SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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C-1

DELEGATURA PROPIEDAD INDUSTRIAL

División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCION

ENTRADA EN FASE NACIONAL

21. **EXPEDIENTE No.** 06-107328

54. **TITULO** HETEROCICLOS MONOCICLICOS COMO INHIBIDORES DE CINASA

51. **CLASIFICACION INTERNACIONAL**

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.**

SS

(FORMA P 10)

Oficina de Comunicaciones

PETITORIO

AS: 102.328

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-107328- -00000-0000
Fec: 2006-10-23 17:06:17 Dep: 2020 NUECREACIONES
Tra: 11 PATENTEIYII
Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 754

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 Province Line 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, Lyndon A M Cornelius, Robert J Schmidt, Gretchen M. Schroeder, Kyoung S Kim. **Dirección:** 222 Riverwoods Drive, New Hope, PA 18938, US; 29 Mill Pond Road, Jackson, NJ 08527, US, 3 South Deer Place, Hainesport, New Jersey 08036, US, 82 Colleen Circle, Ewing, New Jersey 08638, US, 252 Forest Lane, North Brunswick, New Jersey 08902, Estados Unidos de América (Respectivamente). **Nacionalidad o Domicilio:** Estados Unidos de América	

5 PCT (86)
Solicitud Internacional No PCT/US2005/014120 Fecha 22-04-2005
Publicación Internacional No WO/2005/117867A2 Fecha 15-12-2005

6 Título (54): HETEROCICLOS MONOCICLICOS COMO INHIBIDORES DE CINASA

7 Clasificación Internacional (51) A61K 31/44 A 61 P 35/00
C 07 D 213/68

8 Prioridad SI ☒ NO ☐	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
	US	23-04-2004	60/564,842
	US	23-12-2004	60/639,178
	US	21-04-2005	11/111,144

9 Comprobante de pago No. 06-76,627 **Fecha** 20-10-2006

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

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
- [ ] Documento de cesión del inventor al solicitante o a su causante
- [ ] Declaraciones
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [ ] Copia del examen preliminar efectuado por la IPEA.
- [ ] Traducción del examen preliminar efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 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.

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

As. 102.328

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-107328- -00000-0000
Fec: 2006-10-23 17:06:17 Dep: 2020 NUECREACIONES
Tra: 11 PATENTEIYII
Eve: 378 FASENACIONALI
Act 411 PRESENTACION Folios: 754

RECIBO OFICIAL DE CAJA : 06 - 76,627
FECHA : OCTUBRE 4 DE 2006

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO POPULAR	050-00110-6	58188063	04/10/2006	32,860,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	463,000.00
		TOTAL : $	463,000.00

SON: CUATROCIENTOS SESENTA Y TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

A·102328

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 December 2005 (15.12.2005)

PCT

(10) International Publication Number
WO 2005/117867 A2

(51) International Patent Classification[7]: A61K 31/44, C07D 213/68, 213/73, 213/74, 213/75, 239/34, 239/46, 401/04, 401/06, 401/12, 401/14, 417/12, A61P 35/00

(21) International Application Number: PCT/US2005/014120

(22) International Filing Date: 22 April 2005 (22.04.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/564,842	23 April 2004 (23.04.2004)	US
60/639,178	23 December 2004 (23.12.2004)	US
11/111,144	21 April 2005 (21.04.2005)	US

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(72) Inventors; and

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

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, 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, 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) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

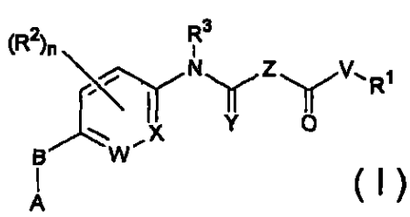
Published:

— *without international search report and to be republished upon receipt of that report*

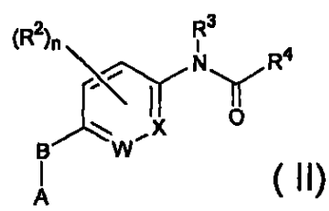
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette

WO 2005/117867 A2

(54) Title: MONOCYCLIC HETEROCYCLES AS KINASE INHIBITORS



(I)



(II)

(57) Abstract: The present invention is directed to compounds having the formula [I + II] and methods for using them for the treatment of cancer.

MONOCYCLIC HETEROCYCLES AS KINASE INHIBITORS

RELATED APPLICATIONS

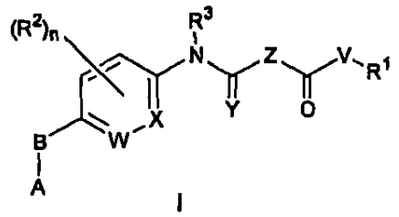
[0001] This application claims priority benefit under Title 35 § 119(e) of United States Provisional Applications Nos. 60/564,842, filed April 23, 2004, and 60/639,178, filed December 23, 2004, the contents of which are herein incorporated by reference.

FIELD OF THE INVENTION

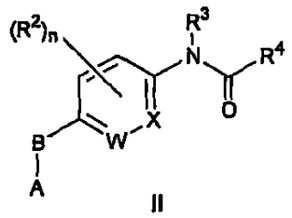
[0002] This invention relates to compounds that inhibit the protein tyrosine kinase activity of growth factor receptors such as c-Met, thereby making them useful as anti-cancer agents. The pharmaceutical compositions that comprise these compounds are also useful in the treatment of diseases, other than cancer, which are associated with signal transduction pathways operating through growth factor and anti-angiogenesis receptors such as c-Met.

SUMMARY OF THE INVENTION

[0003] The present invention is directed to compounds having Formulas I and II as described below that are useful in the treatment of cancer.



I



II

or an enantiomer, diastereomer, hydrate, solvate or pharmaceutically acceptable salt 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, NR^8CH_2, S, SO, SO_2, or CR^9R^{10};

V is NR^{11} or $-(CR^{37}R^{38})_p-$ provided that when VR^{11} is N, R^1 is an alkyl or cycloalkyl;

W and X are each independently C or N;

Y is selected from O, S, and NR^{12};

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

l is 0 to 2;

n is 0 to 4 if W and X are both C, 0 to 3 if one of X or W is N, and 0 to 2 if X and W are both N;

p is 1 to 4;

R^3, R^5, R^6, R^7, R^8, R^{11} and R^{15} are independently selected from H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclo, substituted heterocyclo;

R^4 is selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, and substituted heterocycloalkyl, provided that

(a) if R^4 is phenyl

(i) R^4 is not substituted with both hydroxy and amido; and

(ii) R^4 is not substituted with $-NRSO_2R-$ wherein R is alkyl or aryl;

(b) if R^4 is pyridyl ,R^4 is not substituted with both hydroxy and methoxy; and

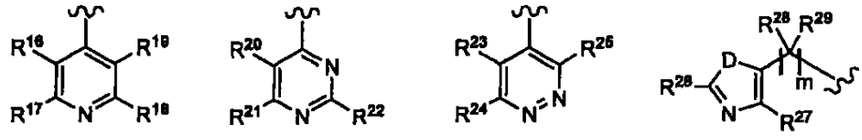
(c) if R^4 is pyrimidinyl, it is not substituted with =O;

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

R^{12} is selected from H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, CN, NO_2 or SO_2NH_2;

R^{13} and R^{14} are independently selected from H, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, substituted heterocycloalkyl or taken together to form a carbocyclic or heterocyclic ring of 3 to 8 atoms;

A is selected from one of the following:



wherein

D is S or O;

m is 0 to 6;

R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26} and R^{27} are independently selected from H, halogen, $NR^{30}R^{31}$, OR^{32}, CO_2R^{33}, $CONR^{34}R^{35}$, SO_2R^{36}, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, -CN, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, or substituted heterocycloalkyl;

R^{28} and R^{29} are independently selected from H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, or taken together to form a carbocyclic or heterocyclic ring of 3 to 8 atoms;

R^{30}, R^{31}, R^{32}, R^{33}, R^{34}, R^{35}, and R^{36} are independently selected from H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, alkoxycarbonyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclo, substituted heterocyclo, heterocycloalkyl, or substituted heterocycloalkyl; and

$R^{37}$and R^{38} are each independently H, halogen, or alkyl.

DESCRIPTION OF THE INVENTION

[0004] The present invention provides for compounds of Formulas I and II defined above, pharmaceutical compositions employing such compounds, and methods of using such compounds in the treatment of cancer.

[0005] 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 are lower alkyl groups having 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, cycloalkyl, heterocycloalkyl, -CN, aryl, heteroaryl, halo (such as F, Cl, Br, I), haloalkyl (such as CCl_3 or CF_3), hydroxyl, alkoxy, alkylthio, alkylamino, -COOH, -COOR, -C(O)R, -OCOR, amino, carbamoyl (-NHCOOR- or -OCONHR-), urea (-NHCONHR-) or thiol (-SH).

[0006] 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.

[0007] 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 alkynyl groups include those listed above for alkyl groups

[0008] The numbers in the subscript after the symbol "C" define the number of carbon atoms a particular group can contain. For example "C_{1-6} 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_{1-6} alkyl" can also refer to C_{1-6} alkylene which bridges two groups; examples include propane-1,3-diyl, butane-1,4-diyl, 2-methyl-butane-1,4-diyl, etc. "C_{2-6} alkenyl" 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_{2-6} alkenyl" can also refer to C_{2-6} 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_{2-6} 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.

[0009] The term "cycloalkyl" herein alone or as part of another group is a species of alkyl containing from 3 to 15 carbon atoms, without alternating or resonating double bonds between carbon atoms. It may contain from 1 to 4 rings. Exemplary groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, adamantyl, etc. Cycloalkyl groups may be substituted at any available point of attachment. Exemplary substituents include one or more of the following groups: halogen, such as F, Br, or Cl, hydroxyl, alkyl, alkoxy, amino, nitro, cyano, thiol, alkylthio, and any of the subsitituents described above for alkyl groups.

[0010] 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.

[0011] The term "alkyloxycarbonyl" 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.

[0012] The term "alkylcarbonyl" herein alone or as part of another group refers to an alkyl group bonded through a carbonyl group.

[0013] The term "alkylcarbonyloxy" herein alone or as part of another group denotes an alkylcarbonyl group bonded through an oxygen linkage.

[0014] 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, alkyl, alkoxy, hydroxy, carboxy, carbamoyl, alkyloxycarbonyl, nitro, alkenyloxy, trifluoromethyl, amino, cycloalkyl, aryl, heteroaryl, cyano, alkyl $S(O)_m$ ($m = 0, 1, 2$), or thiol.

[0015] The term "arylalkyl" or "aralkyl" herein alone or as part of another group denotes an aryl group as described above bonded through an alkyl group, as described above. And example of an aralkyl group is a benzyl group.

[0016] 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

[0017] 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, =O, $-CO_2H$,

–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.

[0018] 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.

[0019] 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.

[0020] Exemplary tricyclic heteroaryl groups include carbazolyl, benzidolyl, phenanthrollinyl, acridinyl, phenanthridinyl, xanthenyl and the like.

[0021] The term "heterocyclic ring" 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. Preferably, a heterocyclic ring is a 5 or 6-membered monocyclic ring and contains 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), alkoxy (preferably lower alkoxy), nitro, monoalkylamino (preferably a lower alkylamino), dialkylamino (preferably a di[lower]alkylamino),cyano, halo, haloalkyl (preferably rifluoromethyl), 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 heterocyclic rings are isoxazolyl, imidazolinyl, thiazolinyl, imidazolidinyl, pyrrolyl, pyrrolinyl, pyranyl, pyrazinyl, piperidyl, morpholinyl and triazolyl. The heterocyclic ring may be attached to the parent structure through a carbon atom or through any heteroatom of the heterocyclyl that results in a stable structure.

[0022] 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.

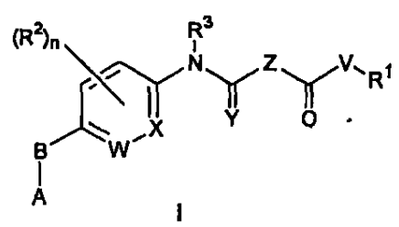
[0023] The term "halogen" or "halo" refers to chlorine, bromine, fluorine or iodine selected on an independent basis.

[0024] 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).

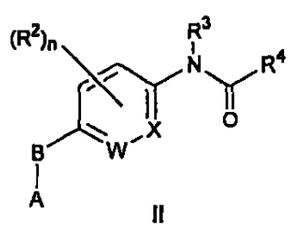
[0025] As used herein, the term "patient" encompasses all mammalian species.

[0026] Suitable examples of salts of the compounds according to the invention with inorganic or organic acids are hydrochloride, hydrobromide, sulfate, methanesulfonate, maleate, fumarate, and phosphate. Salts which are unsuitable for pharmaceutical uses but which can be employed, for example, for the isolation or purification of free compounds I or II, their pharmaceutically acceptable salts, are also included.

[0027] In general, the instant invention comprises compounds having Formula I or II:



I



II

or an enantiomer, diastereomer, hydrate, solvate or pharmaceutically acceptable salt 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, NR^8CH_2, S, SO, SO_2, or CR^9R^{10};

V is NR^{11} or $-(CR^{37}R^{38})_p-$ provided that when V is N, R^1 is an alkyl or cycloalkyl;

W and X are each independently C or N;

Y is selected from O, S, and NR^{12};

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

l is 0 to 2;

n is 0 to 4 if W and X are both C, 0 to 3 if one of X or W is N, and 0 to 2 if X and W are both N,

p is 1 to 4;

R^3, R^5, R^6, R^7, R^8, R^{11} and R^{15} are independently selected from H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclo, substituted heterocyclo;

R^4 is selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, and substituted heterocycloalkyl, provided that

(a) if R^4 is phenyl

(i) R^4 is not substituted with both hydroxy and amido; and

(ii) R^4 is not substituted with $-NRSO_2R-$ wherein R is alkyl or aryl;

(b) if R^4 is pyridyl, R^4 is not substituted with both hydroxy and methoxy; and

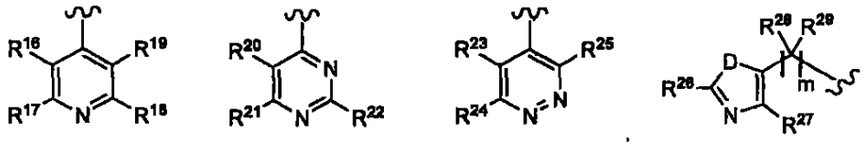
(c) if R^4 is pyrimidinyl, it is not substituted with =O;

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

R^{12} is selected from H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, CN, NO_2 or SO_2NH_2;

R^{13} and R^{14} are independently selected from H, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, substituted heterocycloalkyl or taken together to form a carbocyclic or heterocyclic ring of 3 to 8 atoms;

A is selected from one of the following:



wherein

D is S or O;

m is 0 to 6;

R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26} and R^{27} are independently selected from H, halogen, $NR^{30}R^{31}$, OR^{32}, CO_2R^{33}, $CONR^{34}R^{35}$, SO_2R^{36}, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, -CN, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, or substituted heterocycloalkyl;

R^{28} and R^{29} are independently selected from H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, or taken together to form a carbocyclic or heterocyclic ring of 3 to 8 atoms;

R^{30}, R^{31}, R^{32}, R^{33}, R^{34}, R^{35}, and R^{36} are independently selected from H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, alkoxycarbonyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclo, substituted heterocyclo, heterocycloalkyl, or substituted heterocycloalkyl; and

$R^{37}$and R^{38} are each independently H, halogen, or alkyl.

[0028] In some embodiments of the present invention, R^1 is a substituted or unsubstituted phenyl, such as fluorophenyl, a substituted or unsubstituted C_1 to C_4 alkyl, such as methyl, or a substituted or unsubstituted C_3 to C_8 cycloalkyl, such as cyclohexyl or cyclopentyl.

[0029] In some embodiments of the present invention, R^2 is C_1 to C_4 alkyl, halogen, or haloalkyl.

[0030] In some embodiments of the present invention, R^4 is optionally substituted phenyl, or a 5 or 6 membered nitrogen containing heteraryl group such as pyridyl, pyridinone, pyrazolyl, or pyrrolidyl.

[0031] According to one embodiment of the present invention, B is O, $NHCH_2$, CH_2 or CH(OH); Y is O or S and Z is $-CR^{13}R^{14}$ or $-NR^{15}$ wherein R^{13}, R^{14}, and R^{15} are each H.

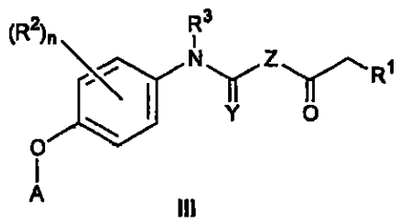
[0032] In some embodiments of the present invention, A is an optionally substituted pyridine or pyrimidine, wherein the substituent is alkyl, alkenyl, alkynyl, halogen, cycloalkyl, heterocycloalkyl, $-NR^{39}COR^{40}$, $-NR^{39}C(O)_2R^{40}$, $-NR^{41}R^{42}$, or $-C(O)NR^{43}R^{44}$, wherein R^{39}, R^{40}, R^{41}, R^{42}, R^{43}, and R^{44} are independently H, lower alkyl, substituted lower alkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, or $-NR^{43}R^{44}$ form a heterocycloalkyl.

[0033] According to some embodiments of the present invention, A is a pyridine substituted with $-NR^{41}R^{42}$, $-NR^{39}COR^{40}$, $-C(O)NR^{43}R^{44}$, halogen, C_1 to C_4 alkyl, optionally substituted with hydroxy, hydroxyalkylamino, alkylamino, aminoalkylamino, or heteroarylalkyl; or $-C{=}C-R^{45}$, $-C{\equiv}C-R^{46}$, wherein R^{45} and R^{46} are alkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, heterocycloalkyl, $-C(O)R^{47}$, $-NR^{39}COR^{40}$, aryl, or heteroaryl; or the pyridine is substituted with aryl, such as phenyl, which may be further substituted with $CONH_2$, methyl, aminoethyl, hydroxyethyl, $-CONHCH_2CH_2NHCH_3$, or CH_2CONH_2, the pyridines may also be substituted with pyridyl or piperidyl groups.

[0034] According to some embodiments of the present invention, A is an optionally substituted pyrimidine. Preferred substituents include $-NR^{41}R^{42}$, or

$-NR^{39}CO_2R^{40}$, wherein R^{41} and $R^2$are preferably H or methyl and R^{39} and R^{40} are preferably, H or alkyl.

In one embodiment of the present invention, compounds have the following formula III:

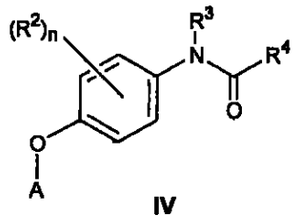


III

wherein

R^1 is optionally substituted phenyl or alkyl; Z is NH or NCH_3 ; R^2 is F, Cl, CH_3 or CF_3, R^3 is H; andY is O or S. In some embodiments, $R^1$is C_3 to C_7 cycloalkyl, substituted or unsubstituted phenyl, or $-(CH_2)_n-R^{50}$ wherein n is 1 to 3, R^{50} is H, substituted or unsubstituted phenyl, amino, amido, CN, $-C(O)_2H$, or $-C(O)_2CH_3$

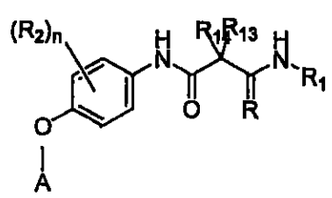
In some embodiments of the present invention, compounds have the following formula Formula IV:



IV

wherein R^2 is halo or H; R^3 is H; R^4 is optionally substituted phenyl, optionally substituted pyrazole, or optionally substituted pyridyl, pyridinone, or pyridine-N-oxide.

In one embodiment of the present invention, compounds are of the following formula V:



V

wherein R^1 is optionally alkyl or cycloalkyl; A is optionally substituted pyrimidine or pyridine; and R_2 is halo or H; and R^{13} and R^{14} are either H or together with the carbon to which they are attached form a cycloalkyl, such as cyclopropyl.

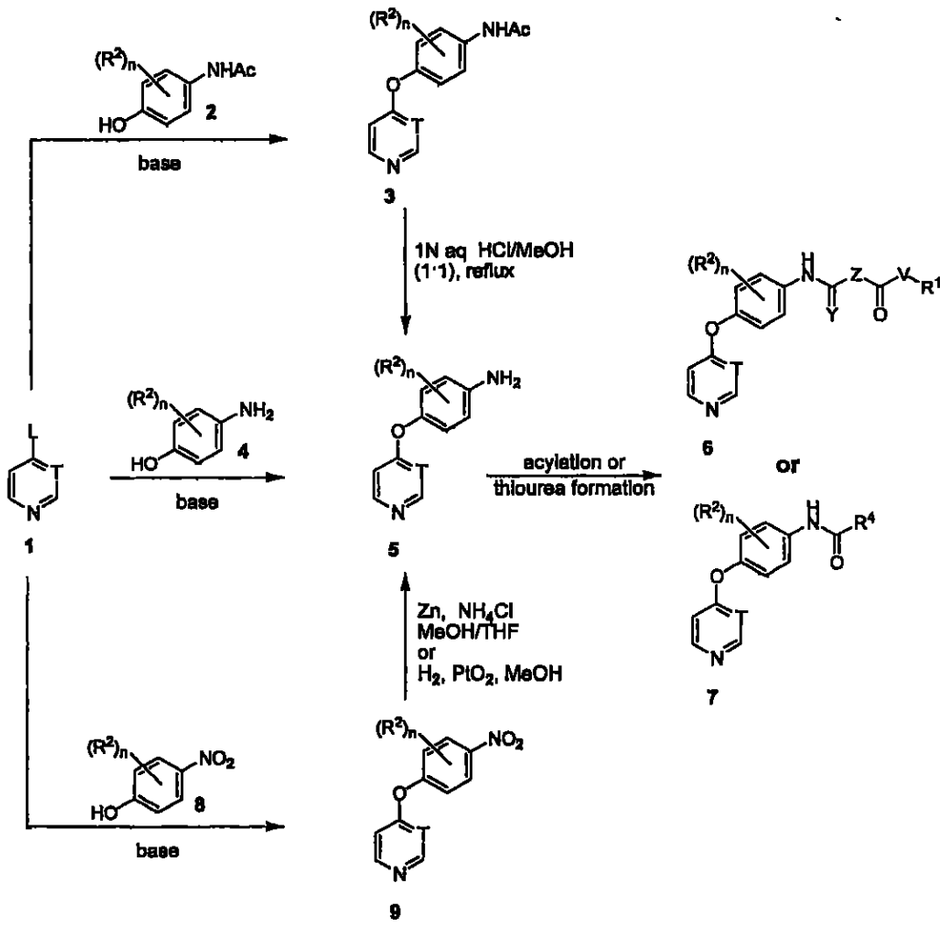
[0035] The invention also provides methods for treating a proliferative disease, such as cancer by administering to a mammalian species in need of such treatment an effective amount of a compound of formulas I or II, as defined above. In another embodiment, the invention provides a method for treating a proliferative disease via modulation of Met kinase by administering to a mammalian species in need of such treatment an effective amount of a compound of formulas 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.

[0036] Certain compounds of Formulas I and II may generally be prepared according to the following Schemes 1-14. The compounds are synthesized readily using synthetic methods known to one skilled in the art. 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

[0037] General routes to the pyridine and pyrimidine analogues described in the invention are illustrated in Scheme 1. An appropriately substituted pyridine or pyrimidine **1** can be treated with functionalized phenols **2**, **4**, and **8** in the presence of a base, such as sodium hydride, sodium hydroxide, or potassium carbonate, to furnish the desired ethers **3**, **5**, and **9**, respectively. Removal of the acetamide protecting group of compound **3** with aqueous HCl in methanol provides the key intermediate **5**. Alternatively, aniline **5** can be obtained from compound **9** via reduction of the nitro group with either zinc dust and ammonium chloride or Adams' catalyst (platinum (IV) oxide) under hydrogenation conditions. Analogues **6** and **7** can then be prepared by acylation of aniline **5** with, for example isocyanates, acid chlorides or by treatment with a carboxylic acid and a coupling reagent, such as: benzotriazol-1-yloxytris(trimethylamino)phosphonium hexafluorophosphate (BOP reagent), bromotripyrrolidinophosphonium hexafluorophosphate (PyBroP), *O*-(1*H*-

benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU). Formation of the acylthiourea of **6** (Y = S, Z = NH) can be accomplished by treating aniline **5** with an appropriately substituted isothiocyanate.

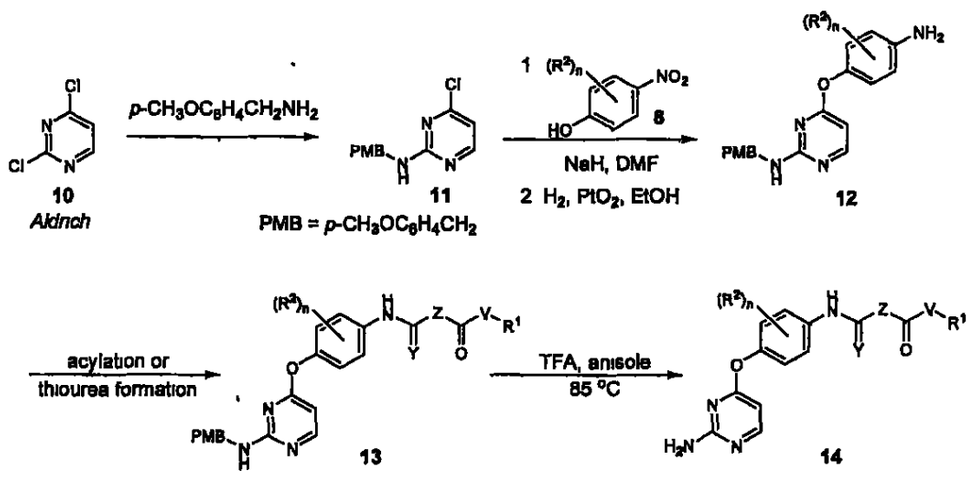
SCHEME 1



T = CR^{19} or N
L = leaving group, such as a halogen or NO_2

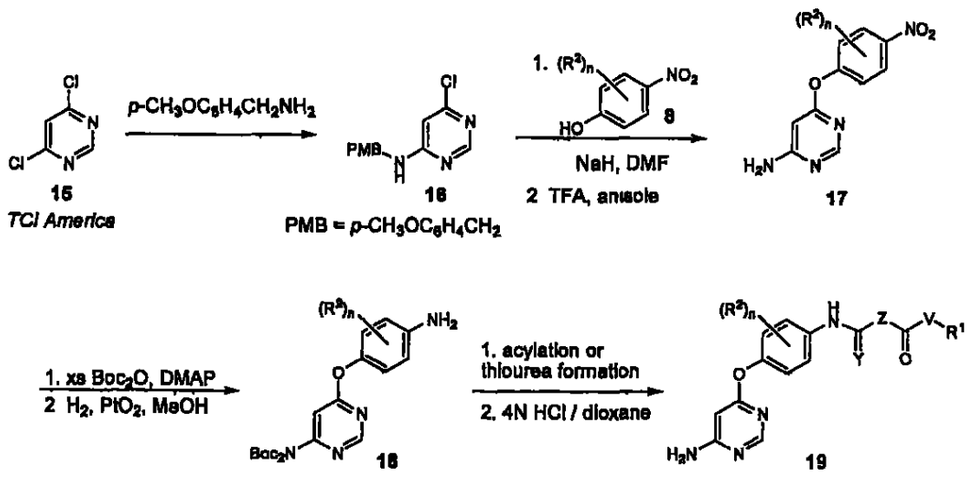
[0038] The two different regioisomeric aminopyrimidine analogues **14** and **19** can be prepared using the synthetic routes outlined in Schemes 2 and 3. PMB-protected aminopyrimidine **11**, derived from commercially available 2,4-dichloropyrimidine (**10**, Aldrich), can be converted to ether **13** via aniline **12** using the same chemistry outlined in Scheme 1. Removal of the PMB group of **13** can be accomplished with trifluoroacetic acid and anisole to generate compound **14**.

SCHEME 2



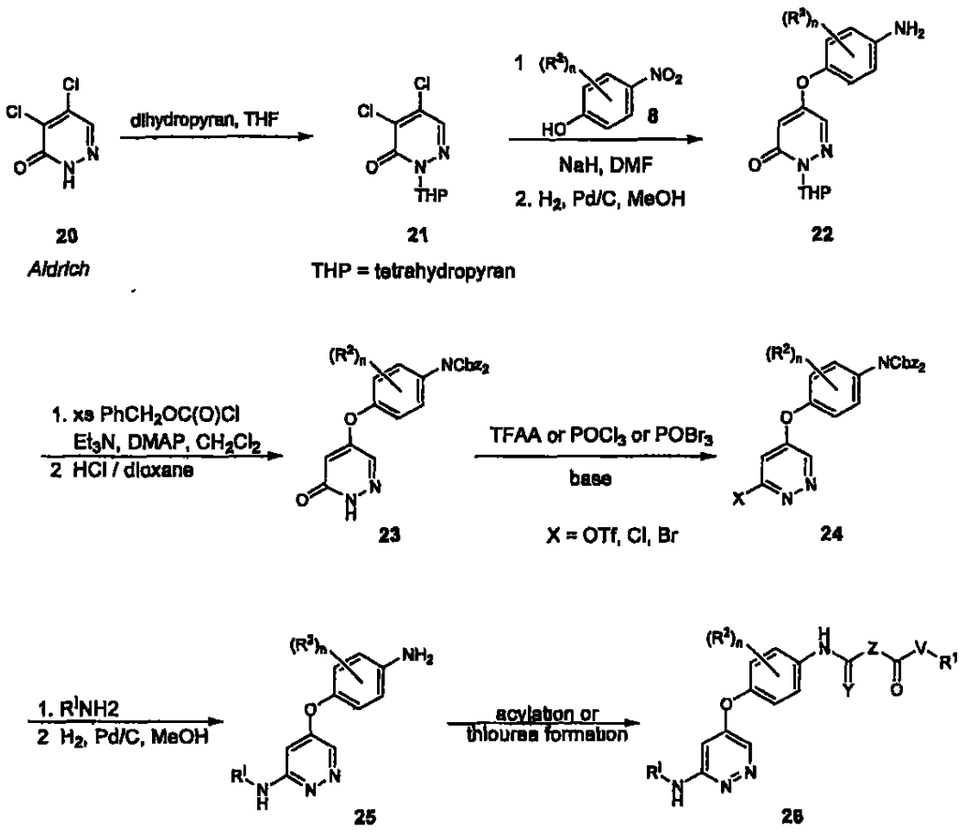
[0039] Similarly, PMB-protected aminopyrimidine **16**, derived from commercially available 4,6-dichloropyrimidine (**15**, TCI America), can be converted to ether **17** following the PMB deprotection step (Scheme 3). Bis-Boc (*t*-butyloxycarbonyl) protection of the amine of **17** with excess di-*tert*-butyl dicarbonate followed by hydrogenation with Adams' catalyst provides aniline **18**. Amine **19** can be obtained from compound **18** following an acylation or thiourea formation step and removal of the Boc protecting groups under acidic conditions.

SCHEME 3



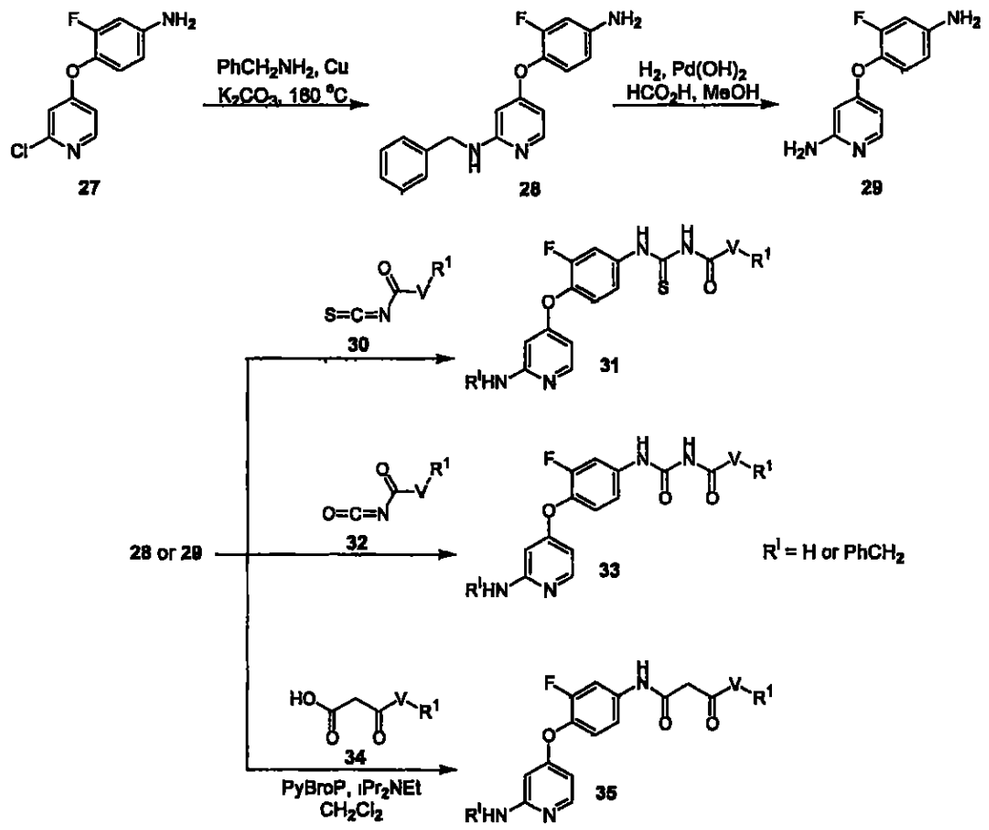
[0040] Aminopyridazine derivative **26** may be prepared using the synthetic route outlined in Scheme 4 which is based on similar chemistry cited in the following references: Chung, H.-A. et al. *J. Heterocyclic Chem.* **1999**, *36*, 905-910 and Bryant R. D. et al. *J. Heterocyclic Chem.* **1995**, *32*, 1473-1476, the disclosures of which are herein incorporated by reference. 4,5-Dichloropyridazin-3(2*H*)-one (**20**, Aldrich) can be protected with, for example a tetrahydropyran (THP) group to give intermediate **21**. Treatment of compound **21** with an appropriately substituted phenol and a base (i.e., sodium hydride) followed by reduction of the nitro containing intermediate under catalytic hydrogenation conditions can provide aniline **22**. Protection of the aniline group of **22** as a bis-benzyl carbamate (Cbz) followed by removal of the THP group under acidic conditions may furnish compound **23**. Treatment of compound **23** with either trifluoroacetic anhydride (TFAA), phosphorous oxychloride or phosphorous oxybromide in the presence of a base, such as triethylamine or diisopropylethylamine may introduce the necessary leaving group at the 3-position of compound **24**. Displacement of the leaving group X of compound **24** with an appropriately substituted amine, followed by removal of the Cbz groups can generate intermediate **25**. Aniline **25** may be converted to the desired 3-aminopyridazine analogue **26** using chemistry previously described in Schemes 1-3.

