8.61 (dd, 1H, J= 7.0, 2.0 Hz), 8.55 (dd, 1H, J= 12.5, 7.0 Hz), 8.15 (dd, 1H, J= 6.5, 2.0 Hz), 8.10 (d, 1H, J= 6.5 Hz), 7.57-7.62 (m, 3H), 7.40-7.44 (m, 3H), 6.75 (t, 1H, J= 7.0 Hz), 6.47 (d, 1H, J= 5.5 Hz),6.29 (m, 1H); EM(ESI) m/z 477.2 $(M + H)^+$.

EJEMPLO 315



1-(3-Fluoro-4-(3-(2-hidroxietil)-1H-pirrolo[2,3-b]piridin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)urea

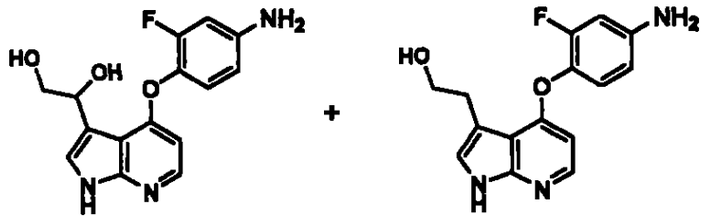


A) 2-(4-(2-Fluoro-4-nitrofenoxi)-1H-pirrolo[2,3-b]piridin-3-il)-2-oxoetil formato

A una solución de 2-bromo-1-(4-(2-fluoro-4-nitrofenoxi)-1H-pirrolo[2,3-b]piridin-3-il)etanona (100 mg, 0.25 mmol, Compuesto A del ejemplo 253) en 1 mL de DMF se agregó formiato de sodio (52 mg, 0.75 mmol, Aldrich). La mezcla de reacción se agitó a temperatura ambiente durante 4 h, y se

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diluyó con K_2HPO_4 acuoso saturado (2 mL). El precipitado que se formó se colectó por filtración, se lavó con H_2O fría (2 mL) y éter (5 mL), y se secó bajo vació para proporcionar el producto deseado (81 mg, 90%) como un sólido café ligero. EM(ESI$^+$) m/z 360.16 $(M + H)^+$.



B) 1-(4-(4-Amino-2-fluorofenoxi)-1H-pirrolo[2,3-b]piridin-3-il)etano-1,2-diol y 2-(4-(4-Amino-2-fluorofenoxi)-1H-pirrolo[2,3-b]piridin-3-il)etanol

A una suspensión de hidruro de aluminio anhidro (266 mg, 2.0 mmol, Alfa Aesar) en 5 mL de 1,2 dimetoxietano a 0°C se agregó hidruro de aluminio litio (1 M soln. en THF, 1.0 mL, 1.0 mmol). Una solución de 2-(4-(2-fluoro-4-nitrofenoxi)-1H-pirrolo[2,3-b]piridin-3-il)-2-oxoetilformato (72 mg, 0.2 mmol) en 5 mL de 1,2-dimetoxietano se agregó gota a gota. La mezcla de reacción se agitó a temperatura ambiente durante 2 h y se apagó por la adición de 5 mL de agua fría. La mezcla se extrajo con EtOAc (3 x 30 mL) y los extractos orgánicos combinados se secaron ($MgSO_4$), se concentraron in vacuo y se purificarón por cromatografía de columna instantánea (ISCO RediSep® cartucho de gel de sílice, eluyendo con 2-10% de MeOH en diclorometano) para dar 1-(4-(4-amino-2-fluorofenoxi)-1H-pirrolo[2,3-b]piridin-3-il)etano-1,2-diol (27 mg, 45%): EM(ESI$^+$) m/z 304.3(M +

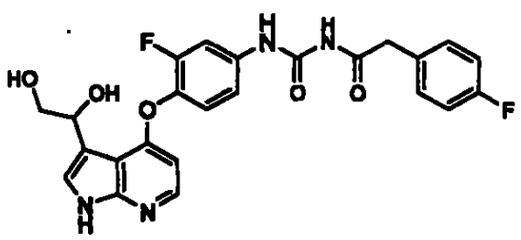
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H)$^+$ y 2-(4-(4-amino-2-fluorofenoxi)-1H-pirrolo[2,3-b]piridin-3-il)etanol (10 mg, 18%): EM(ESI$^+$) m/z 288.3 (M + H)$^+$.

C) 1-(3-Fluoro-4-(3-(2-hidroxietil)-1H-pirrolo[2,3-b]piridin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)urea

Se preparó de 2-(4-(4-amino-2-fluorofenoxi)-1H-pirrolo[2,3-b]piridin-3-il)etanol usando un procedimiento similar como se describe por el ejemplo 264 (4.5 mg, 28%). ^{1}H RMN (CD_3OD) δ 10.74 (s, 1H), 8.06 (d, 1H, J= 5.5 Hz), 7.74 (d, 1H, J= 12.1 Hz), 7.29-7.25 (m, 4H), 7.00-6.96 (m, 3H), 6.51 (d, 1H, J= 5.5 Hz), 3.80 (t, 2H, J= 6.6 Hz), 3.62 (s, 2H), 3.06 (t, 2H, J = 6.6 Hz); EM(ESI$^+$) m/z 467.3 (M + H)$^+$.

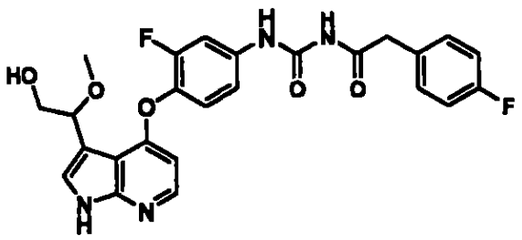
EJEMPLO 316



1-(4-(3-(1,2-Dihidroxietil)-1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea

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EJEMPLO 317



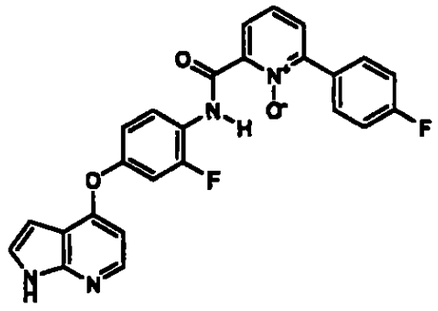
1-(3-Fluoro-4-(3-(2-hidroxi-1-metoxietil)-1H-pirrolo[2,3-b]piridin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)urea

Los ejemplos 316 y 317 se prepararon de 1-(4-(4-amino-2-fluorofenoxi)-1H-pirrolo[2,3-b]piridin-3-il)etano-1,2-diol (Ver: Etapa B del ejemplo 315) usando un procedimiento similar como se describe por el ejemplo 264. La mezcla de reacción se concentró in vacuo y se purificó por CLAR preparativa. Las fracciones deseadas se combinaron, se concentraron in vacuo y se liofilizaron para dar un sólido blanco. El CL/EM indico que el sólido contenia 1-(4-(3-(1,2-dihidroxietil)-1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea y 1-(3-fluoro-4-(3-(2-hidroxi-1-metoxietil)-1H-pirrolo[2,3-b]piridin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)urea. El sólido se purificó nuevamente por cromatografía de columna instantánea (ISCO RediSep® cartucho de gel de sílice, se eluyó con 1-10% MeOR en diclorometano) para proporcionar dos productos: Para 1-(4-(3-(1,2-dihidroxietil)-1H-pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea (6.3

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mg, 16%); ^{1}H RMN (DMSO-d_6) δ 11.57 (s, 1H), 11.03 (s, 1H), 10.59 (s, 1H), 7.99 (d, 1H, J= 5.5 Hz), 7.77 (dd, 1H, J= 12.6, 2.2 Hz), 7.41-7.32 (m, 4H), 7.28 (d, 1H, J= 2.2 Hz), 7.18 (t, 1H, J= 8.8 Hz), 7.01 (t, 2H, J= 8.8 Hz), 6.15 (d, 1H, J= 5.5 Hz), 5.05 (m, 1H), 4.91 (d, 1H, J= 4.4 Hz), 4.60 (t, 1H, J= 5.8 Hz), 3.79-3.75 (m, 1H), 3.75 (s, 2H), 3.47-3.44 (m, 1H); EM(ESI$^+$) m/z 483.3 $(M + H)^+$. Para 1-(3-fluoro-4-(3-(2-hidroxi-1-metoxietil)-1H-pirrolo[2,3-b]piridin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)urea (3.2 mg, 8%); ^{1}H RMN (CD_3OD) δ 8.05 (d, 1H, J= 5.5 Rz), 7.71 (d, 1H, J= 12.1 Hz), 7.37 (s, 1H), 7.28-6.25 (m, 4H), 6.98 (t, 1H, J= 8.2 Hz), 6.45 (d, 1H, J= 5.5 Hz), 3.81 (m, 1H), 3.73-3.71 (m, 2H), 3.63 (s, 2H), 3.34 (s, 3H); EM(ESI$^+$) m/z 497.2 $(M + H)^+$.

EJEMPLO 318

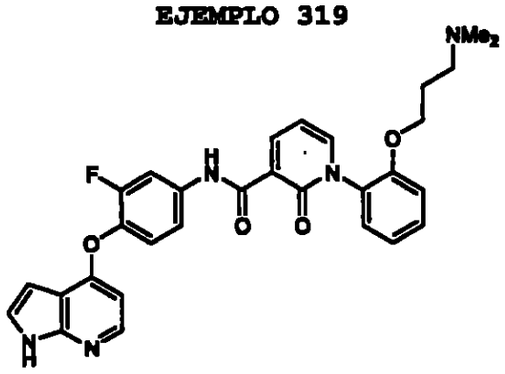


[2-fluoro-4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-fenil]-amida del ácido 6-(4-Fluoro-fenil)-1-oxi-piridina-2-carboxílico

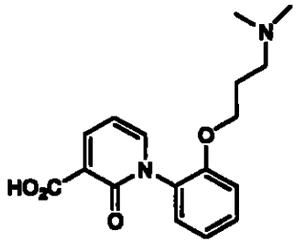
Se preparó en una manera similar como en el ejemplo 241. CLAR t_R = 3.328 min. (YMC S5 ODS 4.6 x 50 mm, 10-90% de metanol acuoso que contiene 0.2% de R_3PO_4, 4 minutos

gradiente, monitoreado a 220 nm); EM(ESI$^+$) m/z 459.2 $(M + H)^+$.

EJEMPLO 319



N-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-1-(2-(3-(dimetilamino)propoxi)fenil)-2-oxo-1,2-dihidropiridina-3-carboxamida, sal de clorohidrato



A) ácido 1-(2-(3-(Dimetilamino)propoxi)fenil)-2-oxo-1,2-dihidropiridina-3-carboxílico

Se preparó en una manera similar como en las etapas A y B del ejemplo 242. ^{1}H RMN (DMSO-d_6) δ 10.53 (br m, 1H), 8.51-8.53 (m, 1H), 8.18-8.20 (m, 1H), 7.48-7.51 (m, 2H), 7.30(d, 1H, J= 7.96Hz), 7.13-7.17 (m, 1H),6.82(t, 1H, J= 6.95 Hz), 4.11-4.18 (m, 2H), 2.66-2.68 (m, 2H), 2.67 (s, 6H), 1.98-2.05 (m, 2H); EMAR(ESI), calculado: 317.1501, encontrado:

674

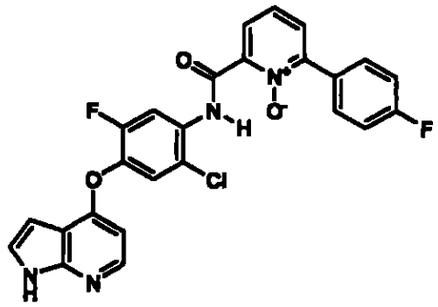
676

317.1490.