SCHEME 4



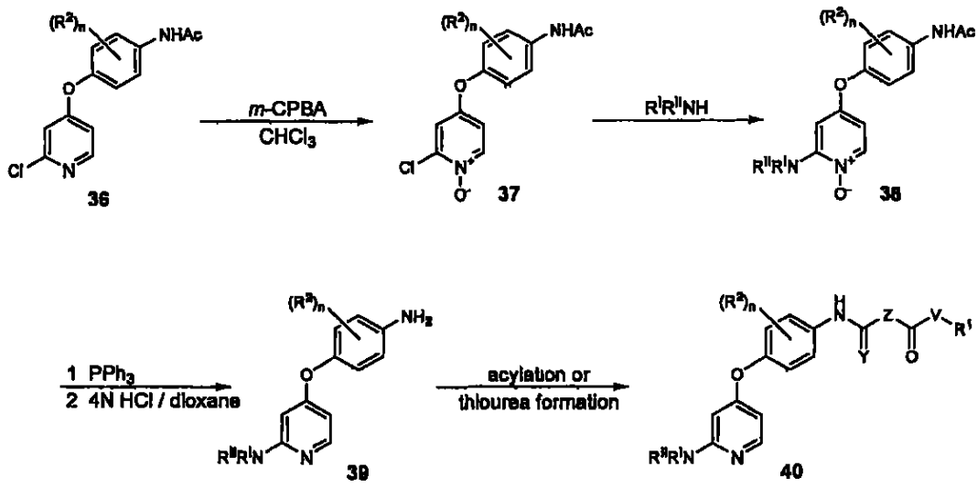
[0041] 2-Aminopyridine derivatives may be prepared using the synthetic routes outlined in Schemes 5 and 6. Aniline **27**, derived from chemistry described in Scheme 1 may be converted to intermediate **28** upon heating with Cu powder and potassium carbonate in benzylamine (Scheme 5). Removal of the benzyl protecting group of compound **28** under catalytic hydrogenation conditions with palladium on carbon provides aminopyridine **29**. Intermediates **28** or **29** can be treated with isothiocyanates **30**, isocyanates **32**, and carboxylic acids **34** in the presence of a coupling reagent to afford acylthiourea **31**, acylurea **33**, and amide **35**, respectively

SCHEME 5



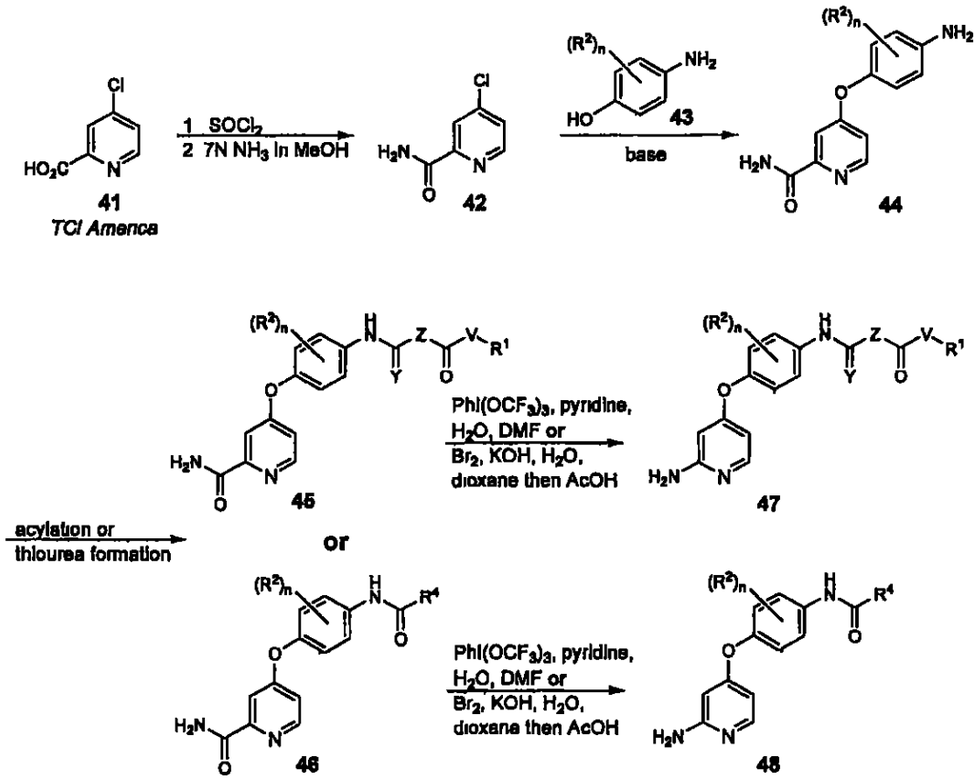
[0042] In a related approach, 2-chloropyridine intermediate **36**, obtained using chemistry described in Scheme 1 can be converted to the *N*-oxide **37** using 3-chloroperoxybenzoic acid (*m*-CPBA) in chloroform (see, WO2004/002410) (Scheme 6). Treatment of compound **37** with an appropriately substituted amine can afford intermediate **38**. Reduction of the *N*-oxide of compound **38** with, for example triphenylphosphine, followed by removal of the acetamide protecting group under acidic conditions can provide aniline **39**. Conversion of aniline **39** to the desired analogue **40** can be accomplished using chemistry previously described in Schemes 1-5.

SCHEME 6



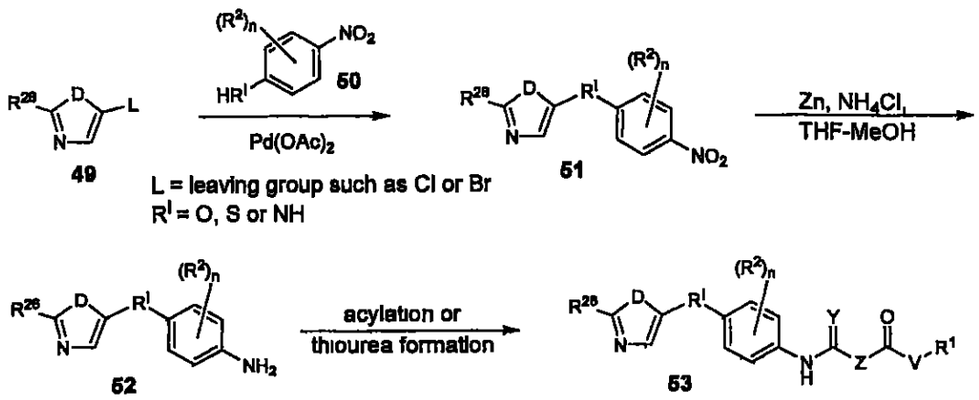
[0043] In an alternative approach to compounds related to **40**, the 2-aminopyridine derivatives **47** and **48** may be prepared according to the synthetic sequence illustrated in Scheme 7. To this end, 4-chloropicolinic acid (**41**, TCI America) can be converted to 4-chloropicolinamide (**42**) using a two step procedure involving thionylchloride followed by ammonia in methanol. Coupling of intermediate **42** with 4-aminophenol derivative **43**, in the the presence of a base, such as potassium *t*-butoxide can afford the picolinamide derivative **44**. Acylation or acylurea formation of intermediate **44** can provide intermediates such as **45** and **46**. Treatment of the picolinamide derivatives **45** and **46** with either bis-(trifluoroacetoxy)-iodobenzene, pyridine and water in DMF or bromine, potassium hydroxide in water promotes a Hofmann rearrangement to generate the desired 2-aminopyridine derivatives **47** and **48**.

SCHEME 7

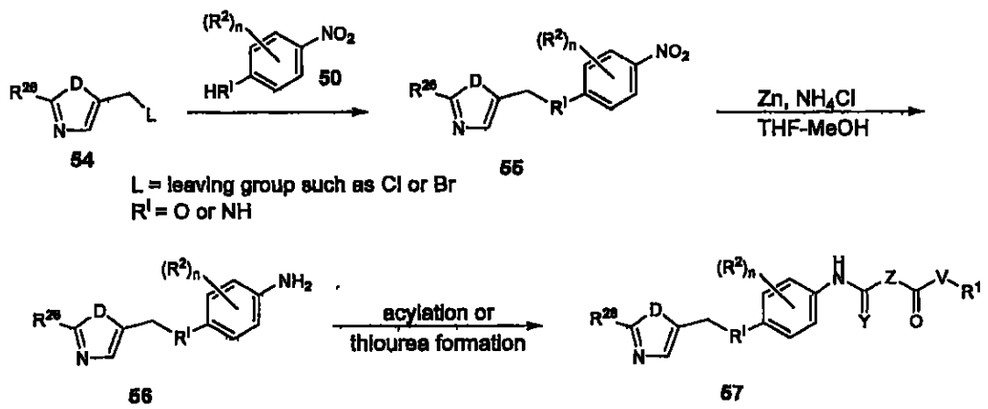


[0044] Thiazole containing compounds **53**, **57** and **62** can be prepared using the synthetic routes described in Schemes 8-10. Displacement of the leaving groups of **49** (Scheme 8) or **54** (Scheme 9) with an aniline / phenol **50** can provide intermediates **51** and **55**, respectively. Reduction of the nitro substituents of **51** and **55** with zinc dust and ammonium chloride in a THF-MeOH mixture should generate anilines **52** and **56**, respectively. Conversion of anilines **52** and **56** to the desired compounds **53** and **57** can be accomplished using chemistry previously described (*vide supra*).

SCHEME 8

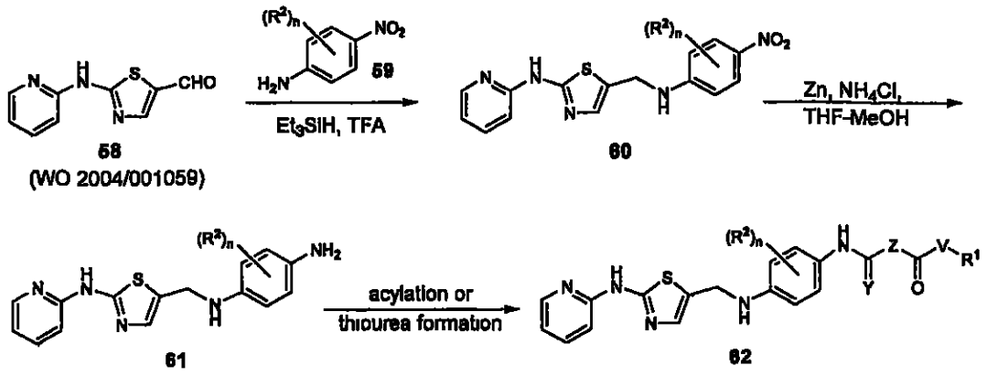


SCHEME 9



[0045] Reductive amination of aldehyde **58** can be achieved using the methods described in WO 2004/001059, herein incorporated by reference in its entirety, using an appropriately substituted aniline **59** can furnish the nitro intermediate **60** (Scheme 10). The desired aminothiazole derivative **62** can then be obtained using chemistry similar to that which was described in Schemes 8 and 9.

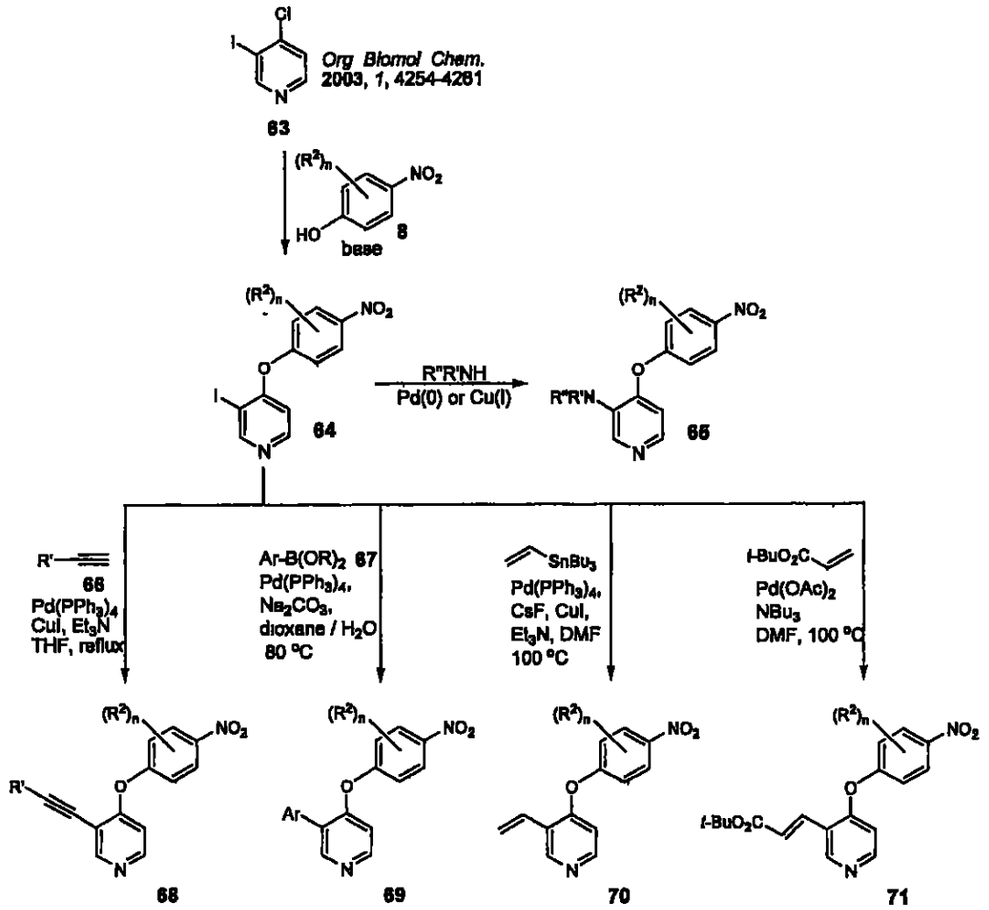
SCHEME 10



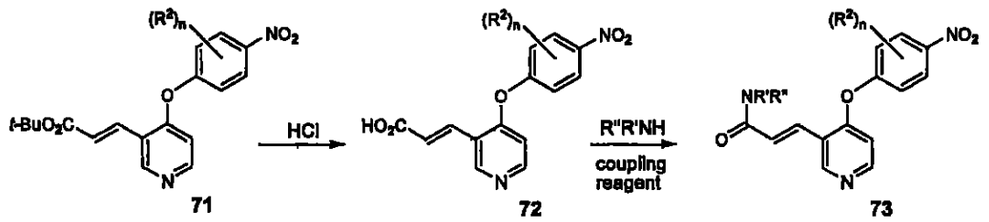
[0046] Incorporation of various substituents at the 3-position of the pyridine nucleus can be accomplished using the chemistry outlined in Scheme 11. To this end, 4-chloro-3-iodopyridine (**63**, Tabanella, S. et al. *Org. Biomol. Chem.* **2003**, *1*, 4254-4261.) can be coupled with the 4-nitrophenol derivative **8** in the presence of a base, such as diisopropylethylamine (Hunig's base) to afford the desired iodide intermediate **64**. A variety of organometallic mediated coupling reactions can then be carried out with the iodide derivative **64**, examples of which are illustrated in Scheme 11. The iodide **64** can be treated with amines (R"R'NH), substituted alkynes **66**, arylboronates **67**, vinylstannanes, and α,β-unsaturated esters in the presence of a palladium or copper catalyst to afford the intermediates **65**, **68-71**, respectively. The nitro moiety of compounds **65** and **68-71** can be reduced with, for example zinc dust and ammonium chloride in a THF-MeOH mixture, and the resulting aniline intermediates can be acylated using chemistry previously described in Schemes 1-5.

[0047] Intermediate **71** can then be converted to the α,β-unsaturated amides **73** (Scheme 12). Compound **72**, derived from acid promoted hydrolysis of ester **71**, can be coupled with various amines (R"R'NH) in the presence of a coupling reagent such as, but not limited to EDCI, TBTU, DCC, to furnish the desired amide intermediate **73**. Reduciton of the nitro moiety of **73** and subsequent acylation of the requisite aniline intermediate can be accomplished using chemistry previously described in Schemes 1-5.

SCHEME 11



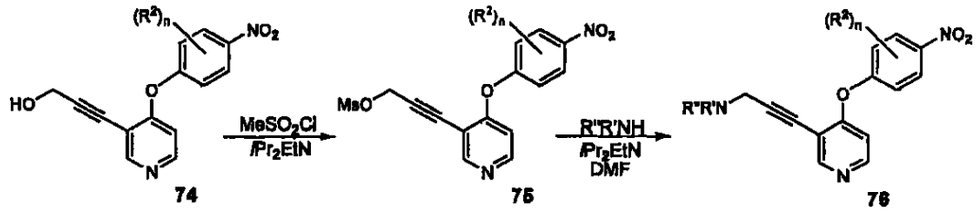
SCHEME 12



[0048] Intermediate **74** can also be further modified to prepare propargylic amines **76** (Scheme 13). Mesylation of the propargylic alcohol **74**, can be accomplished with methanesulfonyl chloride in the presence of a base, such as diisopropylethylamine (Hunig's base) to provide the mesylate **75**. Displacement of the mesylate group of compound **75** with various amines (R"R'NH) can provide the propargylic amines **76**.

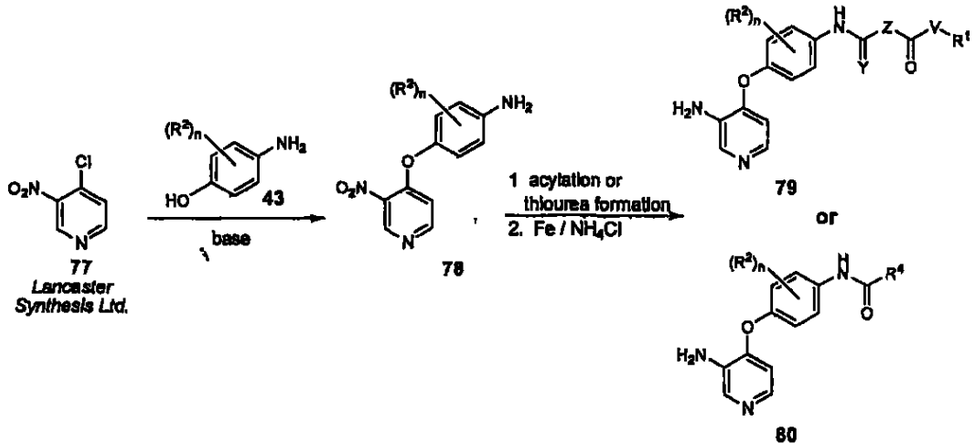
Reduction of the nitro moiety of **76** and subsequent acylation of the requisite aniline intermediate can be accomplished using chemistry previously described in Schemes 1-5.

SCHEME 13



[0049] The 3-aminopyridine derivatives **79** and **80** can be prepared according to the synthetic route described in Scheme 14. To this end, 4-chloro-3-nitropyridine (**77**, Lancaster Synthesis Ltd.) can be coupled with 4-aminophenol in the presence of a base, such as sodium hydride in DMF to afford the nitro intermediate **78**. Chemistry previously described above can be used to convert intermediate **78** to the desired compounds **79** and **80**. The amino substituent of **79** and **80** can also be further modified, for example via alkylation, acylation, arylation or sulfonylation.

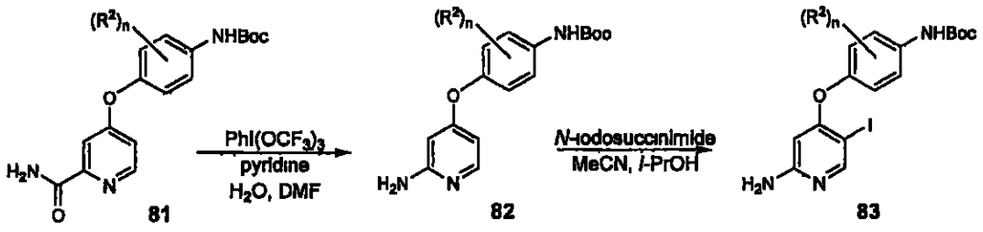
SCHEME 14



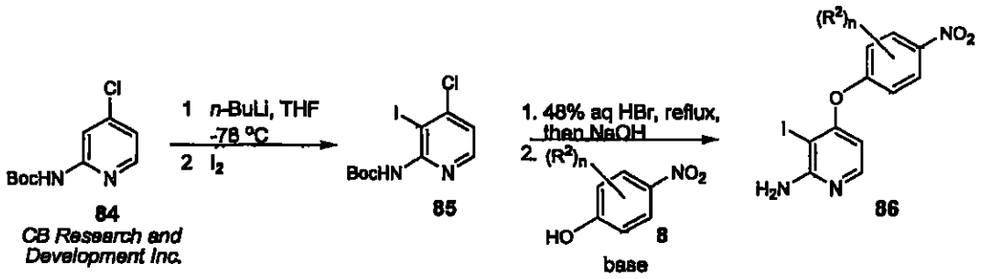
[0050] Incorporation of subsituents on either the 5- or 3- position of the 2-aminopyridine ring can be accomplished using the iodide intermediates **83** and **86**, respectively (Schemes 15 and 16). The 2-carboxamide derivative **81** can be converted to the 2-aminopyridine derivative **82** using the Hofmann rearrangement protocol

previously described in Scheme 7. Iodination of the 5-position of compound **82** can be achieved with *N*-iodosuccinimide in an acetonitrile-isopropanol mixture to afford the desired iodide intermediate **83**. Alternatively, *t*-butyl 4-chloropyridin-2-ylcarbamate (**84**, CB Research and Development Inc.) can be converted to *t*-butyl 4-chloro-3-iodopyridin-2-ylcarbamate (**85**) via a two step process involving *n*-butyllithium in THF at low temperature followed by the addition of iodine. Removal of the *N*-Boc (*t*-butylcarbamate) protecting group of **85** with refluxing aqueous hydrogen bromide followed by coupling of the chloride intermediate with the 4-nitrophenol derivative **8** in the presence diisopropylamine (Hunig's base) in *N*-methylpyrrolidinone (NMP) at elevated temperature can provide the iodide intermediate **86**. The iodide intermediates **83** and **86** can be futher processed using chemistry similar to that previously described in Scheme 11.

SCHEME 15



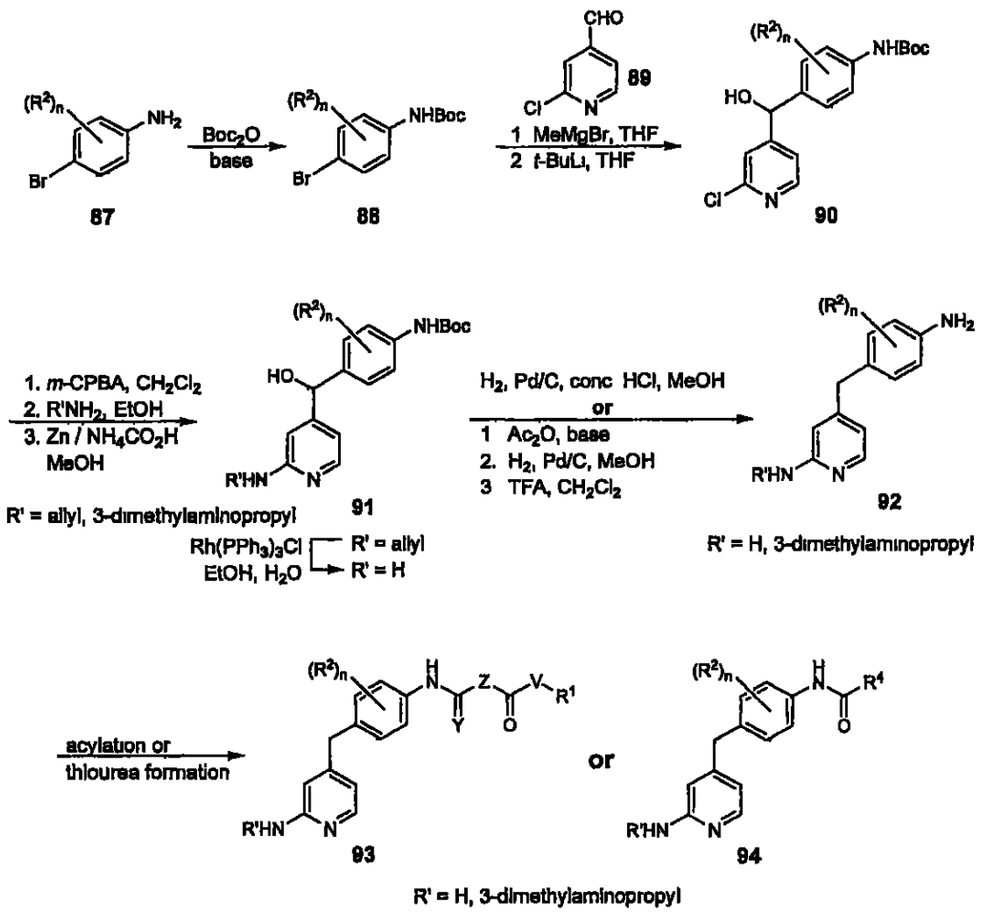
SCHEME 16



[0051] The methylene linked (B = CH_2) analogues **93** and **94** can be prepared according to the synthetic sequence outlined in Scheme 17. Compound **88**, derived from *N*-Boc protection of the 4-bromoaniline derivative **87**, can be treated with methylmagnesium bromide followed by *tert*-butyllithium and 2-chloroisonicotinaldehyde (Frey, L. F. et al. *Tetrahedron Lett* **2001**, *42*, 6815-6818) at

low temperature to provide intermediate **90**. Oxidation of the pyridine ring of **90** with 3-chloroperoxybenzoic acid (*m*-CPBA), followed by displacement of the chloro substituent with an amine ($R'NH_2$) and subsequent reduction of the *N*-oxide intermediate with zinc and ammonium formate in methanol can provide intermediate **91**. When allylamine is used as the nucleophilic amine ($R'NH_2$), the allyl group can be removed from the amine of **91** using a rhodium catalyst in an ethanol-water mixture. Removal of the hydroxyl group of **91** can be accomplished by two different methods. For example, hydrogenolysis of compound **91** in the presence of a palladium catalyst, followed by deprotection of the *N*-Boc group on the aniline under acidic conditions (HCl in methanol) can afford compound **92**. Alternatively, compound **92** can be obtained by acylation of the alcohol of **91** and subsequent hydrogenolysis of the intermediate in the presence of a palladium catalyst and removal of the *N*-Boc protecting group under acidic conditions (trifluoroacetic acid in methylene chloride). Intermediate **92** can then be acylated to furnish the desired compounds **93** and **94** using chemistry previously described in Schemes 1-5.

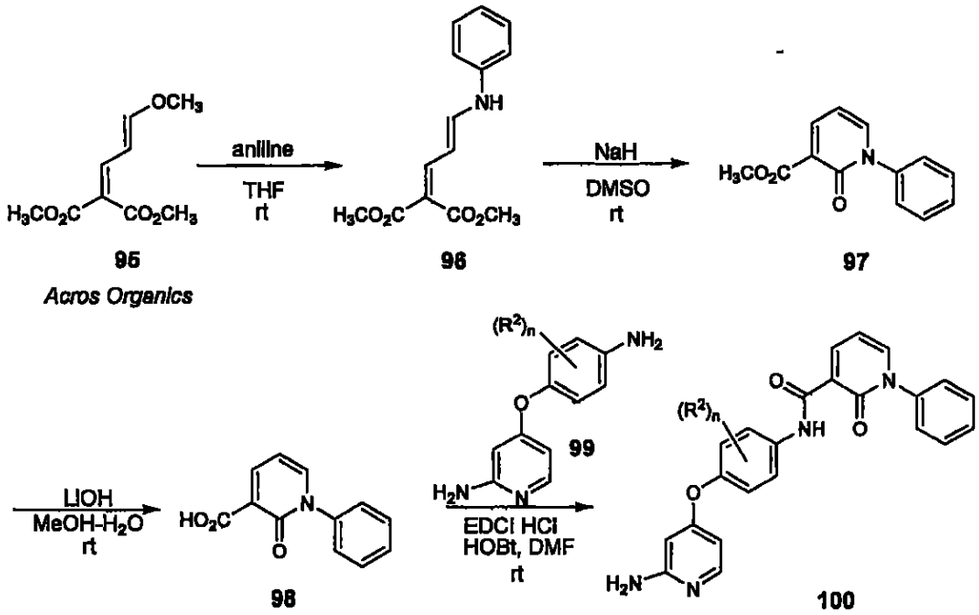
SCHEME 17



87 88 89 90 91 92 93 94

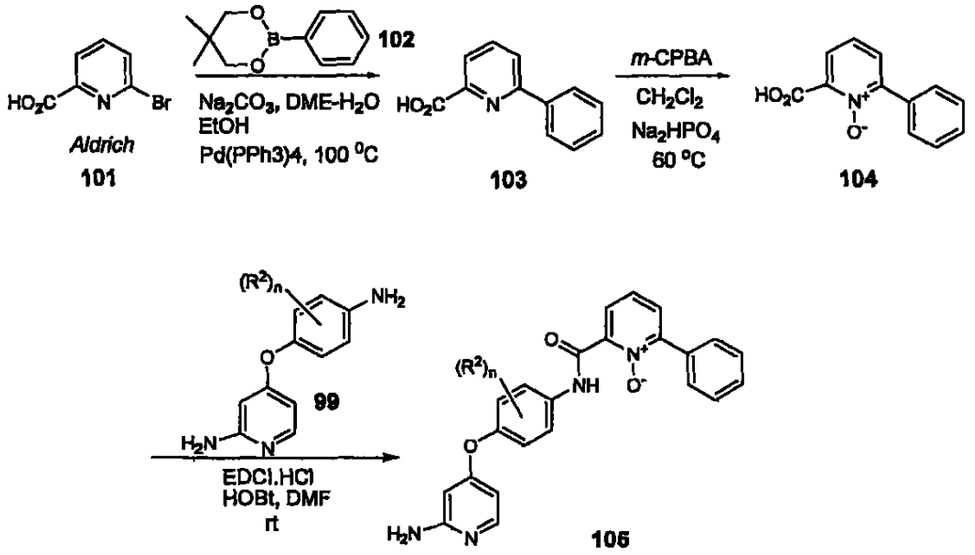
[0052] The heterocyclic amide derivatives **100** and **105** can be prepared according to the synthetic routes described in Schemes 18 and 19. To this end, methyl 2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxylate (**97**) can be obtained in a two step process beginning with commercially available (*E*)-dimethyl 2-(3-methoxyallylidene)malonate (**95**) (Scheme 18). Thus, treatment of compound **95** with aniline at room temperature can provide intermediate **96**, which can then cyclized in the presence of a base, such as sodium hydride in dimethylsulfoxide to generate **97**. Hydrolysis of intermediate **97** under basic conditions can provide 2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxylic acid (**98**). The carboxylic acid **98** can then be coupled with the aniline derivative **99** in the presence of a coupling reagent, such as 1-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) and hydroxybenzotriazole (HOBt) in DMF to furnish the desired compound **100**.

SCHEME 18



[0053] The pyridyl *N*-oxide intermediate **104** (Scheme 19) can be obtained by a two step process in which the commercially available 6-bromopicolinic acid (**101**) is coupled with the phenyl-1,3,2-dioxaborinane **102** (Aldrich) in the presence of a palladium(0) catalyst and sodium carbonate, followed by oxidation of the requisite intermediate **103** at elevated temperature. Coupling of intermediate **104** with the aniline derivative **99** can furnish the desired compound **105**.

SCHEME 19



[0054] 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.

[0055] 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.

[0056] 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.

[0057] 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).

[0058] 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.

[0059] Compounds of Formulas I and II may also be useful in inhibiting tumor angiogenesis and metastasis.

[0060] 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 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.

[0061] Additional cytotoxic agents include, melphalan, hexamethyl melamine, thiotepa, cytarabin, idatrexate, trimetrexate, dacarbazine, L-asparaginase, camptothecin, topotecan, bicalutamide, flutamide, leuprolide, pyridobenzoindole derivatives, interferons, and interleukins.

[0062] 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.

[0063] 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.

[0064] 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.

[0065] 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.

[0066] 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.

[0067] 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.

[0068] 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.

[0069] 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.

[0070] 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 microemulation.

[0071] 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.

[0072] 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.

[0073] 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.

[0074] 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.)

[0075] 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.

[0076] 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.

[0077] 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).

ASSAYS

[0078] 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 salts thereof.

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	

[0079] 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 were incubated for 60 minutes at 27°C and stopped by the addition of cold trichloroacetic acid (TCA) to a final concentration 4%. TCA precipitates were 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 were generated to determine the concentration required to inhibit 50% of kinase activity (IC_{50}). Compounds were 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 were derived by non-linear regression analysis and had a coefficient of variance (SD/mean, n=6) = 16%.

[0080] Preferred compounds of the invention inhibit Met kinase with IC_{50} values between 0.01 to 100 μM. The most preferred compounds have IC_{50} values of less than 0.5 μM.

[0081] Further subject matter of the invention also includes pharmaceuticals for use as described above including controlling cancer, inflammation and arthritis, which contain at least one compounds of Formulas I and II as defined above or at least one of its pharmacologically acceptable acid addition salts, and the use of a compound of the Formulas I and II as defined above for the preparation of a pharmaceutical having activity against proliferative diseases as described previously including against cancer, inflammation and/or arthritis.

[0082] 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

[0083] The invention will now be further described by the following working examples, which are preferred embodiments of the invention. 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).

[0084] 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 = 4 mL/min and detection at 220 nm.

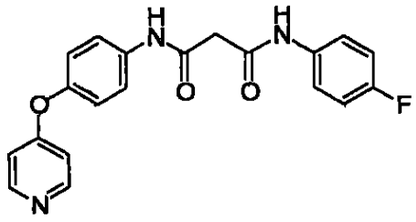
[0085] Preparative Reverse Phase (RP) HPLC was performed with a linear gradient elution using 10% methanol, 90% water, 0.1% TFA (solvent A) and 90% methanol, 10% water, 0.1% TFA (solvent B) and detection at 220 nm on one of the following columns: **A** - Shimadzu S5 ODS-VP 20 × 100 mm column with a flow rate of 20 mL/min; **B** - YMC S5 ODS 30 × 100 mm column with a flow rate of 20 mL/min; **C** - Phenomonex 30 × 250 mm column with a flow rate of 10 mL/min; **D** - YMC S5 ODS 20 × 250 mm column with a flow rate of 10 mL/min; **E** - YMC S10 ODS 50 × 500 mm column with a flow rate of 50 mL/min; or **F** - YMC S10 ODS 30 × 500 mm column with a flow rate of 20 mL/min.

[0086] 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.

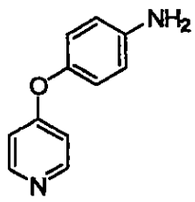
[0087] The following abbreviations are used for commonly used reagents : Boc or BOC: *t*-butyl carbamate; Fmoc: 9*H*-fluorenylmethyl carbamate; TEA: triethylamine; NMM: *N*-methylmorpholine; Ms: methanesulfonyl; DIEA or DIPEA: diisopropylethylamine or Hunig's base; NMP: *N*-methylpyrrolidinone; BOP reagent: benzotriazol-1-yloxytris(trimethylamino)phosphonium hexafluorophosphate; DCC: 1,3-dicyclohexylcarbodiimide; EDCI: 1-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; RT or 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 or HOBT: hydroxybenzotriazole; $Na(OAc)_3BH$: sodium triacetoxyborohydride; HOAc: acetic acid; TFA: trifluoroacetic acid; LiHMDS: lithium bis(trimethylsilyl)amide; DMSO: dimethyl sulfoxide; MeCN: acetonitrile; MeOH: methanol; EtOAc: ethyl acetate; DMF: dimethyl formamide; THF: tetrahydrofuran; DCE: 1,2-dichloroethane; Et_2O: diethyl ether; DCM. dichloromethane or methylene chloride; *m*-CPBA: 4-chloroperoxybenzoic acid.

Example 1

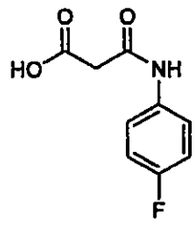


***N*-(4-Fluorophenyl)-*N*-(4-(pyridin-4-yloxy)phenyl)malonamide**



A) 4-(4-Aminophenoxy)pyridine

[0088] A solution of 4-chloropyridine hydrochloride (Aldrich, 3.0 g, 20.0 mmol) in dimethyl sulfoxide (40 mL) was treated with 4-aminophenol (Aldrich, 2.1 g, 20.0 mmol) and sodium hydroxide pellets (2.0 g, 50.0 mmol) and the mixture was heated at 100 °C for 18 h. The mixture was cooled to room temperature, poured onto a mixture of ice-water (300 g) and extracted with Et_2O (3 x 150 mL). The combined extracts were washed with brine, dried ($MgSO_4$) and concentrated to give the 4-(4-aminophenoxy)aniline as a pale yellow solid (3.5 g, 94%). ^1H NMR (DMSO-d_6) δ 8.38 (dd, 2H, J = 5.5, 1.5 Hz), 6.83-6.79 (m, 4H), 6.63-6.59 (m, 2H), 5.13 (br s, 2H); MS(ESI^+) m/z 187.2 $(M + H)^+$.



B) 3-(4-Fluorophenylamino)-3-oxopropanoic acid

[0089] To a solution of ethyl 3-chloro-3-oxopropanoate (Aldrich, 5.0 mL, 40 mmol) in methylene chloride (100 mL) at 0 °C was added diisopropylethylamine (8.4 mL, 48 mmol) followed by 4-fluoroaniline (Aldrich, 3.6 mL, 38 mmol). The reaction mixture 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 upon 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 226.11 $(M+H)^+$.

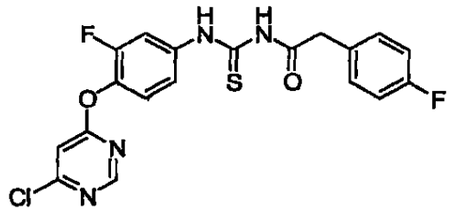
[0090] The above ester was dissolved in 100 mL of ethanol and cooled to 0 °C. 1 N aq. NaOH solution (100 mL) was added and the reaction was stirred at 0 °C for 1 h. The reaction was concentrated *in vacuo* to remove ethanol. The aqueous solution was extracted with EtOAc (50 mL) and was then made acidic with 1N 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 as a yellow solid (6.31 g, 84%) 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 198.43 $(M+H)^+$.

C) *N*-(4-Fluorophenyl)-*N*-(4-(pyridin-4-yloxy)phenyl)malonamide

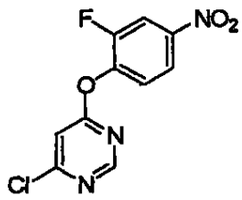
[0091] A solution of 4-(4-aminophenoxy)pyridine (93 mg, 0.50 mmol) in DMF was treated with 3-(4-fluorophenylamino)-3-oxopropanoic acid (99 mg , 0.50 mmol), DIPEA (113 μL, 0.65 mmol) and TBTU (209 mg, 0.65 mmol) and the mixture was stirred at RT for 2 h. The mixture was concentrated to remove the DMF and the residue partitioned between EtOAc and saturated sodium bicarbonate solution. The

EtOAc phase was washed with saturated sodium bicarbonate solution, brine, dried ($MgSO_4$) and concentrated to give the title compound as an off-white foam (140 mg, 76%). ^{1}H NMR (DMSO-d_6) δ 10.30 (s, 1H), 10.24 (s, 1H), 8.43 (dd, 2H , J = 5.5, 1.5 Hz), 7.70 (d, 2H, J = 9.1 Hz), 7.63-7.60 (m, 2H), 7.17-7.14 (m, 4H), 6.89 (dd, 2H, J = 5.5, 1.5 Hz), 3.46 (s, 2H); MS(ESI$^+$) m/z 365.9 $(M + H)^+$.