B) N-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-3-fluorofenil)-1-(2-(3-(dimetilamino)propoxi)fenil)-2-oxo-1,2-dihidropiridina-3-carboxamida, sal de clorohidrato

Se preparó en una manera similar como en la etapa C del ejemplo 242. ^{1}H RMN (CD_3OD) δ 8.62-8.65 (m, 1H), 8.23 (d, 1H, J= 6.90 Hz), 7.98-8.01 (m, 1H), 7.83-7.85 (m, 1H), 7.39-7.50 (m, 2H), 7.31-7.49 (m, 3H), 7.20 (d, 1H, J= 7.93), 7.10-7.13 (m, 1H), 6.80 (d, 1H, J= 6.72 Hz), 6.69 (t, 1H, J= 6.75 Hz), 6.59-6.60 (m, 1H), 4.12 (t, 2H, J= 5.61 Hz), 3.02-3.06 (m, 2H), 2.70 (s, 6H), 2.03-2.04 (m, 2H); EMAR(ESI), calculado: 542.2204, encontrado: 542.2194.

EJEMPLO 320

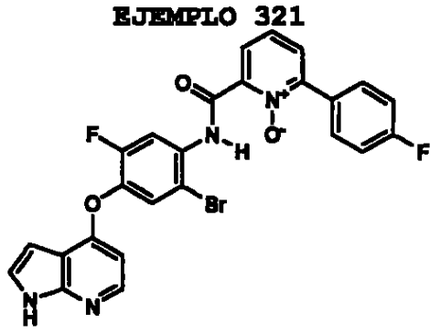


[2-cloro-5-fluoro-4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-fenil]-amida del ácido 6-(4-Fluoro-fenil)-1-oxi-piridina-2-carboxílico

Se preparó en una manera similar como en el ejemplo 241. CLAR t_R = 3.293 min. (Chromolith SpeedROD 4.6 x 50 mm, 10-90% de metanol acuoso que contiene 0.1% de TFA, 4 min gradiente,

monitoreado a 220 nm); EM(ESI$^+$) m/z 493 (M + H)$^+$.

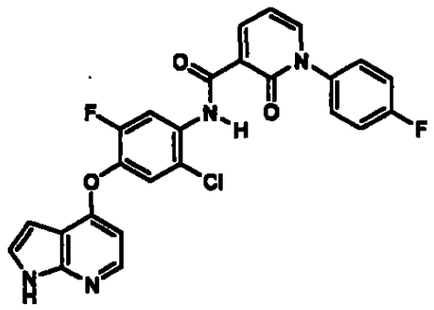
EJEMPLO 321



[2-bromo-5-fluoro-4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-fenil]-amida del ácido 6-(4-Fluoro-fenil)-1-oxi-piridina-2-carboxílico

Se preparó en una manera similar como en el ejemplo 241. CLAR t_R = 3.371 min (Chromolith SpeedROD 4.6 x 50 mm, 10-90% de metanol acuoso que contiene 0.1% de TFA, 4 min gradiente, monitoreado a 220 nm); EM (ESI$^+$) m/z 537 (M + H)$^+$.

EJEMPLO 322

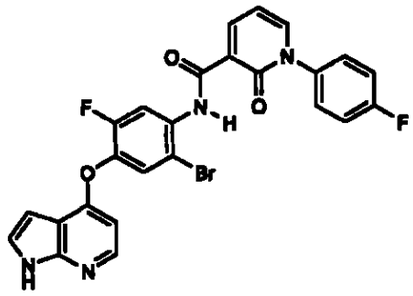


N-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-2-cloro-5-fluorofenil)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridina-3-carboxamida

Se preparó en una manera similar como en la etapa C del

ejemplo 242. CLAR t_R = 3.070 min (Chromolith SpeedROD 4.6 x 50 mm, 10-90% de metanol acuoso que contiene 0.1% de TFA, 4 min gradiente, monitoreado a 220 nm); EM(ESI$^+$) m/z 493 (M + H)$^+$.

EJEMPLO 323

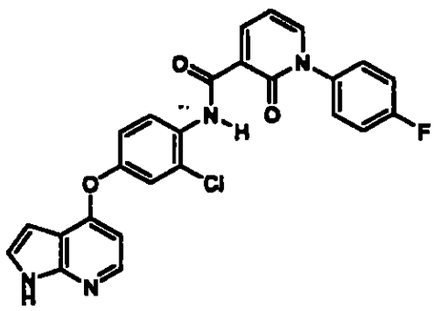


N-(4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-2-bromo-5-fluorofenil)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridina-3-carboxamida

Se preparó en una manera similar como en la etapa C del ejemplo 242. CLAR t_R = 3.115 min (Chromolith SpeedROD 4.6 x 50 mm, 10-90% de metanol acuoso que contiene 0.1% de TFA, 4 min gradiente, monitoreado a 220 nm); EM(ESI$^+$) m/z 538 (M + H)$^+$.

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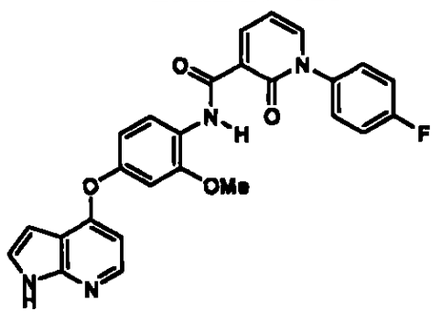
EJEMPLO 324



N-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-2-clorofenil)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridina-3-carboxamida

Se preparó en una manera similar como en la etapa C del ejemplo 242. CLAR t_R = 2.946 min (Chromolith SpeedROD 4.6 x 50 mm, 10-90% de metanol acuoso que contiene 0.1% de TFA, 4 min gradiente, monitoreado a 220 nm); EM(ESI$^+$) m/z 475 $(M + H)^+$.

EJEMPLO 325

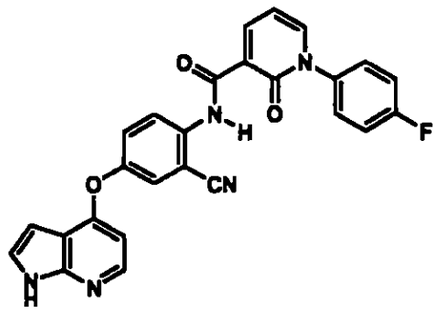


N-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-2-metoxifenil)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridina-3-carboxamida

Se preparó en una manera similar como en la etapa C del ejemplo 242. CLAR t_R = 2.795 min (Chromolith SpeedROD 4.6 x 50 mm, 10-90% de metanol acuoso que contiene 0.1% de TFA, 4 min gradiente, monitoreado a 220 nm); EM(ESI$^+$) m/z 471 $(M + H)^+$.

680

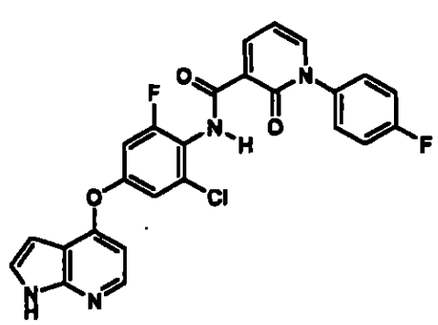
EJEMPLO 326



N-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-2-cianofenil)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridina-3-carboxamida

Se preparó en una manera similar como en la etapa C del ejemplo 242. CLAR t_R = 2.618 min (Chrmmolith SpeedROD 4.6 x 50 mm, 10-90% de metanol acuoso que contiene 0.1% de TFA, 4 min gradiente, monitoreado a 220 nm); EM(ESI^+) m/z 466 $(M + H)^+$.

EJEMPLO 327



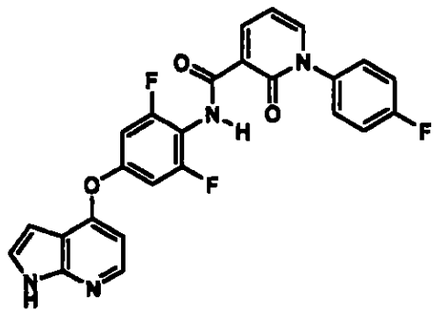
N-(4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-2-cloro-6-fluorofenil)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridina-3-carboxamida

Se preparó en una manera similar como en la etapa C del ejemplo 242. CLAR t_R = 2.805 min (Chromolith SpeedROD 4.6 x 50 mm, 10-90% de

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metanol acuoso que contiene 0.1% de TFA, 4 min gradiente, monitoreado a 220 nm); EM(ESI$^+$) m/z 493 $(M + H)^+$.

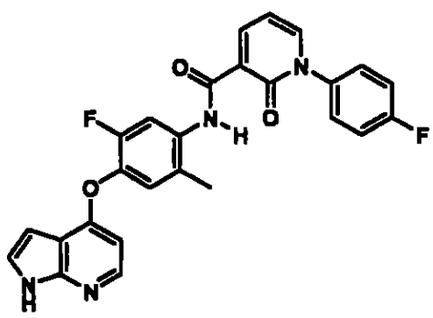
EJEMPLO 328



N-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-2,6-difluorofenil)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridina-3-carboxamida

Se preparó en una manera similar como en la etapa C del ejemplo 242. CLAR t_R = 2.653 min (Chromolith SpeedROD 4.6 x 50 mm, 10-90% de metanol acuoso que contiene 0.1% de TFA, 4 min gradiente, monitoreado a 220 nm); EM(ESI$^+$) m/z 477 $(M + H)^+$.

EJEMPLO 329



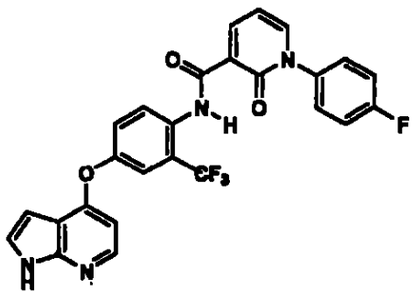
N-(4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-2-metil-4-fluorofenil)-1-

682

(4-fluorofenil)-2-oxo-1,2-dihidropiridina-3-carboxamida

Se preparó en una manera similar como en la etapa C del ejemplo 242. CLAR t_R = 3.010 min (Chromolith SpeedROD 4.6 x 50 mm, 10-90% de metanol acuoso que contiene 0.1% de TFA, 4 min gradiente, monitoreado a 220 nm); EM(ESI$^+$) m/z 473 $(M + H)^+$.

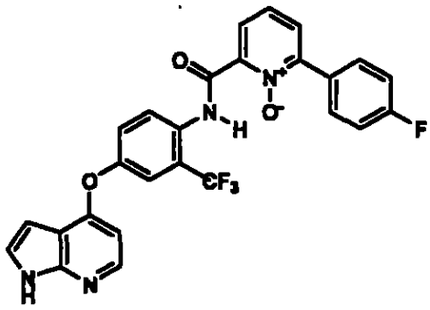
EJEMPLO 330



N-(4-(1H-Pirrolo[2,3-b]piridin-4-iloxi)-2-trifluorometil-fenil)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridina-3-carboxamida

Se preparó en una manera similar como en la etapa C del ejemplo 242. CLAR t_R = 2.943 min (Chromolith SpeedROD 4.6 x 50 mm, 10-90% de metanol acuoso que contiene 0.1% de TFA, 4 min gradiente, monitoreado a 220 nm); EM(ESI$^+$) m/z 509 $(M + H)^+$.

EJEMPLO 331



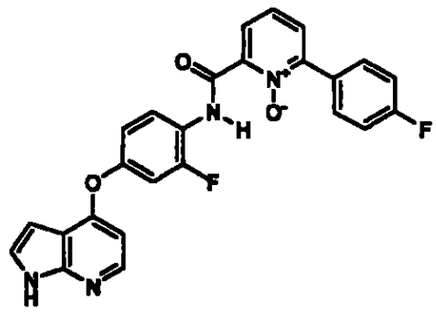
6-(4-Fluoro-fenil)-1-oxi-piridina-2-carboxílico

683

[2-trifluorometil-4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-fenil]-amida

Se preparó en una manera similar como en el ejemplo 241. CLAR t_R = 3.205 min (Chromolith SpeedROD 4.6 x 50 mm, 10-90% de metanol acuoso que contiene 0.1% de TFA, 4 min gradiente, monitoreado a 220 nm); EM(ESI$^+$) m/z 509 $(M + H)^+$.