Example 2

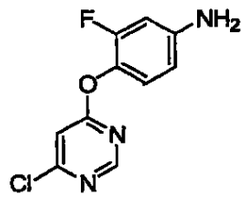


1-(4-(6-Chloropyrimidin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl) thiourea



A) 4-Chloro-6-(2-fluoro-4-nitrophenoxy)pyrimidine

[0092] A mixture of 4,6-dichloropyrimidine (Aldrich, 0.74 g, 5.0 mmol), 2-fluoro-4-nitrophenol (Aldrich, 0.79 g, 5.0 mmol) and DMF (10 ml) was treated with potassium carbonate (0.72 g, 5.2 mmol) and heated at 80 °C for 3 h. The mixture was cooled, diluted with water and extracted with ethyl acetate. The ethyl acetate extract was washed with brine, dried ($MgSO_4$), and concentrated to give the crude product as a yellow solid. The crude product was triturated with isopropyl ether to give 4-chloro-6-(2-fluoro-4-nitrophenoxy)pyrimidine as a yellow solid (1.3 g, 94%). ^{1}H NMR (DMSO-d_6) δ 8.80 (s, 1H), 8.51 (dd, 1H, J = 8.6, 2.5 Hz), 8.31 (d, 1H, J = 9.1 Hz), 7.87 (d, 1H, J = 9.1 Hz), 7.84 (s, 1H).



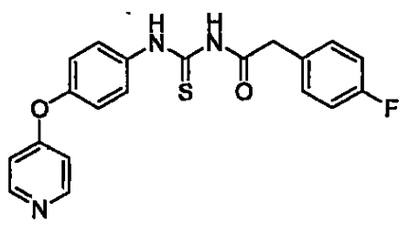
B) 4-Chloro-6-(2-amino-2-fluorophenoxy)pyrimidine

[0093] A solution of 4-chloro-6-(2-fluoro-4-nitrophenoxy)pyrimidine (1.3 g, 4 8 mmol) in methanol (120 mL) was treated with Raney nickel (1.5 g, aqueous slurry) and the reaction mixture was stirred under a blanket of hydrogen (from a latex balloon) at RT for 3 h. The catalyst was filtered off, the filtrate concentrated, and the residue partitioned between CH_2Cl_2 and water. The methylene chloride phase was separated, dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography on silica gel using 1- 2 % MeOH in CH_2Cl_2 as the eluent to give 4-chloro-6-(2-amino-2-fluorophenoxy)pyrimidine as a white solid (600 mg, 52%). ^1H NMR (DMSO-d_6) δ 8.64 (s, 1H), 7.39 (s, 1H), 6.97 (dd, 1H, J= 8.8, 8.8 Hz), 6.46 (dd, 1H, J= 13.1, 2.5 Hz), 6.38 (dd, 1H, J= 8.6, 2.5 Hz), 5.44 (br s, 2H); MS(ESI$^+$) m/z 240.04 $(M + H)^+$.

C) 1-(4-(6-Chloropyrimidin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea

[0094] 4-Fluorophenylacetyl chloride (Lancaster, 0.52 g, 3.0 mmol) was added to a mixture of NaSCN (0.27 g, 3.3 mmol) and EtOAc (12 mL) and the resulting mixture stirred at RT for 30 min. This mixture was added to a solution of 4-chloro-6-(2-amino-2-fluorophenoxy)pyrimidine in 1:1 EtOAc/CH_2Cl_2 (5 ml) and the resulting mixture stirred at RT overnight. The mixture was concentrated and the residue partitioned between EtOAc/ H_2O. The EtOAc phase was separated, washed with brine, dried ($MgSO_4$) and concentrated. The product was purified by flash chromatography using 10 – 35 % EtOAc/ hexanes as the eluent to give the title compound as a yellow crystalline solid (0.85 g, 65%). ^1H NMR (DMSO-d_6) δ 12.40 (s, 1H), 11.81 (s, 1H), 8.67 (s, 1H), 7.90 (dd, 1H, J= 12.1, 2.0 Hz), 7.62 (s, 1H), 7.47-7.41 (m, 2H), 7.38-7.35 (m, 2H), 7.17 (t, 2H, J= 8.8 Hz), 3.81 (s, 2H); MS(ESI$^+$) m/z 434.98 $(M + H)^+$.

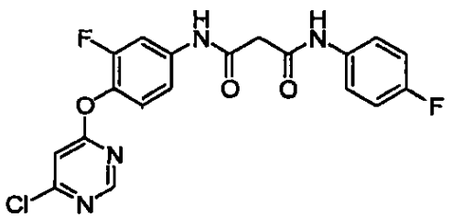
Example 3



1-(2-(4-Fluorophenyl)acetyl)-3-(4-(pyridin-4-yloxy)phenyl)thiourea

[0095] The title compound was prepared using 4-(4-aminophenoxy)pyridine (Compound A of Example 1) and a similar procedure outlined for the preparation of Compound C of Example 2. Yield: 10%. ^{1}H NMR ($CDCl_3$) δ 12.3 (s, 1H), 8.63 (s, 1H), 8.49, (d, 2H, J = 6.2 Hz), 7.71 (d, 2H, J = 8.9 Hz), 7.31-7.27 (m, 2H), 7.14-7.09 (m, 4H), 6.90 (dd, 2H, J = 4.8, 1.4 Hz), 3.73 (s, 2H); MS(ESI$^+$) m/z 382.2 $(M+H)^+$.

Example 4

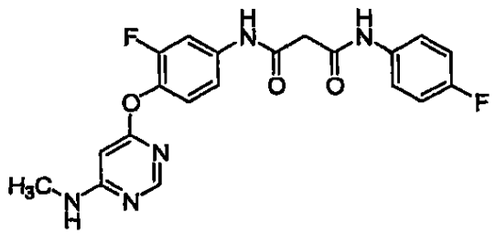


***N*^{1}-(4-(6-Chloropyrimidin-4-yloxy)-3-fluorophenyl)-*N*^{3}-(4-fluorophenyl) malonamide**

[0096] A solution of 4-chloro-6-(2-amino-2-fluorophenoxy)pyrimidine (29 mg, 0.12 mmol, Compound B of Example 2), 3-(4-fluorophenylamino)-3-oxopropanoic acid (26 mg, 0.13 mmol, Compound B of Example 1) in DMF (1.5 mL) was treated with DIPEA (24 µl, 0.14 mmol) and TBTU (46 mg, 0.14 mmol). The reaction mixture was stirred at RT overnight, diluted with EtOAc (25 mL), and the organic phase was washed with brine (3 x 20 mL), dried ($MgSO_4$) and concentrated. The product was purified by flash chromatography using 1-3 % MeOH in CH_2Cl_2 as the eluent to give the title compound as a white solid (35 mg, 78%). ^{1}H NMR (DMSO-d_6) δ 10.49 (s, 1H), 10.25 (s, 1H), 8.65 (s, 1H), 7.78 (d, 1H, J = 12.1 Hz), 7.63-7.57

(m, 3H), 7.40-7.34 (m, 2H), 7.16 (t, 2H, J = 8.8 Hz), 3.48 (s, 2H); MS (ESI^+) m/z 419.21 $(M+H)^+$.

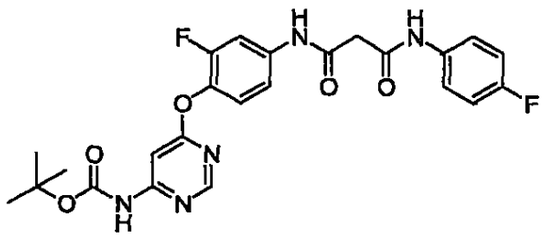
Example 5



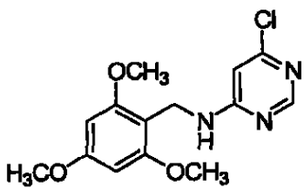
N^1-(3-Fluoro-4-(6-(methylamino)pyrimidin-4-yloxy)phenyl)-N^3-(4-fluorophenyl)malonamide

[0097] A solution of N^1-(4-(6-chloropyrimidin-4-yloxy)-3-fluorophenyl)-N^3-(4-fluorophenyl)malonamide (100 mg, 0.42 mmol, Example 4) in *n*-BuOH (3 mL) was treated with 2 M methylamine/THF (0.2 mL) and heated in a screw cap vial at 80 °C for 12 h. The mixture was concentrated and the residue purified by preparative HPLC using a gradient of MeOH-H_2O containing 0.1 % TFA. The fraction containing the product was lyophilized to give the title compound as a pale yellow solid (60 mg, 34%). ^1H NMR (DMSO-d_6) δ 10.58 (s, 1H), 10.36 (br s, 2H), 8.19 (br s, 1H), 7.76 (d, 1H, J = 12.1 Hz), 7.64-7.62 (m, 2H), 7.36-7.27 (m, 2H), 7.15 (dd, 2H, J = 8.8, 8.8 Hz), 5.95 (br s, 1H), 3.49 (s, 2H), 2.80 (s, 3H); MS(ESI^+) m/z 414.16 $(M+H)^+$.

Example 6

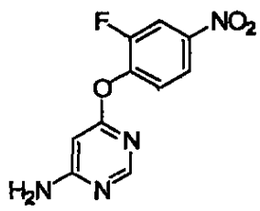


***tert*-Butyl 6-(2-fluoro-4-(3-(4-fluorophenylamino)-3-oxopropanamido)phenoxy)pyrimidin-4-ylcarbamate**



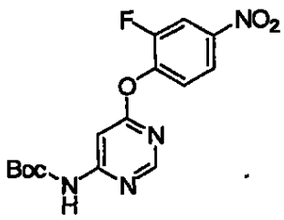
A) *N*-(2,4,6-Trimethoxybenzyl)-6-chloropyrimidin-4-amine

[0098] A mixture of 4,6-dichloropyrimidine (Aldrich, 1.48 g, 10.0 mmol), 2,4,6-trimethoxybenzylamine hydrochloride (2.33 g, 10.0 mmol), DIPEA (4.8 mL, 27.7 mmol), and *n*-BuOH (50 mL) was heated at 100 °C for 2 h. The mixture was cooled, diluted with water (200 mL) and the precipitated product was collected by vacuum filtration on a Büchner funnel. The product was washed with cold water, ether, and vacuum dried to give an off-white solid (2.8 g, 90%). ^{1}H NMR (DMSO-d_6) δ 8.28 (s, 1H), 7.38 (s, 1H), 6.49 (s, 1H), 6.25 (s, 2H), 4.34 (s, 2H), 3.77 (s, 9H).



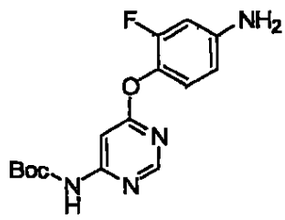
B) 6-(2-Fluoro-4-nitrophenoxy)pyrimidin-4-amine

[0099] A mixture of *N*-(2,4,6-trimethoxybenzyl)-6-chloropyrimidin-4-amine (2.2 g, 7.11 mmol), 2-fluoro-4-nitrophenol (1.1 g, 7.0 mmol), and 2-methoxyethyl ether (50 mL) was heated at 160 °C for 60 h. The reaction mixture was cooled to RT and poured into H_2O (200 mL). The solid was collected, washed with 2 M aqueous Na_2CO_3 and H_2O, and then vacuum dried on a Büchner funnel. The crude product was treated with TFA (20 mL) in dioxane (40 mL) and stirred at RT for 4 h. The reaction mixture was concentrated, the residue partitioned between EtOAc and saturated $NaHCO_3$ solution. The EtOAc phase was separated, dried ($MgSO_4$), concentrated and the crude product purified by flash chromatography using 1-2 % MeOH in CH_2Cl_2 as the eluent to give 6-(2-fluoro-4-nitrophenoxy)pyrimidin-4-amine (440 mg, 31%). ^{1}H NMR (DMSO-d_6) δ 8.31 (dd, 1H, J = 10 4, 2.5 Hz), 8.14 (dd, 1H, J = 9.8, 2.0 Hz), 8.04 (s, 1H), 7.61 (dd, 1H, J = 8.3, 8.3 Hz), 7.07 (s, 2H), 6.02 (s, 1H); MS(ESI$^+$) m/z 251.15 $(M + H)^+$.



C) *tert*-Butyl 6-(2-fluoro-4-nitrophenoxy)pyrimidin-4-ylcarbamate

[00100] A mixture of 6-(2-fluoro-4-nitrophenoxy)pyrimidin-4-amine (439 mg, 1.2 mmol), BOC_2O (261 mg, 1.2 mmol), DMAP (10 mg), and THF (10 mL) was stirred at RT for 1 h then concentrated *in vacuo* to give the crude product. The product was purified by flash chromatography using 1-2 % MeOH in CH_2Cl_2 as the eluent to give *tert*-butyl 6-(2-fluoro-4-nitrophenoxy)pyrimidin-4-ylcarbamate as a white solid (110 mg, 26%). ^{1}H NMR (DMSO-d_6) δ 10.59 (s, 1H), 8.39 (dd, 1H, J = 8.8, 1.1 Hz), 8.32 (dd, 1H, J = 10.3, 2.4 Hz), 8.15 (ddd, 1H, J = 9.1, 2.5, 1.0 Hz), 7.67 (dd, 1H, J = 8.8, 8.8 Hz), 7.45 (s, 1H), 1.44 (s, 9H); MS(ESI) m/z 349.08 (M - H).



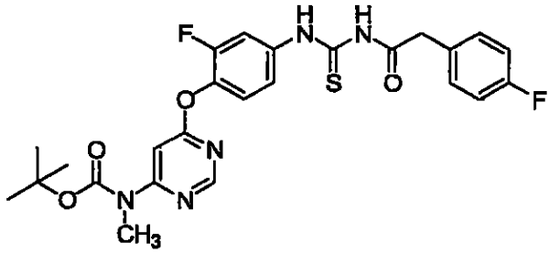
D) *tert*-Butyl 6-(4-amino-2-fluorophenoxy)pyrimidin-4-ylcarbamate

[00101] A solution of *tert*-butyl 6-(2-fluoro-4-nitrophenoxy)pyrimidin-4-ylcarbamate (11 mg, 0.031 mmol) in MeOH (2 mL) was treated with PtO_2 and the reaction mixture was stirred under a blanket of hydrogen (from a latex balloon) for 2 h. The catalyst was filtered off and the filtrate concentrated to give *tert*-butyl 6-(4-amino-2-fluorophenoxy)pyrimidin-4-ylcarbamate (8 mg, 81%). ^{1}H NMR (DMSO-d_6) δ 10.62 (s, 1H), 8.43 (d, 1H, J = 2.5 Hz), 8.36 (dd, 1H, J = 9.8, 2.5 Hz), 8.36 (dd, 1H, J = 9.8, 2.5 Hz), 8.20-8.17 (m, 1H), 7.71 (dd, 1H, J = 8.8, 8.8 Hz), 7.49 (s, 1H), 1.48 (s, 9H).

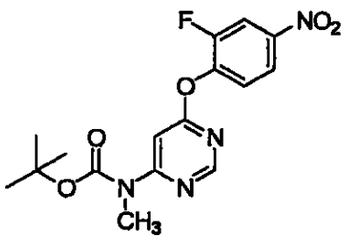
E) *tert*-Butyl 6-(2-fluoro-4-(3-(4-fluorophenylamino)-3-oxopropanamido)phenoxy)pyrimidin-4-ylcarbamate

[00102] The title compound was prepared from *tert*-butyl 6-(4-amino-2-fluorophenoxy)pyrimidin-4-ylcarbamate (8 mg, 0.025 mmol) and (4-fluorophenylamino)-3-oxopropanoic acid (6 mg, 0.031 mmol, Compound B of Example 1), TBTU (11 mg, 0.034 mmol), and DIPEA (6 μL, 0.030 mmol) using a similar procedure described for the preparation of Compound C, Example 1. Flash chromatography using 1-1.5 % MeOH in CH_2Cl_2 as the eluent gave the title compound as a white solid (10 mg, 80%). ^{1}H NMR (DMSO-d_6) δ 10.48 (s, 1H), 10.46 (s, 1H), 10.25 (s, 1H), 8.39 (s, 1H), 7.74-7.77 (m, 1H), 7.62 (d, 1H, J = 5.5 Hz), 7.61 (d, 1H, J = 4.9 Hz), 7.36-7.30 (m, 2H), 7.17-7.13 (m, 2H), 3.48 (s, 2H), 1.46 (s, 9H); MS(ESI$^+$) m/z 500.12 $(M+H)^+$.

Example 7



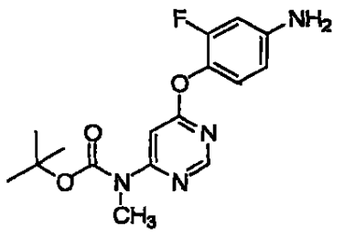
***tert*-Butyl 6-(2-fluoro-4-(3-(4-fluorophenylamino)-3-oxopropanamido)phenoxy)pyrimidin-4-yl(methyl)carbamate**



A) *tert*-Butyl 6-(2-fluoro-4-nitrophenoxy)pyrimidin-4-yl(methyl)carbamate

[00103] A solution of *tert*-butyl 6-(2-fluoro-4-nitrophenoxy)pyrimidin-4-ylcarbamate (Compound C of Example 6, 44 mg, 0.13 mmol) in anhydrous DMF (1 mL) was cooled in an ice bath and treated with 60 % NaH (44 mg, 0.16 mmol) and

stirred at the same temperature for 30 minutes. The reaction mixture was treated with iodomethane (10 μL, 0.15 mmol) and stirred at 0-5 °C for 10 min. The reaction mixture was allowed to warm to room temperature and stirred for 30 min. The mixture was diluted with H_2O (10 mL) and extracted with EtOAc (2 x 10 mL). The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give the product (35 mg, 74%) as a pale yellow solid. ^{1}H NMR (DMSO-d_6) δ 8.57 (d, 1H, J = 1.1 Hz), 8.37 (dd, 1H, J = 9.8, 3.0 Hz), 8.19 (ddd, 1H, J = 9.1, 2.5, 1.0 Hz), 7.71 (dd, 1H, J = 8.8, 8.8 Hz), 7.66 (s, 1H), 3.38 (s, 3H), 1.51 (s, 9H).



B) *tert*-Butyl 6-(4-amino-2-fluorophenoxy)pyrimidin-4-yl(methyl)carbamate

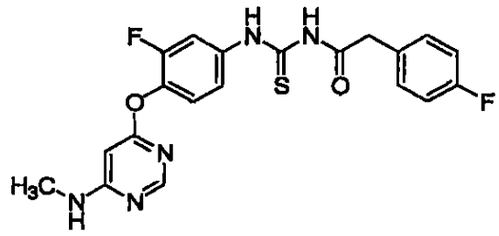
[00104] A mixture of *tert*-butyl 6-(2-fluoro-4-nitrophenoxy)pyrimidin-4-yl(methyl)carbamate in 1:1 EtOH / MeOH (2 mL) was treated with PtO_2 (10 mg) and the reaction mixture was stirred under a blanket of H_2 (from a latex balloon) for 2 h. The reaction mixture was filtered and concentrated to give the desired product (30 mg, 75%)as a light brown solid. MS(ESI$^+$) m/z 365.13 $(M+H)^+$.

C) *tert*-Butyl 6-(2-fluoro-4-(3-(4-fluorophenylamino)-3-oxopropanamido)phenoxy)pyrimidin-4-yl(methyl)carbamate

[00105] The title compound was prepared from *tert*-butyl 6-(4-amino-2-fluorophenoxy)pyrimidin-4-yl(methyl)carbamate (30 mg, 0.068 mmol), 4-fluorophenylacetyl chloride (Lancaster, 15 mg, 0.088 mmol) and NaSCN (9 mg, 0.11 mmol) in EtOAc/ CH_2Cl_2 using a similar procedure described for the preparation of Compound C of Example 2. Flash chromatography on SiO_2 using 1- 40 % EtOAc in hexanes as the eluent gave the title compound (30 mg, 83%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 12.40 (s, 1H), 11.79 (s, 1H), 8.55 (s, 1H), 7.86 (dd, 1H, J = 12.1,

2.5 Hz), 7.54 (d, 1H, J = 1.1 Hz), 7.45-7.35 (m, 4H), 7.20-7.14 (ddd, 2H, J = 8.8, 8.8, 2.1 Hz), 3.81 (s, 2H), 3.36 (s, 3H), 1.49 (s, 9H); MS(ESI$^+$) m/z 530.09 $(M + H)^+$.

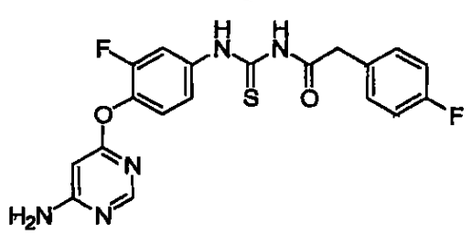
Example 8



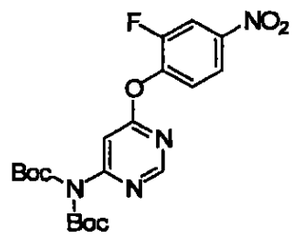
1-(3-Fluoro-4-(6-(methylamino)pyrimidin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea

[00106] *tert*-Butyl 6-(2-fluoro-4-(3-(4-fluorophenylamino)-3-oxopropanamido)phenoxy)pyrimidin-4-yl(methyl)carbamate (Example 7, 25 mg, 0.047 mmol) was treated with 4 M HCl in 1,4-dioxane (3 mL), stirred at RT for 4 h and concentrated *in vacuo*. The residue was partitioned between saturated aq. $NaHCO_3$ solution and EtOAc. The EtOAc phase was separated, dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography on SiO_2 using 1 % MeOH in CH_2Cl_2 as the eluent gave the title compound (10 mg, 50%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 12.37 (s, 1H), 11.77 (s, 1H), 8.09 (s, 1H), 7.82 (d, 1H, J = 11.6 Hz), 7.41-7.35 (m, 5H), 7.32-7.28 (m, 1H), 7.19-7.14 (m, 2H), 3.81 (s, 2H), 2.78 (s, 3H); MS(ESI$^+$) m/z 430.07 $(M + H)^+$.

Example 9

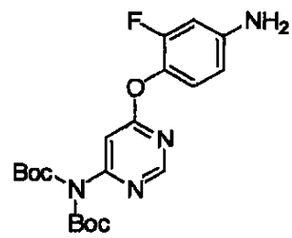


1-(4-(6-Aminopyrimidin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea



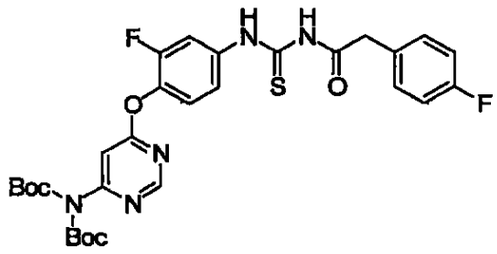
A) 6-(*N,N*-di-*tert*-Butyloxycarbonyl)amino-4-(2-fluoro-4-nitrophenoxy)pyrimidine

[00107] A mixture of 6-(2-fluoro-4-nitrophenoxy)pyrimidin-4-amine (Compound B of Example 6, 150 mg, 0.60 mmol), BOC_2O (275 mg, 1.26 mmol), DMAP (5 mg), and THF (20 mL) was stirred at RT for 2.5 h. The reaction mixture was concentrated *in vacuo* to give the crude product. Flash chromatography on SiO_2 using 5 – 15 % EtOAc in hexanes as the eluent gave the title compound (180 mg, 67%) as white solid. ^{1}H NMR (DMSO-d_6) δ 8.62 (d, 1H, J = 1.0 Hz), 8.42-8.39 (m, 1H), 8.21 (ddd, 1H, J = 9.1, 2.5, 1.0 Hz), 7.77 (dd, 1H, J = 8.8, 8.8 Hz), 7.49 (d, 1H, J = 1.1 Hz), 1.49 (s, 18H); MS(ESI$^+$) m/z 451.12 $(M + H)^+$.



B) 6-(*N,N*-di-*tert*-Butyloxycarbonyl)amino-4-(4-amino-2-fluorophenoxy)pyrimidine

[00108] A mixture of the 6-(*N,N*-di-*tert*-butyloxycarbonyl)amino-4-(2-fluoro-4-nitrophenoxy)pyrimidine (175 mg, 0.38 mmol) in toluene (5 mL) and MeOH (3 mL) was treated with PtO_2 (35 mg) and the reaction mixture was stirred under a blanket of H_2 (from a latex balloon) for 15 h. The catalyst was filtered off, the filtrate concentrated *in vacuo* and the residue was purified by flash chromatography on SiO_2 using 1–10 % MeOH in CH_2Cl_2 as the eluent to give the product (110 mg, 68%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 8.56 (s, 1H), 7.17 (s, 1H), 6.97 (dd, 1H, J = 8.8, 8.8 Hz), 6.46 (dd, 1H, J = 12.6, 2.5 Hz), 6.38 (dd, 1H, J = 8.8, 2.5 Hz), 5.40 (s, 2H), 1.89 (s, 18H).



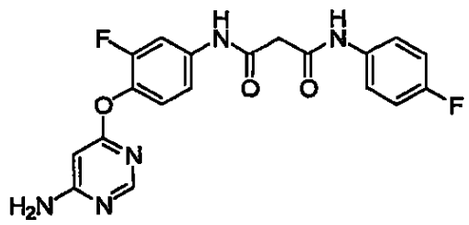
C) 1-(4-(*N,N*-di-*tert*-Butyloxycarbonyl 6-aminopyrimidin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea

[00109] The title compound was prepared from 6-(*N,N*-di-*tert*-butyloxycarbonyl)amino-4-(4-amino-2-fluorophenoxy)pyrimidine (20 mg, 0.048 mmol), 4-fluorophenylacetyl chloride (Lancaster, 10 mg, 0.062 mmol), and NaSCN (95 mg, 0.062 mmol) in EtOAc / CH_2Cl_2 using a similar procedure described for the preparation of Compound C of Example 2. Flash chromatography on SiO_2 using 10-20 % EtOAc in hexanes as the eluent gave the title compound (23 mg, 77%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 12.40 (s, 1H), 11.79 (s, 1H), 8.59 (s, 1H), 7.88 (dd, 1H, J = 12.5, 1.8 Hz), 7.46-7.41 (m, 2H), 7.38-7.35 (m, 3H), 7.17 (dd, 2H, J = 8.8, 8.8 Hz), 3.81 (s, 2H), 1.47 (s, 18H); MS(ESI$^+$) m/z 616.12 $(M+H)^+$.

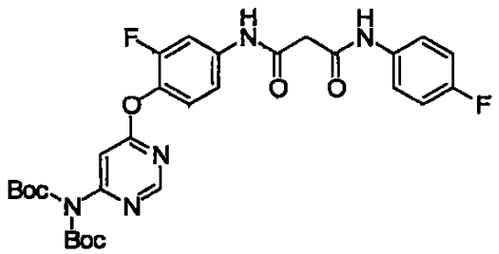
D) 1-(4-(6-Aminopyrimidin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea

[00110] A mixture of 1-(4-(*N,N*-di-*tert*-butylcarbonyl 6-aminopyrimidin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea (18 mg, 0.029 mmol) and 4 M HCl in dioxane (1.5 mL) was stirred at RT for 18 h and then concentrated to give the crude product. The crude product was partitioned between EtOAc and saturated aq. $NaHCO_3$ solution. The EtOAc phase separated, dried ($MgSO_4$), concentrated *in vacuo* and the residue was purified by flash chromatography on SiO_2 using 1- 2 % MeOH in CH_2Cl_2 to give the title compound (12 mg, 99%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 12.38 (s, 1H), 11.77 (s, 1H), 8.05 (s, 1H), 7.83 (dd, 1H, J = 12.3, 1.8 Hz), 7.41-7.35 (m, 3H), 7.31 (dd, 2H, J = 8.8, 8.8 Hz), 7.17 (t, 1H, J = 8.8 Hz), 7.02 (s, 2H), 5.89 (s, 1H), 3.81 (s, 2H); MS(ESI$^+$) m/z 416.06 $(M+H)^+$.

Example 10



N^1-1-(4-(6-Aminopyrimidin-4-yloxy)-3-fluorophenyl)-N^3-(4-fluorophenyl)malonamide



A) N^1-(4-(*N,N*-di-*tert*-Butylcarbonyl 6-aminopyrimidin-4-yloxy)-3-fluorophenyl)-N^3-(4-fluorophenyl)malonamide

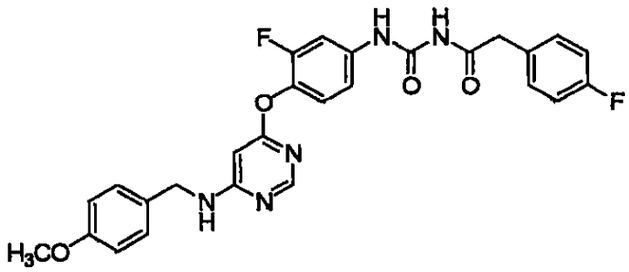
[00111] The title compound was prepared from a mixture of 6-(*N,N*-di-*tert*-butyloxycarbonyl)amino-4-(4-amino-2-fluorophenoxy)pyrimidine (Compound B of Example 9, 20 mg, 0.048 mmol), 3-(4-fluorophenylamino)-3-oxopropanoic (Compound B of Example 1, 14 mg, 0.072 mmol), DIPEA (12 μL, 0.069 mmol) in DMF using a similar procedure described for the preparation of Compound C of Example 1. Flash chromatography on SiO_2 using 15-50 % EtOAc in hexanes as the eluent gave the title compound (23 mg, 80%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 10.47 (s, 1H), 10.24 (s, 1H), 8.58 (d, 1H, J = 1 Hz), 7.77 (dd, 1H, J = 12.9, 1.8 Hz), 7.63-7.60 (m, 2H), 7.37-7.36 (m, 2H), 7.32 (s, 1H), 7.15 (t, 2H, J = 8.8 Hz), 1.47 (s, 18H); MS(ESI$^+$) m/z 600.17 $(M + H)^+$.

B) N^1-(4-(6-Aminopyrimidin-4-yloxy)-3-fluorophenyl)-N^3-(4-fluorophenyl)malonamide

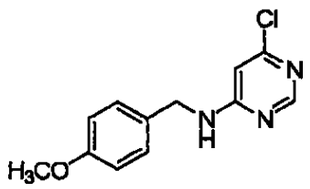
[00112] The title compound was prepared from *N*-1-(4-(*N,N*-di-*tert*-butylcarbonyl 6-aminopyrimidin-4-yloxy)-3-fluorophenyl)-*N*-3-(4-fluorophenyl)malonamide (20

mg, 0.032 mmol) using a similar procedure described for the preparation of Compound D of Example 9 to give the title compound (13 mg, 98%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 10.42 (s, 1H), 10.24 (s, 1H), 8.03 (s, 1H), 7.73 (d, 1H, J = 11.0 Hz), 7.61 (dd, 2H, J = 9.2, 4.9 Hz), 7.33-7.30 (m, 1H), 7.28-7.23 (m, 1H), 7.18-7.13 (m, 2H), 6.89 (s, 2H), 5.80 (s, 1H), 3.47 (s, 2H); MS(ESI$^+$) m/z 400.09 $(M + H)^+$.

Example 11

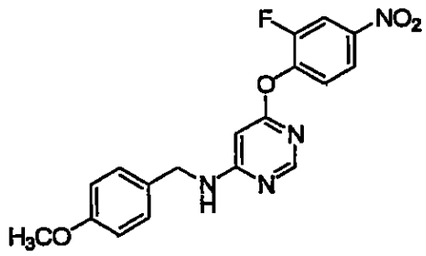


1-(4-(6-(4-Methoxybenzylamino)pyrimidin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea



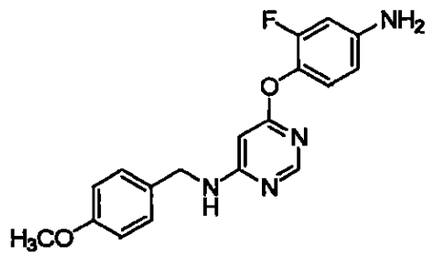
A) *N*-(4-Methoxybenzyl)-6-chloropyrimidin-4-amine

[00113] A mixture of 4,6-dichloropyrimidine (Aldrich, 3.6 g, 24.2 mmol), 4-methoxybenzylamine (2.7 g, 19.7 mmol), DIPEA (5 ml, 28.8 mmol), and *n*-BuOH was heated at reflux for 3 h. The mixture was concentrated and the residue treated with H_2O (150 mL) and EtOAc (175 mL). The EtOAc phase was separated, washed with saturated aq. $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated to give the title compound (4.5 g) which was used without further purification. ^{1}H NMR (DMSO-d_6) δ 8.29 (s, 1H), 8.13 (br s, 1H), 7.25 (d, 2H, J = 8.2 Hz), 6.90 (d, 2H, J = 8.2 Hz), 6.56 (s, 1H), 4.48 (s, 2H), 3.75 (s, 3H).



B) *N*-(4-Methoxybenzyl)-6-(2-fluoro-4-nitrophenoxy)pyrimidin-4-amine

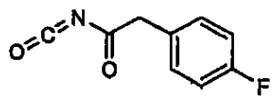
[00114] A mixture of *N*-(4-methoxybenzyl)-6-chloropyrimidin-4-amine (2.3 g, 9.2 mmol), 2-fluoro-4-nitrophenol (1.45 g, 9.2 mmol), DIPEA (15 mL), and 2-methoxyethyl ether (75 mL) was heated at 160 °C in a sealed pressure bottle for 50 h. The mixture was cooled, poured onto crushed ice (200 g), treated with EtOAc (200 mL). After vigorously stirring for 10 min, the insoluble material was filtered off. The EtOAc phase was washed with saturated aq. Na_2CO_3 solution (100 mL), brine (3 x 100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The gummy solid obtained was triturated with isopropyl ether to give the title compound (1.75 g, 76%) as a brown solid. ^{1}H NMR (DMSO-d_6) δ 8.32 (dd, 1H, J = 10.2, 2.0 Hz), 8.15 (d, 2H, J = 9.2 Hz), 8.05 (br s, 1H), 7.61 (dd, 1H, J = 8.4, 8.4 Hz), 7.26 (d, 2H, J = 8.5 Hz), 6.91 (d, 2H, J = 8.5 Hz), 6.14 (br s, 1H), 4.48 (br s, 2H), 3.74 (s, 3H).



C) *N*-(4-Methoxybenzyl)-6-(4-amino-2-fluorophenoxy)pyrimidin-4-amine

[00115] A solution of *N*-(4-methoxybenzyl)-6-(2-fluoro-4-nitrophenoxy)pyrimidin-4-amine (150 mg, 0.41 mmol) in 1:1 MeOH / THF (20 mL) was treated with ammonium chloride (0.22 g, 4.1 mmol), and zinc dust (<20 microns, 0.27 g, 4.2 mmol). The reaction mixture was stirred at RT for 1 h. An additional portion of zinc dust (150 mg) was added to the mixture and the reaction mixture was stirred at RT for 1 h and heated at 70 °C for 20 min. The mixture was filtered to remove the inorganic solids, concentrated *in vacuo*, and the residue partitioned between EtOAc and brine.

The EtOAc phase was separated, washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound (145 mg, 99%). ^{1}H NMR (DMSO-d_6) δ 8.10 (br s, 1H), 7.76 (br s, 1H), 7.21 (d, 2H, J = 8.6 Hz), 6.88 (d, 3H, J = 8.6 Hz), 6.44 (dd, 1H, J = 12.7, 2.0 Hz), 6.36 (dd, 1H, J = 8.3, 2.3 Hz), 5.79 (s, 1H), 4.41 (br s, 2H), 3.73 (s, 3H); MS(ESI$^+$) m/z 341.18 $(M + H)^+$.



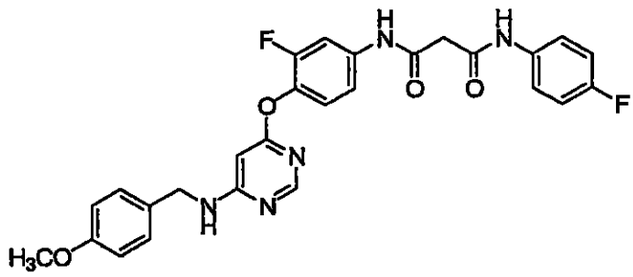
D) 2-(4-Fluorophenyl)acetyl isocyanate

[00116] Silver cyanate (0.912 g, 6.08 mmol, 1.05 eq) was added to a solution of 4-fluorophenylacetyl chloride (Lancaster, 0.794 ml, 5.79 mmol, 1.0 eq) in toluene (16 ml) at room temperature. The reaction mixture was shielded from light and heated to reflux. After 60 minutes, the mixture was cooled to room temperature and filtered (Acrodisc, PTFE 0.2μM) to give a 0.36 M solution of 2-(4-fluorophenyl)acetyl isocyanate in toluene, which was used without further purification.

E) 1-(4-(6-(4-Methoxybenzylamino)pyrimidin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea

[00117] A solution of *N*-(4-methoxybenzyl)-6-(4-amino-2-fluorophenoxy)pyrimidin-4-amine (88 mg, 0.26 mmol) in THF (2 mL) was treated with 0.36 M 2-(4-fluorophenyl)acetyl isocyanate in toluene (0.72 mL, 0.26 mmol) and the reaction mixture was stirred at RT for 1 h. The mixture was concentrated *in vacuo* and the solid obtained was triturated with isopropyl ether to give the title compound (125 mg, 93%) as an off-white solid. ^{1}H NMR (DMSO-d_6) δ 11.00 (s, 1H), 10.50 (s, 1H), 8.09 (s, 1H), 7.85 (br s, 0.5 H), 7.66 (d, 1H, J = 12.6 Hz), 7.36-7.15 (m, 9.5 H), 6.88 (d, 1H, J = 8.1 Hz), 5.91 (s, 1H), 4.42 (br s, 2H), 3.72 (s, 2H), 3.71 (s, 3H); MS(ESI$^+$) m/z 520.14 $(M + H)^+$.

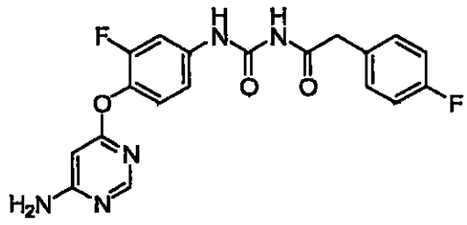
Example 12



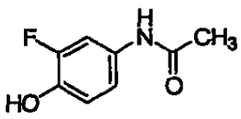
***N*^{1}-(4-(6-(4-Methoxybenzylamino)pyrimidin-4-yloxy)-3-fluorophenyl)-*N*^{3}-(4-fluorophenyl)malonamide**

[00118] The title compound was prepared from *N*-(4-methoxybenzyl)-6-(4-amino-2-fluorophenoxy)pyrimidin-4-amine (Compound C of Example 11, 200 mg, 0.59 mmol), 3-(4-fluorophenylamino)-3-oxopropanoic acid (Compound B of Example 1, 128 mg, 0.65 mmol), TBTU (228 mg, 0.71 mmol), and DIPEA (123 μL, 0.71 mmol) in DMF using a similar procedure described for the preparation of Compound C of Example 1. The crude product was purified by trituration with isopropyl ether to give the title compound (250 mg, 82%) as an off-white solid. ^{1}H NMR (DMSO-d_6) δ 10.43 (s, 1H), 10.25 (s, 1H), 8.09 (s, 1H), 7.85 (s, 1H), 7.72 (dd, 1H, J = 9.1, 5.0 Hz), 7 62 (dd, 2H, J = 8.8, 5.0 Hz), 7.31-7.21 (m, 4H), 7.15 (dd, 2H, J = 8.8, 8.8 Hz), 6.88 (m, 2H), 5.90 (s, 1H), 4.42 (br s, 2H), 3.71 (s, 3H), 3.46 (s, 2H); MS(ESI$^+$) m/z 520.14 $(M + H)^+$.

Example 13

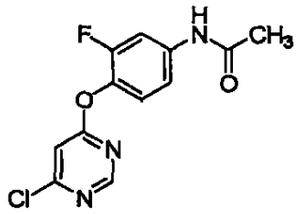


1-(4-(6-Aminopyrimidin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea



A) *N*-(3-Fluoro-4-hydroxyphenyl)acetamide

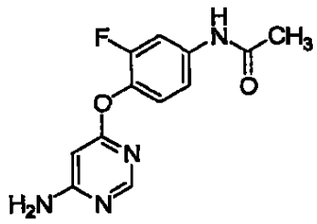
[00119] The title compound was prepared from the commercially available 2-fluoro-4-nitrophenol according the procedure of Burckhalter, J. H. et al. (*J Am. Chem Soc.* **1948**, *70*, 1363). Nitrophenol (5.73 g, 36.5 mmol) and acetic anhydride (3.72 g, 36.5 mmol) were dissolved in acetic acid (20 mL) and PtO_2 (150 mg) was then added. The reaction mixture was shaken under H_2 atmosphere (50 psi) at RT for 24 h. The precipitate which formed was collected by vacuum filtration and the filter paper was washed with acetic acid (25 mL). The combined filtrate and washing was concentrated *in vacuo* to give the title compound (2.0 g). The solid that remained on the filter paper was treated with MeOH to dissolve the product and the Pt_2O filtered off. The filtrate was concentrated *in vacuo* and the solid obtained was triturated with 1:1 EtOAc/hexanes (200 mL) to give a second crop of the title compound (1.8 g, 62% overall). ^{1}H NMR (DMSO-d_6) δ 9.83 (s, 1H), 9.51 (s, 1H), 7.50 (dd, 1H, J = 13.6, 2.5 Hz), 7.03 (d, 1H, J = 8.5 Hz), 6.84 (dd, 1H, J = 9.3, 9.3 Hz), 1.98 (s, 3H), MS(ESI$^+$) m/z 170.23 $(M + H)^+$.



B) *N*-(4-(6-Chloropyrimidin-4-yloxy)-3-fluorophenyl)acetamide

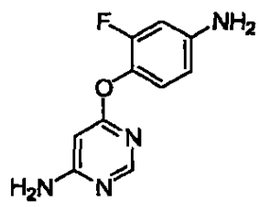
[00120] A mixture of 4,6-dichloropyrimidine (1.50 g, 10.0 mmol), *N*-(3-fluoro-4-hydroxyphenyl)acetamide (1.70 g, 10.0 mmol), K_2CO_3 (1.8 g, 13.0 mmol), and DMF (15 mL) was heated at 70 °C for 1.5 h. The mixture was concentrated to half its original volume and cooled in an ice bath. The mixture was treated with H_2O (100 mL) to precipitate the product which was collected by vacuum filtration. The product was washed with H_2O and vacuum dried on the funnel overnight to give the title compound (2.0 g, 71%) as a gray solid. ^{1}H NMR (DMSO-d_6) δ 10. 26 (s, 1H), 8.67

(s, 1H), 7.78 (dd, 1H, J = 12.6, 2.0 Hz), 7.56 (s, 1H), 7.37-7.30 (m, 2H), 2.08 (s, 3H); MS(ESI$^+$) m/z 282.10 $(M+H)^+$.



C) *N*-(4-(6-Aminopyrimidin-4-yloxy)-3-fluorophenyl)acetamide

[00121] A mixture of *N*-(4-(6-aminopyrimidin-4-yloxy)-3-fluorophenyl)acetamide (1.0 g, 3.5 mmol) and ca. 7 M NH_3 in MeOH (5 mL) was heated at 100 °C in a sealed pressure bottle for 2 h. The mixture was concentrated *in vacuo* and the residue partitioned between EtOAc and saturated aq. $NaHCO_3$ solution. The EtOAc phase was separated, washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography on SiO_2 using first 50% EtOAc in hexanes then 5% MeOH in CH_2Cl_2 as eluents gave the title compound (175 mg, 20%) as a brown solid. ^{1}H NMR (DMSO-d_6) δ 10.17 (s, 1H), 8.02 (s, 1H), 7.70 (dd, 1H, J = 13.2, 2.2 Hz), 7.26 (dd, 1H, J = 8.8, 2.2 Hz), 7.22 (dd, 1H, J = 8.8, 8.8 Hz), 6.89 (br s, 2H), 2.05 (s, 3H); MS(ESI$^+$) m/z 263.15 $(M+H)^+$.



D) 6-(4-Amino-2-fluorophenoxy)pyrimidin-4-amine

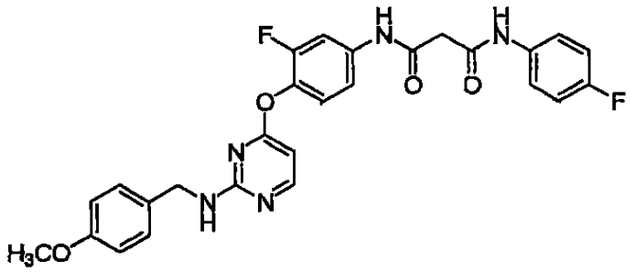
[00122] A mixture of *N*-(4-(6-aminopyrimidin-4-yloxy)-3-fluorophenyl)acetamide (175 mg, 0.67 mmol), 1 M HCl (6 mL), and MeOH (2 mL) was heated at reflux for 3 h. The reaction mixture was cooled, made basic (pH 8) with aqueous Na_2CO_3 solution and extracted with EtOAc (2 x 25 mL). The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound (140 mg, 96%) as a brown solid. ^{1}H NMR (DMSO-d_6) δ 8.02 (s, 1H), 6.89 (dd, 1H, J = 9.0, 9.0 Hz), 6.80

(br s, 2H), 6.43 (dd, 1H, J = 12.7, 2.8 Hz), 6.35 (dd ,1H, J = 8.8, 2.2 Hz), 5.67 (s, 1H), 5.34 (br s, 2H).

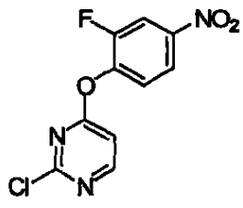
E) 1-(4-(6-Aminopyrimidin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea

[00123] The title compound was prepared from 6-(4-amino-2-fluorophenoxy)pyrimidin-4-amine (92 mg, 0.42 mmol) and 0.36 M 2-(4-fluorophenyl)acetyl isocyanate in toluene (Compound D of Example 11, 1.3 mL, 0.45 mmol) in THF as described above for Example 11. The crude product was purified by trituration using 1:1 EtOH / H_2O followed by absolute EtOH. The product was vacuum dried to give the title compound (100 mg, 60%). A second, slightly less pure crop of the product (45 mg, 27%) was obtained by extracting the combined filtrates and washing with EtOAc. ^{1}H NMR (DMSO-d_6) δ 10.99 (s, 1H), 10.50 (s, 1H), 8.01 (s, 1H), 7.65 (dd, 1H, J = 12.6, 2.1 Hz), 7.33 (dd, 2H, J = 8.1, 6.0 Hz), 7.28 (dd, 1H, J = 8.6, 2.0 Hz), 7.22 (dd, 1H, J = 8.8, 8.8 Hz), 7.17-7.12 (m, 2H), 6.89 (br s, 2H), 5.80 (s, 1H), 3.71 (s, 2H); MS(ESI$^+$) m/z 400.09 $(M + H)^+$.

Example 14

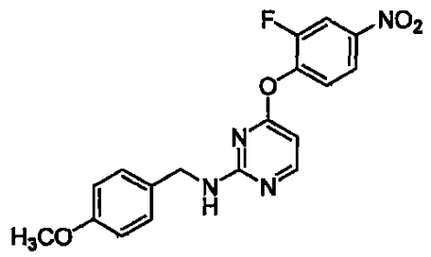


N^1-(4-(2-(4-Methoxybenzylamino)pyrimidin-4-yloxy)-3-fluorophenyl)-N^3-(4-fluorophenyl)malonamide



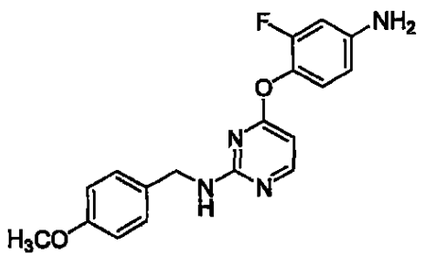
A) 2-Chloro-4-(2-fluoro-4-nitrophenoxy)pyrimidine

[00124] A mixture of 2,4-dichloropyrimidine (Aldrich, 0.74 g, 5.0 mmol), 2-fluoro-4-nitrophenol (Avacado, 0.79 g, 5.0 mmol), K_2CO_3 (0.76 g, 5.5 mmol), and DMF (50 mL) was heated at 100 °C for 2 h. The mixture was cooled and diluted with saturated $NaHCO_3$ solution (100mL) and extracted with EtOAc. The EtOAc extract was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give a mixture of the 2-phenoxy- and 4-phenoxypyrimidine regioisomers as a yellow solid. The regioisomers were separated by flash chromatography using 10-40 % EtOAc in hexanes as the eluent to give the title compound (0.71 g, 53%) as a white solid. ^1H NMR (DMSO-d_6) δ 8.76 (dd, 1H, J = 6.0, 1.6 Hz), 8.43 (dt, 1H, J = 9.8, 2.2 Hz), 8.23 (dd, 1H, J = 8.8, 1.6 Hz), 7.80 (dt, 1H, J = 9.8, 2.2 Hz), 7.48 (dd, 1H, J = 6.0, 2.2 Hz).



B) *N*-(4-Methoxybenzyl)-4-(2-fluoro-4-nitrophenoxy)pyrimidin-2-amine

[00125] A mixture of 2-chloro-4-(2-fluoro-4-nitrophenoxy)pyrimidine (0.66 g, 2.44 mmol), 4-methoxybenzylamine (0.34 g, 3.45 mmol), K_2CO_3 (0.37 g, 2.66 mmol), and DMF (15 mL) was heated at 100 °C for 1h. The mixture was cooled, diluted with H_2O (100 mL) and extracted with EtOAc (100 mL). The organic phase was washed twice each with saturated $NaHCO_3$ solution and brine. The organics were dried ($MgSO_4$) and concentrated to give the crude product. Flash chromatography on SiO_2 using 1- 3 % MeOH in CH_2Cl_2 as the eluent gave the title compound (275 mg, 29%) as a pale yellow solid. ^1H NMR (DMSO-d_6) δ 8.40-8.21 (m, 2H), 8.16 (dd, 1H, J = 8.8, 1.7 Hz), 7.98 (br s, 0.5H), 7.73-7.55 (m, 1.5 H), 7.16 (br s, 1H), 6.85-6.71 (m, 3H), 6.37 (s, 1H), 4.43 (br s, 1H), 3.95 (br s, 1H), 3.69 (s, 3H).



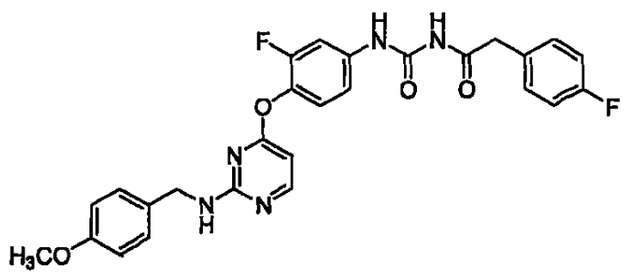
C) *N*-(4-Methoxybenzyl)-4-(4-amino-2-fluorophenoxy)pyrimidin-2-amine

[00126] The title compound was obtained by the reduction of *N*-(4-methoxybenzyl)-4-(2-fluoro-4-nitrophenoxy)pyrimidin-2-amine (270 mg, 0.73 mmol) with zinc dust (475 mg, 7.3 mmol) and NH_4Cl (387 mg, 7.3 mmol) in 1:1 THF / MeOH (20 mL) using a similar procedure described for Compound C of Example 11. Flash chromatography on SiO_2 using 1- 3 % MeOH in CH_2Cl_2 as the eluent gave the title compound (235 mg, 95%) as a brown film. ^{1}H NMR (DMSO-d_6) δ 8.01 (s, 1H), 7.65 (br s, 0.5 H), 7.49 (br s, 0.5H), 7.08 (br s, 1H), 6.83 (br s, 2H), 6.81 (m, 1H), 6.69 (br s, 2H), 6.39 (br s, 0.5H), 6.31 (br s, 0.5H), 6.01 (m, 1H), 5.26 (br s, 2H), 4.24 (br s, 1H), 3.95 (br s, 1H), 3.61 (s, 3H); MS(ESI$^+$) m/z 341.16 $(M+H)^+$.

D) N^1-(4-(2-(4-Methoxybenzylamino)pyrimidin-4-yloxy)-3-fluorophenyl)-N^3-(4-fluorophenyl)malonamide

[00127] The title compound was obtained from *N*-(4-methoxybenzyl)-4-(4-amino-2-fluorophenoxy)pyrimidin-2-amine (34 mg , 0.10 mmol), 3-(4-fluorophenylamino)-3-oxopropanoic acid (Compound B of Example 1, 22 mg, 0.11 mmol), TBTU (39 mg, 0.12 mmol) and DIPEA (23 mL, 0.17 mmol) using a similar procedure described for the preparation of Compound C of Example 1. The crude product was triturated with 3:1 isopropyl ether / EtOAc to give the title compound (35 mg, 61%) as an off-white solid. ^{1}H NMR (DMSO-d_6) δ 10.47 (br s, 1H), 10.26 (s, 1H), 8.15 (s, 1H), 7.77 (m, 3H), 7.61 (m, 2H), 7.35-7.25 (m, 2H), 7.15 (dd, 2H, J = 8.8, 8.8 Hz), 6.81-6.73 (m, 2H), 6.24 (s, 1H), 4.32 (br s, 1H), 3.96 (br s, 1H), 3.68 (s, 1H), 3.48 (s, 2H); MS(ESI$^+$) m/z 520.14 $(M+H)^+$.

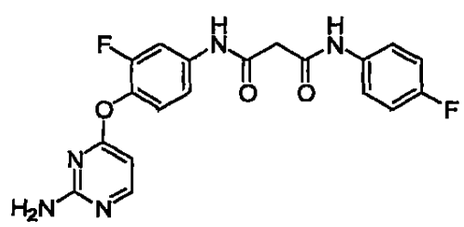
Example 15



1-(4-(2-(4-Methoxybenzylamino)pyrimidin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea

[00128] A solution of *N*-(4-methoxybenzyl)-4-(4-amino-2-fluorophenoxy)pyrimidin-2-amine (Compound C of Example 14, 34 mg, 0.10 mmol) in THF (1 ml) was treated with 0.36 M 2-(4-fluorophenyl)acetyl isocyanate in toluene (Compound D of Example 11, 0.31 mL, 0.11 mmol) and the mixture stirred at RT for 1 h. The mixture was concentrated *in vacuo* and the solid obtained was triturated first with 3:1 isopropyl ether / EtOAc and then CH_2Cl_2 to give the title compound (32 mg, 62%) as an off-white solid. ^{1}H NMR (DMSO-d_6) δ 10.47 (s, 1H), 10.26 (s,1H), 8.15 (s, 1H), 7.76 (d, 1H, J = 12.6 Hz), 7.61 (dd, 3H, J = 9.1, 5.0 Hz), 7.29 (s, 2H), 7.31-7.21 (m, 3H), 6.81 (s, 3H), 6.24 (s, 1H), 4.32 (s, 1H), 3.96 (s, 1H), 3.68 (s, 3H), 3.48 (s, 2H); MS(ESI$^+$) m/z 520.14 $(M + H)^+$.

Example 16

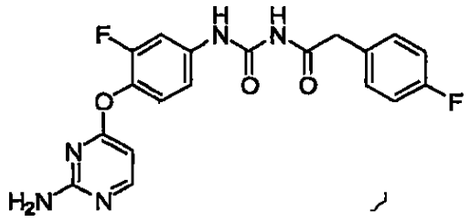


***N*^{1}-(4-(2-Aminopyrimidin-4-yloxy)-3-fluorophenyl)-*N*^{3}-(4-fluorophenyl)malonamide**

[00129] A mixture of *N*^{1}-(4-(2-(4-methoxybenzylamino)pyrimidin-4-yloxy)-3-fluorophenyl)-*N*^{3}-(4-fluorophenyl)malonamide (Example 14, 25 mg, 0.048 mmol), anisole (52 mg, 0.48 mmol) in TFA (1 mL) was heated at 85 °C for 6 h. The TFA was removed under vacuum and the residue partitioned between EtOAc and saturated aq.

$NaHCO_3$ solution. The EtOAc phase was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. Flash chromatography on SiO_2 using EtOAc then 1-2 % MeOH in CH_2Cl_2 as eluents gave the title compound (12 mg, 63%) as an off-white solid. ^1H NMR (DMSO-d_6) δ 11.00 (s, 1H), 10.51 (s, 1H), 8.02 (s, 1H), 7.66 (dd, 1H, J = 12.6, 2.0 Hz), 7.42-7.31 (m, 2H), 7.32-7.27 (m, 1H), 7.23 (t, 2H, J = 8.6 Hz), 7.16 (t, 2H, J = 9.1 Hz), 6.91 (s, 2H), 3.73 (s, 2H); MS(ESI$^+$) m/z 400.11 $(M + H)^+$.

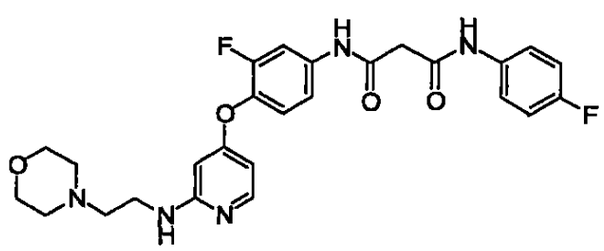
Example 17



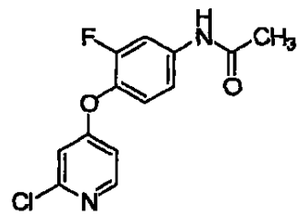
1-(4-(2-Aminopyrimidin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea

[00130] The title compound was prepared from 1-(4-(2-(4-methoxybenzylamino)pyrimidin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea (Example 15, 20 mg, 0.039 mmol) using a similar procedure described for Example 16. Flash chromatography on SiO_2 using EtOAc then 1-2 % MeOH in CH_2Cl_2 as eluents gave the title compound (10 mg, 62%) as an off-white solid. ^1H NMR (DMSO-d_6) δ 11.01 (s, 1H), 10.52 (s, 1H), 8.20 (d, 1H, J = 6 0 Hz), 7.70 (dd, 1H, J = 12.1, 2.0 Hz), 7.36-7.30 (m, 6H), 7.16 (dd, 2H, J = 8.8, 8.8 Hz), 6.45 (d, 1H, J = 6.1 Hz), 3.73 (s, 2H); MS(ESI$^+$) m/z 400.09 $(M + H)^+$.

Example 18

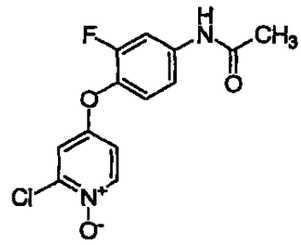


***N*^{1}-(3-Fluoro-4-(2-(2-morpholinoethylamino)pyridin-4-yloxy)phenyl)-*N*^{3}-(4-fluorophenyl)malonamide, hydrochloride salt**



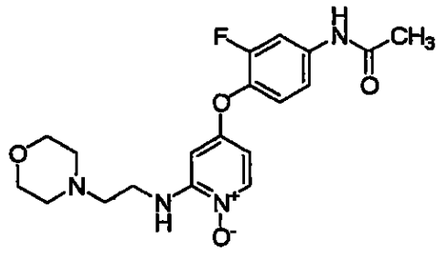
A) *N*-(4-(2-Chloropyridin-4-yloxy)-3-fluorophenyl)acetamide

[00131] A mixture of *N*-(3-fluoro-4-hydroxyphenyl)acetamide (Compound A of Example 13, 1.33 g, 7.87 mmol), 2-chloro-4-nitropyridine (Aldrich, 1.24 g, 7.87 mmol), K_2CO_3 (1.6 g, 11.8 mmol), and DMF (25 mL) was heated at 100 °C for 9 h. The reaction mixture was concentrated *in vacuo* and the residue partitioned between EtOAc and saturated $NaHCO_3$ solution. The EtOAc phase was washed with brine, dried ($MgSO_4$), and concentrated. Flash chromatography using 30 -80 % EtOAc in hexanes as the eluent gave the title compound (1.6 g, 73%) as a pale yellow solid. ^{1}H NMR (DMSO-d_6) δ 10.24 (s, 1H), 8.65 (s, 1H), 7.89-7.64 (m, 1H), 7.56 (s, 1H), 7.46-7.19 (m, 2H), 2.06 (s, 3H); MS(ESI$^+$) m/z 281.16 $(M + H)^+$.



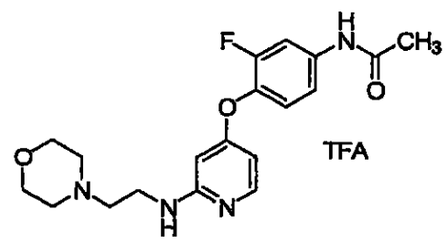
B) *N*-(4-(2-Chloropyridin-4-yloxy-1-oxide)-3-fluorophenyl)acetamide

[00132] A mixture of *N*-(4-(2-chloropyridin-4-yloxy)-3-fluorophenyl)acetamide (0.98 g, 3.5 mmol), *m*-chloroperoxybenzoic acid (> 90 %, 1 3 g, 7.6 mmol), and $CHCl_3$ (50 mL) was stirred at RT for 60 h. The mixture was concentrated and the residue triturated with Et_2O (2 x 100 mL) to give the title compound (0.89 g, 87%) as a pale yellow solid. ^{1}H NMR (DMSO-d_6) δ 10.25 (s, 1H), 8.34 (d, 1H, J = 7.1 Hz), 7 80 (d, 1H, J = 13.2 Hz), 7.49 (d, 1H, J = 3.3 Hz), 7.33 (d, 2H, J = 4.9 Hz), 7.02 (dd, 1H, J = 7.1, 3.3 Hz), 2.06 (s, 3H); MS(ESI$^-$) m/z 295.04 (M - H).



C) ***N*-(3-Fluoro-4-(2-(2-morpholinoethylamino)pyridin-4-yloxy-1-oxide)phenyl)acetamide**

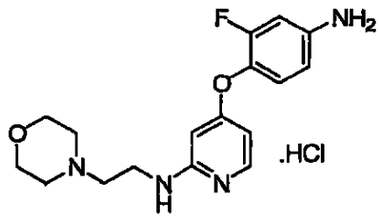
[00133] A mixture of *N*-(4-(2-chloropyridin-4-yloxy-1-oxide)-3-fluorophenyl)acetamide (205 mg, 0.62 mmol), 4-(2-aminoethyl)morpholine (Aldrich, 169 mg, 1.30 mmol), and absolute EtOH was heated at reflux 16 h. The reaction mixture was concentrated *in vacuo*, the residue treated with H_2O (3 mL) and applied to a 10g Varian C-18 cartridge. The cartridge was eluted first with H_2O then with 30 % MeOH in H_2O. The fractions which contained the desired product were pooled, concentrated to 5 mL volume, and extracted 3 times with EtOAc. The combined extracts were washed with brine, dried ($MgSO_4$) and concentrated to give the title compound (100 mg, 40%). ^{1}H NMR (DMSO-d_6) δ 10.22 (s, 1H), 7.84 (d, 1H, J = 6.1 Hz), 7.77 (dd, 1H, J = 13.2, 2.2 Hz), 7.31 (dd, 1H, J = 8.8, 2.2 Hz), 7.24 (t, 1H, J = 8.8 Hz), 6.41 (m, 1H), 6.13 (dd, 1H, J = 5.5, 2.2 Hz), 5.81 (d, 1H, J = 2.2 Hz), 3.60-3.52 (m, 4H), 3.31-3.28 (m, 2H), 2.38 (t, 2H, J = 7.1 Hz), 2.34 (m, 4H), 2.06 (s, 3H); MS(ESI$^+$) m/z 405.22 $(M + H)^+$.



D) ***N*-(3-Fluoro-4-(2-(2-morpholinoethylamino)pyridin-4-yloxy)phenyl)acetamide, trifluoroacetic acid salt**

[00134] A mixture of *N*-(3-fluoro-4-(2-(2-morpholinoethylamino)pyridin-4-yloxy-1-oxide)phenyl)acetamide (100 mg, 0.26 mmol), and triphenylphosphine polymer supported (1.4 -2.0 mmol/g) on polystyrene (500 mg) and DMF (2 mL) was stirred at

135 °C for 15 h. The mixture was filtered to remove the resin and the resin washed with DMF and EtOAc. The filtrate and washings were combined and concentrated. The crude product was purified by preparative HPLC (Shimadzu S5 VP-ODS 20 x 100 mm) to give the title compound (45 mg, 46%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 10.33 (s, 1H), 8.02 (d, 1H, J = 6.6 Hz) 7.84 (dd, 1H, J = 13.2, 2.0 Hz), 7.39-7.31 (m, 2H), 6.52 (s, 1H), 6.10 (s, 1H), 3.83 (br s, 4H), 3.64 (m, 2H), 3.28 (m, 6H), 2.08 (s, 3H); MS(ESI$^+$) m/z 375.12 $(M + H)^+$.



E) 4-(4-Amino-2-fluorophenoxy)-*N*-(2-morpholinoethyl)pyridin-2-amine, hydrochloride salt

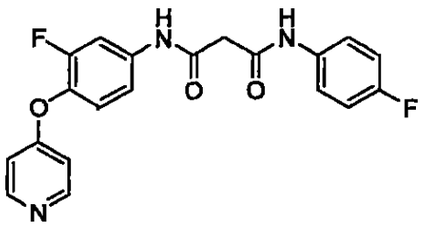
[00135] A mixture of *N*-(3-fluoro-4-(2-(2-morpholinoethylamino)pyridin-4-yloxy)phenyl)acetamide trifluoroacetate (40 mg), MeOH (1 mL), and 6 M HCl (0.2 mL) was heated at reflux for 3 h. The reaction mixture was concentrated on a rotary evaporator and the residue lyophilized to give the title compound (30 mg, 76%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.12 (br s, 1H), 8.85 (br s, 1H), 7.95 (d, 1H, J = 7.2 Hz), 7.08 (dd, 1H, J = 8.8, 8.8 Hz), 6.65-6.63 (m, 2H), 6.54 (d, 1H, J = 8.3 Hz), 6.31 (br s, 1H), 3.85 (m, 6H), 3 33 (m, 6H); MS(ESI$^-$) m/z 373.14 (M - H)

F) N^1-(3-Fluoro-4-(2-(2-morpholinoethylamino)pyridin-4-yloxy)phenyl)-N^3-(4-fluorophenyl)malonamide

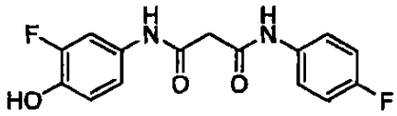
[00136] The title compound was prepared from a mixture of 4-(4-amino-2-fluorophenoxy)-*N*-(2-morpholinoethyl)pyridin-2-amine, hydrochloride salt (15 mg, 0.043 mmol), 3-(4-fluorophenylamino)-3-oxopropanoic acid (Compound B of Example 1, 10 mg, 0.052 mmol), TBTU (17 mg, 0.052 mmol), DIPEA (30 μL), and DMF (1 mL) using a similar procedure described for the preparation of Compound C of Example 1. The crude product was purified by preparative HPLC (Shimadzu S5

VP-ODS 20 x 100 mm). The product obtained from HPLC purification was treated with 1 M HCl and lyophilized to give the title compound (10 mg, 40%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 10.37 (s, 1H), 10.05 (s, 1H), 9.90 (br s, 1H), 7.90 (d, 1H, J = 6.1 Hz), 7.75 (d, 1H, J = 13.2 Hz), 7.58-7.55 (m, 2H), 7.53-7.50 (m, 1H), 7.40 (d, 1H, J = 8.8 Hz), 7.24 (t, 1H, J = 8.8 Hz), 7.08 – 7.03 (m, 3H), 6.39 (d, 1H, J = 6.1 Hz), 6.11 (s, 1H), 3.80 -3.81 (m, 4H), 3.67- 3.65 (m, 2H), 3.47 (br s, 2H), 3.20 (br s, 4H); MS(ESI$^+$) m/z 512.12 $(M+H)^+$.

Example 19



N^1-(3-Fluoro-4-(pyridin-4-yloxy)phenyl)-N^3-(4-fluorophenyl)malonamide



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

[00137] To a solution of 2-fluoro-4-nitrophenol (Avacado, 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 4-amino-2-fluorophenol as a brown solid which was used without further purification (656 mg, 81%).

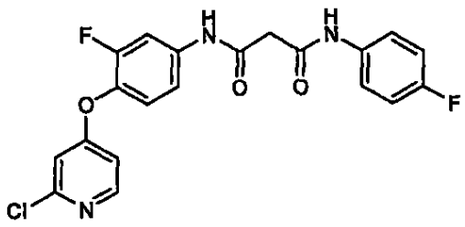
[00138] 3-(4-Fluorophenylamino)-3-oxopropanoic acid (Compound B of Example 1, 197 mg, 1.00 mmol) was dissolved in dimethylformamide (4 mL). Triethylamine (140 μL, 1.00 mmol) was added and the solution was cooled to 0 °C. 4-Amino-2-fluorophenol (Step A of Example 19, 127 mg, 1.00 mmol) was added followed by benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (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 7.61-7.57 (m, 2H), 7.51 (dd, 1H, J = 13, 2.5 Hz), 7.08-6.99 (m, 3H), 6.88 (t, 1H, J = 9.4 Hz), 3.51 (s, 2H); MS(ESI$^+$) m/z 307.44 $(M+H)^+$.

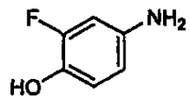
B) N^1-(3-Fluoro-4-(pyridin-4-yloxy)phenyl)-N^3-(4-fluorophenyl)malonamide.

[00139] N^1-(3-Fluoro-4-hydroxyphenyl)-N^3-(4-fluorophenyl)malonamide (31 mg, 0.10 mmol), copper(II) acetate (27 mg, 0.15 mmol), pyridin-4-ylboronic acid (25 mg, 0.20 mmol), and pyridine (16 μL, 0.20 mmol) were placed in a pressure tube in that order. The tube was charged with methylene chloride (0.5 mL) and sealed. The reaction was stirred at 120 °C for 5 h. The reaction mixture was filtered through silica gel using 5% methanol / ethyl acetate. After concentration, the crude product was purified by prep 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*. The product was treated with 4N HCl in dioxane and concentrated. Lyophilization with water gave the title compound (8 mg, 21%) as a yellow solid. ^{1}H NMR (CD_3OD) δ 8.31 (d, 2H, J = 6.1 Hz), 7.72 (dd, 1H, J = 12.7, 2.4 Hz), 7.49-7.46 (m, 2H), 7.27-7.25 (m, 1H), 7.15 (t, 1H, J = 8.8 Hz), 6.97 (t, 2H, J = 8.7 Hz), 6.85 (dd, 2H, J = 5.1, 1.2 Hz), 3.46 (s, 2H); MS(ESI$^+$) m/z 384.21 $(M+H)^+$.

Example 20

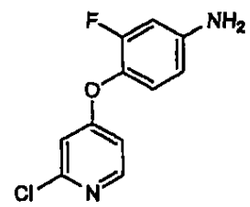


N^1-(4-(2-Chloropyridin-4-yloxy)-3-fluorophenyl)-N^3-(4-fluorophenyl)malonamide



A) 2-Fluoro-4-aminophenol

[00140] A mixture of platinum oxide (0.010 g) and 2-fluoro-4-nitrophenol (Aldrich, 1.24 g, 7.78 mmol, 1.0 eq) in MeOH (100 ml) were stirred under a H_2 atmosphere at 50 psi at room temperature. The reaction mixture was filtered through celite and the filtrate concentrated *in vacuo* to afford the title compound (1.00 g, 100%), as a solid which was used without further purification. ^{1}H NMR (DMSO-d_6) δ 8.57 (s, 1H), 6.46-6.47 (m, 1H), 6.33-6.46 (m, 1H), 6.19-6.21 (m, 1H), 4.79 (s, 2H); MS(ESI$^+$) m/z 128 $(M+H)^+$.



B) 4-(2-Chloropyridin-4-yloxy)-3-fluorobenzenamine

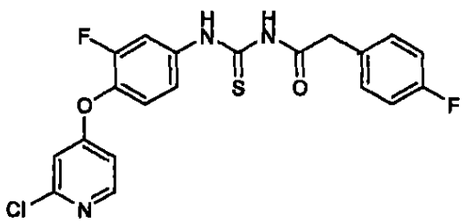
[00141] Sodium hydride (60%, 0.104 g, 2.60 mmol, 1.1 eq) was added to a solution of 2-fluoro-4-aminophenol (0.30 g, 2.36 mmol, 1.0 eq) in DMF (6.5 mL) at room temperature and the reaction mixture was stirred for 30 minutes. 2-Chloro-4-nitropyridine (Aldrich, 0.374 g, 2.36 mmol, 1.0 eq) was added and the reaction mixture was heated to 90 °C for 12 h. The reaction mixture was cooled to room temperature, quenched with saturated aqueous NaCl solution and extracted with ethyl

acetate (3 x 70 mL). The combined organic extracts were washed with 10% aq. LiCl solution (3 x 70 mL), dried over Na_2SO_4, filtered and the filtrate concentrated *in vacuo* to afford the title compound (0.430 g, 76%) which was used without further purification. ^{1}H NMR (DMSO-d_6) δ 8.27 (d, 1H, J = 5.7 Hz), 6.90-7.04 (m, 3H), 6.42-6.54 (m, 2H), 5.54 (s, 2H); MS(ESI$^+$) m/z 239 $(M+H)^+$; HRMS (ESI$^+$) calcd.: 239.0387, found: 239.0391.