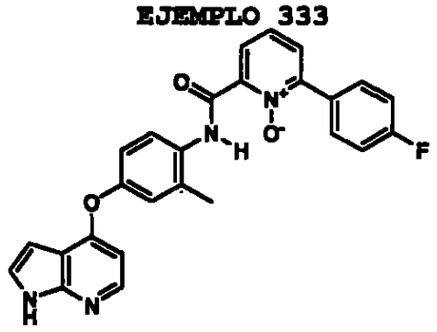
EJEMPLO 332



[2-fluoro-4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-fenil]-amida del ácido 6-(4-Fluoro-fenil)-1-oxi-piridina-2-carboxílico

Se preparó en una manera similar como en el ejemplo 241. CLAR t_R = 1.103 min. (YMC S5 ODS 4.6 x 50 mm, 10-90% de metanol acuoso que contiene 0.1% de H_3PO_4, 4 min gradiente, monitoreado a 220 nm); EM(ESI$^+$) m/z 459 $(M + H)^+$.

EJEMPLO 333

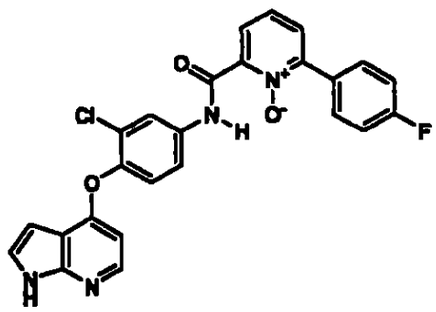


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[2-metil-4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-fenil]-amida del ácido 6-(4-Fluoro-fenil)-1-oxi-piridina-2-carboxílico

Se preparó en una manera similar como en el ejemplo 241. CLAR t_R = 3.120 min (Chromolith SpeedROD 4.6 x 50 mm, 10-90% de metanol acuoso que contiene 0.1% de TFA, 4 min gradiente, monitoreado a 220 nm); EM(ESI$^+$) m/z 455 $(M + H)^+$.

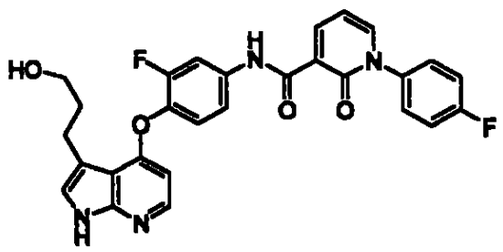
EJEMPLO 334



[5-Fluoro-4-(1H-pirrolo[2,3-b]piridin-4-iloxi)-fenil]-amida del ácido 6-(4-Fluoro-fenil)-1-oxi-piridina-2-carboxílico

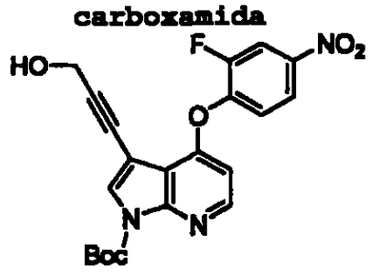
Se preparó en una manera similar como en el ejemplo 241. CLAR t_R = 3.200 min. (Chromolith SpeedROD 4.6 x 50 mm, 10-90% de metanol acuoso que contiene 0.1% de TFA, 4 min gradiente, monitoreado a 220 nm); EM(ESI$^+$) m/z 475 $(M + H)^+$.

EJEMPLO 335



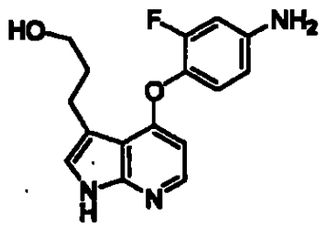
685

N-(3-Fluoro-4-(3-(3-hidroxipropil)-1H-pirrolo[2,3-b]piridin-4-iloxi)fenil)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridina-3-carboxamida



A) tert-Butil 4-(2-fluoro-4-nitrofenoxi)-3-(3-hidroxiprop-1-inil)-1H-pirrolo[2,3-b]piridina-1-carboxilato

Una corriente de Argón que se burbujeó a través de una mezcla de tert-butil 4-(2-fluoro-4-nitrofenoxi)-3-yodo-1H-pirrolo[2,3-b]piridina-1-carboxilato (400 mg, 0.8 mmol, Compuesto B del ejemplo 283), alcohol de propargilo (90 mg, 1.6 mmol), $Pd(dppf)_2Cl_2:CH_2Cl_2$ (66 mg, 0.08 mmol), y CuI (40 mg) en trietilamina (0.8 mL) y THF (6 mL) durante 5 minutos. La mezcla de reacción se selló en un tubo y se calentó a 75°C durante 1h. La mezcla se diluyó con CH_2Cl_2 y se lavó con salmuera. La fase orgánica se secó sobre $MgSO_4$ y se concentró in vacuo. El residuo crudo se purificó por cromatografía de columna instantánea (gel de sílice, 30% EtOAc/ CH_2Cl_2) para proporcionar el producto deseado (220 mg, 64% rendimiento) como un sólido amarillo. CL/EM (ESI^+) m/z 428 $(M + H)^+$.



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B) 3-(4-(4-Amino-2-fluorofenoxi)-1H-pirrolo[2,3-b]piridin-3-il)propan-1-ol

Una mezcla de tert-butil 4-(2-fluoro-4-nitrofenoxi)-3-(3-hidroxiprop-1-inil)-1H-pirrolo[2,3-b]piridina-1-carboxilato (50 mg, 0.15 mmol) y 10% de Pd/C (que contiene 50% de H_2O, 120 mg) en THF (10 mL) y MeOH (2 mL) se hidrogenó a través de una almohadilla de Celite®. La mezcla cruda se purificó por CLAR preparativa para proporcionar el producto deseado (6 mg, 13% rendimiento) como un sólido blanco. CL/EM (ESI) m/z 302 $(M + H)^+$.

C) N-(3-Fluoro-4-(3-(3-hidroxipropil)-1H-pirrolo[2,3-b]piridin-4-iloxi)fenil)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridina-3-carboxamida

A una mezcla agitada de 3-(4-(4-amino-2-fluorofenoxi)-1H-pirrolo[2,3-b]piridin-3-il)propan-1-ol (5 mg, 0.0166 mmol), ácido 1-(4-fluorofenil)-2-oxo-1,2-dihidropiridina-3-carboxílico (5.8 mg, 0.025 mmol, Compuesto B del ejemplo 242), y HATU (Perseptive Biosystems, 10 mg, 0.025 mmol) en DMF (0.5 mL), se agregó DIPEA (0.1 mL). La mezcla de reacción se agitó a temperatura ambiente durante 2 h y se concentró in vacuo. El residuo se purificó por CLAR preparativa para dar el compuesto del título (6 mg, sal HCl, 66% rendimiento) como un sólido blanco. ^1H RMN (CD_3OD) δ 8.71 (dd, 1H, J= 7.2, 2.0 Hz), 8.22 (d, 1H, J= 6.8 Hz), 8.10 (dd, 1H, J= 12.4, 2.0 Hz),

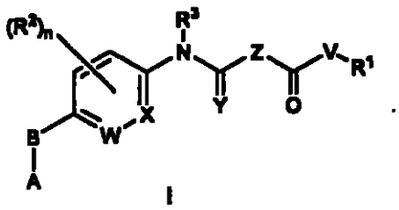
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8.00 (dd, 1H, J= 6.4, 2.0 Hz), 7.25-7.60 (m, 7H), 7.70-7.80 (m, 2H), 3.64 (t, 2H, J= 6.4 Hz), 3.05 (t, 2H, J= 7.2 Hz), 2.00 (m, 2H); CL/EM (ESI^+) m/z 517 $(M + H)^+$.

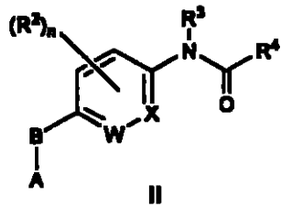
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REIVINDICACIONES

1. Un compuesto de conformidad con la Fórmula I ó II:



I



II

que incluye sales farmacéuticamente aceptables del mismo, caracterizado porque:

R^1 es H, alquilo, alquilo substituido, cicloalquilo, cicloalquilo substituido, arilalquilo, arilalquilo substituido, arilo, arilo substituido, alquenilo, alquenilo substituido, alquinilo, alquinilo substituido, heteroarilo, heteroarilo substituido, heterociclo, heterociclo substituido, heteroarilaquilo, heteroarilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido;

cada R^2 es independientemente, H, halógeno, ciano, NO_2, OR^5, NR^6R^7, alquilo, alquilo substituido, cicloalquilo, cicloalquilo substituido, arilo, arilo substituido, heteroarilo, heteroarilo substituido, heterociclo, heterociclo substituido, arilalquilo, arilalquilo substituido, heterocicloalquilo, o heterocicloalquilo substituido;

B es O, NR^8, S, SO, SO_2, CR^9R^{10};

V es NR^{11} o $-(CR^{47}R^{48})_p-$;

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W o X son independientemente C o N;

Y es O, S, o NR^{12};

Z es $-CR^{13}R^{14}-$, $-(CR^{13}R^{14})_mNR^{15}-$;

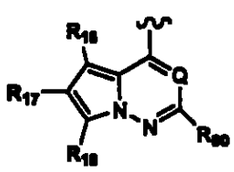
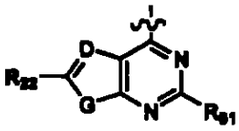
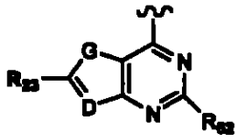
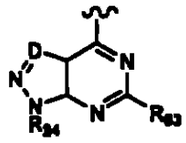
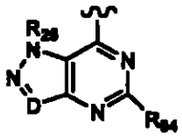
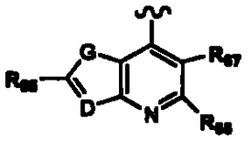
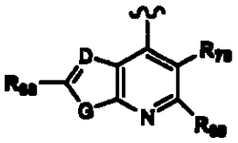
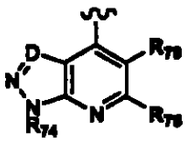
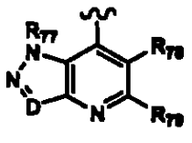
l tiene un valor de 0 hasta 4;

m tiene un valor 0 a 2;

n tiene un valor 0 a 4;

p tiene un valor 0 a 4, con la condición de que si p es 0, R^1 no es fenilo;

A es:

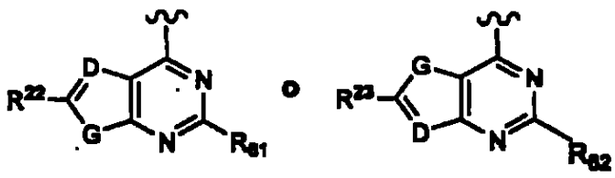










Q es CR^{19};

D es CR^{20} o N;

G es S, O, o NR^{21}, con la condición de que si A es

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y G es S, R^4 no es un grupo fenilo substituido;

R^3, R^5, R^6, R^7, R^8, R^{11} y R^{15} son cada uno independientemente H, alquilo, alquilo substituido, cicloalquilo, cicloalquilo substituido, arilo, arilo substituido, heteroarilo, heteroarilo substituido, heterocicloalquilo, o heterocicloalquilo substituido;

R^4 es arilo, arilo substituido, heteroarilo, heteroarilo substituido, heterocicloalquilo, o heterocicloalquilo substituido;

R^9 y R^{10} son independientemente H, halógeno, alquilo, alquilo substituido, cicloalquilo, cicloalquilo substituido, arilo, arilo substituido, heteroarilo, heteroarilo substituido, heterocicloalquilo, o heterocicloalquilo substituido;

R^{12} es H, alquilo, alquilo substituido, CN, NO_2 o SO_2NH_2;

R^{13}, R^{14}, R^{15}, R^{47} y R^{48} son independientemente H, halógeno, alquilo, alquilo substituido, cicloalquilo, cicloalquilo substituido, arilo, arilo substituido, heteroarilo, heteroarilo substituido, heterociclo,

heterociclo substituido o tomados juntos para formar un anillo heterocíclico o carbocíclico desde 3 hasta 8 átomos;