C) **N^1-(4-(2-Chloropyridin-4-yloxy)-3-fluorophenyl)-N^3-(4-fluorophenylmalonamide**

[00142] Diisopropylethylamine (0.091 mL, 0.525 mmol, 2.5 eq) was added to a solution of 4-(2-chloropyridin-4-yloxy)-3-fluorobenzenamine (0.050 g, 0.21 mmol, 1.0 eq), 3-(4-fluorophenylamino)-3-oxopropanoic acid (Compound B of Example 1, 0.041 g, 0.21 mmol, 1.0 eq), and PyBroP (0.117 g, 0.252 mmol, 1.2 eq) in CH_2Cl_2 (1.0 mL) at 0 °C The reaction mixture was warmed to room temperature and stirred for 12 h. The reaction mixture was quenched with saturated aqueous NaCl solution, and the mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and the filtrate concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (Merck, 40-63 μM, 230-240 mesh, eluting 3/1 ethyl acetate / hexane) to afford the title compound (0.056 g, 64%) as a solid. ^{1}H NMR (DMSO-d_6) δ 10.61 (s, 1H), 10.34 (s, 1H), 8.36-8.38 (m, 1H), 7.91-7.93 (m, 1H), 7.67-7.71 (m, 2H), 7.46-7.48 (m, 2H), 7.04-7.26 (m, 4H), 3.56 (s, 2H); MS(ESI$^+$) m/z 418 $(M+H)^+$; HRMS (ESI$^+$) calcd.: 418.0770, found: 418.0767.

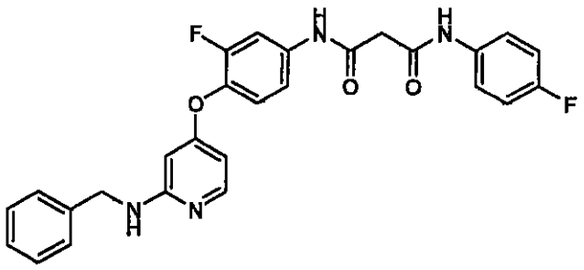
Example 21



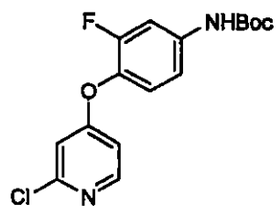
1-(4-(2-Chloropyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea

[00143] 4-Fluorophenylacetylchloride (Aldrich, 0.072 mL, 0.525 mmol, 2.5 eq) was added to a solution of sodium thiocyanate (0.056 g, 0.695 mmol, 3.3 eq) in ethyl acetate (2.0 mL) at room temperature and the reaction mixture was stirred for 1.5 h to afford a solution of 2-(4-fluorophenyl)ethanoyl isothiocyanate (0.263 M). A solution of 4-(2-chloropyridin-4-yloxy)-3-fluorobenzenamine (0.050 g, 0.21 mmol, 1.0 eq) in CH_2Cl_2 (1.0 mL) was added dropwise to the 2-(4-fluorophenyl)ethanoyl isothiocyanate solution and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was concentrated *in vacuo* and the resulting residue was purified by silica gel flash chromatography (Merck, 40-63 μM, 230-240 mesh, eluting 3/1 hexane/ ethyl acetate) to afford the title compound (0.058 g, 64%) as a solid. ^1H NMR (DMSO-d_6) δ 12.46 (s, 1H), 11.84 (s, 1H), 8.35-8.33 (m, 1H), 8.02-8.33 (m, 1H), 6.99-7.52 (m, 8H), 3.84 (s, 2H); MS(ESI$^+$) m/z 434 $(M+H)^+$; HRMS (ESI$^+$) calcd.· 434.0542, found: 434.0547.

Example 22



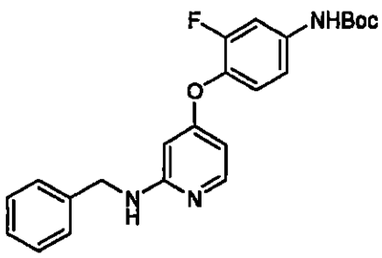
N^1-(4-(2-(Benzylamino)pyridin-4-yloxy)-3-fluorophenyl)-N^3-(4-fluorophenyl) malonamide



A) *tert*-Butyl 4-(2-chloropyridin-4-yloxy)-3-fluorophenylcarbamate

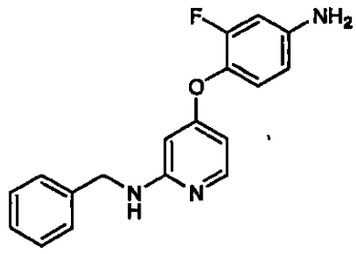
[00144] Di-tert-butyl dicarbonate (0.920 g, 4.22 mmol, 4.5 eq) was added to a solution of 4-(2-chloropyridin-4-yloxy)-3-fluorobenzenamine (Compound B of

Example 20, 0.224 g, 0.939 mmol, 1.0 eq) and triethylamine (0.391 mL, 3.00 mmol, 3.0 eq) in THF (10 mL) and the reaction mixture was heated at 55 °C for 14 h. The reaction mixture was cooled to room temperature and quenched with 1N HCl. The solution was extracted with CH_2Cl_2 (3 x 70 mL), the combined organic extracts washed with 1N NaOH (100 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (Merck, 40-63 μM, 230-240 mesh, eluting 4:1 hexane/ ethyl acetate) to afford the title compound (0.270 g, 85%). ^{1}H NMR (DMSO-d_6) δ 8.35-8.36 (m, 1H), 7.55-7.57 (m, 1H), 7.45-7.46 (m, 1H), 7.21-7.24 (m, 1H), 6.96-6.97 (m, 2H), 1.40 (s, 9H); MS(ESI$^+$) m/z 339 $(M+H)^+$; HRMS (ESI$^+$) calcd.: 339.0912, found: 339.0915.



B) *tert*-Butyl-4-(2-(benzylamino)pyridin-4-yloxy)-3-fluorophenylcarbamate

[00145] *tert*-Butyl 4-(2-chloropyridin-4-yloxy)-3-fluorophenylcarbamate (0.100 g, 0.295 mmol, 1.0 eq) was added to a degassed solution of dppf.$PdCl_2$ (Matrix Scientific, 0.011 g, 0.0148 mmol, 0.05 eq), dppf (0.012 g, 0.022 mmol, 0.075 eq), and NaO*t*-Bu (0 040 g, 0.414 mmol, 1.4 eq) in toluene at room temperature. Benzylamine (0.045 mL, 0.414 mmol, 1.4 eq) was added to the reaction mixture and the resulting solution was stirred at 80 °C for 4 h. The reaction mixture was cooled to room temperature, quenched with 1N HCl and the solution extracted with $CHCl_3$ (3 x 50 mL). The combined organic extracts were washed with 1 N NaOH (70 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (Merck, 40-63 μM, 230-240 mesh, eluting 2:1 hexane / ethyl acetate) to afford the title compound (0.020 g, 17%). ^{1}H NMR ($CDCl_3$) δ 7.80-7.90 (m, 1H), 7.35-7.45 (m, 1H), 7.19-7.24 (m, 3H), 6.91-6.93 (m, 2H), 6.59 (br m, 1H), 6.10-6.20 (m, 1H), 5.75 (br m, 1H), 5.30-5.40 (m, 1H), 4.34 (s, 2H), 1.46 (s, 9H); MS(ESI$^+$) m/z 410 $(M+H)^+$; HRMS (ESI$^+$) calcd.: 410.1880, found: 410.1884.



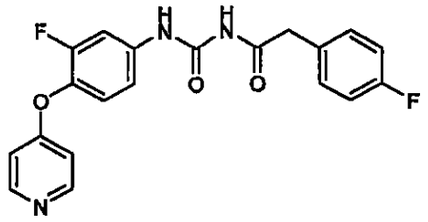
C) 4-(4-Amino-2-fluorophenoxy)-*N*-benzylpyridin-2-amine, hydrochloride salt

[00146] Anhydrous HCl in dioxane (4N, 2.00 mL, 8.00 mmol, 165 eq) was added to *tert*-butyl 4-(2-(benzylamino)pyridin-4-yloxy)-3-fluorophenylcarbamate (0.020 g, 0.0489 mmol, 1.0 eq) and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was concentrated *in vacuo* to afford the title compound (0.017 g, 100%) a solid that was used without further purification. MS(ESI$^+$) m/z 310 $(M+H)^+$; HRMS (ESI$^+$) calcd.: 310.1356, found: 310.1364.

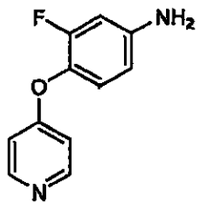
D) N^1-(4-(2-(Benzylamino)pyridin-4-yloxy)-3-fluorophenyl)-N^3-(4-fluorophenyl) malonamide

[00147] Diisopropylethylamine (0.014 mL, 0.081 mmol, 3.5 eq) was added to a solution of 4-(4-amino-2-fluorophenoxy)-*N*-benzylpyridin-2-amine, hydrochloride salt (0.008 g, 0.023 mmol, 1.0 eq), 3-(4-fluorophenylamino)-3-oxopropanoic acid (Compound B of Example 1, 0.005 g, 0.023 mmol, 1.0 eq), and PyBroP (0.013 g, 0.028 mmol, 1.2 eq) in CH_2Cl_2 (1.0 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 16 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by reverse phase HPLC chromatography (YMC-ODS-A, C-18, S10, 30x500 mm, eluting 20-90% aqueous MeOH with 0.1%TFA, 30 min. gradient). The appropriate fractions were concentrated *in vacuo*, neutralized with sat. aqueous $NaHCO_3$ solution and the mixture extracted with $CHCl_3$ (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the title compound (0.0025 g, 45%) as a solid. MS(ESI$^+$) m/z 489 $(M+H)^+$; HRMS(ESI$^+$) calcd.: 489.1738, found: 489.1743.

Example 23



1-(3-Fluoro-4-(pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea



A) 3-Fluoro-4-(pyridin-4-yloxy)benzenamine

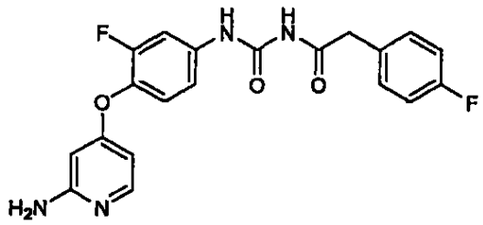
[00148] Potassium hydride (30%, 0.520 g, 3.90 mmol, 3.0 eq) was added to a solution of 2-fluoro-4-aminophenol (Compound A of Example 20, 0.254 g, 2.00 mmol, 1.5 eq) in DMF (5.0 mL) at room temperature and the reaction mixture was stirred for 15 minutes. 4-Chloro-pyridine (Aldrich , 0.200 g, 1.30 mmol, 1.0 eq) was added and the reaction mixture was heated to 150 °C for 2 h. The reaction mixture was cooled to room temperature, quenched with 1N NaOH and the solution extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were washed with 1N aqueous NaOH (2 x 30 mL) followed by 10% aqueous LiCl (3 x 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the title compound as a solid. ^{1}H NMR (DMSO-d_6) δ 8.44-8.46 (m, 2H), 6.89-7.03 (m, 1H), 6.87-6.88 (m, 2H), 6.44-6.56 (m, 2H), 5.51 (s, 2H); MS(ESI$^+$) m/z 205 $(M+H)^+$; HRMS(ESI$^+$) calcd.: 205.0777, found: 205.0775.

B) 1-(3-Fluoro-4-(pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea

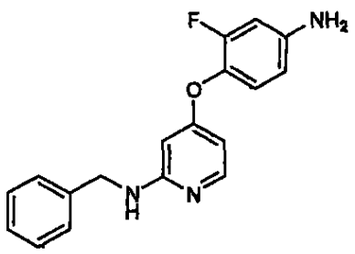
[00149] Silver cyanate (0.912 g, 6.08 mmol, 1.05 eq) was added to a solution of 4-fluorophenylacetyl chloride (Aldrich, 0.794 mL, 5.79 mmol, 1.0 eq) in toluene (16 mL) at room temperature shielded from light. The reaction mixture was heated to reflux for 60 minutes and then cooled to room temperature. The reaction mixture was

filtered (Acrodisc, PTFE 0.2μM) and the resultant 2-(4-fluorophenyl)acetyl isocyanate solution (0.36 M, 0.75 mL, 0.27 mmol, 1.1 eq) was added to a solution of 3-fluoro-4-(pyridin-4-yloxy)benzenamine (0.050 g, 0.245 mmol, 1.0 eq) in CH_2Cl_2 (2.0 mL) at room temperature. The reaction mixture was stirred at room temperature for 1 h, quenched with saturated aqueous NaCl solution and the mixture was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (Merck, 40-63 μM, 230-240 mesh, eluting 0-5% MeOH in $CHCl_3$) to afford the title compound (0.043 g, 46%) as a solid. ^{1}H NMR (DMSO-d_6) δ 11.06 (s, 1H), 10.60 (s, 1H), 8.47 (s, 2H), 7.77-7.80 (m, 1H), 6.92-7.48 (m, 8H), 3.75 (s, 2H); MS(ESI$^+$) m/z 384 $(M+H)^+$; HRMS(ESI$^+$) calcd.: 384.1160, found: 384.1147.

Example 24



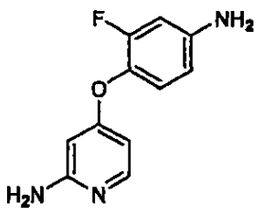
1-(4-(2-Aminopyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea



A) 4-(4-Amino-2-fluorophenoxy)-*N*-benzylpyridin-2-amine

[00150] Benzylamine (9.1 mL, 83.8 mmol, 20 eq) was added to 4-(2-chloropyridin-4-yloxy)-3-fluorobenzenamine (Compound B of Example 20, 1.0 g, 4.19 mmol, 1.0 eq), copper powder (0.266 g, 4.19 mmol, 1.0 eq) and K_2CO_3 (0.578 g, 4.19 mmol, 1.0 eq) in a sealed tube and the reaction mixture was heated to 160 °C for 12 h. The reaction mixture was cooled to room temperature and quenched with saturated

aqueous NaCl solution. The solution was extracted with ethyl acetate (3 x 100 mL), the combined organic extracts dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by preparative reverse phase HPLC (YMC C-18 ODS-A S10 50 x 500 mm, eluting 10-90% aqueous MeOH with 0.1% TFA, 30 minute gradient) and the appropriate fractions were concentrated *in vacuo*. The concentrate was neutralized with saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the title compound (0.675 g, 52%) as a solid. ^1H NMR (CD_3OD) δ 7.78-7.80 (m, 1H), 7.28-7.30 (m, 5H), 6.80-6.90 (m, 1H), 6.52-6.55 (m, 2H), 6.18-6.20 (m, 1H), 5.87-5.88 (m, 1H), 4.40 (s, 2H); MS(ESI^+) m/z 310 $(M+H)^+$; HRMS(ESI^+) calcd.: 310.1356, found: 310.1360.



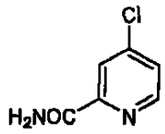
B) 4-(4-Amino-2-fluorophenoxy)pyridin-2-amine

[00151] Palladium hydroxide on carbon (10%, 0.050 g) was added to a solution of 4-(4-amino-2-fluorophenoxy)-*N*-benzylpyridin-2-amine (0.245 g, 0.790 mmol, 1.0 eq) in 5% HCO_2H-MeOH (10 mL) under a blanket of hydrogen (from a balloon) at room temperature. The reaction mixture was stirred at room temperature for 12 h, filtered through Celite® and the filtrate concentrated *in vacuo*. The residue was purified by reverse phase preparative HPLC (YMC ODS-A S10 30 x 500 mm., 10-90% aqueous MeOH with 0.1% TFA, 30 minute gradient) and the appropriate fractions were concentrated *in vacuo*. The concentrate was neutralized with saturated aqueous $NaHCO_3$ solution and the mixture was extracted with $CHCl_3$ (3 x 35 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the title compound (0.045 g, 26%) as a solid. ^1H NMR (CD_3OD) δ 7.62-7.63 (m, 1H), 6.77-6.82 (m, 1H), 6.38-6.47 (m, 2H), 6.09-6.11 (m, 1H), 5.83-5.84 (m, 1H); MS(ESI^+) m/z 220 $(M+H)^+$; HRMS(ESI^+) calcd.: 220.0886, found: 220.0877.

C) 1-(4-(2-Aminopyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea

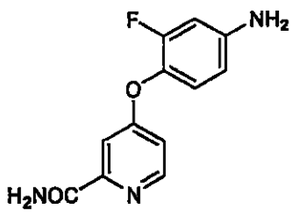
[00152] 2-(4-Fluorophenyl)acetyl isocyanate (Compound D of Example 11, 0.362 M, 0.351 mL, 0.127 mmol, 1.3 eq) was added to a solution of 4-(4-amino-2-fluorophenoxy)pyridin-2-amine (0.022 g, 0.100 mmol, 1.0 eq) in CH_2Cl_2 (2.0 mL) at room temperature. The reaction mixture was stirred for 13 h at room temperature and then concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (Merck gel 40-63μM, 230-240 mesh, 1:1 ethyl acetate/hexane) to afford the title compound (0.025 g, 64%) as a solid. ^{1}H NMR (CD_3OD) δ 7.62-7.67 (m, 2H), 7.23-7.29 (m, 2H), 7.07-7.12 (m, 2H), 6.95-6.99 (m, 2H), 6.12-6.14 (m, 1H), 5.86-5.87 (m, 1H), 3.61 (s, 2H); MS(ESI$^+$) m/z 399 $(M+H)^+$; HRMS(ESI$^+$) calcd.: 399.1269, found: 399.1269.

[00153] Alternatively, **Example 24** was prepared in the following manner:



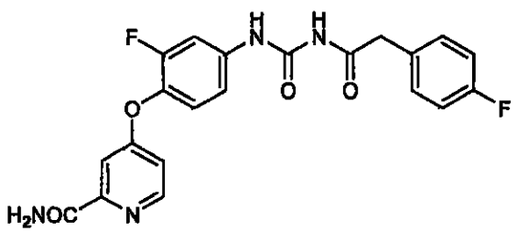
A') 4-Chloropicolinamide

[00154] A heterogeneous mixture of 4-chloropicolinic acid (TCI America, 5.4 g, 34.2 mmol, 1.0 eq) and thionyl chloride (30 mL) were heated at 80 °C for 2h. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The residue was treated with an ammonia in MeOH solution (7N, 45 mL) in an ice bath and the reaction mixture was stirred for 15 minutes. The ice bath was then removed and the reaction was warmed to room temperature and then stirred for 3 h. The reaction mixture was concentrated *in vacuo* and the residue purified by recrystallization from EtOAc to afford the product (5.14 g, 96%) as a solid. ^{1}H NMR (DMSO-d_6) δ 8.61-8.63 (m, 1H), 8.21 (m, 1H), 8.03-8.04 (m, 1H), 7.76-7.83 (m, 2H), MS(ESI$^+$) m/z 157 $(M+H)^+$.



B') **4-(4-Amino-2-fluorophenoxy)picolinamide**

[00155] A solution of 4-amino-2-fluorophenol (Compound A of Example 20, 0.81 g, 6.4 mmol, 1.0 eq) in DMF (6.5 mL) was treated with potassium *tert*-butoxide (0.79 g, 7.1 mmol, 1.1 eq) at room temperature and the reaction mixture was stirred for 1h. 4-Chloropicolinamide (1.0 g, 6.4 mmol, 1.0 eq) was added and the reaction mixture was heated to 110 °C for 8 h. The reaction was cooled to room temperature and the reaction mixture quenched with water. The resulting heterogeneous solution was filtered and the solid material was washed with water. The solid was triturated with a small amount of MeOH followed by Et_2O. The solid was filtered and dried *in vacuo* to afford the product (1.3 g, 82%) as a solid. ^{1}H NMR (DMSO-d_6) δ 8.49-8.50 (m, 1H), 8.12 (br s, 1H), 7.71 (br s, 1H), 7.35-7.36 (m, 1H), 7.14-7.16 (m, 1H), 7.01-7.06 (m, 1H), 6.44-6.47 (m, 2H), 5.53 (s, 2H); MS(ESI$^+$) m/z 248 $(M + H)^+$.



C') **1-(4-(2-Carbamoylpyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea**

[00156] A solution of 2-(4-fluorophenyl)acetyl isocyanate (Compound D of Example 11, 0.29 M in toluene, 54.9 mL, 15.9 mmol, 2.1 eq) was added to 4-(4-amino-2-fluorophenoxy)picolinamide (1.86 g, 7.53 mmol, 1.0 eq) in 10/3 DCM/DMF (65 mL) at room temperature and the reaction mixture was stirred for 17 h. The reaction mixture was concentrated *in vacuo* and the residue redissolved in $CHCl_3$. The organic layer was washed with saturated aqueous NaCl, the organic fraction separated, dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was

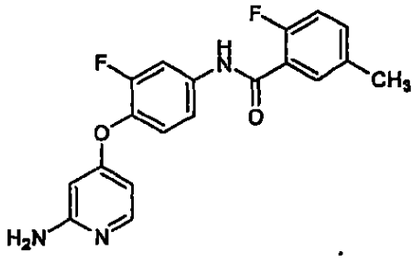
purified by silica gel chromatography (eluting 1/3 hexane/EtOAc, then to elute product 5% MeOH in $CHCl_3$), and the appropriate fractions concentrated *in vacuo* to afford the product (2.2 g, 69%) as a solid. ^{1}H NMR (DMSO-d_6) δ 11.07 (s, 1H), 10.62 (s, 1H), 8.54 (d, 1H, J = 5.60 Hz), 8.16-8.19 (m, 1H), 7.76-7.84 (m, 2H), 7.35-7.49 (m, 5H), 7.16-7.23 (m, 3H), 3.76 (s, 2H); MS(ESI$^+$) m/z 427 $(M + H)^+$. HRMS (ESI$^+$) calcd.: 427.1218, found: 427.1214.

D') 1-(4-(2-Aminopyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, hydrochloride salt

[00157] Bis-(trifluoroacetoxy)-iodobenzene (Aldrich, 3.09 g, 7.20 mmol, 1.4 eq) was added to a solution of 1-(4-(2-carbamoylpyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea (2.19 g, 5.14 mmol, 1.0 eq), water (0.241 mL, 13.4 mmol, 2.6 eq) and pyridine (1.62 mL, 20 mmol, 3.9 eq) in DMF (20 mL) at room temperature and the reaction mixture was stirred for 5 h. The reaction mixture was quenched with 1 N HCl and the aqueous solution extracted with Et_2O, discarding the organic layer. The aqueous layer was neutralized with 1 N NaOH and extracted with EtOAc. The combined organic layers were washed with 10% aq LiCl, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (eluting with 0-5% MeOH in $CHCl_3$) and the appropriate fractions were concentrated *in vacuo*. The residue was dissolved in THF (50 mL) cooled to 0 °C and treated with anhydrous HCl (4N, 10 mL, 40 mmol, 7.8 eq). The reaction mixture was allowed to warm to room temperature and stirred for 2h resulting in a heterogeneous solution. The solution was filtered and the solid washed with Et_2O and dried *in vacuo* to afford the title compound (1.38 g, 63%) as a solid. ^{1}H NMR (DMSO-d_6)

δ 11.09 (s, 1H), 10.65 (s, 1H), 7.97–8.00 (m, 1H), 7.83–7.90 (m, 3H), 7.35–7.48 (m, 4H), 7.15–7.21 (m, 2H), 6.70–6.72 (m, 1H), 6.16–6.17 (m, 1H), 3.77 (s, 2H); MS(ESI$^+$) m/z 399 $(M + H)^+$. HRMS (ESI$^+$) calcd.: 399.1269; found: 399.1258. Elem analysis for $C_{20}H_{16}N_4O_3F_2$ 1.0 HCl..0.22 H_2O Calcd.: C; 54.75, H; 4.01, N; 12.77, Cl; 8.08. Found: C; 54.75, H; 4.35, N; 4.35, Cl; 8.06.

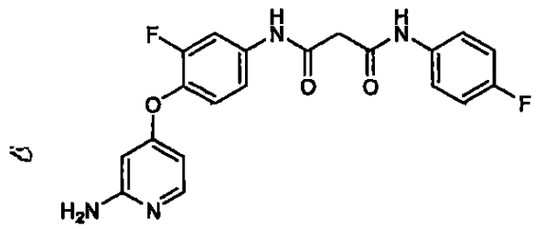
Example 25



***N*-(4-(2-Aminopyridin-4-yloxy)-3-fluorophenyl)-2-fluoro-5-methylbenzamide**

[00158] Diisopropylethylamine (0.035 mL, 0.200 mmol, 2.0 eq) was added to a solution of 4-(4-amino-2-fluorophenoxy)pyridin-2-amine (Compound B of Example 24, 0.022 g, 0.100 mmol, 1.0 eq), 2-fluoro-5-methyl benzoic acid (Aldrich, 0.015 g, 0.100 mmol, 1.0 eq), EDCI (0.021 g, 0.11 mmol, 1.1 eq) and HOBT (0.014 g, 0.100 mmol, 1.0 eq) in DMF (0.700 mL) at room temperature. The reaction mixture was stirred at room temperature for 8 h, quenched with saturated aqueous $NaHCO_3$ solution and extracted with $CHCl_3$ (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by reverse phase preparative HPLC (YMC ODS-A S10 30 x 500 mm, 30-90% aqueous MeOH with 0.1% TFA, 30 minute gradient) and the appropriate fractions were concentrated *in vacuo*. The concentrate was neutralized with saturated aqueous $NaHCO_3$ solution and the mixture extracted with $CHCl_3$ (3 x 30 mL). The combined organics were dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the title compound (0.014 g, 40%) as a solid. ^1H NMR (CD_3OD) δ 7.67-7.80 (m, 2H), 7.36-7.45 (m, 3H), 7.03-7.14 (m, 2H), 6.14-6.16 (m, 1H), 5.89-5.90 (m, 1H), 2.29 (s, 3H); MS(ESI^+) m/z 356 $(M+H)^+$; HRMS(ESI^+) calcd.: 356.1211, found: 356.1203.

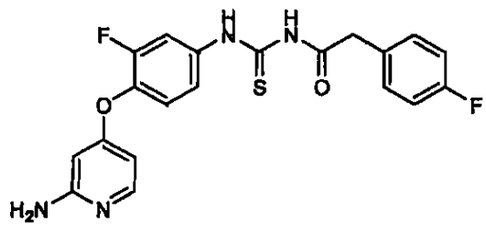
Example 26



***N*^{1}-(4-(2-Aminopyridin-4-yloxy)-3-fluorophenyl)-*N*^{3}-(4-fluorophenylmalonamide**

[00159] Diisopropylethylamine (0.105 mL, 0.604 mmol, 3.3 eq) was added to a solution of 4-(4-amino-2-fluorophenoxy)pyridin-2-amine (Compound B of Example 24, 0.040 g, 0.183 mmol, 1.0 eq), 3-(4-fluorophenylamino)-3-oxopropanoic acid (Compound B of Example 1, 0.054 g, 0.274 mmol, 1.5 eq), and PyBroP (0.139 g, 0.298 mmol, 1.6 eq) in CH_2Cl_2 (2.0 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 18 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and the solution extracted with $CHCl_3$ (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (Merck 40-63μM, 230-240 mesh, eluting 0-6% MeOH in $CHCl_3$ to afford the title compound (0.056 g, 77%) as a solid. ^{1}H NMR (CD_3OD) δ 7.67-7.68 (m, 2H), 7.48-7.52 (m, 2H), 7.13-7.25 (m, 1H), 7.10-7.12 (m, 1H), 6.94-6.99 (m, 2H), 6.16-6.17 (m, 1H), 5.88-5.89 (m, 1H), 3.30 (s, 2H); MS(ESI) m/z 399 ($M - H^+$); HRMS(ESI$^+$) calcd.: 399.1269, found: 399.1261.

Example 27

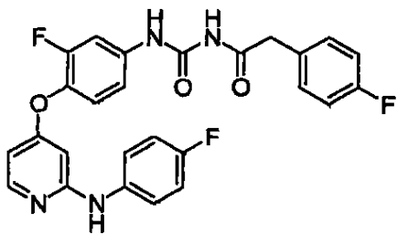


1-(4-(2-Aminopyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)thiourea

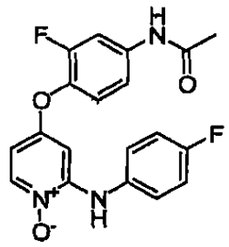
[00160] 4-Fluorophenylacetylchloride (Aldrich, 0.017 mL, 0.126 mmol, 2.5 eq) was added to a solution of sodium thiocyanate (0.014 g, 0.176 mmol, 3.5 eq) in ethyl

acetate (1.0 mL) at room temperature and the reaction mixture was stirred for 1.5 h to afford a 2-(4-fluorophenyl)ethanoyl isothiocyanate solution (0.126 M). 4-(4-Amino-2-fluorophenoxy)pyridin-2-amine (Compound B of Example 24, 0.011 g, 0.050 mmol, 1.0 eq) was dissolved in CH_2Cl_2 (1.0 mL) and 2-(4-fluorophenyl)ethanoyl isothiocyanate (0.126 M, 0.50 mL, 0.063 mmol, 1.3 eq) was added and the reaction mixture was stirred at room temperature for 20 h. The reaction mixture was concentrated *in vacuo* and the resulting residue was purified by silica gel flash chromatography (Merck, 40-63 μM, 230-240 mesh, eluting 0-6% MeOH in $CHCl_3$) to afford the title compound (0.008 g, 38%) as a solid. ^{1}H NMR (CD_3OD) δ 7.85-7.95 (m, 1H), 7.67-7.69 (m, 1H), 7.13-7.28 (m, 4H), 6.95-7.00 (m, 2H), 6.05-6.15 (m, 1H), 5.90-5.91 (m, 1H), 3.65 (s, 2H); MS(ESI$^+$) m/z 415 $(M+H)^+$; HRMS(ESI$^+$) calculated: 415.1040, found: 415.1041.

Example 28



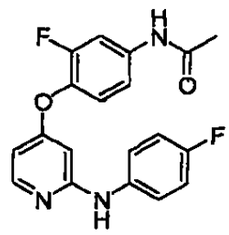
1-(3-Fluoro-4-(2-(4-fluorophenylamino)pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea



A) ***N*-(3-Fluoro-4-(2-(4-fluorophenylamino)pyridin-4-yloxy-1-oxide)phenyl)acetamide**

[00161] A mixture *N*-(4-(2-chloropyridin-4-yloxy-1-oxide)-3-fluorophenyl)acetamide (Compound B of Example 18, 62 mg, 0.21 mmol), 4-

fluoroaniline (47 mg, 0.42 mmol), and 2-methoxyethyl ether (91 mL) was heated at 140 °C for 15 min. The mixture was cooled to RT, diluted with EtOAc (20 mL), washed with saturated $NaHCO_3$ solution and brine (several times), dried ($MgSO_4$), and concentrated *in vacuo* to give a 4:1 mixture of the title compound and the parent pyridine as a light brown oil (45 mg, 58%). The product was used in the subsequent step without any further purification. MS(ESI$^+$) m/z 372.1 $(M + H)^+$.



B) *N*-(3-Fluoro-4-(2-(4-fluorophenylamino)pyridin-4-yloxy)phenyl)acetamide

[00162] A mixture of *N*-(3-fluoro-4-(2-(4-fluorophenylamino)pyridin-4-yloxy-1-oxide)phenyl)acetamide (45 mg), triphenylphosphine polymer supported (~3 mmol/g) on polystyrene (200 mg, Fluka) and DMF (3 mL) was heated at 135 °C for 48 h. The resin was filtered off, washed with DMF and EtOAc. The filtrate and washings were combined and concentrated *in vacuo*. The crude product was purified by flash chromatography using 30-80 % EtOAc in hexanes as the eluent to give the title compound (22 mg, 51%) as a pink solid. ^{1}H NMR (DMSO-d_6) δ 10.24 (s, 1H), 8.99 (s, 1H), 8.03 (d, 1H, J = 6.3 Hz), 7.80 (dd, 1H, J = 13.0, 2.1 Hz), 7.63-7.60 (m, 2H), 7.36-7.29 (m, 2H), 7.05 (dd, 1H, J = 9.1, 8.6 Hz), 6.44 (dd, 1H, J = 5.5, 2.2 Hz), 6.09 (d, 1H, J = 2 Hz), 2.07 (s, 3H); MS(ESI$^+$) m/z 356.7 $(M + H)^+$.



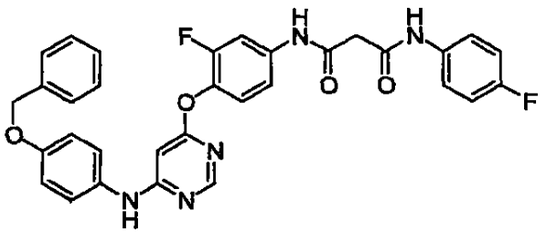
C) 4-(4-Amino-2-fluorophenoxy)-N-(4-fluorophenyl)pyridin-2-amine

[00163] A mixture of *N*-(3-fluoro-4-(2-(4-fluorophenylamino)pyridin-4-yloxy)phenyl)acetamide (18 mg, 0.051 mmol), 6 M HCl (0.1 mL, 0.60 mmol) and MeOH (1.5 mL) was heated at reflux for 2 h. The mixture was concentrated *in vacuo* and the residue made basic with saturated aq. $NaHCO_3$ solution then extracted with EtOAc. The extract was dried (MgSO4) and concentrated *in vacuo* to give the title compound (14 mg, 88%) as a red gum. ^{1}H NMR (DMSO-d_6) δ 8.97 (s, 1H), 7.98 (d, 1H, J = 5.8 Hz), 7.64 -7.60 (m, 2H), 7.05 (dd, 2H, J = 9.1, 8.8 Hz), 6.97 (dd, 1H, J = 9.4, 8.8 Hz), 6.51 (dd, 1H, J = 13.3, 2.6 Hz), 6.40 (ddd, 2H, J = 9.0, 6.2, 2.1 Hz), 6.08 (d, 1H, J = 2.0 Hz), 5.44 (br s, 2H); MS(ESI$^+$) m/z 314.17 $(M + H)^+$.

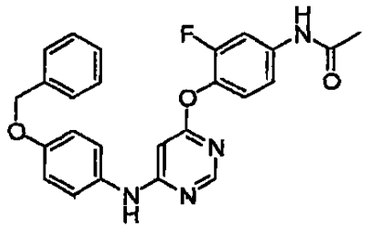
D) 1-(3-Fluoro-4-(2-(4-fluorophenylamino)pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea

[00164] A solution 4-(4-amino-2-fluorophenoxy)-*N*-(4-fluorophenyl)pyridin-2-amine (11 mg, 0.035 mmol) in THF (1 mL) was cooled in an ice bath and treated with a solution of 2-(4-fluorophenyl)acetyl isocyanate in toluene (Compound D of Example 11, 250 μL, 0.070 mmol) and stirred at RT for 2 h. The mixture was concentrated *in vacuo* and the residue triturated with isopropyl ether to give the title compound (11 mg, 65%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.04 (s, 1H), 10.56 (s, 1H), 9.01 (s, 1H), 8.03 (d, 1H, J = 5.6 Hz), 7.77 (dd, 1H, J = 13.3, 2.0 Hz), 7.63-7.60 (m, 2H), 7.41-7.31 (m, 5H), 7.19-7.14 (m, 2H), 7.05 (dd, 1H, J = 9.1, 8.5 Hz), 6.43 (dd, 1H, J = 6.2, 2.1 Hz), 6.10 (d, 1H, J = 2.1 Hz), 3.74 (s, 2H); MS(ESI$^+$) m/z 493.2 $(M + H)^+$.

Example 29

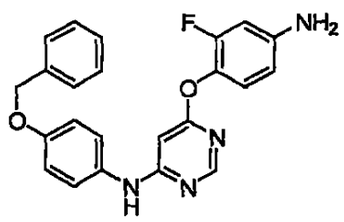


N^1-(4-(6-(4-(Benzyloxy)phenylamino)pyrimidin-4-yloxy)-3-fluorophenyl)-N^3-(4-fluorophenyl)malonamide



A) *N*-(4-(6-(4-(Benzyloxy)phenylamino)pyrimidin-4-yloxy)-3-fluorophenyl)acetamide

[00165] A mixture of *N*-(4-(6-chloropyrimidin-4-yloxy)-3-fluorophenyl)acetamide (Compound B of Example 13, 281 mg, 1.00 mmol) , 4-benzyloxyaniline (Aldrich, 398 mg, 2.00 mmol), and 2-methoxyethyl ether (2 mL) was heated at 160 °C for 45 min. The cooled mixture was treated with H_2O (50 mL) and extracted with EtOAc (100 mL). The EtOAc extract was washed with brine (3 x 25 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound (200 mg, 22%) as a purple solid. ^1H NMR (400 MHz, DMSO-d_6) δ 10.19 (s, 1H), 9.43 (s, 1H), 8.23 (s, 1H), 7.72 (dd, 1H, J = 12.5, 2.0 Hz), 7.44-7.42 (m, 4H), 7.38 (dd, 2H, J = 8.0, 6.9 Hz), 7.33-7.23 (m, 3H), 6.98 (d, 2H, J = 9.0 Hz), 6.07 (s, 1H), 5.07 (s, 2H), 2.05 (s, 3H); MS(ESI$^+$) m/z 445.13 $(M + H)^+$.