R^{16}, R^{17}, R^{18}, R^{20}, R^{22}, R^{23}, R^{60}, R^{61}, R^{62}, R^{63}, R^{64}, R^{65}, R^{66}, R^{67}, R^{68}, R^{69}, R^{70}, R^{75}, R^{76}, R^{78}, y R^{79}, son independientemente H, halógeno, NO_2, ciano, OR^{26}, $NR^{27}R^{28}$, CO_2R^{29}, $C(O)NR^{30}R^{31}$, SO_2R^{32}, $SO_2NR^{33}R^{34}$, $NR^{35}SO_2R^{36}$, $NR^{37}C(O)R^{38}$, $NR^{39}CO_2R^{40}$, $-CO(CH_2)_1R^{41}$; $-CONH(CH_2)_1R^{42}$, alquilaminoalquilo, alquilaminoalquinilo, alquilo C_1 hasta C_6, alquilo C_1 hasta C_6 substituido, cicloalquilo C_3 hasta C_7, cicloalquilo C_3 hasta C_7 substituido, alquenilo, alquenilo substituido, alquinilo, alquinilo substituido, hidroxialquilo, arilo, arilo substituido, heteroarilo, heteroarilo substituido, arilalquilo, arilalquilo substituido, heterocicloalquilo, o heterocicloalquilo substituido;

R^{19} es H o ciano;

R^{21} y R^{24} son independientemente H, alquilo C_1 hasta C_6 o alquilo C_1 hasta C_6 substituido;

R^{25}, R^{74} y R^{77} son independientemente H, alquilo, alquilo substituido, cicloalquilo, cicloalquilo substituido, arilo, arilo substituido, arilalquilo, arilalquilo substituido, heteroarilo, heteroarilo substituido, heterocicloalquilo, o heterocicloalquilo substituido

R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, R^{33}, R^{34}, R^{35}, R^{36}, R^{37}, R^{38}, R^{39}, R^{40}, R^{41}, y R^{42} son independientemente H, alquilo, alquilo substituido, cicloalquilo, cicloalquilo substituido, arilo,

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arilo substituido, arilalquilo, arilalquilo substituido, heteroarilo, heteroarilo substituido, heterocicloalquilo, o heterocicloalquilo substituido.

2. El compuesto de conformidad con la reivindicación 1, caracterizado porque R^1 es alquilo C_1 a C_6 opcionalmente substituido, alquenilo, alquinilo, cicloalquilo C_3 a C_7 opcionalmente substituido, heterocicloalquilo C_3 a C_7, fenilo opcionalmente substituido, bifenilo opcionalmente substituido o un heteroarilo bicíclico o monocíclico C_5 a C_{11} opcionalmente substituido.

3. El compuesto de conformidad con la reivindicación 2, caracterizado porque R^1 se selecciona del grupo que consiste de fenilo, opcionalmente substituido con Cl, F, OCH_3, alquilo, alquenilo, alquinilo, hidroxi, amido, fenoxi, CH_2CN, bencilo, $NHCO_2CH_3$; bifenilo, piridilo, azepanilo, pirazolilo, tiazolilo, indolilo, indazolilo, indenilo, ciclopropilo, isopropilo, feniletilo, aminoalquilo, bencilo, amidoalquilo, morfolina y furanilmetilo.

4. El compuesto de conformidad con la reivindicación 1, caracterizado porque R^2 es H, metilo, alcoxilo, halo, haloalquilo o ciano.

5. El compuesto de conformidad con la reivindicación 1, caracterizado porque R^4 es un fenilo opcionalmente substituido, un piridilo opcionalmente substituido, un pirrolidinilo opcionalmente substituido, un piridil-N-oxi

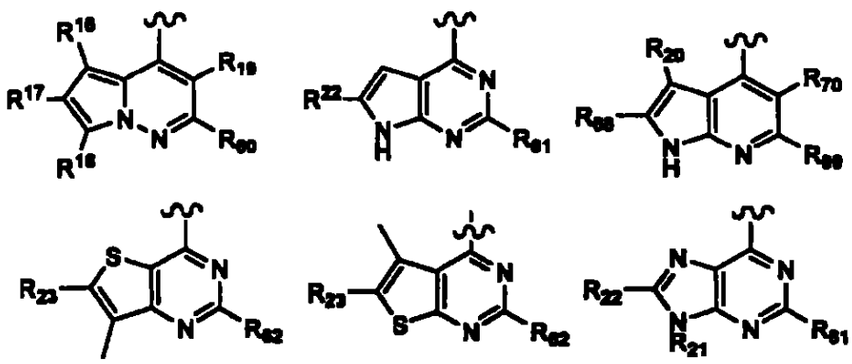
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opcionalmente substituido, o una piridinona opcionalmente substituida.

6. El compuesto de conformidad con la reivindicación 5, caracterizado porque el fenilo, piridilo, piridinona o N-oxi piridilo se substituye con hidroxilo, halo, alquilo C_1 a C_4, cicloalquilo C_3 a C_7, $-COCH_3$, alcoxi, amino, heterocicloalquilo, aminoalquilamino, ciano, alquiltiol, fenilo o alquilaminoalcoxilo.

7. El compuesto de conformidad con la reivindicación 6, caracterizado porque el sustituto es F, Br, Cl, metilo, pentilo, metoxi, fenilo, morfolinilo, NH_2 o $NHCHNH_2$.

8. El compuesto de conformidad con la reivindicación 1, caracterizado porque A es



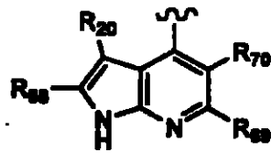
9. El compuesto de conformidad con la reivindicación 8, caracterizado porque R^{19} es H o CN; R^{16} y R^{17} son independientemente H, alquilo C_1 a C_4, alcoxi C_1 a C_4, o $-C(O)_2R^{29}$ en donde R^{29} es alquilo C_1 a C_4; y R^{18} es H.

10. El compuesto de conformidad con la reivindicación 8, caracterizado porque, R^{22} y R^{61} son H.

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11. El compuesto de conformidad con la reivindicación 8, caracterizado porque, R^{68}, R^{69} y R^{70} son H; R^{20} es alquilo C_1 a C_4; alquenilo; alquinilo; heterocicloarilo C_5 a C_6; $CO(CH_2)_1R^{41}$ y R^{41} es alquilo C_1 a C_4; haloalquilo; amino; alquilamino; heterocicloalquilo C_5 a C_7; heteroarilo C_5 a C_7; $C(O)_2R^{29}$ en donde R^{29} es etilo; CN; alcoxi; fenilmetilo; alquilaminoalquinilo; alquilaminoalquilo; hidroxialquilo o metoxialquilo.

12. El compuesto de conformidad con la reivindicación 8, caracterizado porque A es,



13. El compuesto de conformidad con la reivindicación 1, caracterizado porque, Y es O u S.

14. El compuesto de conformidad con la reivindicación 1, caracterizado porque, B es O.

15. El compuesto de conformidad con la reivindicación 1, caracterizado porque, Z es $-CR^{13}R^{14}$ o NR^{15} en donde R^{13}, R^{14} y R^{15} son cada uno H o R^{13} y R^{14} junto con el carbono al cual se enlazan forman un ciclopropilo.

16. El compuesto de conformidad con la reivindicación 1, caracterizado porque R^4 es fenilo.

17. El compuesto de conformidad con la reivindicación 1, caracterizado porque R^4 es piridilo.

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18. El compuesto de conformidad con la reivindicación 1, caracterizado porque R^4 es pirrolidinilo.

19. El compuesto de conformidad con la reivindicación 1, caracterizado porque R^4 es piridil-N-oxi.

20. El compuesto de conformidad con la reivindicación 1, caracterizado porque R^4 es piridinona.

21. El compuesto de conformidad con la reivindicación 12, caracterizado porque R^{20} es $-COCH_2-R$, donde R es amino, pirrolidina o piperazina.

22. El compuesto de conformidad con la reivindicación 12, caracterizado porque R^{20} es piridina o tiazol.

23. El compuesto de conformidad con la reivindicación 12, caracterizado porque R^{20} es $-COC(Cl)_3$ o $CONHCH_2$piridina.

24. El compuesto de conformidad con la reivindicación 12, caracterizado porque R^{20} es CH_2piperidina, CH_2fenilo, -C≡C-amino, ciano, $-CO_2CH3$, - CH_2OH, CH_2OMe, hidroxietilo, $-CHOH(CH_2)_2OH$ o $CH(OCH_3)CH_3$.

25. El compuesto de conformidad con la reivindicación 1, caracterizado porque tiene un valor IC50 menor que aproximadamente 5 μM.

26. El compuesto de conformidad con la reivindicación 1, caracterizado porque tiene un valor IC50 menor que aproximadamente 1 μM.

27. Un método para el tratamiento contra el cáncer, caracterizado porque comprende administrarle a un paciente

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que lo necesita, una cantidad farmacéuticamente efectiva de un compuesto que tiene la fórmula I ó II de conformidad con la reivindicación 1.

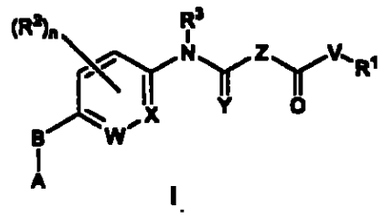
28. Una composición farmacéutica caracterizada porque comprende una cantidad terapéuticamente efectiva de un compuesto de conformidad con la reivindicación 1, en un portador farmacéuticamente aceptable.

29. El método de conformidad con la reivindicación 18, caracterizado porque además comprende administrarle al paciente al menos otro agente anticancerígeno.

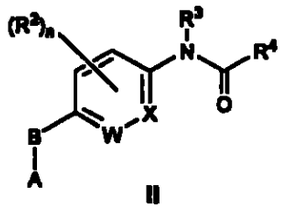
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RESUMEN DE LA INVENCIÓN

En general, la invención actual comprende compuestos de las Fórmulas I y II



I



II

que incluyen sales farmacéuticamente aceptables de los mismos. Los compuestos de la invención son útiles como inhibidores de proteína cinasa y, por lo tanto, son útiles para el tratamiento contra el cáncer y otras enfermedades mediadas por la proteína cinasa.

10601-WO-PCT
102.718
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PATENT C OPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
BRISTOL-MYERS SQUIBB COMPANY
Attn. Gibbons, Maureen
P.O. Box 4000
Route 206 and Province Line Road
Princeton, NJ 08543-4000
UNITED STATES OF AMERICA

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing (day/month/year)	07/04/2006
Applicant's or agent's file reference: 10601-PCT	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No.: PCT/US2005/022682	International filing date (day/month/year): 28/06/2005
Applicant: BRISTOL-MYERS SQUIBB COMPANY	

1. [x] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 338.82.70

   For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. [ ] With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   Shortly after the expiration of 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

   Within 19 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise, the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

RECEIVED
BMS PATENT LAW

Name and mailing address of the International Searching Authority: European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer: Eva Brell

APR 17 2006

Docketed Item claims amended
Due Date 4/17/06
Attorney M. Gibbons

Form PCT/ISA/220 (January 2004)

PATENT CO PERATION TREATY

PCT

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
10601-PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2005/022682	28/06/2005	28/06/2004
Applicant		
BRISTOL-MYERS SQUIBB COMPANY		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the language, the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. [ ] Certain claims were found unsearchable (See Box No. II)

3. [ ] Unity of invention is lacking (see Box No III)

4. With regard to the title,
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the abstract,
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the drawings,
   a. the figure of the drawings to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant
      [ ] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [ ] none of the figures is to be published with the abstract

INTEI \TI NAL SEARCH REPORT

I.. .ational application No
PCT/US2005/022682

A. CLASSIFICATION OF SUBJECT MATTER
C07D487/04 C07D495/04 C07D471/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 415 987 A (EISAI CO., LTD) 6 May 2004 (2004-05-06) claim 2 cited as WO0232872	1-29
A	WO 01/09134 A (NOVARTIS AG; NOVARTIS-ERFINDUNGEN VERWALTUNGSGESELLSCHAFT M.B.H; COLLI) 8 February 2001 (2001-02-08) claim 1	1-29
A	WO 97/16452 A (NOVARTIS AG; ZIMMERMANN, JUERG; CAPRARO, HANS-GEORG; PETERLI, PATRICIA) 9 May 1997 (1997-05-09) claim 1	1-29

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 March 2006	07/04/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Wolf, C

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/022682

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 27,29 in respect of industrial applicability
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 27,29 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2005/022682

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1415987 A	06-05-2004	AU 9598601 A	29-04-2002
		CA 2426461 A1	25-04-2002
		CN 1478078 A	25-02-2004
		HU 0302603 A2	28-11-2003
		WO 0232872 A1	25-04-2002
		JP 3712393 B2	02-11-2005
		MX PA03003362 A	01-08-2003
		NO 20031731 A	19-06-2003
		NZ 525324 A	24-03-2005
		US 2004053908 A1	18-03-2004
WO 0109134 A	08-02-2001	AT 251160 T	15-10-2003
		AU 767349 B2	06-11-2003
		AU 6567700 A	19-02-2001
		BR 0012888 A	09-04-2002
		CA 2379560 A1	08-02-2001
		CN 1365360 A	21-08-2002
		CZ 20020299 A3	17-04-2002
		DE 60005684 D1	06-11-2003
		DE 60005684 T2	29-07-2004
		DK 1200435 T3	02-02-2004
		EP 1200435 A1	02-05-2002
		ES 2208395 T3	16-06-2004
		HU 0201935 A2	28-11-2002
		JP 2003506375 T	18-02-2003
		MX PA02001102 A	20-08-2002
		NO 20020467 A	20-03-2002
		NZ 516667 A	28-05-2004
		PL 354477 A1	26-01-2004
		PT 1200435 T	27-02-2004
		SK 1262002 A3	02-07-2002
		TR 200200234 T2	21-06-2002
		US 6589950 B1	08-07-2003
		ZA 200200783 A	12-02-2003
WO 9716452 A	09-05-1997	AT 236161 T	15-04-2003
		AU 7296896 A	22-05-1997
		BR 9611157 A	30-03-1999
		CA 2234609 A1	09-05-1997
		CN 1202896 A	23-12-1998
		DE 69627195 D1	08-05-2003
		DE 69627195 T2	29-01-2004
		EP 0874846 A1	04-11-1998
		ES 2196181 T3	16-12-2003
		HK 1016580 A1	06-02-2004
		JP 11514336 T	07-12-1999
		PT 874846 T	29-08-2003

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2005/022682	28.06.2005	28.06.2004

International Patent Classification (IPC) or both national classification and IPC
INV. C07D487/04 C07D495/04 C07D471/04

Applicant
BRISTOL-MYERS SQUIBB COMPANY

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Wolf, C Telephone No. +49 89 2399-8285

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2005/022682

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ in written format

      ☐ in computer readable form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in computer readable form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2005/022682

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 27,29 in respect of industrial applicability

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 27,29 in respect of industrial applicability

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form ☐ has not been furnished

☐ does not comply with the standard

the computer readable form ☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-29
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-29
Industrial applicability (IA)	Yes:	Claims	1-26,28
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III.

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

For the assessment of the present claims 27,29 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item V.

The following documents are cited in the International Search Report:

D1: EP-A-1 415 987 (EISAI CO., LTD) 6 May 2004 (2004-05-06)
D2: WO 01/09134 A (NOVARTIS AG; NOVARTIS-ERFINDUNGEN VERWALTUNGSGESELLSCHAFT M.B.H; COLLI) 8 February 2001 (2001-02-08)
D3: WO 97/16452 A (NOVARTIS AG; ZIMMERMANN, JUERG; CAPRARO, HANS-GEORG; PETERLI, PATRICIA) 9 May 1997 (1997-05-09).

In the light of D1 the subject matter claimed appears to be not novel and to lack an inventive step (Articles 33(2) and (3) PCT).

D1 discloses antitumor active agents of formula II in claim 2 whose general formula II overlaps with the general formula claimed in claim 1 of the present application.

D2 and D3 disclose similarly structured pharmacologically active compounds which differ from the compounds as claimed in the substituent(s) R^1 respectively R_1 as defined in the prior art documents.

2. The assessment of inventive step of the subject matter claimed can only be based

upon subject matter which is novel. However, the following is to be noted:

The technical problem underlying the present application was the provision of further antitumor active compounds.

As far as the subject matter claimed is novel it is structurally closely related to the subject matter disclosed in D1. It would be expected by a skilled person faced with the task of solving said technical problem that such similarly structured compounds exhibit a simila pharmacological profile as the prior art. The solution to the technical problem thus appears to be obvious in the light of D1.

Re Item VII.

Claim 29 contains a reference back to claim 18 which is not correct.

Re Item VIII.

1. The terms "substituted" in the claims render the scope of the claimed range unclear (Article 6 PCT).

2. The Applicant is invited to indicate the reason for the provisos in the claims. If it was intended to delimit the subject matter claimed from any further prior art not cited yet, the referring documents should be indicated.

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

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INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims,description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by canceling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

TRATADO DE COOPERACION DE PATENTES

PCT

REPORTE DE BUSQUEDA INTERNACIONAL

(Artículo 18 y Reglas 43 y 44 del PCT)

Referencia de archivo del solicitante o apoderado: 10601-PCT	PARA UNA ACCIÓN ADICIONAL	Ver forma PCT/ISA/220 Si es aplicable el artículo 5 a continuación
No. de solicitud internacional: PCT/US2005/022682	Fecha de presentación internacional *(día/mes/año)*: 28/06/2005	(primera) Fecha de prioridad *(día/mes/año)*: 28/06/2004
Solicitante: BRISTOL-MYERS SQUIBB COMPANY		

Este reporte de búsqueda internacional ha sido preparado por esta Autoridad de Búsqueda Internacional y se transmite al solicitante de acuerdo al Artículo 18. Una copia se transmite a la Oficina Internacional.

Este reporte de búsqueda internacional consiste de un total de 3 hojas.

[X] También está acompañado de una copia de cada documento de la técnica previa citado en este reporte.

I. Base del reporte:

a. Con respecto al **idioma**, la búsqueda internacional se llevó a cabo con base a:

[X] la solicitud internacional en el idioma a la que fué enviado.

[ ] una traducción de la solicitud internacional en _____, que es el idioma de una traducción enviada para el proposito de búsqueda internacional (Reglas 12.3(a) y 23.1(b)).

[ ] Con respecto a cualquier **secuencia de nucleótidos/aminoácidos** descrita en la solicitud internacional, la búsqueda internacional se llevó a cabo con base a la secuencia listada, ver Bloque No. I

2. [ ] **Ciertas reivindicaciones son inescrutables** (ver Bloque II)

3. [ ] **Se pierde la unidad de la invención** (ver Bloque III)

4. Con respecto al **título**,

[X] El texto se aprobó como se presenta por el solicitante

[ ] El texto se estableció por esta Autoridad para leerse como sigue:

5. Con respecto al **resumen**:

[X] El texto se aprobó como se presenta por la solicitud

[ ] El texto se estableció, según la regla 38.2 (b) por esta Autoridad como aparece en el Bloque IV. El solicitante tiene un mes a partir de la fecha de envío de esta búsqueda internacional para enviar sus comentarios a esta Autoridad

6. Con respecto a las **figuras**:

a. La figura de los dibujos a ser publicados en el resumen es la Figura No. _____.

[ ] Como se sugiere por el solicitante

[ ] Debido a que el solicitante se equivocó al sugerir una figura

[ ] Debido a que esta figura caracteriza mejor la invención

b. [ ] Ninguna de las figuras es publicada con el resumen

REPORTE DE BÚSQUEDA INTERNACIONAL

Solicitud Internacional No.:
PCT/US2005/022682

A. CLASIFICACIÓN DEL TEMA

C07D487/04 C07D495/04 C07D471/04

De conformidad con la Clasificación Internacional de Patentes (IPC) tanto para clasificación nacional como para IPC

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B. CAMPOS BUSCADOS

Documentación mínima buscada (sistema de clasificación seguido por los símbolos de clasificación)

C07D

Documentación buscada aparte de la documentación mínima para indicar que los documentos se incluyen en los campos buscados

Base de datos electrónica consultada durante la búsqueda internacional (nombre de la base de datos y cuando es práctico, búsqueda de términos usados)

EPO-Internal, CHEM ABS Data, WPI Data, BEILSTEIN Data

C. DOCUMENTOS CONSIDERADOS COMO RELEVANTES

Categoría*	Cita del documento, con indicaciones y si es adecuado, de los párrafos relevantes	Reivindicación relevante No.
X	EP 1 415 987 A (EISAI CO., LTD) 6 de Mayo de 2004 (06-05-2004) citadas WO/0232872 reivindicación 2	1-29
A	WO 01/09134 A (NOVARTIS AG; NOVARTIS-ERFINDUNGEN VERWALTUNGSGESELLSCHAFT M.B.H.; COLLI) 8 de Febrero de 2001 (08-02-2001) reivindicación 1	1-29
A	WO 97/16452 A (NOVARTIS AG; ZIMMERMANN, JUERG; CAPRARO, HANS-GEORG; PETERLI, PATRICIA) 9 de Mayo de 1997 (09-05-1997) reivindicación 1	1-29

--/--

☐ Se enlistan a continuación documentos adicionales del bloque C

☒ Miembros de la familia de patentes se enlistan en el anexo

* Categorías especiales de los documentos citados:

"A" documentos que definen el estado general de la técnica que no se consideran de relevancia particular

"E" documentos principales que están publicados sobre o después de la fecha internacional de recepción

"L" documento que se involucra en las reivindicaciones de prioridad o que se menciona para establecer la fecha de publicación de otra cita u otra razón especial (como se especifica)

"O" documentos que se refieren a un descubrimiento hablado, utilidad, demostración u otros medios

"P" documento publicado antes de la fecha de recepción internacional pero después de la fecha de prioridad reivindicada

"T" último documento publicado después de la fecha de publicación internacional o de fecha de prioridad y que no esté en desacuerdo con la solicitud pero que se cite para entender los principios de la teoría que apoyan la invención

"X" documento de relevancia particular: la invención reivindicada no puede considerarse novedosa o no puede considerarse por involucrar una etapa inventiva cuando el documento se considera solo

"Y" documento de relevancia particular: la invención reivindicada no puede considerarse por involucrar una etapa inventiva cuando el documento se combina con uno o más documentos, cuya combinación sea obvia para una persona experta en la técnica

"&" documento miembro de la misma familia de patentes

Fecha de terminación de la búsqueda internacional	Fecha de envío del reporte de búsqueda internacional
30 de Marzo de 2006	07/04/2006

Nombre y dirección de correo de la ISA/	Oficial autorizado
Oficina Europea de Patentes, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. No. (+31-70) 340-2040, Tx. 31651 epo nl, Fax: (+31-70) 340-3016	Wolf,C

REPORTE DE BUSQUEDA INTERNACIONAL

No. de solicitud internacional
PCT/US2005/022682

Bloque I Observaciones en donde ciertas reivindicaciones se encontraron inescrutables (Continuación del ítem 2 de la primera hoja)

Este reporte internacional no ha sido establecido con respecto a ciertas reivindicaciones bajo el Artículo 17(2) del PCT por las siguientes razones:

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1. [X] Reivindicaciones Nos.: **27, 29 con respecto a la aplicación industrial**
debido a que se relacionan con temas que no requieren ser buscados por esta Autoridad, a saber:

Aunque las reivindicaciones 27, 29 conciernen a un método de tratamiento del cuerpo humano/animal, se ha llevado a cabo la búsqueda basándose en los supuestos efectos del compuesto/composición.

2. [ ] Reivindicaciones Nos.:
debido a que se relacionan con partes de la solicitud internacional que no cumplen con los requerimientos prescritos a tal extensión que ninguna búsqueda internacional significativa se puede llevar a cabo, específicamente:

3. [ ] Reivindicaciones Nos.:
debido a que son reivindicaciones dependientes y no están redactadas de acuerdo con las segundas y terceras oraciones de la Regla 6.4(a).