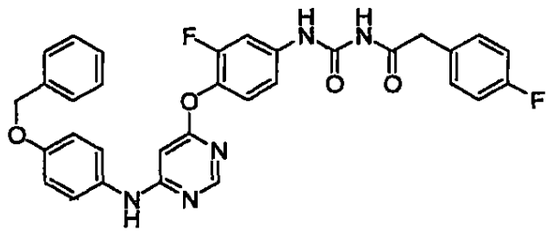
B) 6-(4-Amino-2-fluorophenoxy)-*N*-(4-(benzyloxy)phenyl)pyrimidin-4-amine

[00166] A mixture of *N*-(4-(6-(4-(benzyloxy)phenylamino)pyrimidin-4-yloxy)-3-fluorophenyl)acetamide (150 mg, 0.34 mmol), 6 M HCl (0.5 mL) and MeOH (3 mL) was heated at reflux for 2 h. The mixture was concentrated to remove the MeOH and the residue treated with saturated $NaHCO_3$ solution and extracted with EtOAc. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound (123 mg, 90%) as a pink solid. ^{1}H NMR (DMSO-d_6): δ 9.37 (s, 1H), 8.24 (s, 1H), 7.46-7.31 (m, 7H), 6.99-6 92 (m, 3H), 6.48 (dd, 1H, J = 12.5, 2.7 Hz), 6.39 (dd, 1H, J = 8.6, 2.7 Hz), 5.97 (s, 1H), 5.39 (br s, 2H), 5 08 (s, 2H); MS(ESI$^+$) m/z 403.09 $(M + H)^+$.

C) N^1-(4-(6-(4-(Benzyloxy)phenylamino)pyrimidin-4-yloxy)-3-fluorophenyl)-N^3-(4-fluorophenyl)malonamide

[00167] The title compound was prepared from a mixture 6-(4-amino-2-fluorophenoxy)-*N*-(4-(benzyloxy)phenyl)pyrimidin-4-amine (45 mg, 0.11 mmol), 3-(4-fluorophenylamino)-3-oxopropanoic acid (Compound B of Example 1, 24 mg, 0.12 mmol), TBTU (48 mg, 0.15 mmol), DIPEA (0.26 mL, 0.15 mmol), and DMF (1 mL) using a similar procedure described for the preparation of Compound C of Example 1. The crude product was triturated with isopropyl ether to give the title compound (56 mg, 88%) as a pink solid. ^{1}H NMR (DMSO-d_6) δ 10.47 (s, 1H), 10.27 (s, 1H), 9.45 (s, 1H), 8.25 (s, 1H), 7.77 (dd, 1H, J = 12.7, 2.0 Hz), 7.65-7.62 (m, 2H), 7.46 (d, 4H, J = 7.3 Hz), 7.40 (dd, 2H, J = 7.6, 7.3 Hz), 7.37-7.29 (m, 3H), 7.17 (dd, 2H, J = 9.0, 8.3 Hz), 7.00 (d, 2H, J = 9.0 Hz) 6.09 (s, 1H), 5.09 (s, 2H) 3.49 (s, 2H); MS(ESI$^+$) m/z 582.3 $(M + H)^+$.

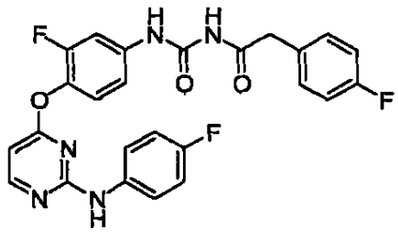
Example 30



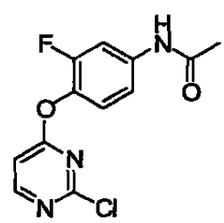
1-(4-(6-(4-(Benzyloxy)phenylamino)pyrimidin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea

[00168] The title compound was prepared from 6-(4-amino-2-fluorophenoxy)-*N*-(4-(benzyloxy)phenyl)pyrimidin-4-amine (Compound B of Example 29, 45 mg, 0.11 mmol) and a solution of 2-(4-fluorophenyl)acetyl isocyanate in toluene (Compound D of Example 11, 0.13 mmol) in THF using a similar procedure described for the preparation of Compound E of Example 11. The crude product was triturated with isopropyl ether to give the title compound (58 mg, 90%) as a pink solid. ^{1}H NMR (DMSO-d_6) δ 11.02 (s, 1H), 10.54 (s, 1H), 9.46 (s, 1H), 8.24 (s, 1H), 7.70 (dd, 1H, J = 12.7, 2.4 Hz), 7.46-7.26 (m, 9H), 7.18 (dd, 2H, J = 9.6, 8.3 Hz), 7.00 (d, 2H, J = 9.6 Hz), 6.11 (s, 1H), 5.09 (s, 2H), 3.75 (s, 2H); MS(ESI$^+$) m/z 582.3 $(M + H)^+$.

Example 31

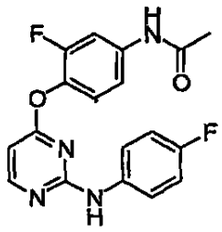


1-(3-Fluoro-4-(2-(4-fluorophenylamino)pyrimidin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea



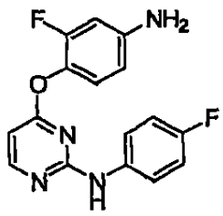
A) *N*-(4-(2-Chloropyrimidin-4-yloxy)-3-fluorophenyl)acetamide

[00169] A mixture of 2,4-dichloropyrimidine (Aldrich, 1.5 g, 10.0 mmol), *N*-(3-fluoro-4-hydroxyphenyl)acetamide (0.85 g, 5.0 mmol), K_2CO_3 (0.76 g, 5.5 mmol), and CH_3CN (100 mL) was heated at reflux for 2 h. The mixture was concentrated and the residue partitioned between EtOAc and saturated $NaHCO_3$ solution. The EtOAc phase was washed with sat $NaHCO_3$ solution, brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography using a gradient form 30 % EtOAc in hexanes to 100 % EtOAc to give the title compound (1.1 g, 78%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 10.22 (s, 1H), 8.63 (d, 1H, J = 5.6 Hz), 7.74 (dd, 1H, J = 12.6, 2.4 Hz), 7.34-7.26 (m, 3H), 2.01 (s, 3H).



B) *N*-(3-Fluoro-4-(2-(4-fluorophenylamino)pyrimidin-4-yloxy)phenyl)acetamide

[00170] A mixture of *N*-(4-(2-chloropyrimidin-4-yloxy)-3-fluorophenyl)acetamide (100 mg, 0.36 mmol), 4-fluoroaniline (Aldrich, 40 mg, 0.36 mmol), and 1,4-dioxane (3 mL) was heated at reflux for 2 h. The mixture was concentrated *in vacuo* and the residue triturated with ether to give a gray solid. The product was dissolved in MeOH, treated with silica gel (150 mg) and the mixture concentrated to dryness. The compound was concentrated down on silica gel and applied to a silica gel column and eluted first with EtOAc then with 100:1 MeOH / NH_4OH in CH_2Cl_2 to give the title compound (40 mg, 31%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 10.19 (s, 1H), 9.61 (s, 1H), 8.33 (d, 1H, J = 5.6 Hz), 7.71 (d, 1H, J = 12.7 Hz), 7.40 (s, 2H), 7.30-7.26 (m, 2H), 6.86 (dd, 2H, J = 8.3, 8.3 Hz), 6.50 (d, 1H, J = 5.4 Hz), 2.05 (s, 3H); MS(ESI$^+$) m/z 357.13 $(M + H)^+$.



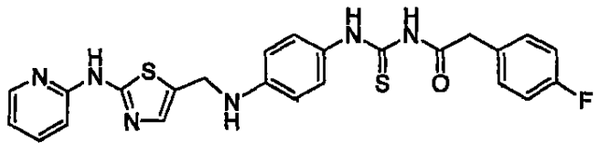
C) 4-(4-Amino-2-fluorophenoxy)-*N*-(4-fluorophenyl)pyrimidin-2-amine

[00171] A mixture of *N*-(3-fluoro-4-(2-(4-fluorophenylamino)pyrimidin-4-yloxy)phenyl)acetamide (32 mg, 0.09 mmol), 6 M HCl (0.2 mL) and MeOH (2 mL) was heated at reflux for 2 h. The mixture was cooled, diluted with EtOAc (20 mL), washed with saturated $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated *in vacuo*. Flash chromatography on SiO_2 using 30-40 % EtOAc in hexanes containing 1 % Et_3N gave the title compound (15 mg, 46%) as a white solid. ^1H NMR (DMSO-d_6) δ 9.55 (s, 1H), 8.25 (d, 1H, J = 5.5 Hz), 7.43 (br s, 2H), 6.92-6.85 (m, 3H), 6.45 (dd, 1H, J = 13.5, 2.1 Hz), 6.38-6.35 (m, 2H), 5.35 (br s, 2H). MS(ESI$^+$) m/z 315.17 $(M + H)^+$.

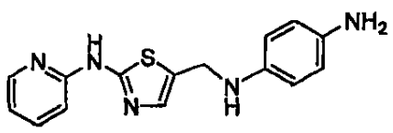
D) 1-(3-Fluoro-4-(2-(4-fluorophenylamino)pyrimidin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea

[00172] A solution of 4-(4-amino-2-fluorophenoxy)-*N*-(4-fluorophenyl)pyrimidin-2-amine (10 mg, 0.032 mmol) in THF (1 mL) was cooled in an ice bath and treated with a solution of 2-(4-fluorophenyl)acetyl isocyanate in toluene (Compound D of Example of 11, 228 μL, 0.064 mmol) and stirred at RT for 2 h. The reaction mixture was concentrated *in vacuo* and the residue triturated with isopropyl ether to give the title compound (15 mg, 93%) as a white solid. ^1H NMR (DMSO-d_6) δ 11.06 (s, 1H), 10.56 (s, 1H), 9.68 (s, 1H), 8.39 (d, 1H, J = 5.7 Hz), 7.76 (dd, 1H, J = 13 5, 2.1 Hz), 7.43 (br s, 2H), 7.46-7.35 (m, 6H), 7.18 (dd, 2H, J = 8.8, 8.8 Hz), 6.57 (d, 1H, J = 5.4 Hz), 3.76 (s, 2H); MS(ESI$^+$) m/z 492.0 $(M + H)^+$.

Example 32



1-(2-(4-Fluorophenyl)acetyl)-3-(4-((2-(pyridin-2-ylamino)thiazol-5-yl)methylamino)phenyl)thiourea



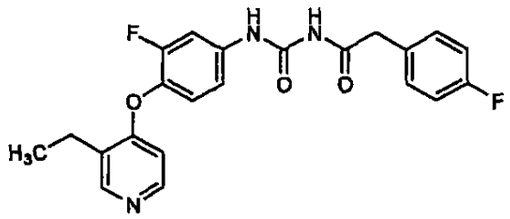
A) N^1-((2-(Pyridin-2-ylamino)thiazol-5-yl)methyl)benzene-1,4-diamine

[00173] A solution of 2-(pyridine-2-ylamino)-thiazole-5-carbaldehyde (0.10 g, 0.49 mmol, WO2004/001059), benzene-1,4-diamine (0.105 g, 0.97 mmol) and triethylsilane (0.19 mL, 1.2 mmol) in CH_2Cl_2-TFA (3:1, 4 mL) was stirred at ambient temperature for 4 h. The reaction mixture was concentrated *in vacuo* and the residue partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$ solution. The organic phase was washed with saturated aqueous $NaHCO_3$ solution, brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product which contained the title compound along with the starting aldehyde and benzene-1,4-diamine was carried on directly into the next step.

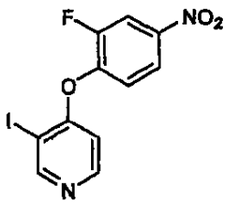
B) 1-(2-(4-Fluorophenyl)acetyl)-3-(4-((2-(pyridin-2-ylamino)thiazol-5-yl)methylamino)phenyl)thiourea

[00174] 4-Fluorophenylacetyl chloride (7.4 μL, 0.053 mmol) was added to a suspension of NaSCN (4.5 mg, 0.055 mmol) in EtOAc (0.5 mL) and the resulting mixture was stirred at RT for 30 min. This mixture was then added to a solution of the above mixture obtained in A (14.5 mg) in CH_2Cl_2 (0.5 ml) and the resulting mixture was stirred at ambient temperature for 2 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by flash chromatography on SiO_2 using a 2-5% MeOH-$CHCl_3$ gradient elution to give the title compound (2 mg) as an orange film. MS(ESI$^+$) m/z 493.2 $(M + H)^+$.

Example 33

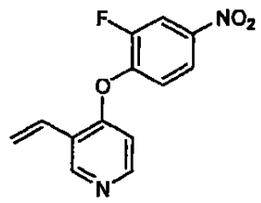


1-(4-(3-Ethylpyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, hydrochloride salt



A) 4-(2-Fluoro-4-nitrophenoxy)-3-iodopyridine

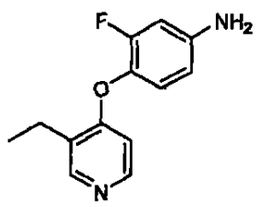
[00175] A mixture of 4-chloro-3-iodopyridine (1.50 g, 6.30 mmol, prepared according to Tabanella, S. et al. *Org. Biomol. Chem.* **2003**, *1*, 4254-4261.), 2-fluoro-nitrophenol (Lancaster, 2 0 g, 12.7 mmol), DIPEA (5 mL), and NMP (10 mL) was heated at 150 °C. After 12 h, more 2-fluoro-nitrophenol (0.50 g, 3.18 mmol) was added to the reaction mixture and heating was continued for 4 h. Most of the volatile components were removed under vacuum at 75 °C, the residue treated with saturated aq. $NaHCO_3$ solution (150 mL) and extracted with EtOAc (2 x 100 mL). The combined extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product. Purification by flash chromatography on silica gel, using 0 -100 % CH_2Cl_2 / hexanes then 2% MeOH / CH_2Cl_2 gave the title compound (1.0 g, 43%) as a yellow solid. ^1H NMR (DMSO-d_6) δ 8.96 (s, 1H), 8.47 (d, 2H, J = 5.5 Hz), 8.44 (dd, 1H, J = 2.7, 9.2 Hz), 7.49 (dd, 1H, J = 8.8, 8.2 Hz), 7.07 (d, 1H, J = 5 5 Hz); MS(ESI$^+$): *m/z* 361.05 $(M + H)^+$.



B) 4-(2-Fluoro-4-nitrophenoxy)-3-vinylpyridine

[00176] A solution of 4-(2-fluoro-4-nitrophenoxy)-3-iodopyridine (200 mg, 0.56 mmol), tributylvinyltin (212 mg, 0.67 mmol) in DMF (1 mL) was treated with CsF (169 mg, 1.12 mmol) followed by $(Ph_3P)_4Pd$ (36 mg, 0.031 mmol) and CuI (10 mg, 0.056 mmol) and the mixture was heated at 45 °C for 1 h. The mixture was cooled, diluted with CH_2Cl_2 (15 mL) and H_2O (10 mL), shaken vigorously and then filtered through Celite®. The filter cake was washed with 1:1 CH_2Cl_2 / EtOAc and the washings were combined with the filtrate. The solution was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give a brown oil. The crude product was purified by flash chromatography on SiO_2 using 0-2 % MeOH / CH_2Cl_2 to give a semi-pure product. The product was treated with 2 M HCl / Et_2O (10 mL) and the precipitated hydrochloride derivative collected by filtration and washed with Et_2O and EtOAc to a yellow solid (145 mg, 87%). ^{1}H NMR (DMSO-d_6) δ 9.11 (s, 1H), 8.64 (s, 1H), 8.51-8.48 (m, 1H), 8.24 (d, 1H, J= 7.7 Hz), 7.83-7.79 (m, 1H), 7.28 (d, 1H, J= 6.0 Hz), 7.02-6.95 (m, 1H), 6.24 (d, 1H, J= 17.6 Hz), 5.68 (d, 1H, 11.5 Hz); MS(ESI$^+$): *m/z* 261.18 $(M+H)^+$.

[00177] The above hydrochloride salt was converted to the free-base as follows: The pyridine hydrochloride (230 mg) was stirred with $NaHCO_3$ (25 mL) and EtOAc (20 mL) until homogeneous and the EtOAc phase separated, washed with brine, dried ($MgSO_4$) and concentrated. The title compound (190 mg) was obtained as a yellow oil.



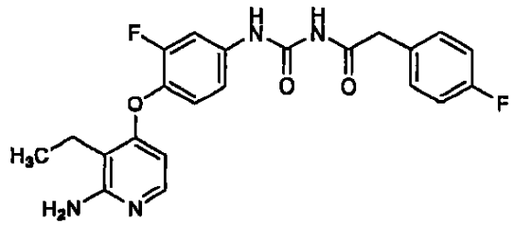
C) 4-(3-Ethylpyridin-4-yloxy)-3-fluorobenzenamine

[00178] A solution of 4-(2-fluoro-4-nitrophenoxy)-3-vinylpyridine (80 mg, 0.30 mmol) in 1:1 EtOAc / MeOH (2 mL) was hydrogenated over 10 % palladium-carbon (30 mg) for 1 h using H_2 from a latex balloon. Pt_2O (10 mg) was added to the mixture and the reaction continued for 1 h. The mixture was filtered through Celite® and concentrated *in vacuo* to give the title compound (50 mg, 63%) as a yellow oil. ^1H NMR (DMSO-d_6) δ 8.33 (s, 1H), 8.22 (d, 1H, J = 5.6 Hz), 6.96 (dd, 1H, J = 8.7, 9.1 Hz), 6.50 (dd, 1H, J = 2.0, 13.7 Hz), 6.56 (d, 1H, J = 5.6 Hz), 6.41 (dd, 1H, J = 2.5, 6 1 Hz), 2.69 (q, 2H, J = 7.6 Hz), 1.21 (t, 3H, J = 7.6 Hz).

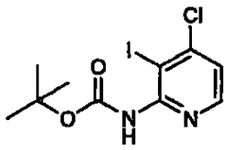
D) 1-(4-(3-Ethylpyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, hydrochloride salt

[00179] A solution of 4-(3-ethylpyridin-4-yloxy)-3-fluorobenzenamine (23 mg, 0.10 mmol) in CH_2Cl_2 (1 mL) was treated with a solution of 0.3 M solution of 2-(4-fluorophenyl)acetyl isocyanate in toluene (Compound D of Example 11, 0.33 mL, 0.11 mmol) and the mixture was stirred at room temperature for 2.5 h. The mixture was concentrated under vacuum and the residue triturated with 1:1 isopropyl ether / EtOAc to give a yellow solid. The product was treated with absolute MeOH (1 mL) and 2 M HCl / Et_2O (1 mL), stirred at room temperature for 5 min and concentrated under vacuum to give the title compound (15 mg, 36%) as a pale yellow solid. ^1H NMR (DMSO-d_6) δ 11.04 (s, 1H), 10.57 (s, 1H), 8.41 (s, 1H), 8.26 (d, 1H, J = 5.6 Hz), 7.76 (dd, 1H, J = 2.0, 12.7 Hz), 7.40 – 7.28 (m, 4H), 7.19-7.14 (m, 3H), 6.54 (d, 1H, J = 5.6 Hz), 3.73 (s, 2H), 2.72 (q, 2H, J = 7.6 Hz), 1.23 (t, 3H, J = 7.6 Hz); MS(ESI$^+$): m/z 412.20 $(M + H)^+$.

Example 34

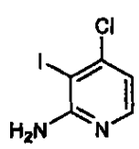


1-(4-(2-Amino-3-ethylpyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, trifluoroacetic acid salt



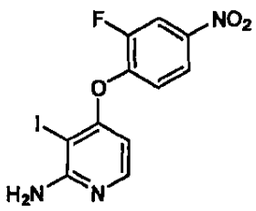
A) (4-Chloro-3-iodopyridin-2-yl)-carbamic acid *tert*-butyl ester

[00180] A solution of (4-chloro-pyridin-2-yl)-carbamic acid *tert*-butyl ester (CB Research and Development Inc., 5.0 g, 22.0 mmol), TMEDA (8 mL) in anhydrous THF (100 mL) was placed under a nitrogen atmosphere and cooled to -70 °C and treated dropwise with 2.5 M *n*-BuLi in hexanes (22.0 mL, 54.8 mmol) over a period of 30 min. The mixture was stirred at -70 °C for 1 h then treated dropwise with a solution of I_2 (14 g, 110 mmol) in anhydrous THF (16 mL) at -70 °C. After the addition was complete, the reaction was stirred at -70 °C for 30 min then allowed to warm to room temperature. The mixture was treated with a solution of sodium hydrogensulfite (16 g) in H_2O (100 mL) and stirred for 30 min then extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The product was purified by flash chromatography on SiO_2 eluting with 0 – 5 % MeOH / CH_2Cl_2 to give the title compound (5.8 g, 78%) as white solid. ^1H NMR (DMSO-d_6) δ 9.46 (s, 1H), 8.29 (d, 1H, J = 5.6 Hz), 7.46 (d, 1H, J = 5.0 Hz), 1.44 (s, 9H); MS(ESI): *m/z* 352.99 (M-H)$^-$.



B) 4-Chloro-3-iodopyridin-2-amine

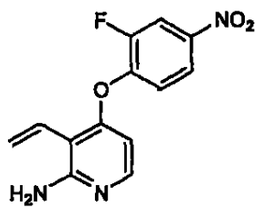
[00181] A suspension of (4-chloro-3-iodo-pyridin-2-yl)-carbamic acid *tert*-butyl ester (5.6 g, 15.8 mmol) in 48 % hydrobromic acid was heated at 100 °C for 10 min to give a clear solution. The mixture was cooled, treated with crushed ice and made basic with 6 M NaOH. The precipitated product was collected by vacuum filtration, washed with H_2O and sucked partially on the funnel to give a white solid. The product was dissolved in THF and the solution dried over $MgSO_4$ and concentrated *in vacuo* to give the title compound (3.7 g, 93%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 7.84 (d, 1H, J = 5.1 Hz), 6.73 (d, 1H, J = 5.6 Hz), 6.51 (br s, 2H); MS(ESI$^+$): *m/z* 254.97 $(M+H)^+$.



C) 4-(2-Fluoro-4-nitrophenoxy)-3-iodopyridin-2-amine

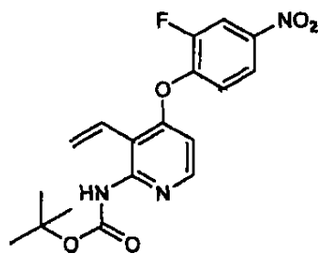
[00182] A mixture of 4-chloro-3-iodopyridin-2-amine (3.6 g, 14.2 mmol) and 2-fluoro-4-nitrophenol (Lancaster, 4.5 g, 28.4 mmol), DIPEA (3.6 mL, 20.7 mmol) and NMP (8 mL) was placed in a glass pressure vessel and heated rapidly to 170 °C and the heating continued for 18 h. The volatile components were distilled off under reduced pressure and the viscous residue poured into ice-water (150 mL). The mixture was sonicated for 15 min in order to break up the gummy solid and the pH of the mixture was adjusted to 7.5 with saturated aq. $NaHCO_3$ solution. The solid was collected by vacuum filtration, washed with H_2O, sucked partially dry on the funnel. The partially dried solid was suspended in toluene (150 mL) and the mixture concentrated *in vacuo* and the process repeated 3 times to give a brown solid. The product was dissolved in MeOH (150 mL), treated with 4 M HCl /1,4-dioxane (8 mL) and stirred at room temperature for 5 min and then the mixture was concentrated *in vacuo*. The hydrochloride thus obtained was washed and triturated with EtOAc and partitioned between EtOAc and saturated aq. $NaHCO_3$ solution. The EtOAc phase was separated washed with brine, and then dried ($MgSO_4$). The EtOAc solution was

treated with activated charcoal, stirred at room temperature for 10 min and the charcoal filtered off. The solution was concentrate *in vacuo* to give the title compound (3.9 g, 74%) as a yellow solid. ^{1}H NMR (DMSO-d_6) δ 8.39 (dd, 1H, J= 2.5, 10.7 Hz), 8.12 (dd, 1H, J= 1.5, 9.2 Hz), 7.86 (d, 1H, J= 5.6 Hz), 7.32 (dd, 1H, J = 8.6, 8.6 Hz), 6.40 (br s, 2H), 6.18 (d, 1H, J= 5.6 Hz).



D) 4-(2-Fluoro-4-nitrophenoxy)-3-vinylpyridin-2-amine

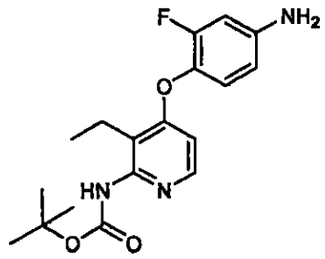
[00183] The title compound was prepared from 4-(2-fluoro-4-nitrophenoxy)-3-iodopyridin-2-amine and tributylvinyltin via a Stille coupling reaction in the same manner as described in Step B of Example 33. ^{1}H NMR (DMSO-d_6) δ 8.35 (dd, 1H, J = 10.7, 3.1 Hz), 8.09 (d, 1H, J= 9.2 Hz), 7.85 (d, 1H, J= 5.6 Hz), 7.31-7.15 (m, 1H), 6.54 (dd, 1H, J= 17.8, 11.7 Hz), 6.24 (br s, 2H), 6.20 (d, 1H, J= 5.6 Hz), 5.71 (d, 1H, J= 17.8 Hz), 5.46 (d, 1H, J= 11.7 Hz); MS(ESI$^+$): *m/z* 276.17 $(M+H)^+$.



E) *tert*-Butyl 4-(2-fluoro-4-nitrophenoxy)-3-vinylpyridin-2-ylcarbamate

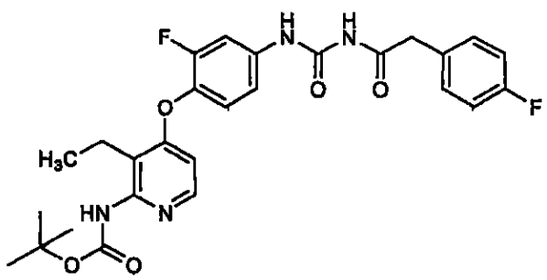
[00184] A solution of 4-(2-fluoro-4-nitrophenoxy)-3-vinylpyridin-2-amine (60 mg, 0.22 mmol) in 1,4-dioxane (0.5 mL) and *tert*-butyl alcohol (1.5 mL) was treated with Boc_2O (140 mg, 0.64 mmol) and heated at 65 °C for 5 h. The mixture was cooled, partitioned between EtOAc and saturated aq. $NaHCO_3$ solution. The EtOAc phase was separated, washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography on SiO_2 to give the title compound (50 mg, 60%) as a yellow solid. ^{1}H NMR (DMSO-d_6) δ 9.37 (s, 1H), 8.41

(dd, 1H, J = 10.7, 2.5 Hz), 8.22 (d, 1H, J = 5.6 Hz), 8.15 (d, 1H, J = 8.6 Hz), 7.42 (t, 1H, J = 8.6 Hz), 6.86 (d, 1H, J = 5.6 Hz), 6.58 (dd, 1H, J = 17.8, 11.7 Hz), 5.82 (d, 1H, J = 16.3 Hz), 5.52 (d, 1H, J = 11.7 Hz), 1.42 (s, 9H); MS(ESI$^+$): *m/z* 376.18 $(M+H)^+$.



F) *tert*-Butyl 4-(4-amino-2-fluorophenoxy)-3-ethylpyridin-2-ylcarbamate

[00185] A solution of *tert*-butyl 4-(2-fluoro-4-nitrophenoxy)-3-vinylpyridin-2-ylcarbamate (48 mg, 0.13 mmol) was hydrogenated over 10 % palladium-carbon (10 mg) and Pt_2O (5 mg) for 1.5 h using H_2 from a rubber balloon. The mixture was filtered through Celite® and the filtrate concentrated *in vacuo* to give the title compound (40 mg, 89%) as a pale yellow solid. ^{1}H NMR (DMSO-d_6) δ 9.04 (s, 1H), 8.03 (d, 1H, J = 5.6 Hz), 6.95 (dd, 1H, J = 8.6, 8.6 Hz), 6.50 (dd, 1H, J = 2.5, 13.2 Hz), 6.41 (dd, 1H, J = 2.5, 9.4 Hz), 6.36 (d, 1H, J = 5.6 Hz), 5.44 (s, 2H), 2.67-2.62 (m, 2H), 1.43 (s, 9H), 1.11 (t, 3H, J = 7.1 Hz); MS(ESI$^+$): *m/z* 348.22 $(M+H)^+$.



G) *tert*-Butyl 3-ethyl-4-(2-fluoro-4-(3-(2-(4-fluorophenyl)acetyl)ureido)phenoxy)pyridin-2-ylcarbamate

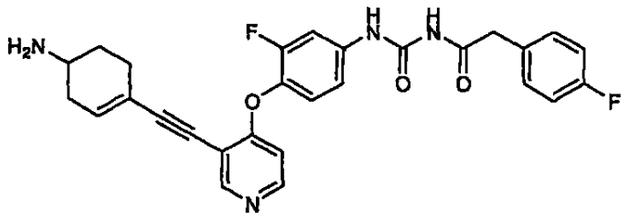
[00186] The title compound was prepared from tert-butyl 4-(4-amino-2-fluorophenoxy)-3-ethylpyridin-2-ylcarbamate (20 mg, 0.058 mmol) and 0.3 M

solution of 2-(4-fluorophenyl)acetyl isocyanate in toluene (232 μL, 0.070 mmol) in THF in the same manner as Step D of Example 33. MS(ESI$^+$): *m/z* 527.31 $(M + H)^+$.

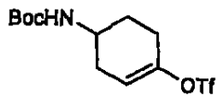
H) 1-(4-(2-Amino-3-ethylpyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, trifluoroacetic acid salt

[00187] A solution of *tert*-butyl 3-ethyl-4-(2-fluoro-4-(3-(2-(4-fluorophenyl)acetyl)ureido)phenoxy)pyridin-2-ylcarbamate (16 mg, 0.03 mmol) was dissolved in anhydrous THF (0.5 mL) and treated with 4 M HCl / 1,4-dioxane (1.5 mL) and stirred at room temperature for 3 h. The mixture was concentrated *in vacuo* and the product purified by preparative HPLC method A to give the title compound (5 mg, 36%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.06 (s, 1H), 10.6 (s, 1H), 7.80 – 7.79 (m, 4H), 7.43 – 7.33 (m, 4H), 7.16 (dd, 2H, J = 8.9, 8.9 Hz), 6.19 (d, 1H, J = 7.1 Hz), 3.73 (s, 2H), 2.71 -2.66 (m, 2H), 1.10 (t, 3H, J = 7.1 Hz); MS(ESI$^+$): *m/z* 427.18 $(M + H)^+$.

Example 35



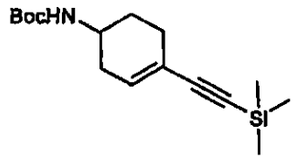
1-(4-(3-(2-(4-Aminocyclohex-1-enyl)ethynyl)pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea



A) 4-(*tert*-Butoxycarbonyl)cyclohex-1-enyl trifluoromethanesulfonate

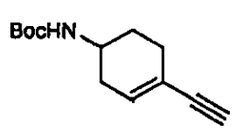
[00188] A solution of *N*-Boc-4-aminocyclohexanone (Astatech Inc., 213 mg, 1.0 mmol) in THF (7 mL) was cooled to -70 °C and treated with a solution 0.5 M KHMDS in toluene (2.4 ml, 1.2 mmol). The mixture was stirred at -70 °C for 20 min, treated dropwise with a solution of phenyltrifluoromethanesulfonimide (392 mg, 1.1

mmol) in THF (4 mL) and stirred at –70 °C for 25 min. The mixture was quenched with saturated aq. NH_4Cl solution, diluted with EtOAc, washed with 10 % Na_2CO_3 and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography on SiO_2 eluting with 10 -25 % EtOAc / hexanes to give the title compound (180 mg, 52%) as a white solid. ^1H NMR (DMSO-d_6) δ 5.68 (s, 1H), 4.50 (s, 1H), 3.82 (s, 1H), 2.68–2.25 (m, 3H), 2.22–1.89 (m, 2H), 1.87–1.63 (m, 1H), 1.43 (s, 9H).



B) *tert*-Butyl 4-(2-(trimethylsilyl)ethynyl)cyclohex-3-enylcarbamate

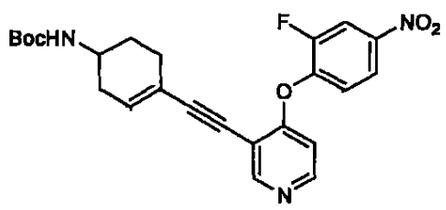
[00189] A mixture of 4-(tert-butoxycarbonyl)cyclohex-1-enyl trifluoromethanesulfonate (170 mg, 0.49 mmol), trimethylsilylacetylene (138 μL, 0.98 mmol), Et_3N (0.68 mL) and THF (8 mL) in a reaction flask was purged with argon and treated in turn with CuI (14 mg, 0.072 mmol) and $(Ph_3P)_4Pd$ (27 mg, 0.024 mmol). The reaction mixture was stirred at room temperature for 25 min, and then diluted with EtOAc (50 mL), washed with saturated aq. $NaHCO_3$ solution and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography on SiO_2 eluting with 0 -25 % EtOAc / hexanes to give the title compound (116 mg, 81%) as a yellow solid. ^1H NMR (DMSO-d_6) δ 6.06 (s, 1H), 4.50 (s, 1H), 3.76 (s, 1H), 2.46 (d, 1H, J = 18.8 Hz), 2.36–2.14 (m, 2H), 2.00–1.78 (m, 2H), 1.66–1.50 (m, 1H), 1.43 (s, 9H), 0.27-0.05 (m, 9H).



C) *tert*-Butyl 4-ethynylcyclohex-3-enylcarbamate

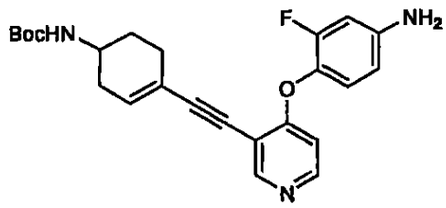
[00190] A solution of tert-butyl 4-(2-(trimethylsilyl)ethynyl)cyclohex-3-enylcarbamate (112 mg, 0.38 mmol) in THF was cooled to -15 °C, treated with 1.0 M tetrabutylammonium fluoride in THF (Aldrich, 440 μL, 0.44 mmol) and the mixture

stirred at –15 °C for 40 min. The mixture was treated with 5 % Na_2CO_3 (25 mL) and extracted with ether. The ether extract was washed with 5 % Na_2CO_3 and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound (83 mg, 99%) as a brown oil. ^{1}H NMR (DMSO-d_6) δ 6.09 (s, 1H), 4.51 (s, 1H), 3.77 (s, 1H), 2.82 (s, 1H), 2.47 (d, 1H, J = 18.3 Hz), 2.35–2.16 (m, 2H), 2.04-1.79 (m, 2H), 1.72 – 1.51 (m, 1H), 1.43 (s, 9H).



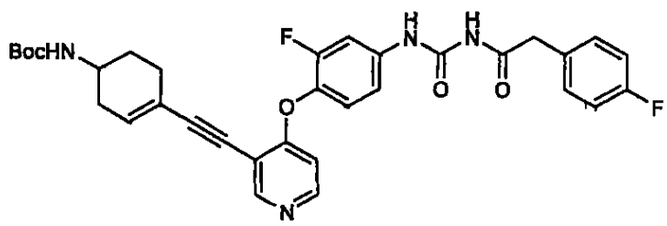
D) *tert*-Butyl 4-(2-(4-(2-fluoro-4-nitrophenoxy)pyridin-3-yl)ethynyl)cyclohex-3-enylcarbamate

[00191] A solution of 4-(2-fluoro-4-nitrophenoxy)-3-iodopyridine (Compound A of Example 33, 130 mg, 0.36 mmol) and *N*-Boc-4-ethynylcyclohex-3-enamine (80 mg, 0.36 mmol) in anhydrous THF (2 mL) was treated with Et_3N (2 mL) and the degassed by vacuum/argon purge. The solution was treated with tetrakistriphenylphosphine palladium (20 mg, 0.0018 mmol) and CuI (10 mg, 0.054 mmol) and then heated at reflux for 2 h. The mixture was cooled and partitioned between saturated aq. $NaHCO_3$ solution and EtOAc. The EtOAc phase was separated, washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with 0-40 % EtOAc / hexanes to give the title compound (124 mg, 76%) as a yellow solid. ^{1}H NMR (DMSO-d_6) δ 8.68 (s, 1H), 8.51 (d, 1H, J = 5.6 Hz), 8.43 (dd, 1H, J = 2.5, 10. 7 Hz), 8.15 (d, 1H, J = 9.2 Hz), 7.49 (dd, 1H, J = 8.6, 8.6 Hz), 7.14 (d, 1H, J = 5.6 Hz), 6.85 (d, 1H, J = 7.1 Hz), 6.04- 6.00 (m, 1H), 3.48 – 3.35 (m, 1H), 2.36 – 2.25 (m, 1H), 2.17 – 2.04 (m, 2H), 2.03 – 1.89 (m, 1H), 1.78 – 1.69 (m, 1H), 1.46 – 1.35 (m, 1H), 1.36 (s, 9H); MS(ESI$^+$): *m/z* 454.27 $(M + H)^+$.