Bloque II Observaciones en donde se carece de unidad de la invención (Continuación del ítem 3 de la primera hoja)

La Autoridad de Búsqueda Internacional encontró múltiples invenciones en esta solicitud internacional, como sigue:

1. [ ] Ya que todas las cuotas de búsqueda adicionales fueron pagadas a tiempo por la solicitante, este reporte de búsqueda cubre todas las reivindicaciones escrutables.
2. [ ] Ya que todas las reivindicaciones escrutables pudieron ser buscadas sin esfuerzo que justifique una cuota adicional, esta Autoridad no invita al pago de ninguna cuota adicional.
3. [ ] Ya que solamente algunas de las cuotas de búsqueda adicionales requeridas fueron pagadas oportunamente por la solicitante, este reporte de búsqueda internacional cubre solamente aquellas reivindicaciones para las cuales se pagaron cuotas, específicamente las reivindicaciones Nos.:

[ ] Ninguna cuota de búsqueda adicional requerida fue pagada oportunamente por la solicitante. Consecuentemente, este reporte de búsqueda internacional está restringido a la invención primero mencionada en las reivindicaciones; está cubierta por las reivindicaciones Nos.:

Observación en protesta

[ ] Las cuotas de búsqueda adicionales estuvieron acompañadas por la protesta de la solicitante.

[ ] Ninguna protesta acompañó el pago de las cuotas de búsqueda adicional.

REPORTE DE BUSQUEDA INTERNACIONAL

Información sobre miembros de la familia de patentes

No. de solicitud internacional
PCT/US2005/022682

Documento de patente citado en el Reporte de Búsqueda		Fecha de publicación	Miembro(s) de la familia de patente(s)		Fecha de publicación
EP 1415987	A	06-05-2004	AU	9598601 A	29-04-2002
			CA	2426461 A1	25-04-2002
			CN	1478078 A	25-02-2004
			HU	0302603 A2	28-11-2003
			WO	0232872 A1	25-04-2002
			JP	3712393 B2	02-11-2005
			MX	PA03003362 A	01-08-2003
			NO	20031731 A	19-06-2003
			NZ	525324 A	24-03-2005
			US	2004053908 A1	18-03-2004
WO 0109134	A	08-02-2001	AT	251160 T	15-10-2003
			AU	767349 B2	06-11-2003
			AU	6567700 A	19-02-2001
			BR	0012888 A	09-04-2002
			CA	2379560 A1	08-02-2001
			CN	1365360 A	21-08-2002
			CZ	20020299 A3	17-04-2002
			DE	60005684 D1	06-11-2003
			DE	60005684 T2	29-07-2004
			DK	1200435 T3	02-02-2004
			EP	1200435 A1	02-05-2002
			ES	2208395 T3	16-06-2004
			HU	0201935 A2	28-11-2002
			JP	2003506375 T	18-02-2003
			MX	PA02001102 A	20-08-2002
			NO	20020467 A	20-03-2002
			NZ	516667 A	28-05-2004
			PL	354477 A1	26-01-2004
			PT	1200435 T	27-02-2004
			SK	1262002 A3	02-07-2002
			TR	200200234 T2	21-06-2002
			US	6589950 B1	08-07-2003
			ZA	200200783 A	12-02-2003
WO 9716452	A	09-05-1997	AT	236161 T	15-04-2003
			AU	7296896 A	22-05-1997
			BR	9611157 A	30-03-1999
			CA	2234609 A1	09-05-1997
			CN	1202896 A	23-12-1998
			DE	69627195 D1	08-05-2003
			DE	69627195 T2	29-01-2004
			EP	0874846 A1	04-11-1998
			ES	2196181 T3	16-12-2003
			HK	1016580 A1	06-02-2004
			JP	11514336 T	07-12-1999
			PT	874846 T	29-08-2003

PATENT COOPERATION TRE TY

PCT/US2005/022682

10601-WO-PCT

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

RECEIVED
BMS PATENT LAW

GIBBONS, Maureen
Bristol-Myers Squibb Compar
P.O. Box 4000
Princeton, New Jersey 08543-4000
ETATS-UNIS D'AMERIQUE

SEP 12 2005

914

Docketed Item
Due Date
Attorney MG

Date of mailing *(day/month/year)* 01 September 2005 (01.09.2005)	
Applicant's or agent's file reference 10601-PCT	IMPORTANT NOTIFICATION
International application No. PCT/US2005/022682	International filing date *(day/month/year)* 28 June 2005 (28.06.2005)
International publication date *(day/month/year)*	Priority date *(day/month/year)* 28 June 2004 (28.06.2004)
Applicant BRISTOL-MYERS SQUIBB COMPANY et al	

1. By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. *(If applicable)* The letters "NR" appearing in the right-hand column denote a priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

3. *(If applicable)* An asterisk (*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b) (the priority document was received after the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as the priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
28 June 2004 (28.06.2004)	60/583,459	US	17 August 2005 (17.08.2005)
23 September 2004 (23.09.2004)	60/612,563	US	17 August 2005 (17.08.2005)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 338 82 70

Authorized officer
ALi SOLEIMAN
Facsimile No. (41-22) 338.71.30
Telephone No. +41 22 338 8554

PCT REQUEST

Original (for SUBMISSION)

0	For receiving Office use only	
0-1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	

0-4	Form - PCT/RO/101 PCT Request	
0-4-1	Prepared Using	PCT-SAFE [EASY mode] Version 3.50 (Build 0002.162)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	United States Patent and Trademark Office (USPTO) (RO/US)
0-7	Applicant's or agent's file reference	10601-PCT
I	Title of invention	FUSED HETEROCYCLIC KINASE INHIBITORS
II	Applicant	
II-1	This person is:	applicant only
II-2	Applicant for	all designated States except US
II-4	Name:	BRISTOL-MYERS SQUIBB COMPANY
II-5	Address:	Route 206 and Province Line Road Princeton, New Jersey 08543-4000 United States of America
II-6	State of nationality	US
II-7	State of residence	US
II-8	Telephone No.	609-252-4000
II-9	Facsimile No.	609-252-4526
III-1	Applicant and/or inventor	
III-1-1	This person is:	applicant and inventor
III-1-2	Applicant for	US only
III-1-4	Name (LAST, First)	BORZILLERI, Robert M.
III-1-5	Address:	222 Riverwoods Drive New Hope, Pennsylvania 18938 United States of America
III-1-6	State of nationality	US
III-1-7	State of residence	US

III-2	Applicant and/or Inventor	
III-2-1	This person is:	applicant and inventor
III-2-2	Applicant for	US only
III-2-4	Name (LAST, First)	CHEN, Zhong
III-2-5	Address:	30 Kingston Terrace Princeton, New Jersey 08540 United States of America
III-2-6	State of nationality	CN
III-2-7	State of residence	US
III-3	Applicant and/or Inventor	
III-3-1	This person is:	applicant and inventor
III-3-2	Applicant for	US only
III-3-4	Name (LAST, First)	HUYNH, Tram N.
III-3-5	Address:	26 Manley Road Pennington, New Jersey 08534 United States of America
III-3-6	State of nationality	US
III-3-7	State of residence	US
III-4	Applicant and/or Inventor	
III-4-1	This person is:	applicant and inventor
III-4-2	Applicant for	US only
III-4-4	Name (LAST, First)	VACCARO, Wayne
III-4-5	Address:	1706 Westover Road Yardley, Pennsylvania 19067 United States of America
III-4-6	State of nationality	US
III-4-7	State of residence	US
III-5	Applicant and/or Inventor	
III-5-1	This person is:	applicant and inventor
III-5-2	Applicant for	US only
III-5-4	Name (LAST, First)	CHEN, Xiao Tao
III-5-5	Address:	3708 Powder Horn Drive Furlong, Pennsylvania 18925 United States of America
III-5-6	State of nationality	US
III-5-7	State of residence	US

III-6	Applicant and/or inventor	
III-6-1	This person is:	applicant and inventor
III-6-2	Applicant for	US only
III-6-4	Name (LAST, First)	KIM, Kyoung S.
III-6-5	Address:	252 Forest Lane North Brunwick, New Jersey 08902 United States of America
III-6-6	State of nationality	US
III-6-7	State of residence	US
III-7	Applicant and/or inventor	
III-7-1	This person is:	applicant and inventor
III-7-2	Applicant for	US only
III-7-4	Name (LAST, First)	CAI, Zhen-Wei
III-7-5	Address:	36 Hills Drive Belle Mead, New Jersey 08502 United States of America
III-7-6	State of nationality	US
III-7-7	State of residence	US
IV-1	Agent or common representative; or address for correspondence The person identified below is hereby/ has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name (LAST, First)	GIBBONS, Maureen
IV-1-2	Address:	Bristol-Myers Squibb Company P.O. Box 4000 Princeton, New Jersey 08543-4000 United States of America
IV-1-3	Telephone No.	609-252-3453
IV-1-4	Facsimile No.	609-252-4526
IV-1-6	Agent's registration No.	44,121
IV-2	Additional agent(s)	additional agent(s) with same address as first named agent
IV-2-1	Name(s)	DUNCAN,Sammy(46,675); WINSLOW,Anastasia(40,875); O'BRIEN,Maureen(42,043); GOLIAN,Paul, D.(42,591); BABAJKO,Suzanne(32,880); BAXAM,Deanna(45,266); SUN,Jing G.(45,914); BOGIE,Terence(44,544); BERGEN,Briana C.(39,123); D'AMICO,Stephen(46,652); DAVIS,Stephen(26,693);

		DUNCAN,Laurelee(44,096); KILCOYNE,John(33,100); KLEIN,Christopher(34,363); KORSEN,Elliott(32,705); LAMERDIN,John(44,858); LANGE,Keith(44,201); PEIST,Kenneth(45,006); PROVOOST,Jonathan(44,292); RODNEY,Burton(22,076); SHER,Audrey(39,024); ALGIERI,Aldo(31,697); DUBOFF,Samuel(25,969); EPPERSON,James(52,867); MAKUJINA,Shah(41,174); RYAN,Richard(30,491); VANATTEN,Mary, K.(39.408); VOLLES,Warren, K.(33,810); GU,Henry H.(55,227); MINGO,Pamela(48,256); GREENBLATT,Gary(47,609); PARLET,Nickki L.(44,996); WANG,Joseph C.(44,391); WILLE,Louis J.(32,954); CHIN,Jennifer T.(47,487); PATEL,Rena(41,412); KRIEGER,Stuart E.(28,731); COHEN,Jacqualine M.(51,574)
V	DESIGNATIONS	
V-1	The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.	
VI-1	Priority claim of earlier national application	
VI-1-1	Filing date	28 June 2004 (28.06.2004)
VI-1-2	Number	60/583,459
VI-1-3	Country	US
VI-2	Priority claim of earlier national application	
VI-2-1	Filing date	23 September 2004 (23.09.2004)
VI-2-2	Number	60/612,563
VI-2-3	Country	US

PCT REQUEST

Original (for SUBMISSION)

VI-3	Priority document request The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):	VI-1, VI-2	
VII-1	International Searching Authority Chosen	European Patent Office (EPO) (ISA/EP)	
VIII	Declarations	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	
IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	6	✓
IX-2	Description	269	-
IX-3	Claims	6	-
IX-4	Abstract	1	✓
IX-5	Drawings	0	-
IX-7	TOTAL	282	
	Accompanying Items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-9	Original separate power of attorney	✓	-
IX-17	PCT-SAFE physical media	-	✓
IX-18	Figure of the drawings which should accompany the abstract		
IX-20	Language of filing of the international application	English	
X-1	Signature of applicant, agent or common representative		
X-1-1	Name (LAST, First)	GIBBONS, Maureen	
X-1-2	Name of signatory		
X-1-3	Capacity		

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FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/EP
10-6	Transmittal of search copy delayed until search fee is paid	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	

PCT (ANNEX - FEE CALCULATION SHEET)

Original (for SUBMISSION)

(This sheet is not part of and does not count as a sheet of the international application)

0	For receiving Office use only	
0-1	International Application No.	
0-2	Date stamp of the receiving Office	

0-4	Form PCT/RO/101 (Annex) PCT Fee Calculation Sheet				
0-4-1	Prepared Using		PCT-SAFE [EASY mode] Version 3.50 (Build 0002.162)		
0-9	Applicant's or agent's file reference		10601-PCT		
2	Applicant		BRISTOL-MYERS SQUIBB COMPANY		
12	Calculation of prescribed fees		fee amount/multiplier	Total amounts (USD)	
12-1	Transmittal fee	T	⇨	300	
12-2-1	Search fee	S	⇨	1000	
12-2-2	International search to be carried out by		EP		
12-3	International filing fee (first 30 sheets)	H	1211		
12-4	Remaining sheets		246		
12-5	Additional amount	(X)	13		
12-6	Total additional amount	I2	3198		
12-7	I1 + I2 =	I	4409		
12-12	EASY Filing reduction	R	-87		
12-13	Total international filing fee (I-R)	I	⇨	4322	
12-14	Fee for priority document Number of priority documents requested		2		
12-15	Fee per document	(X)	20		
12-16	Total priority document fee:	P	⇨	40	
12-17	TOTAL FEES PAYABLE (T+S+I+P)		⇨	5662	
12-19	Mode of payment		authorization to charge deposit account		
12-20	Deposit account instructions The receiving Office		United States Patent and Trademark Office (USPTO) (RO/US)		
12-20-1	Authorization to charge the total fees indicated above.		✓		
12-20-2	Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.		✓		
12-20-3	Authorization to charge the fee for priority document.		✓		
12-21	Deposit account No.		19-3880		
12-22	Date		27 June 2005 (27.06.2005)		
12-23	Name and signature		GIBBONS, Maureen		

PCT (ANNEX - FEE CALCULATION SHEET)

Original (for SUBMISSION)

(This sheet is not part of and does not count as a sheet of the international application)

REMARKS

13-1-1	Applicant Remarks	[The abstract contains a chemical structure. The place where it should be inserted is indicated by brackets with the following text "INSERT CHEMICAL STRUCTURE HERE".