E) *tert*-Butyl 4-(2-(4-(4-amino-2-fluorophenoxy)pyridin-3-yl)ethynyl)cyclohex-3-enylcarbamate

[00192] A mixture of *tert*-butyl 4-(2-(4-(2-fluoro-4-nitrophenoxy)pyridin-3-yl)ethynyl)cyclohex-3-enylcarbamate (110 mg, 0.24 mmol), iron powder, ~325 mesh (150 mg, 2.7 mmol), NH_4Cl (280 mg, 5.3 mmol), DMF (1 mL), H_2O (1 mL) and EtOH (1 mL) was heated at 100 °C for 30 minutes. The mixture was filtered through a pad of Celite® using DMF to wash the filter cake and the filtrate made basic to pH 8 with saturated aq. $NaHCO_3$ solution. The mixture was extracted twice with EtOAc and dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound (105 mg) which was used without any further purification. MS(ESI$^+$): *m/z* 424.27 $(M + H)^+$.



F) *tert*-Butyl 4-(2-(4-(2-fluoro-4-(3-(2-(4-fluorophenyl)acetyl)ureido)phenoxy)pyridin-3-yl)ethynyl)cyclohex-3-enylcarbamate

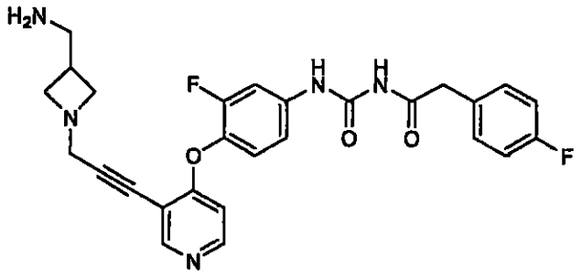
[00193] A solution of *tert*-butyl 4-(2-(4-(4-amino-2-fluorophenoxy)pyridin-3-yl)ethynyl)cyclohex-3-enylcarbamate (50 mg, 0.12 mmol) in dry CH_2Cl_2 (2 mL) was treated with a 0.3 M solution of 2-(4-fluorophenyl)acetyl isocyanate in toluene (Compound D of Example 11, 0.8 mL, 0.24 mmol) and the mixture stirred at rt for 1 h. The solvents were evaporated under vacuum and the residue purified by flash chromatography on silica gel eluting with 10-60 % EtOAc / hexanes to give the title compound (50 mg, 69%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.03 (s, 1H), 10.57 (s, 1H), 8.57 (s, 1H), 8.36 (d, 1H, J = 5.7 Hz), 7.78 (dd, 1H, J = 1 8, 13 1 Hz),

7.41 – 7.29 (m, 3H), 7.16 (dd, 3H, J = 8.6, 8.6 Hz), 6.85 (d, 1H, J = 8.3 Hz), 6.70 (d, 1H, J = 5.7 Hz), 6.13 – 6.08 (m, 1H), 3.73 (s, 2H), 3.51 – 3.41 (m, 1H), 2.38 – 2.27 (m, 1H), 2.27 – 2.20 (m, 2H), 1.82 – 1.72 (m, 1H), 1.54 – 1.28 (m, 2H), 1.37 (s, 9H); ESI MS): *m/z* 603.24 $(M + H)^+$.

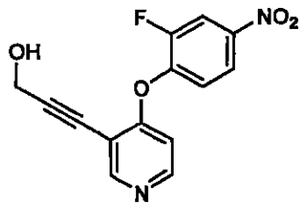
G) 1-(4-(3-(2-(4-Aminocyclohex-1-enyl)ethynyl)pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, dihydrochloride salt

[00194] A solution of *tert*-butyl 4-(2-(4-(2-fluoro-4-(3-(2-(4-fluorophenyl)acetyl)ureido)phenoxy)pyridin-3-yl)ethynyl)cyclohex-3-enylcarbamate (40 mg, 0.066 mol) in anhydrous 1,4-dioxane (2 mL) was cooled to -10 °C and treated with 4 M HCl / 1,4-dioxane (4 mL). The mixture was stirred at -5 °C for 2.5 h then at rt for 1 h. The mixture was concentrated under vacuum without any heating to give the title compound (32 mg, 84%) as a yellow solid. ^{1}H NMR (DMSO-d_6) δ 11.05 (s, 1H), 10.61 (s, 1H), 8.69 (s, 1H), 8.44 (d, 1H, J = 6.1 Hz), 8.06 (d, 1H, J = 2.0 Hz), 7.80 (dd, 1H, J = 12.7, 2.0 Hz), 7.46–7.38 (m, 1H), 7.35 (dd, 1H, J = 8.6, 5.6 Hz), 7.19–7.13 (m, 1H), 6.82 (d, 1H, J = 5.6 Hz), 6.17 (s, 1H), 3.74 (s, 2H), 3.73-3.62 (m, 2H), 3.62-3.54 (m, 1H), 3.34–3.22 (m, 1H), 2.31 (s, 1H), 1.99–1.96 (m, 1H), 1.71-1.66 (m, 1H); MS(ESI$^+$): *m/z* 503.12 $(M + H)^+$.

Example 36

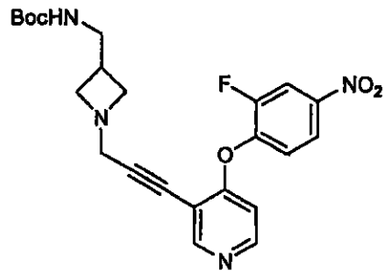


1-(4-(3-(3-(3-(Aminomethyl)azetidin-1-yl)prop-1-ynyl)pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, trihydrochloride salt



A) 3-(4-(2-Fluoro-4-nitrophenoxy)pyridin-3-yl)prop-2-yn-1-ol

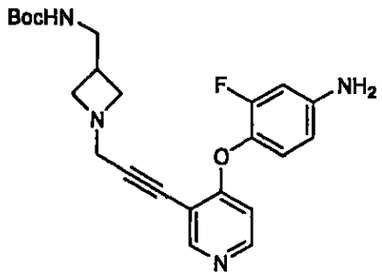
[00195] A solution of 4-(2-fluoro-4-nitrophenoxy)-3-iodopyridine (Compound A of Example 33, 300 mg, 0.83 mmol), propargylalcohol (Aldrich, 145 μL, 2.50 mmol), Et_3N (2 mL) and anhydrous THF (2 mL) was degassed by vacuum/argon purge and treated with $Pd(Ph_3P)_4$ (31 mg, 0.027 mmol) and CuI (10 mg, 0.054 mmol). The mixture was heated at reflux under argon atmosphere for 10 min, cooled to rt and diluted with EtOAc (25 mL) and H_2O (20 mL). The EtOAc phase was washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel using 0-3 % MeOH / CH_2Cl_2 to give the desired product (185 mg, 77%) as a pale yellow solid. ^{1}H NMR (DMSO-d_6) δ 8.69 (s, 1H), 8.49 (d, 1H, J = 5.6 Hz), 8.43 (dd, 1H, J = 10.7, 2.5 Hz), 8.17 (d, 1H, J = 9.2 Hz), 7.57 (t, 1H, J =8.6 Hz), 7.04 (d, 1H, J = 5.6 Hz), 5.40 (t, 1H, J = 6.1), 4.28 (d, 2H, J = 6.1 Hz); MS(ESI$^+$): *m/z* 289.13 $(M + H)^+$.



B) *tert*-Butyl (1-(3-(4-(2-fluoro-4-nitrophenoxy)pyridin-3-yl)prop-2-ynyl)azetidin-3-yl)methylcarbamate

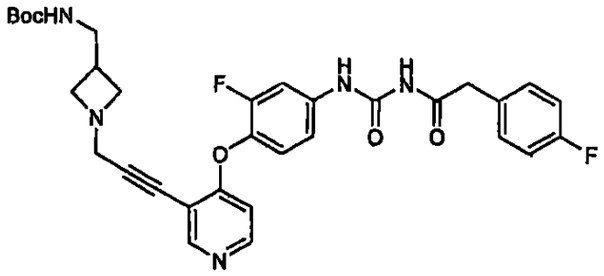
[00196] A solution of 3-(4-(2-fluoro-4-nitrophenoxy)pyridin-3-yl)prop-2-yn-1-ol (43 mg, 0.15 mmol) and DIPEA (45 μL, 0.26 mmol) in anhydrous THF (1.5 mL) was cooled to 0 °C and treated with methanesulfonyl chloride (15 mg, 0.11 mmol) in portions. After stirring at 0 °C for 1 h, the mixture was concentrated under reduced pressure. The residue was treated with DMF (1.0 mL), DIPEA (45 μL, 0.26 mmol)

and azetidin-3-ylmethyl-carbamic acid *tert*-butyl ester (Beta Pharma Inc., 145 mg, 0.78 mmol) and stirred at rt for 2 h. The reaction mixture was partitioned between EtOAc and saturated aq. $NaHCO_3$ solution and the EtOAc phase separated, washed with brine dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 eluting with 1-5 % MeOH / CH_2Cl_2 to afford the title compound (33 mg, 48%) as a colorless oil. ^1H NMR (DMSO-d_6) δ 8.74 (s, 1H), 8.51 (d, 1H, J = 5.6 Hz), 8.41 (dd, 1H, J = 10.7, 2.5 Hz), 8.15 (d, 1H, J = 9.2 Hz), 7.53 (t, 1H, J = 8.6 Hz), 7.09 (d, 1H, J = 6.1 Hz), 6.86 (t, 1H, J = 5.6 Hz), 3.39 (s, 2H), 3.24-3.14 (m, 2H), 3.07-2.98 (m, 2H), 2.94-2.87 (m, 2H), 2.37-2.26 (m, 1H), 1.33 (s, 9H); MS(ESI$^+$): *m/z* 401.20 (100), $[(M-C_4H_9)]^+$; *m/z* 457.20 (25), $(M+H)^+$.



C) *tert*-Butyl (1-(3-(4-(4-amino-2-fluorophenoxy)pyridin-3-yl)prop-2-ynyl)azetidin-3-yl)methylcarbamate

[00197] The title compound was prepared by the reduction of *tert*-butyl (1-(3-(4-(2-fluoro-4-nitrophenoxy)pyridin-3-yl)prop-2-ynyl)azetidin-3-yl)methylcarbamate (30 mg, 0.66 mmol) in the same manner as in Step E of Example 35 using Fe powder (50 mg, 0.091 mmol) and NH_4Cl (96 mg, 1.82 mmol). The product was used in subsequent reactions without any purification. MS(ESI$^+$): *m/z* 371.24 (100), $[(M-C_4H_9)]^+$; *m/z* 427.27 (25), $(M+H)^+$.



D) *tert*-Butyl (1-(3-(4-(2-fluoro-4-(3-(2-(4-fluorophenyl)acetyl)ureido)phenoxy)pyridin-3-yl)prop-2-ynyl)azetidin-3-yl)methylcarbamate

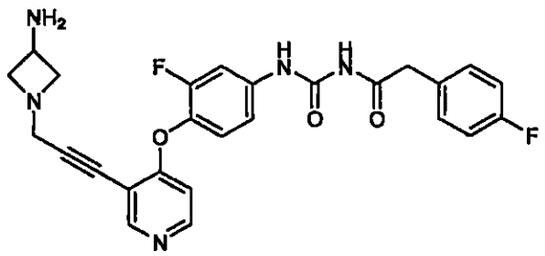
[00198] The title compound was prepared from *tert*-butyl (1-(3-(4-(4-amino-2-fluorophenoxy)pyridin-3-yl)prop-2-ynyl)azetidin-3-yl)methylcarbamate (25 mg, 0.059 mmol) and a 0.3 M solution of 2-(4-fluorophenyl)acetyl isocyanate in toluene (Compound D of Example 11, 0.37 mL, 0.11 mmol) in the same manner as Step D of Example 33 to give the title compound as a white solid (20 mg, 57%). ^{1}H NMR (DMSO-d_6) δ 11.04 (s, 1H), 10.58 (s, 1H), 8.63 (s, 1H), 8.37 (d, 1H, J = 5.5 Hz), 7.78 (d, 1H, J = 12.6 Hz), 7.40 – 7.33 (m, 4H), 7.16 (dd, 2H, J = 8.8, 8.9 Hz), 6.89 – 6.87 (m, 1H), 6.68 (d, 1H, J = 5.5 Hz), 3.73 (s, 2H), 3.45 (s, 2H), 3.26-3.24 (m, 2H), 3.07–3.04 (m, 2H), 2.98 – 2.96 (m, 2H), 2.38 – 2.35 (m, 2H), 1.32 (s, 9H); MS(ESI$^+$): *m/z* 606.26 $(M + H)^+$.

E) 1-(4-(3-(3-(3-(Aminomethyl)azetidin-1-yl)prop-1-ynyl)pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, trihydrochloride salt

[00199] *tert*-Butyl (1-(3-(4-(2-fluoro-4-(3-(2-(4-fluorophenyl)acetyl)ureido)phenoxy)pyridin-3-yl)prop-2-ynyl)azetidin-3-yl)methylcarbamate (20 mg, 0.033 mmol) was dissolved in CH_2Cl_2 (2 mL) and treated with TFA (0.5 mL) and the mixture stirred at room temperature for 1.5 h. The mixture was concentrated *in vacuo* and purified by preparative HPLC (Column A) to give the TFA salt. The TFA salt was dissolved in absolute MeOH and treated with 1.0 M HCl / ether stirred for 5 min and concentrated *in vacuo* to give the title compound (9 mg, 45%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.07 (s, 1H), 10 06 (s, 1H), 8.96 (m, 1H), 8.61 – 8.52 (m, 1H), 8.36 – 8.25 (s, 2H), 7.82 (d, 1H, J = 12.2 Hz), 7.45 – 7.42 (m, 2H), 7.37 – 7.33 (m, 2H), 7.18 – 7.14 (m, 2H), 6.92 (d, 1H, J = 6.1 Hz), 4.48 (s, 2H), 4.27 – 3.98 (m, 2H), 3.76 (s, 2H), 3.30 - 3.20 (m, 1H), 3.16 – 3.00 (m, 2H); MS(ESI$^+$): *m/z* 506.18 $(M + H)^+$.

[00200] Examples **37-40** were prepared in a similar manner to that which is described in Example 36.

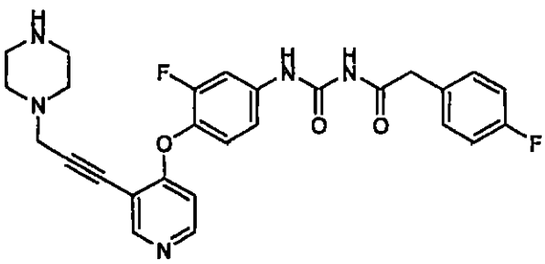
Example 37



1-(4-(3-(3-(3-Aminoazetidin-1-yl)prop-1-ynyl)pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, trihydrochloride salt

[00201] MS(ESI$^+$): *m/z* 492.17 $(M + H)^+$

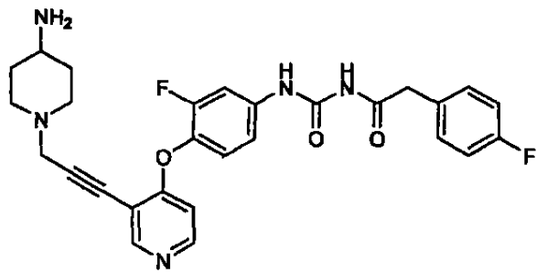
Example 38



1-(3-Fluoro-4-(3-(3-(piperazin-1-yl)prop-1-ynyl)pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea, trihydrochloride salt

[00202] ^{1}H NMR (DMSO-d_6) δ 11.07 (s, 1H), 10.63 (s, 1H), 9.44 (s, 1H), 8.91 (s, 1H), 8.50 (d, 1H, J = 6.2 Hz), 7.84-7.78 (m, 1H), 7.45-7.39 (m, 2H), 7.38-7.32 (m, 2H), 7.16 (t, 2H, J = 8.8 Hz), 6.85 (d, 1H, J = 6.2 Hz), 4.26 (s, 2H), 3.75 (s, 2H), 3.34 (br s, 4H), 2.49 (br s, 4H); MS(ESI$^+$): *m/z* 506.23 $(M + H)^+$.

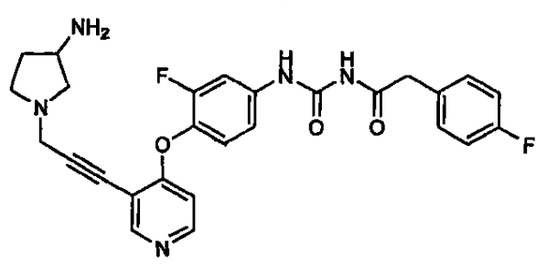
Example 39



1-(4-(3-(3-(4-Aminopiperidin-1-yl)prop-1-ynyl)pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, trihydrochloride salt

[00203] ^{1}H NMR (DMSO-d_6) δ 11.07 (s, 1H), 10.62 (s, 1H), 8.81 (s, 1H), 8.48 (d, 1H, J = 6.1 Hz), 8.31 (s, 2H), 7.80 (dd, 1H, J = 2.2, 12.7 Hz), 7.44 – 7.33 (m, 4H), 7.19 – 7.13 (m, 2H), 6.78 (d, 1H, J = 5.7 Hz), 4.40 (s, 2H), 3.74 (s, 2H), 3.64 – 3.60 (m, 2H), 3.34 – 3.22 (m, 1H), 3.19 – 3.13 (m, 2H), 2.16 – 2.13 (m, 2H), 1.99 -1.88 (m, 2H); MS(ESI$^+$): *m/z* 506.23 $(M + H)^+$.

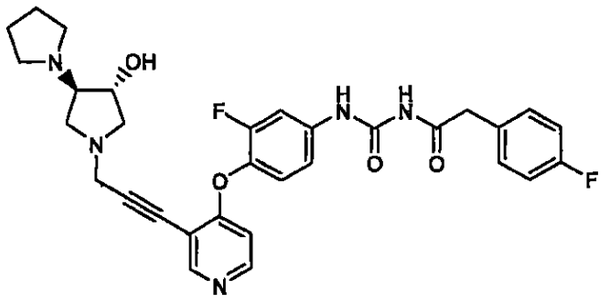
Example 40



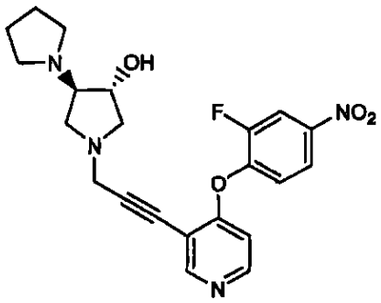
(±)-1-(4-(3-(3-(3-Aminopyrrolidin-1-yl)prop-1-ynyl)pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, trihydrochloride salt

[00204] ^{1}H NMR (DMSO-d_6) δ 11.08 (s, 1H), 10.65 (s, 1H), 8.96 (s, 1H), 8.54 (d, 1H, J = 6.1 Hz), 7.83 (d, 1H, J = 12.7 Hz), 7.43 (s, 2H), 7.37 – 7.33 (m, 2H), 7.16 – 7.14 (m, 2H), 6.90 (d, 1H, J = 5.6 Hz), 4.62 (s, 2H), 4.06 – 3.87 (m, 1H), 3.75 (s, 2H), 3.70 – 3.55 (m, 3H), 3.49 – 3.44 (m, 2H), 2.25 – 2.08 (m, 1H); MS(ESI$^+$): *m/z* 506.22 $(M + H)^+$.

Example 41



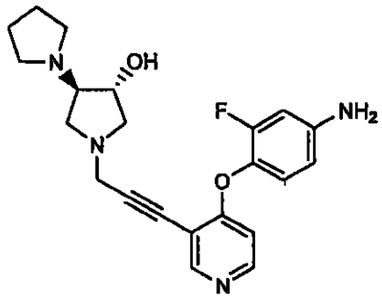
1-(3-Fluoro-4-(3-(3-((3R,4R)-3-hydroxy-4-(pyrrolidin-1-yl)pyrrolidin-1-yl)prop-1-ynyl)pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea, trihydrochloride salt



A) (3*R*,4*R*)-1-(3-(4-(2-Fluoro-4-nitrophenoxy)pyridin-3-yl)prop-2-ynyl)-4-(pyrrolidin-1-yl)pyrrolidin-3-ol

[00205] A solution of 3-(4-(2-fluoro-4-nitrophenoxy)pyridin-3-yl)prop-2-yn-1-ol (Compound A of Example 36, 43 mg, 0.15 mmol) and DIPEA (45 μL, 0.26 mmol) in anhydrous THF (1.5 mL) was cooled to 0 °C and treated with methanesulfonyl chloride (15 mg, 0.11 mmol) in portions. After stirring at 0 °C for 1 h, the mixture was concentrated under reduced pressure. The residue was treated with DMF (1.0 mL), DIPEA (45 μL, 0.26 mmol) and (3*R*,4*R*)-4-(pyrrolidin-1-yl)pyrrolidin-3-ol (Lexicon Pharmaceutical Corp., 94 mg, 0.6 mmol) and stirred at rt for 2 h. The reaction mixture was partitioned between EtOAc and saturated aq. $NaHCO_3$ solution and the EtOAc phase separated, washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography on SiO_2 eluting with 0-1.5 % MeOH / CH_2Cl_2 to give the title compound (38 mg, 59%) as a brown oil. ^1H NMR (DMSO-d_6) δ 8.72 (s, 1H), 8.54 (d, 1H, J = 5.6 Hz), 8.40 (dd, 1H, J =

10.7, 2.5 Hz), 8.14 (d, 1H, J = 9.2 Hz), 7.43 (t, 1H, J = 8.6 Hz), 7 15 (d, 1H, J = 5.6 Hz), 4.99-4.81 (m, 1H), 4.11-4.10 (m, 0.5H), 3.92-3.84 (m, 1H), 3.54 (s, 2H), 3.59-3.50 (m, 0.5H), 3.16-3.15 (m, 1H), 2.79-2.75 (m, 1H), 2.60-2.32 (m, 4H), 1.70-1.59 (m, 4H); MS(ESI$^+$): *m/z* 427.24 $(M + H)^+$.



B) (3*R*,4*R*)-1-(3-(4-(4-Amino-2-fluorophenoxy)pyridin-3-yl)prop-2-ynyl)-4-(pyrrolidin-1-yl)pyrrolidin-3-ol

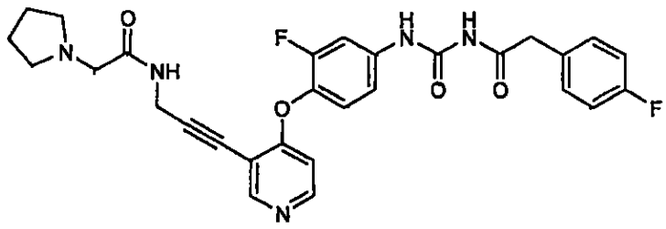
[00206] A mixture of (3*R*,4*R*)-1-(3-(4-(2-fluoro-4-nitrophenoxy)pyridin-3-yl)prop-2-ynyl)-4-(pyrrolidin-1-yl)pyrrolidin-3-ol (35 mg, 0.082 mmol), DMF (1 mL), EtOH (1 mL) and H_2O (1 mL) was treated with Fe powder (67 mg, 1.2 mmol, 2.4 mmol) and heated at 100 °C for 45 min. The mixture was filtered through Celite®, made basic with $NaHCO_3$ and concentrate *in vacuo*. The residue was partitioned between EtOAc and saturated aq. $NaHCO_3$ solution. The EtOAc phase was dried ($MgSO_4$) and concentrated *in vacuo* to give the crude aniline (16 mg, 50%) which was used directly in the next step without further purification. MS(ESI$^+$): *m/z* 397.28 $(M + H)^+$.

C) 1-(3-Fluoro-4-(3-(3-((3*R*,4*R*)-3-hydroxy-4-(pyrrolidin-1-yl)pyrrolidin-1-yl)prop-1-ynyl)pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea, trihydrochloride salt

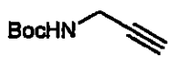
[00207] The title compound was prepared from (3*R*,4*R*)-1-(3-(4-(4-amino-2-fluorophenoxy)pyridin-3-yl)prop-2-ynyl)-4-(pyrrolidin-1-yl)pyrrolidin-3-ol (16 mg, 0.04 mmol) and a 0.3 M solution of 2-(4-fluorophenyl)acetyl isocyanate in toluene (Compound D of Example 11, 0.13 mL, 0.04 mmol) in a manner similar to that of Step D of Example 33. The product was purified by preparative HPLC (Column A) and converted to the hydrochloride salt in the same manner as in Step E of Example

36 to give the title compound (9 mg, 33%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.06 (s, 1H), 10.62 (s, 1H), 8.86 (s, 1H), 8.45 (d, 1H, J = 6.1 Hz), 7.81 (d, 1H, J = 12.2 Hz), 7.45 – 7.40 (m, 4H), 7.33 – 7.28 (m, 4H), 7.16 (dd, 2H, J = 9.2, 8.6 Hz), 6.80 (d, 1H, J = 6.1 Hz), 4.64 (s, 1H), 4.34 (s, 2H), 3.84 – 3.70 (m, 4H), 2.70 – 3.55 (m, 2H), 3.55 – 2.98 (m, 3H), 2.08 – 1.92 (m, 2H), 1.92 – 1.75 (m, 2H); MS(ESI$^+$): *m/z* 576.25 $(M+H)^+$.

Example 42

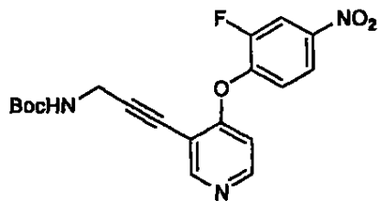


1-(3-Fluoro-4-(3-(3-(2-(pyrrolidin-1-yl)acetamido)prop-1-ynyl)pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea, dihydrochloride salt



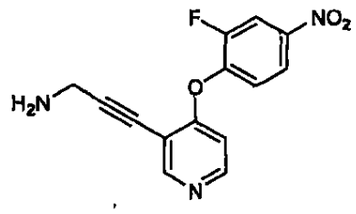
A) *N*-Boc-propargylamine

[00208] Di-*tert*-butyl-dicarbonate (21.8 mg, 100.0 mmol) was dissolved in THF (25 mL) and the solution cooled to 0 °C and treated dropwise with a solution of propargylamine (Aldrich, 5.0 g, 90.0 mmol) keeping the temperature below 15 °C. The mixture was stirred at rt for 1.5 h then concentrated under vacuum. The residue was dissolved in hexanes and filtered through a column of silica gel using 0-100% CH_2Cl_2 / hexanes to elute the product. The eluent containing the product was concentrated *in vacuo* to give a colorless oil which was dissolved in hexanes (150 mL) and cooled to 0 °C to give white crystals. The crystals were collected by filtration and dried under vacuum to give the title compound (10.5 g, 75%). ^{1}H NMR ($CDCl_3$) δ 4.75 (s, 1H), 3.95 (s, 2H), 2.25–2.24 (m, 1H), 1.48 (s, 9H).



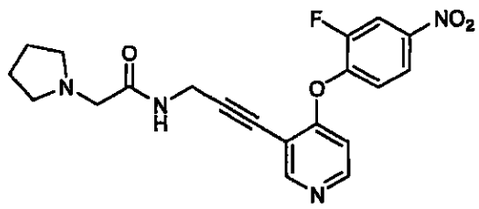
B) *tert*-Butyl 3-(4-(2-fluoro-4-nitrophenoxy)pyridin-3-yl)prop-2-ynylcarbamate

[00209] The title compound was prepared from *N*-Boc-propargylamine (98 mg, 0.63 mmol) and 4-(2-fluoro-4-nitrophenoxy)-3-iodopyridine (Compound A of Example 33, 150 mg, 0.42 mmol) via a Sonagashira cross coupling reaction using $Pd(Ph_3P)_4$ (9 mg, 0.008 mmol) and CuI (1.5 mg, 0.008 mmol) in 1:1 Et_3N / THF (3 mL) according to Step C of Example 35. The title compound (124 mg, 76%) was obtained as a red oil. ^1H NMR (DMSO-d_6) δ 8.66 (s, 1H), 8.50 (d, 1H, J = 5.6 Hz), 8.40 (dd, 1H, J = 2.5, 10.7 Hz), 8.15 (d, 1H, J = 9.2 Hz), 7.52 (dd, 1H, J = 8.1, 8.6 Hz), 7.33–7.30 (m, 1H), 7.07 (d, 1H, J = 5.6 Hz), 3.95 (d, 2H, J = 5.6 Hz), 1.35 (s, 9H); MS(ESI$^+$): *m/z* 388.21 $(M + H)^+$.



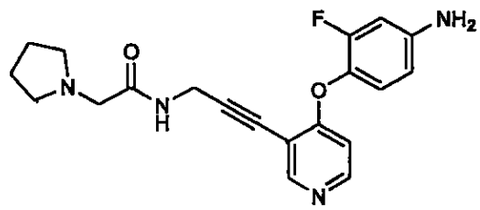
C) 3-(4-(2-Fluoro-4-nitrophenoxy)pyridin-3-yl)prop-2-yn-1-amine

[00210] A solution of *tert*-butyl 3-(4-(2-fluoro-4-nitrophenoxy)pyridin-3-yl)prop-2-ynylcarbamate (300 mg, 0.78 mmol) in CH_2Cl_2 (10 mL) was treated with TFA (2 mL) and stirred at rt for 45 min. The mixture was concentrated under vacuum and the residue was partitioned between EtOAc and saturated aq. $NaHCO_3$ solution. The EtOAc phase was separated and washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound (180 mg, 80%) as a red oil. ^1H NMR (DMSO-d_6) δ 8.65 (s, 1H), 8.47 (d, 1H, J = 5.6 Hz), 8.43 (dd, 1H, J = 10.7, 2.5 Hz), 8.17 (d, 1H, J = 8.6 Hz), 7.54 (t, 1H, J = 8.6 Hz), 7.04 (d, 1H, J = 5.6 Hz), 3.49 (s, 2H); MS(ESI$^+$): *m/z* 288.17 $(M + H)^+$.



D) *N*-(3-(4-(2-Fluoro-4-nitrophenoxy)pyridin-3-yl)prop-2-ynyl)-2-(pyrrolidin-1-yl)acetamide

[00211] A solution of 3-(4-(2-fluoro-4-nitrophenoxy)pyridin-3-yl)prop-2-yn-1-amine (80 mg, 0.26 mmol) in anhydrous CH_2Cl_2 (2.5 mL) was cooled to 0 °C and treated with chloroacetyl chloride (40 mg, 0.37 mmol) the mixture was stirred at rt for 1 h. The mixture was concentrated under vacuum to removed the solvent and excess reagent and the residue redissolved in CH_3CN (1.5 mL), treated with pyrrolidone (55 mg, 0.78 mmol) and stirred at rt for 4 h. The mixture was partitioned between EtOAc and saturated aq. $NaHCO_3$ solution and the organic phase separated, washed with brine, dried ($MgSO_4$) and concentrated to give crude product. The residue was purified by flash chromatography on silica gel eluting with 0-10 % MeOH/ CH_2Cl_2 to afford the title compound (40 mg, 39%) as a brown oil. ^{1}H NMR (DMSO-d_6) δ 8.66 (s, 1H), 8 50 (d, 1H, J = 6.1 Hz), 8.41 (dd, 1H, J = 2.8, 10.4 Hz), 8.18 – 8.15 (m, 2H), 7.51 (dd, 1H, J = 8.3, 8.8 Hz), 7.06 (d, 1H, J = 5.5 Hz) 4.10 (d, 2H, J = 5.5 Hz), 3.01 (s, 2H), 2.47 – 2.43 (m, 4H), 1.67 – 1.63 (m, 4H); MS(ESI$^+$): *m/z* 399.27 $(M + H)^+$.



E) *N*-(3-(4-(4-Amino-2-fluorophenoxy)pyridin-3-yl)prop-2-ynyl)-2-(pyrrolidin-1-yl)acetamide

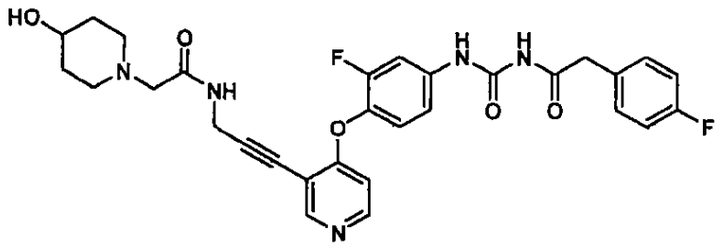
[00212] The title compound was prepared by the reduction of *N*-(3-(4-(2-fluoro-4-nitrophenoxy)pyridin-3-yl)prop-2-ynyl)-2-(pyrrolidin-1-yl)acetamide (35 mg, 0.088 mmol) in the manner similar to that of Step E of Example 35 using Fe powder (67 mg, 1.21 mmol) and NH_4Cl (128 mg, 2.42 mmol). The product was used in subsequent

reactions without any purification. Yellow oil (30 mg, 93%). MS(ESI$^+$): *m/z* 319.24 $(M + H)^+$.

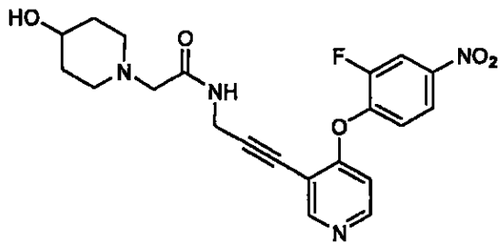
F) 1-(3-Fluoro-4-(3-(3-(2-(pyrrolidin-1-yl)acetamido)prop-1-ynyl)pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea, dihydrochloride salt

[00213] The title compound was prepared from *N*-(3-(4-(4-amino-2-fluorophenoxy)pyridin-3-yl)prop-2-ynyl)-2-(pyrrolidin-1-yl)acetamide (32 mg, 0.088 mmol) and 0.3 M solution of 2-(4-fluorophenyl)acetyl isocyanate in toluene (Compound D of Example 11, 0.40 ml, 0.12 mmol) using THF (0.5 ml) in a manner similar to that of Step D of Example 33. The product was purified by preparative HPLC (Column B). The fraction containing the product was treated with excess 1 M hydrochloric acid, concentrated *in vacuo* and lyophilized to give the title compound (30 mg, 63%) as a pale yellow solid. ^{1}H NMR (DMSO-d_6) δ 11. 07 (s, 1H), 10.62 (s, 1H), 10.09 (s, 1H), 9.17 – 9.14 (m, 1H), 8.65 (s, 1H), 8.43 (d, 1H, J = 5.6 Hz), 7.81 (dd, 1H, J = 2.5, 12.7 Hz), 7.44 – 7.33 (m, 4H), 7.19 – 7.12 (m, 2H), 4.31 (d, 2H, J = 5.6 Hz), 4 05 (d, 2H, J = 5.6 Hz), 3.74 (s, 2H), 3.56 – 3.51 (m, 2H), 3.05 – 2.99 (m, 2H), 1.96 – 1.90 (m, 2H), 1.88 - 1.79 (m, 2H); MS(ESI$^+$): *m/z* 548 26 $(M + H)^+$.

Example 43

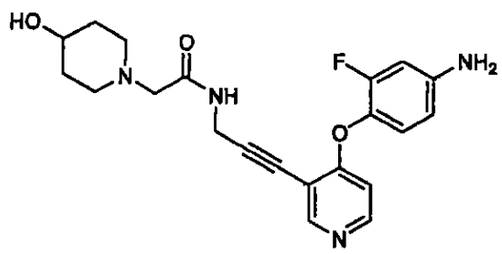


1-(3-Fluoro-4-(3-(3-(2-(4-hydroxypiperidin-1-yl)acetamido)prop-1-ynyl)pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea, dihydrochloride salt



A) *N*-(3-(4-(2-Fluoro-4-nitrophenoxy)pyridin-3-yl)prop-2-ynyl)-2-(4-hydroxypiperidin-1-yl)acetamide

[00214] The title compound was prepared from 3-(4-(2-fluoro-4-nitrophenoxy)pyridin-3-yl)prop-2-yn-1-amine (Compound A of Example 36, 80 mg, 0.26 mmol), 4-hydroxypiperidine (79 mmol, 0.78 mmol) and chloroacetyl chloride (40 mg, 0.36 mmol) in the same manner as for Step D of Example 42. The residue was purified by flash chromatography on silica gel eluting with 1-3 % MeOH / CH_2Cl_2 to give a white foam (40 mg, 36%). ^{1}H NMR (DMSO-d_6) δ 8.65 (s, 1H), 8.49 (d, 1H, J = 5.5 Hz), 8.41 (dd, 1H, J = 10.4, 2.7 Hz), 8.18 – 8.12 (m, 2H), 7.55-7.50 (m, 1H), 7.05 (d, 1H, J = 6.0 Hz), 4.54 (d, 1H, J = 3.8 Hz), 4.11 (d, 2H, J = 6.0 Hz), 3.43-3.36 (m, 1H), 2.86 (s, 2H), 2.64-2.58 (m, 2H), 2.12-2.05 (m, 2H), 1.67-1.61 (m, 2H), 1.44-1.36 (m, 2H); MS(ESI$^+$): *m/z* 429.18 $(M + H)^+$.