In general, the instant invention comprises compounds of Formulas I and II [PLEASE INSERT CHEMICAL STRUCTURES I & II HERE]
including pharmaceutically acceptable salts thereof. The compounds of the invention are useful as protein kina inhibitors and therefore are useful for treating cancer and other protein kinase mediated diseases.

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PCT PETITORIO

Original (para ENTREGA)

0	**Para uso de oficina receptora solamente**	
0-1	Número de solicitud internacional	
0-2	Fecha de presentación internacional	
0-3	Nombre de la oficina receptora y "Solicitud Internacional de PCT"	
0-4	**Forma - PCT/RO/101 PCT Petitorio**	
0-4-1	Preparada utilizando	PCT- SAFE [Modo FÁCIL] Versión 3.50 (diseñada 0002.162)
0-5	**Petición** El suscrito pide que la presente solicitud internacional sea procesada de acuerdo con el Tratado de Cooperación en Materia de Patentes.	
0-6	**Oficina receptora (especificada por la solicitante)**	Oficina de Patentes y Marcas de los EE.UU. (USPTO) (RO/US)
0-7	**Referencia de archivo de la solicitante o apoderado**	10601 - PCT
I	**Título de la invención**	INHIBIDORES DE CINASA HETEROCICLICOS FUSIONADOS
II	**Solicitante**	
II-1	Esta persona es :	solicitante solamente
II-2	Solicitante para:	todos los países designados excepto US
II-4	Nombre:	**BRISTOL-MYERS SQUIBB COMPANY**
II-5	Dirección:	Route 206 y Province Line Road Princeton, Nueva Jersey 08543-4000 Estados Unidos de Norteamérica
II-6	País de nacionalidad:	US
II-7	País de residencia:	US
II-8	Telefono No.	609-252-4000
II-9	Facsímile No.	609-252-4526
III-1	**Solicitante y/o inventor**	
III-1-1	Esta persona es:	solicitante e inventor
III-1-2	Solicitante para:	solamente US
III-1-4	Nombre (apellido, nombre):	BORZILLERI, Robert M.
III-1-5	Dirección:	222 Riverwoods Drive New Hope, Pennsylvania 18938 Estados Unidos de Norteamérica
III-1-6	Estado o nacionalidad	US
III-1-7	País de residencia	US

10601-PCT

PCT PETITORIO

Original (para ENTREGA)

III-2	**Solicitante y/o inventor**	
III-2-1	Esta persona es:	solicitante e inventor
III-2-2	Solicitante para	solamente US
III-2-4	Nombre (APELLIDO, nombre)	CHEN, Zhong
III-2-5	Dirección	30 Kingston Terrace Princeton, Nueva Jersey 08540 Estados Unidos de Norteamérica
III-2-6	Estado o nacionalidad	CN
III-2-7	País de residencia	US
III-3	**Solicitante y/o inventor**	
III-3-1	Esta persona es:	solicitante e inventor
III-3-2	Solicitante para	solamente US
III-3-4	Nombre (APELLIDO, nombre)	HUYNH, Tram N.
III-3-5	Dirección	26 Manley Road Pennington, Nueva Jersey 08534 Estados Unidos de Norteamérica
III-3-6	Estado o nacionalidad	US
III-3-7	País de residencia	US
III-4	**Solicitante y/o inventor**	
III-4-1	Esta persona es:	solicitante e inventor
III-4-2	Solicitante para	solamente US
III-4-4	Nombre (APELLIDO, nombre)	VACCARO, Wayne
III-4-5	Dirección	1706 Westover Road Yardley, Pennsylvania 19067 Estados Unidos de Norteamérica
III-4-6	Estado o nacionalidad	US
III-4-7	País de residencia	US
III-5	**Solicitante y/o inventor**	
III-5-1	Esta persona es:	solicitante e inventor
III-5-2	Solicitante para	solamente US
III-5-4	Nombre (APELLIDO, nombre)	CHEN, Xiao Tao
III-5-5	Dirección	3708 Powder Horn Drive Furlong, Pennsylvania 18925 Estados Unidos de Norteamérica
III-5-6	Estado o nacionalidad	US
III-5-7	País de residencia	US

10601-PCT

PCT PETITORIO

Original (para ENTREGA)

III-6	**Solicitante y/o inventor**	
III-6-1	Esta persona es:	solicitante e inventor
III-6-2	Solicitante para	solamente US
III-6-4	Nombre (APELLIDO, nombre)	KIM, Kyoung S.
III-6-5	Dirección	252 Forest Lane North Brunwick, Nueva Jersey 08902 Estados Unidos de Norteamérica
III-6-6	Estado o nacionalidad	US
III-6-7	País de residencia	US
III-7	**Solicitante y/o inventor**	
III-7-1	Esta persona es:	solicitante e inventor
III-7-2	Solicitante para	solamente US
III-7-4	Nombre (APELLIDO, nombre)	CAI, Zhen-Wei
III-7-5	Dirección	36 Hills Drive Belle Mead, Nueva Jersey 08502 Estados Unidos de Norteamérica
III-7-6	Estado o nacionalidad	US
III-7-7	País de residencia	US
IV-1	**Apoderado o representante común o dirección de correspondencia.** La persona identificada a continuación es/ha sido citada para actuar a nombre de la (s) solicitante (s) ante las autoridades internacionales competentes como:	Apoderado
IV-1-1	Nombre:	GIBBONS, Maureen
IV-1-2	Dirección:	Bristol-Myers Squibb Company P.O. Box 4000 Princeton, Nueva Jersey 08543-4000 Estados Unidos de Norteamérica
IV-1-3	Número de teléfono	609-252-3453
IV-1-4	Número de facsímil:	609-252-4526
IV-1-6	Apoderado con No. de registro	44,121
IV-2	**Apoderados adicionales**	apoderados adicionales con la misma dirección que el apoderado nombrado inicialmente
IV-2-1	Nombre(s)	DUNCAN, Sammy (46,675); WINSLOW, Anastasia (40,875); O'BRIEN, Maureen (42,043); GOLIAN, Paul, D. (42,591); BABAJKO, Suzanne (32,880); BAXAM, Deanna (45,266); SUN, Jing G. (45,914); BOGIE, Terence (44,544); BERGEN, Briana C. (39,123); D'AMICO, Stephen (46,652); DAVIS, Stephen (26,693);

10601-PCT

PCT PETITORIO

Original (para ENTREGA)

		DUNCAN, Laurelee (44,096); KILCOYNE, John (33,100); KLEIN, Christopher (34,363); KORSEN, Elliott (32,705); LAMERDIN, John (44,858); LANGE, Keith (44,201); PEIST, Kenneth (45,006); PROVOOST, Jonathan (44,292); RODNEY, Burton (22,076); SHER, Audrey (39,024); ALGIERI, Aldo (31,697); DUBOFF, Samuel (25,969); EPPERSON, James (52,867); MAKUJINA, Shah (41,174); RYAN, Richard (30,491); VANATTEN, Mary, K. (39,408); VOLLES, Warren, K. (33,810); GU, Henry H. (55,227); MINGO, Pamela (48,256); GREENBLATT, Gary (47,609); PARLET, Nickki L. (44,996); WANG, Joseph C. (44,391); WILLE, Louis J. (32,954); CHIN, Jennifer T. (47,487); PATEL, Rena (41,412); KRIEGER, Stuart E. (28,731); COHEN, Jacqueline M. (51,574)
V	**DESIGNACIONES**	
V-1	**La presentación de ésta petición constituye bajo la Regla 4.9(a), la designación de todos los Estados Contrayentes subordinados por el PCT en la fecha de presentación internacional, para la cesión de todo tipo de protección disponible y cuando sea aplicable para la cesón tanto de la patentes regionales como nacionales.**	
VI-1	**Reivindicación prioritaria de la solicitud nacional anterior**	
VI-1-1	Fecha de presentación	28 Junio 2004 (28.06.2004)
VI-1-2	Número	60/583,459
VI-1-3	País	US
VI-2	**Reivindicación prioritaria de la solicitud nacional anterior**	
VI-2-1	Fecha de presentación	23 Septiembre 2004 (23.09.2004)
VI-2-2	Número	60/612,563
VI-2-3	País	US

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PCT PETITORIO

Original (para ENTREGA)

VI-3	**Prioridad del documento de requisición** Se requiere que la oficina receptora prepare y transmita al Buró Internacional una copia certificada de las solicitudes anteriores identificadas anteriormente como ítem(s):	VI-1, VI-2	
VII-1	**Autoridad de búsqueda internacional escogida**	Oficina Europea de Patentes (EPO) (ISA/EP)	
VIII	**Declaraciones**	Número de Declaraciones	
VIII-1	Declaración en cuanto a la identidad del inventor	-	
VIII-2	Declaración en cuanto al derecho de la solicitante, así como la fecha de presentación internacional, a solicitar y a que se le otorgue una patente	-	
VIII-3	Declaración en cuanto al derecho de la solicitante, así como la fecha de presentación internacional, a reclamar la prioridad de la solicitud anterior.	-	
VIII-4	Declaración de calidad de invención (sólo para los propósitos de la designación de los Estados Unidos de América)	-	
VIII-5	Declaración en cuanto a revelaciones no perjudiciales o excepciones a carencia de novedad	-	
IX	**Lista de verificación**	Número de hojas	archivo(s)electrónico (s) anexo(s)
IX-1	Petitorio (incluyendo hojas de declaración)	2	√
IX-2	Descripción (excluyendo la parte del listado de secuencias)	269	-
IX-3	Reivindicaciones	6	-
IX-4	Extracto	1	√
IX-5	Dibujos	0	-
IX-7	TOTAL	282	
	Items adjuntos	Documento(s) anexos	Archivo(s) electrónicos anexos
IX-8	Hoja de cálculo de derechos	√	-
IX-9	Copia de poder general	√	-
IX-17	Medio físico PCT-SAFE	-	√
IX-19	**Figura de los dibijos que debe acompañar el resumen**		
IX-20	**Idioma de presentación de la solicitud internacional**	Inglés	
X-1	**Firma de la solicitante o apoderado o representante común**	(Rúbrica) GIBBONS, Maureen	
X-1-1	Nombre (Apellido, Nombre)		
X-1-2	Nombre del firmante		
X-1-3	Capacidad		

10601-PCT

PCT PETITORIO

Original (para **ENTREGA**)

PARA USO DE LA OFICINA RECEPTORA SOLAMENTE

10-1	**Fecha de recibo real de la solicitud internacional propuesta**	
10-2 10-2-1 10-2-2	**Dibujos:** Recibido: No recibido:	
10-3	**Fecha corregida de la recepción actual debida a documentos o dibujos recibidos más tarde pero oportunamente que complican la solicitud internacional propuesta**	
10-4	**Fecha de la recepción oportuna de las correcciones requeridas en virtud del Artículo 11(2) del PCT**	
10-5	**Autoridad de búsqueda internacional**	ISA/EP
10-6	**Transmisión de copia de búsqueda retrasada hasta que se pague el derecho de búsqueda**	

PARA USO DE LA OFICINA INTERNACIONAL SOLAMENTE

11-1	**Fecha de recepción de la copia de registro por la oficina internacional**	

APOSTILLE

730

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA

2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
MAURA O KNOBL

3. ACTING IN THE CAPACITY OF:
NOTARY PUBLIC OF NEW JERSEY

4. BEARS THE SEAL/STAMP OF:
MAURA O KNOBL, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY

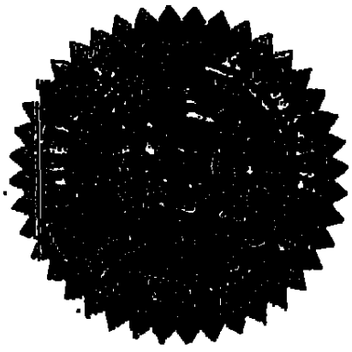
6. THE 13TH DAY OF JANUARY 2006

7. BY: John E McCormac, CPA, NEW JERSEY TREASURER

8. NO. A248886

9. SEAL/STAMP:

10. SIGNATURE





Brigard & Castro
BOGOTA - COLOMBIA

PODER

Yo (nosotros)

domiciliado(s) en

Nombro(amos) a: **JUAN PABLO CADENA SARMIENTO** y/o **CARLOS H. PALACIO EASTMAN** y/o **MARTIN E. TORRES CARDOZO**, de Bogotá, Colombia, apoderados verdaderos y legales con poder especial, amplio y suficiente, para recabar de las oficinas y autoridades colombianas administrativas, judiciales y de policía, en cualquier instancia o recurso, la obtención de patentes de invención, registros de marcas, diseños industriales, modelos de utilidad, depósitos de nombres comerciales, lemas comerciales y enseñas, registros de derechos de autor y contratos sobre los mismos, obtención de certificados de obtentor de variedades vegetales, así como sus prórrogas, renovaciones, anotaciones de traspaso, cambios de nombre y/o domicilio; elaborar, tramitar y registrar contratos de licencia y licencias de cualesquiera clases; intervenir como demandante o como demandado en cualquier instancia y recurso ante cualquier juez, corporación, funcionario público o autoridad en acciones judiciales, administrativas y de policía tales como: oposiciones al registro de marcas; acciones de caducidad, cancelación y nulidad; acciones reivindicatorias, acciones derivadas de la obtención o explotación de licencias; acciones de competencia desleal; demandas penales; acciones de indemnización de perjuicios, reclamos y observaciones a solicitudes de patentes, diseños industriales, modelos de utilidad, en el ejercicio de medidas cautelares y en otras acciones o medidas similares.

A este efecto, lo(s) faculto(amos) para elevar solicitudes, formular descripciones, enmiendas, protestas, declaraciones, oposiciones, cancelaciones, nulidades, apelaciones y reclamos; pagar impuestos, cuotas y gravámenes prescritos por la ley; renunciar o desistir a derechos concedidos o en curso de concesión; recibir toda clase de documentos y valores, dando el descargo respectivo, y, en general, para dar ante dichas autoridades todos los pasos necesarios al efecto indicado y tomar todas las medidas que creyeren conducentes al resguardo de mis (nuestros intereses), con todas las demás facultades legales necesarias.

Este poder comprende la facultad de ratificar o confirmar en mi (nuestro) nombre lo actuado así como la facultad de desistir, transigir, comprometer, y la de sustituirlo en todo o en parte y revocar sustituciones. Asimismo nombro(amos) a: **JUAN PABLO CADENA SARMIENTO** y/o **CARLOS H. PALACIO EASTMAN** y/o **MARTIN E. TORRES CARDOZO**, domiciliado(s) en la Carrera 7 No. 16-56 Piso 9, mis (nuestros) apoderados en Colombia, con facultades para recibir notificaciones y designar apoderados judiciales y extrajudiciales.

Otorgado y firmado en

hoy de de 200_

Firma

Nombre
Cargo

POWER OF ATTORNEY

731

I (We) BRISTOL-MYERS SQUIBB COMPANY

domiciled in Princeton, New Jersey, USA

Hereby appoints **JUAN PABLO CADENA SARMIENTO** and/or **CARLOS H. PALACIO EASTMAN** and/or **MARTIN E. TORRES CARDOZO**, of Bogotá, Colombia, my (our) true and lawful attorneys with special, ample and sufficient power to obtain from the Colombian administrative, judicial and police offices and authorities, in any instance, privileges of patents of invention, registration of trademarks, industrial designs and utility models; registration of commercial names, slogans and emblems, registration of copyright and contracts related thereto, certificates of obtainers of vegetables varieties, as well as extensions, renewals and recordal of assignments and changes of name and domicile related to the above; to prepare, prosecute and register licenses of any kind; to act as plaintiff or defendant in any instance or recourse, and before any judge, corporation, public official or authority in judicial, administrative and police actions, such as: oppositions to the registration of trademarks; caducity, cancellation and nullity actions; claim actions derived from the obtaining or exploitation of licenses, action of unfair competition; criminal proceedings, actions for payment of damages; claims or observations on patent applications, models, industrial designs and utility models; in the exercise of preventive measures and in other actions or similar proceedings.

To that effect they hereby empowered to file applications, formulate descriptions, amendments, protests, declarations, oppositions, cancellations, nullities, appeals and claims; to pay taxes, quotas and assessments prescribed by law, renounce or waive the rights granted or in the process of granting; to receive all kinds of documents and valuables, giving the respective release of receipt, and, in general, to take before said authorities the necessary steps to such effect, and any measures that they may deem pertinent to the safeguard of my (our) interest(s) with all the other necessary legal powers.

This power includes the faculty to ratify or confirm desist, settle and compromise on my (our) behalf, and to substitute this power in whole or in part and to revoke substitutions. At the same time I (We) hereby appoints **JUAN PABLO CADENA SARMIENTO**. and/or **CARLOS H. PALACIO EASTMAN** and/or **MARTIN E. TORRES CARDOZO**, domiciled in Carrera 7 No. 16-56, Piso 9, my (our) attorney(s) in fact, with powers to receive notifications and designate judicial and extrajudicial attorneys.

Granted and signed in

this 27 day of January of 2006

Signature

Name Suzanne E. Babajko
Title Senior Patent Counsel

DESPACHO NOTARIAL DEL CIRCULO DE BOGOTA D.C. QUE ESTA COPIA ES FIEL FOTOSTATICA DEL ORIGINAL QUE HE TENIDO A LA VISTA
ROSA FALLA LA SECA
NOTARIA

732

CERTIFICADO NOTARIAL (SOCIEDAD)

Hoy de de
personalmente compareció ante mí

a quien conozco, y de quien me consta que firmó el anterior documento, debidamente juramentado declaró y dijo que él (ella) es

de

Sociedad legalmente constituida para un período de duración que aún no ha terminado; que el declarante está autorizado por dicha compañía para conferir este poder; que el sello estampado por él al pie de tal poder, en nombre y representación de la expresada compañía, es el sello oficial de ella; y que el objeto para el cual se confiere este instrumento está comprendido dentro del objeto social de la sociedad.

El suscrito Notario hace constar que tuvo a la vista las pruebas de la existencia de la sociedad.

Estado de
con fecha

y que quien confiere el presente poder es su representante.

Notario Público (sello)

NOTARIAL CERTIFICATE (CORPORATION)

On this 11 day of January of 2006 personally appeared before me SUZANNE E. BABAJKO

to me known, and known to me to be the person who signed the foregoing instrument who being by me duly sworn did depose and say that he (she) is the
SENIOR PATENT COUNSEL

of BRISTOL-MYERS SQUIBB COMPANY

Which is legally constituted for a term not yet expired, that deponent is authorized by said Company to confer this Power of Attorney: that the seal affixed hereunto by the deponent in the name and on behalf of said Corporation is the corporate seal thereof; and that the purpose for which this instrument is granted is included within the corporate purpose of company.

The undersigned Notary Public attests that he has seen the documents that prove the existence of the company.

State of
under date of

and that he (she) who grants the present power of attorney is its Representative.

Public Notary (Seal)

CERTIFICADO NOTARIAL PERSONA NATURAL

Hoy de de , compareció(eron) ante mí

a quien (es) conozco y me consta que es(son) la(s) persona(s) firmante(s) del documento que precede y quien(es) declara(n) que otorgan el mismo para los fines y propósitos que en él se expresan.

Notario Público (sello)

NOTARIAL CERTIFICATE NATURAL PERSON

On this 11th day of January of 2006
personally appeared before me
Suzanne E. Babajko
who is(are) known to me and who I attest executed the foregoing document and he (they) declared he (they) grant(s) the document for the uses and purposes therein expressed.

Maura O. Knobl
Notary Public

MAURA O. KNOBL
NOTARY PUBLIC OF NEW JERSEY
My Commission Expires July 25, 2006

COMO NOTARIO CUARENTA Y SIETE ENCARGADO DEL CIRCULO DE PONTA, HAGO CONSTAR QUE ESTA COPIA FOTOSTATICA CONCUERDA CON EL ORIGINAL QUE HE TENIDO A LA VISTA EN LA REPUBLICA DE PANAMA
27 NOV. 2006
ROSA FALLA LASSO
NOTARIO CUARENTA Y SIETE ENCARGADO

LEGALIZACION POR APOSTILLA ES REQUERIDA.

LEGALIZATION BY APOSTILLE IS REQUIRED.

TRADUCCION AL ESPAÑOL del Documento de Poder otorgado por **BRISTOL-MYERS SQUIBB COMPANY** domiciliada en **Princeton, New Jersey, Estados Unidos de América.**

APOSTILLA
(CONVENCION DE LA HAYA DEL 5 DE OCTUBRE DE 1961)

1. PAÍS: ESTADOS UNIDOS DE AMÉRICA

2. ESTE DOCUMENTO PUBLICO HA SIDO FIRMADO POR:
MAURA O KNOBL

3. ACTUANDO EN CAPACIDAD DE:
NOTARIO PUBLICO DE NEW JERSEY

4. LLEVA EL SELLO/TIMBRE DE:
MAURA O KNOBL, NOTARIO

CERTIFICADO

5. EN TRENTON, NEW JERSEY

6. EL 13 DE ENERO DE 2006

7. POR: John E. McCormac, CPA, TESORERO DE NEW JERSEY

8. NO. A248886

9. SELLO/TIMBRE:

10. FIRMA

(Firma)

COMO NOTARIO CUARENTA Y SIETE ENCARGADO DEL CIRCULO DE PODER, HAGO CONSTAR QUE ESTA COPIA FOTOSTATICA CORRESPONDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
MADRID D.C. REPUBLICA DE COLOMBIA
27 NOV. 2006
ROSA FALLA LADSECA
NOTARIO CUARENTA Y SIETE ENCARGADO

732

734

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-128811- -00000-0000
Fec: 2006-12-22 15:22:54 Dep: 2020 NUECREACIONES
Tra: 11 PATENTEYII
Eva: 378 FASENACIONALI
Act 411 PRESENTACION Folios: 731

Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE

PCT

PATENTE DE INVENCION [ ] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de 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 [ ]

COMPLETA [ ] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Firma Responsable

Fecha 22 DIC. 2006

Carrera 13 No. 27-00 Piso 5, 7 y 10
Conmutador: 3 82 08 40
Fax: 350 52 20
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

735

Bogotá,
2020

Doctor(a)
CADENA SARMIENTO JUAN PABLO
Apoderado(a) y/o Representante de
BRISTOL MYERS SQUIBB COMPANY

REFERENCIA	Radicación No.	06 128811
	Solicitud internacional	PCT/US2005/022682
	Fecha inicio fase nacional	28/01/2007
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	1519

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 02 FEB. 2007
adpa10