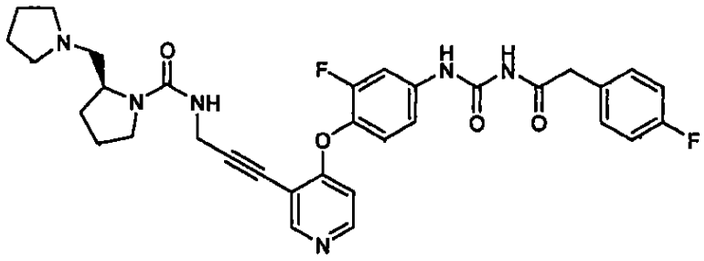
B) *N*-(3-(4-(4-Amino-2-fluorophenoxy)pyridin-3-yl)prop-2-ynyl)-2-(4-hydroxypiperidin-1-yl)acetamide

[00215] The title compound was prepared by the reduction *N*-(3-(4-(2-fluoro-4-nitrophenoxy)pyridin-3-yl)prop-2-ynyl)-2-(4-hydroxypiperidin-1-yl)acetamide (33 mg, 0.077 mmol) in a manner similar to that of Step E of Example 35 using Fe (powder, 67 mg, 1.21 mmol), NH_4Cl (128 mg, 2.42 mmol). The product (30 mg, 100%) was obtained as a yellow oil which was used directly in the subsequent step. MS(ESI$^+$): *m/z* 399.27 $(M + H)^+$.

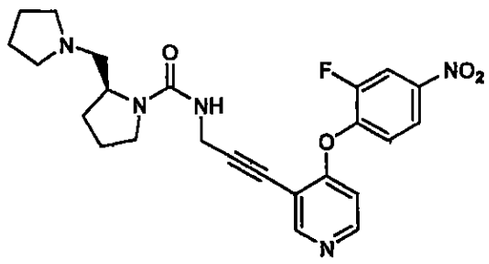
C) **1-(3-Fluoro-4-(3-(3-(2-(4-hydroxypiperidin-1-yl)acetamido)prop-1-ynyl)pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea, dihydrochloride salt**

[00216] The title compound was prepared from *N*-(3-(4-(4-amino-2-fluorophenoxy)pyridin-3-yl)prop-2-ynyl)-2-(4-hydroxypiperidin-1-yl)acetamide (25 mg, 0 063 mmol) and 0.3 M solution of 2-(4-fluorophenyl)acetyl isocyanate in toluene (Compound D of Example 11, 0.40 mL, 0.12 mmol) using THF (0.5 ml) in a manner similar to that of Step D of Example 33. The product was purified by preparative HPLC (Column B). The fraction containing the product was treated with excess 1 N hydrochloric acid, concentrated and lyophilized to give the title compound (10 mg, 30%) as a pale yellow solid. ^{1}H NMR (DMSO-d_6) δ 11.08 (s, 1H), 10.64 (s, 1H), 9.83 – 9.72 (m, 1H), 9.25 – 9.20 (m, 1H), 8.66 (s, 1H), 8.45 (d, 1H, J =6.1 Hz), 7.83 (dd, 1H, J = 2.0, 13.2 Hz), 7.46 - 7.35 (m, 3H), 7.21 – 7.11 (m, 2H), 6.77 (d, 1H, J = 6.1 Hz), 4.33 -4.31 (m, 2H), 3.99 – 3.94 (m, 2H), 3.92 – 3.89 (m, 1H), 3.76 (s, 2H), 3.46 – 3.40 (m, 2H), 3.29 – 3.21 (m, 2H), 3.10 – 3.00 (m, 1H), 1.98 – 1.87 (m, 2H), 1 72 – 1.62 (m, 2H); MS(ESI$^+$): *m/z* 528.25 $(M + H)^+$.

Example 44

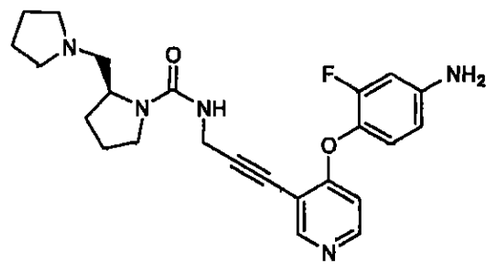


(*S*)-1-(3-Fluoro-4-(3-(3-(2-(pyrrolidin-1-ylmethyl)pyrrolidine-1-carboxamido)prop-1-ynyl)pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea, dihydrochloride salt



A) (*S*)-*N*-(3-(4-(2-Fluoro-4-nitrophenoxy)pyridin-3-yl)prop-2-ynyl)-2-(pyrrolidin-1-ylmethyl)pyrrolidine-1-carboxamide

[00217] 3-(4-(2-Fluoro-4-nitrophenoxy)pyridin-3-yl)prop-2-yn-1-amine (Compound A of Example 36, 55 mg, 0.19 mmol) was dissolved in CH_2Cl_2 (5 mL), treated with 4-nitrophenyl chloroformate (0.38 mg, 0.19 mmol) and pyridine (15 μL, 0.19 mmol). The reaction mixture was stirred at rt. After 1 h, the mixture was treated with Et_3N (30 mL, 0.20 mmol) and (*S*)-(+)-1-(2-pyrrolidinylmethyl)pyrrolidone (Aldrich, 32 mg, 0.21 mmol) and stirred at rt for 15 h. The mixture was then diluted with CH_2Cl_2 (50 mL), washed with 1 M NaOH and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product. The residue was purified by flash chromatography on silica gel eluting with 0-10 % MeOH / CH_2Cl_2 to give the title compound (53 mg, 60%) as a yellow oil. ^{1}H NMR (DMSO-d_6) δ 8.65 (s, 1H), 8.49 (d, 1H, J = 6.1 Hz), 8.41 (dd, 1H, J = 2.8 Hz, 10.5 Hz), 8.16 (d, 1H, J = 7.7 Hz), 7.52 (dd, 1H, J = 8.3, 8.8 Hz), 7.05 (d, 1H, J = 6.1 Hz), 4.11 – 4.06 (m, 2H), 3.99 – 3.95 (m, 2H), 3.76 (s, 2H), 3.16 – 3.11 (m, 2H), 2.57 – 2.48 (m, 2H), 2.43 – 2.41 (m, 2H), 3.36 – 2.34 (m, 2H), 1.90 – 1.86 (m, 2H), 1.76 – 1.62 (m, 3H); MS(ESI$^+$): *m/z* 468.27 $(M + H)^+$.



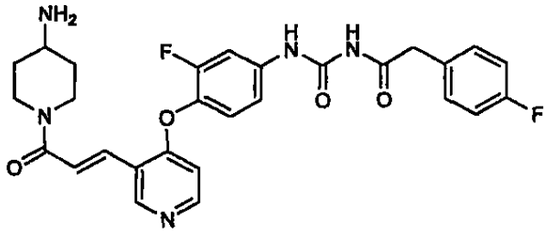
B) (*S*)-*N*-(3-(4-(4-Amino-2-fluorophenoxy)pyridin-3-yl)prop-2-ynyl)-2-(pyrrolidin-1-ylmethyl)pyrrolidine-1-carboxamide

[00218] The title compound was prepared by the reduction of (*S*)-*N*-(3-(4-(2-fluoro-4-nitrophenoxy)pyridin-3-yl)prop-2-ynyl)-2-(pyrrolidin-1-ylmethyl)pyrrolidine-1-carboxamide (50 mg, 0.11 mmol) in a manner similar to that of Step E of Example 35 using Fe (powder, 67 mg, 1.21 mmol), NH_4Cl (128 mg, 2.42 mmol). The product (36 mg, 75%) was obtained as a yellow oil which was used directly in the subsequent step. MS(ESI$^+$): *m/z* 438.30 $(M + H)^+$.

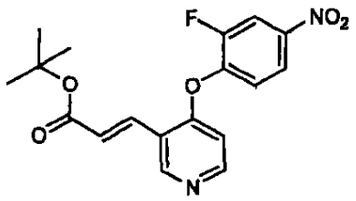
C) (S)-1-(3-Fluoro-4-(3-(3-(2-(pyrrolidin-1-ylmethyl)pyrrolidine-1-carboxamido)prop-1-ynyl)pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea, dihydrochloride salt

[00219] The title compound was prepared from (*S*)-N-(3-(4-(4-amino-2-fluorophenoxy)pyridin-3-yl)prop-2-ynyl)-2-(pyrrolidin-1-ylmethyl)pyrrolidine-1-carboxamide (36 mg, 0.057 mmol) and 0.3 M solution of 2-(4-fluorophenyl)acetyl isocyanate in toluene (Compound D of Example 11, 0.37 mL, 0.11 mmol) in the same manner as in Step D of Example 33. The product was purified by preparative HPLC (Column B) and converted to its hydrochloride according to Step C of Example 43 to give the title compound (10 mg, 25%) as an amber colored oil. ^{1}H NMR (DMSO-d_6) δ 11.06 (s, 1H), 10.60 (s, 1H), 9.56 (s, 1H), 8.58 (s, 1H), 8.38 (d, 1H, J =5.6 Hz), 7.80 (dd, 1H, J = 2.6, 12.7 Hz), 7.42 (dm, 1H, J = 10.6 Hz), 7.38–7.31 (m, 2H), 7.30–7.25 (m, 1H), 7.20–7.10 (m, 2H), 6.69 (d, 1H, J = 6.1 Hz), 4.26–4.12 (m, 2H), 3.79–3.69 (m, 3H), 3.56 (s, 2H), 3.31–3.18 (m, 2H), 3.17–2.93 (m, 2H), 2.14–2.02 (m, 4H), 2.03–1.76 (m, 5H), 1.71–1.61 (m, 1H); MS(ESI$^+$): *m/z* 617.20 $(M + H)^+$.

Example 45

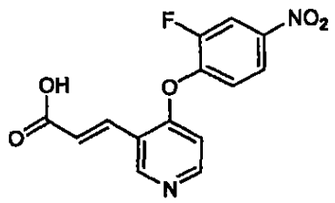


(*E*)-1-(4-(3-(3-(4-Aminopiperidin-1-yl)-3-oxoprop-1-enyl)pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, ditrifluoroacetic acid salt



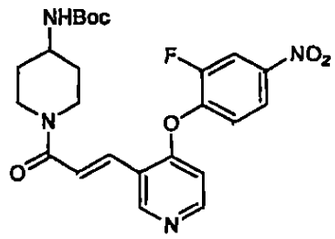
A) (*E*)-*tert*-Butyl 3-(4-(2-fluoro-4-nitrophenoxy)pyridin-3-yl)acrylate

[00220] A mixture of 4-(2-fluoro-4-nitrophenoxy)-3-iodopyridine (Compound A of Example 33, 150 mg, 0.42 mmol), *tert*-butylacrylate (Aldrich, 107 mg, 0.84 mmol), tri-*n*-butylamine (0.21 mL, 0.92 mmol) and DMF (2 mL) was degassed by vacuum/argon purge and then treated with $Pd(OAc)_2$ (17 mg, 0.078 mmol). The mixture was heated at 100-130 °C for under argon for 45 min, then the mixture was cooled to rt, partitioned between EtOAc and saturated aq. $NaHCO_3$ solution. The phases were separated and the EtOAc extracts were washed with saturated aq. $NaHCO_3$ solution and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography on SiO_2 eluting with 0-20 % EtOAc / CH_2Cl_2 to give the title compound (118 mg, 78%) as a pale yellow oil which solidified at room temperature. ^1H NMR (DMSO-d_6) δ 9.02 (s, 1H), 8.49 (d, 1H, J = 5.5 Hz), 8.46 (dd, 1H, J = 2.5, 11.7 Hz), 8.21 (dm, 1H, J = 9.2 Hz), 7.74 (d, 1H, J = 16.3 Hz), 7.65 (dd, 1H, J = 8.1, 8.6 Hz), 6.95 (d, 1H, J = 6.1 Hz), 6.77 (d, 1H, J = 16.3 Hz), 1.47 (s, 9H); MS(ESI$^+$): *m/z* 361.15 $(M+H)^+$.



B) (*E*)-3-(4-(2-Fluoro-4-nitrophenoxy)pyridin-3-yl)acrylic acid

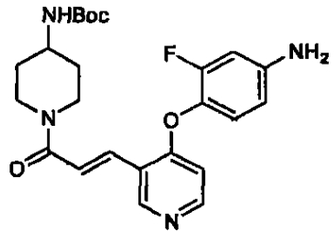
[00221] (*E*)-*tert*-Butyl 3-(4-(2-fluoro-4-nitrophenoxy)pyridin-3-yl)acrylate (115 mg, 0.32 mmol) was treated with 1:1 TFA / CH_2Cl_2 (6 mL) and stirred at room temperature for 1.5 h. The mixture was concentrated under vacuum and the residue treated with MeOH (5 mL) and 2 M HCl / Et_2O (15 mL) and concentrated under vacuum. A second treatment with MeOH (5 mL) and 2 M HCl / Et_2O (15 mL) and reconcentration gave the title compound (120 mg). ^{1}H NMR (DMSO-d_6) δ 9.17 (s, 1H), 8.62 (d, 1H, J = 6.6 Hz), 8.50 (dd, 1H, J = 2.6, 10.1 Hz), 8.25 (d, 1H, J = 9.1 Hz), 7.78 (d, 1H, J = 16.3 Hz), 7.74 (dd, 1H, J = 8.1, 8.6 Hz), 7.17 (d, 1H, J = 6.1 Hz), 6.87 (d, 1H, J = 16.3 Hz); MS(ESI$^+$): *m/z* 305.11 $(M + H)^+$.



C) (*E*)-*tert*-Butyl 1-(3-(4-(2-fluoro-4-nitrophenoxy)pyridin-3-yl)acryloyl)piperidin-4-ylcarbamate

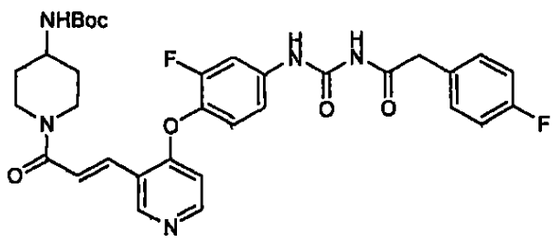
[00222] A solution of (*E*)-3-(4-(2-fluoro-4-nitrophenoxy)pyridin-3-yl)acrylic acid (143 mg, 0.42 mmol), 4-*N*-Boc-aminopiperidine (Aldrich, 84 mg, 0.42 mmol) in DMF (1.5 mL) was treated with DIPEA (160 μL, 0.92 mmol), and TBTU (160 mg, 0.50 mmol) and the mixture stirred at rt for 2 h. The mixture was diluted with EtOAc, washed with saturated aq. $NaHCO_3$ solution and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting first with 30-100 % EtOAc / hexanes then 5 % MeOH / CH_2Cl_2 to give the title compound (110 mg, 54%) as a light brown solid. ^{1}H NMR (DMSO-d_6) δ 9.15 (s, 1H), 8.48 (d, 1H, J = 5.6 Hz), 8.44 (dd, 1H, J = 2.5, 10.5 Hz), 8.18 (d, 1H, J =

9.2 Hz), 7.69 (d, 1H, J = 15.3 Hz), 7.58 (dd, 1H, J = 8.6, 8.6 Hz), 7.50 (d, 1H, J = 15.7 Hz), 6.97 (d, 1H, J = 5.6 Hz), 6.89 (d, 1H, J = 7.6 Hz), 4.31 – 4.16 (m, 2H), 3.55 – 3.46 (m, 1H), 3.20 – 3.14 (m, 1H), 2.83 – 2.81 (m, 1H), 1.82 – 1.71 (m, 2H), 1.34 – 1.18 (m, 2H), 1.37 (s, 9H); MS(ESI$^+$): *m/z* 431.04 (100) [(M-C_4H_9) $^+$H]$^+$; *m/z* 487 10 (90) $(M + H)^+$.



D) (*E*)-*tert*-Butyl 1-(3-(4-(4-amino-2-fluorophenoxy)pyridin-3-yl)acryloyl)piperidin-4-ylcarbamate

[00223] The title compound was prepared by the reduction of (*E*)-*tert*-butyl 1-(3-(4-(2-fluoro-4-nitrophenoxy)pyridin-3-yl)acryloyl)piperidin-4-ylcarbamate (100 mg, 0.21 mmol) in a manner similar to that of Step E of Example 35 using Fe powder (55 mg, 2.7 mmol), NH_4Cl (280 mg, 5.3 mmol). The product (90 mg, 95%) was obtained as a light brown solid which was used directly in the subsequent step. MS(ESI$^+$): *m/z* 457.18 $(M + H)^+$.



E) (*E*)-*tert*-Butyl 1-(3-(4-(2-fluoro-4-(3-(2-(4-fluorophenyl)acetyl)ureido)phenoxy)pyridin-3-yl)acryloyl)piperidin-4-ylcarbamate

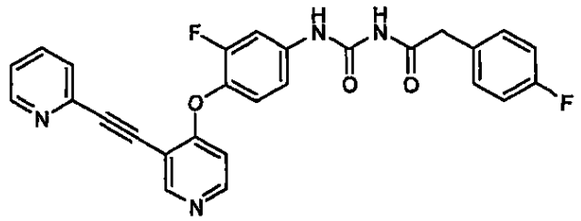
[00224] The title compound was prepared from (*E*)-*tert*-butyl 1-(3-(4-(4-amino-2-fluorophenoxy)pyridin-3-yl)acryloyl)piperidin-4-ylcarbamate (42 mg, 0.092 mmol) and 0.3 M solution of 2-(4-fluorophenyl)acetyl isocyanate in toluene (Compound D of

Example 11, 0.50 mL, 0.15 mmol) in a manner similar to that of Step D of Example 33. The crude product was adsorbed onto silica gel and purified by flash chromatography eluting with 0-5 % MeOH / EtOAc to give the product (20 mg, 33%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.05 (s, 1H), 10.59 (s, 1H), 9.03 (s, 1H), 8.37 (d, 1H, J = 5.6 Hz), 7.82-7.74 (m, 2H), 7.47 (d, 1H, J = 15.8 Hz), 7.42-7.33 (m, 4H), 7.20-7.13 (m, 2H), 6.89 (d, 1H, J = 8.1 Hz), 6.63 (d, 1H, J = 5.6 Hz), 4.31 (d, 1H, J = 13.7 Hz), 4.19 (d, 1H, J = 12.7 Hz), 3.74 (s, 2H), 3.56-3.47 (m, 1H), 3.22-3.13 (m, 1H), 2.84-2.76 (m, 1H), 1.76 (s, 2H), 1.37 (s, 9H), 1.32-1.20 (m, 2H); MS(ESI$^+$): *m/z* 636.23 $(M+H)^+$.

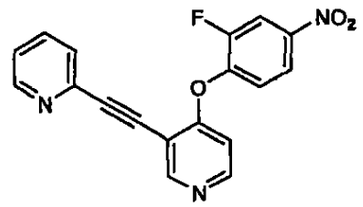
F) (*E*)-1-(4-(3-(3-(4-Aminopiperidin-1-yl)-3-oxoprop-1-enyl)pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, ditrifluoroacetic acid salt

[00225] (*E*)-*tert*-Butyl 1-(3-(4-(2-fluoro-4-(3-(2-(4-fluorophenyl)acetyl)ureido)phenoxy)pyridin-3-yl)acryloyl)piperidin-4-ylcarbamate (15 mg, 0.024 mmol) was dissolved in anhydrous MeOH (0.5 mL), treated with 4 M HCl / 1,4-dioxane (1.5 mL) and stirred at rt for 1 h. The mixture was concentrated under vacuum to give the crude product which was purified by preparative HPLC (Column A). The fraction containing the product was treated with excess 1 M hydrochloric acid, concentrated and lyophilized to give the title compound (8 mg, 44%) as a pale yellow solid. ^{1}H NMR (DMSO-d_6) δ 11.07 (s, 1H), 10.61 (s, 1H), 9.10 (s, 1H), 8.44 (s, 1H), 7.91 (m, 3H), 7.86-7.69 (m, 2H), 7.55–7.28 (m, 5H), 7.23–7.08 (m, 2H), 6.80–6.72 (m, 1H), 5.61–5.33 (m, 1H), 4.45–4.20 (m, 2H), 3.74 (s, 2H), 3.39–3.07 (m, 2H), 2.82–2.68 (m, 1H), 1.91–1.51 (m, 2H), 1.50–1.15 (m, 1H), MS(ESI$^+$): *m/z* 536.16 $(M+H)^+$.

Example 46

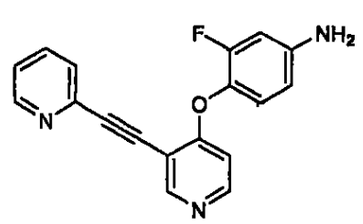


1-(3-Fluoro-4-(3-(2-(pyridin-2-yl)ethynyl)pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea, dihydrochloride salt



A) 2-(2-(4-(2-Fluoro-4-nitrophenoxy)pyridin-3-yl)ethynyl)pyridine

[00226] A mixture of 4-(2-fluoro-4-nitrophenoxy)-3-iodopyridine (Compound A of Example 33, 50 mg, 0.14 mmol) and 2-ethynylpyridine (Aldrich, 57 mg, 0.54 mmol), THF (1 mL) and Et_3N (1 mL) was degassed by vacuum / argon purge and treated in turn with CuI (3 mg, 0.016 mmol) and $(Ph_3P)_4Pd$ (10 mg, 0.009 mmol). The mixture was heated at 60 °C 45 minutes, cooled, partitioned between EtOAc and saturated sodium bicarbonate and the EtOAc phase dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product. Purification of the residue by flash column chromatography on SiO_2 eluting with 0-1.5 % MeOH / CH_2Cl_2 gave the title compound (42 mg, 89%) as a brown solid. ^1H NMR (DMSO-d_6) δ 8.91 (s, 1H), 8.60 (d, 1H, J = 4.5 Hz), 8.45 (dd, 1H, J = 2.6, 10.7 Hz), 8.19 (d, 1H, J = 9.1 Hz), 7.86–7.83 (m, 1H), 7.66 (dd, 1H, J = 8.7, 8.7 Hz), 7.57 (d, 1H, J = 7.6 Hz), 7 45 -7.42 (m, 2H), 7.14 (d, 1H, J = 4.5 Hz); MS(ESI$^+$): *m/z* 336.20 $(M + H)^+$.



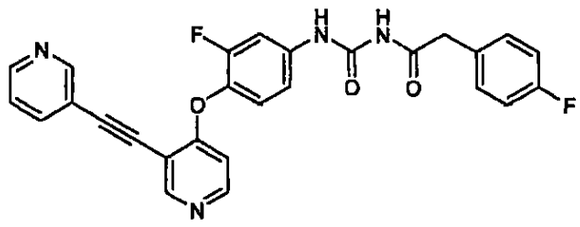
B) 3-Fluoro-4-(3-(2-(pyridin-2-yl)ethynyl)pyridin-4-yloxy)benzenamine

[00227] The title compound was prepared from 2-(2-(4-(2-fluoro-4-nitrophenoxy)pyridin-3-yl)ethynyl)pyridine (30 mg, 0.090 mmol) in a manner similar to that of Step E of Example 35 to give the title compound (20 mg) as a brown solid. MS(ESI$^+$): *m/z* 306.20 $(M + H)^+$.

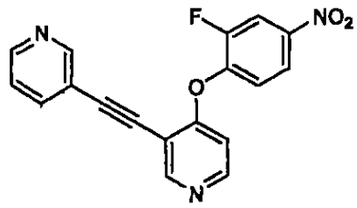
C) 1-(3-Fluoro-4-(3-(2-(pyridin-2-yl)ethynyl)pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea, dihydrochloride salt

[00228] The title compound was prepared from 3-fluoro-4-(3-(2-(pyridin-2-yl)ethynyl)pyridin-4-yloxy)benzenamine (19 mg, 0.062 mmol) and 0.3 M solution of 2-(4-fluorophenyl)acetyl isocyanate in toluene (Compound D of Example 11, 0.50 mL, 0.15 mmol) in a manner similar to that of Step D of Example 33. Purification of the reaction mixture by flash chromatography on SiO_2 eluting with 0 - 100 % EtOAc / CH_2Cl_2 gave a white solid which was converted to the hydrochloride in a manner similar to Step D of Example 33 to give the title compound (19 mg, 60%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.07 (s, 1H), 10.61 (s, 1H), 8.79 (s, 1H), 8.63 (d, 1H, J = 5.6 Hz), 8.47 (d, 1H, J = 5.6 Hz), 7.89 – 7.86 (m, 1H), 7.83 (dd, 1H, J = 1.5, 12.7 Hz), 7.67 (d, 1H, J = 7.6 Hz), 7.47 – 7.43 (m, 2H), 7.39 – 7.35 (m, 1H), 7.30 – 7.27 (m, 1H), 7.20 – 7.16 (m, 2H), 7.14 – 7.10 (m, 1H), 6.77 (d, 1H, J = 5.6 Hz), 3.75 (s, 2H); MS(ESI$^+$): *m/z* 485.17 $(M + H)^+$.

Example 47

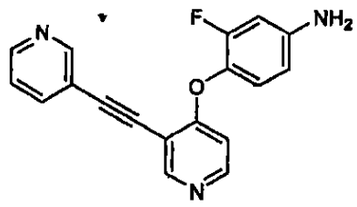


1-(3-Fluoro-4-(3-(2-(pyridin-3-yl)ethynyl)pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea, dihydrochloride salt



A) 3-(2-(4-(2-Fluoro-4-nitrophenoxy)pyridin-3-yl)ethynyl)pyridine

[00229] A mixture of 4-(2-fluoro-4-nitrophenoxy)-3-iodopyridine (Compound A of Example 33, 50 mg, 0.14 mmol) and 3-ethynylpyridine (57 mg, 0.54 mmol), THF (1 mL) and Et_3N (1 mL) was degassed by vacuum / argon purge and treated in turn with CuI (3 mg, 0.016 mmol), and $(Ph_3P)_4Pd$ (10 mg, 0.009 mmol). The mixture was heated at 60 °C 45 minutes, cooled, partitioned between EtOAc and saturated sodium bicarbonate and the EtOAc phase dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by flash chromatography on SiO_2 eluting with 0-1.5 % MeOH / CH_2Cl_2 gave the title compound (33 mg, 77%) as a brown solid. ^1H NMR (DMSO-d_6) δ 8.86 (s, 1H), 8.65 (s, 1H), 8.61 – 8.57 (m, 2H), 8.45 (dd, 1H, J = 2.6, 10.7 Hz), 8.18 (d, 1H, J = 9.2 Hz), 7.90 (d, 1H, J = 9.2 Hz), 7.62 (dd, 1H, J = 8.7, 8.7 Hz), 7.46 (dd, 1H, J = 4.6 , 8.1 Hz), 7.17 (d, 1H, J = 5.6 Hz); MS(ESI$^+$): *m/z* 336.19 $(M + H)^+$.



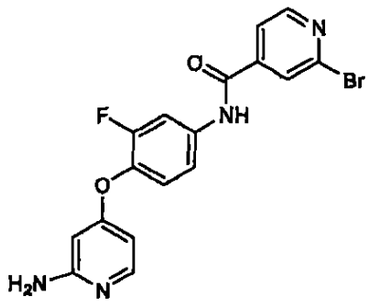
B) 3-Fluoro-4-(3-(2-(pyridin-3-yl)ethynyl)pyridin-4-yloxy)benzenamine

[00230] The title compound was prepared from 3-(2-(4-(2-fluoro-4-nitrophenoxy)pyridin-3-yl)ethynyl)pyridine (30 mg, 0.090 mmol) in a manner similar to Step E of Example 35 to give the title compound as a brown solid (25 mg, 93%). MS(ESI$^+$): *m/z* 306.20 $(M + H)^+$.

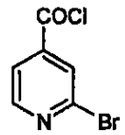
C) **1-(3-Fluoro-4-(3-(2-(pyridin-3-yl)ethynyl)pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea, dihydrochloride salt**

[00231] The title compound was prepared from 3-fluoro-4-(3-(2-(pyridin-3-yl)ethynyl)pyridin-4-yloxy)benzenamine (22 mg, 0.072 mmol) and 0.3 M solution of 2-(4-fluorophenyl)acetyl isocyanate in toluene (Compound D of Example 11, 0.50 mL, 0.15 mmol) in a manner similar to Step D of Example 33. Purification of the reaction mixture by flash column chromatography on SiO_2 eluting with 0-100 % EtOAc / CH_2Cl_2 gave a white solid which was converted to the hydrochloride in a manner similar to Step D of Example 33 to give the title compound (15 mg, 38%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.04 (s, 1H), 10.59 (s, 1H), 8.76 (s, 1H), 8.74 (d, 1H, J = 1.1 Hz), 8.60 (dd, 1H, J = 5.6, 1.1 Hz), 8.45 (d, 1H, J = 6.1 Hz), 7.98 (d, 1H, J = 7.7 Hz), 7.80 (d, 1H, J = 12.1 Hz), 7.47 – 7.45 (m, 1H), 7.41 (s, 2H), 7.36 – 7.34 (m, 2H), 7.16 (dd, 2H, J = 8.8, 8.9 Hz), 6.78 (d, 1H, J = 5.5 Hz), 3.74 (s, 2H); MS(ESI$^+$): 485.13 *m/z*.

Example 48



***N*-(4-(2-Aminopyridin-4-yloxy)-3-fluorophenyl)-2-bromoisonicotinamide, trifluoroacetic acid salt**



A) **2-Bromo-isonicotinicacyl chloride**

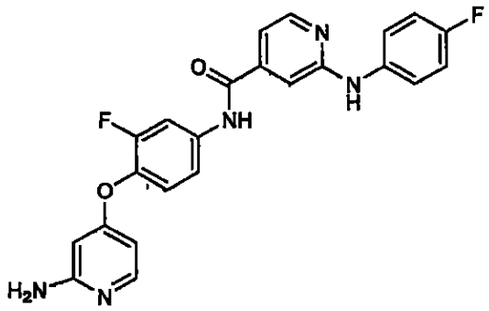
[00232] A solution of 2-bromo-isonicotinic acid (Lancaster, 70 mg, 0.34 mmol) in thionyl chloride (1.2 mL) was heated at reflux temperature for 1.5 h. The mixture was

concentrated and the crude product of 2-bromoisonicotinoyl chloride was used directly in the next step without further purification.

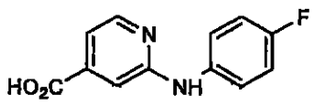
B) *N*-(4-(2-Aminopyridin-4-yloxy)-3-fluorophenyl)-2-bromoisonicotinamide

[00233] To the above residue was added a solution of 4-(4-amino-2-fluorophenoxy)pyridine-2-amine (Compound B of Example 24, 70 mg, 0.32 mmol) in CH_2Cl_2 (3 mL) at rt, and the reaction was stirred for 1 h. The reaction mixture was concentrated and the residue was purified by preparative HPLC to obtain the title compound (75 mg, 45 %) as a yellow solid (TFA salt). ^{1}H NMR (DMSO-d_6) δ 11.03 (s, 1H), 8.62 (d, 1H, J = 5.0 Hz), 8.17 (s, 1 H), 7.89-8.04 (m, 4H), 7.71 (d, 1H, J = 8.8 Hz), 7.51 (t, 1H, J = 9.3 Hz), 6.72 (dd, 1H, J = 7.1, 2.2 Hz), 6.18 (d, 1H, J = 2.2 Hz); MS(ESI$^+$) m/z 403, 405 $(M+H)^+$.

Example 49



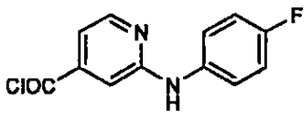
***N*-(4-(2-Aminopyridin-4-yloxy)-3-fluorophenyl)-2-(4-fluorophenylamino) isonicotinamide, bis-trifluoroacetic acid salt**



A) 2-(4-Fluorophenylamino)isonicotinic acid

[00234] To a mixture of 2-fluoro-isonicotinic acid (Aldrich, 423 mg, 3.0 mmol) and 4-fluoroaniline (555 mg, 5.0 mmol) in DMF (18 mL) at rt was added NaH (500 mg of 60% in oil), and the mixture was heated at 85 °C for 75 min. Acetic acid (0.7 mL) was added to the reaction mixture and it was concentrated *in vacuo*. To the residue were added EtOAc (100 mL) and water (20 mL), stirred for 20 min and the

solid was filtered, washed with EtOAc and dried to obtain the desired product (600 mg, 50 %) as a tan solid. ^{1}H NMR (DMSO-d_6) δ 8.98 (s, 1H), 8.43 (s, 1H), 8.04 (d, 1H, J = 4.9 Hz), 7.69 (dd, 2H, J = 8.8, 4.9 Hz), 7.24 (s, 1H), 7.05 (dd, 2H, J = 8.2, 6.0 Hz); MS(ESI$^+$) m/z 233.3 $(M + H)^+$.



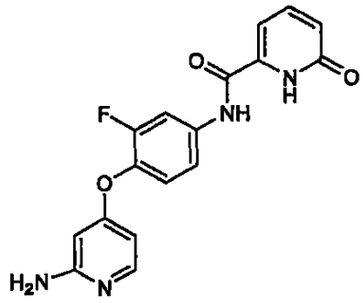
B) 2-(4-Fluorophenylamino)isonicotinicacyl chloride

[00235] A mixture of 2-(4-fluorophenylamino)isonicotinic acid (464 mg, 2.0 mmol) and thionyl chloride (10 mL) was heated at reflux temperature for 2 h. The reaction was concentrated *in vacuo*, and the crude product was used directly in the next step.

C) *N*-(4-(2-Aminopyridin-4-yloxy)-3-fluorophenyl)-2-(4-fluorophenylamino)isonicotinamide

[00236] A solution of 4-(4-amino-2-fluorophenoxy)pyridine-2-amine (Compound B of Example 24, 450 mg, 2.1 mmol) in 1,2-dichloroethane (10 mL) was added slowly to a solution of acylchloride obtained above in 1,2-dichloroethane (10 mL) at ice bath temperature with stirring. The reaction mixture was allowed to stand at rt overnight. To the reaction mixture were added EtOAc (150 mL) and saturated aq. $NaHCO_3$ solution (50 mL). The EtOAc layer was separated, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by preparative HPLC to obtain the title compound (69 mg, 6.3 %) as a yellow solid (bis-TFA salt). ^{1}H NMR (DMSO-d_6) δ 10.90 (s, 1H), 9.32 (s, 1H), 8.27 (d, 1H, J = 5.5 Hz), 7.92-7.07 (m, 11H), 6.68 (dd, 1H, J = 7.1, 2.2 Hz), 6.10 (d, 1H, J = 2.2 Hz); MS(ESI$^+$) m/z 217.9 $(M + H)^+$.

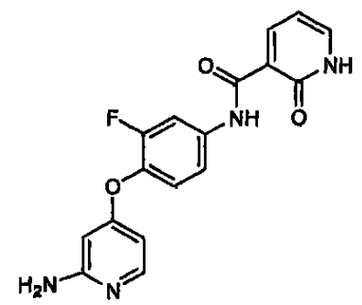
Example 50



***N*-(4-(2-Aminopyridin-4-yloxy)-3-fluorophenyl)-6-oxo-1,6-dihydropyridine-2-carboxamide, trifluoroacetic acid salt**

[00237] To a solution of 6-hydroxypicolinic acid (Aldrich, 28 mg, 0.20 mmol) and HOBt (28 mg, 0.21 mmol) in DMF (2 mL) at rt was added EDCI.HCl (50 mg, 0.26 mmol) followed by 4-(4-amino-2-fluorophenoxy)pyridine-2-amine (Compound B of Example 24, 42 mg, 0.19 mmol), and the reaction mixture was stirred overnight at rt. Purification of the reaction mixture by preparative HPLC afforded the desired product (24 mg, 25 %) as a light brown solid (TFA salt). ^{1}H NMR (CD_3OD) δ 8.03 (dd, 1H, J = 12.6, 2.2 Hz), 7.79-7.36 (m, 5H), 6.85 (d, 1H, J = 8.8 Hz), 6.67 (dd, 1H, J = 7.2, 4.4 Hz), 6.22 (d, 1H, J = 2.2 Hz); MS(ESI$^+$) m/z 341.3 $(M + H)^+$.

Example 51

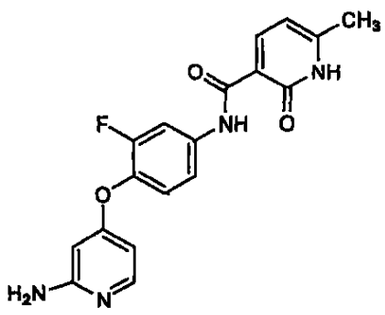


***N*-(4-(2-aminopyridin-4-yloxy)-3-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, trifluoroacetic acid salt**

[00238] To a solution of 2-hydroxynicotinic acid (Aldrich, 42 mg, 0.30 mmol) and HOBt (18 mg) in DMF (2 mL) at rt was added EDCI.HCl (80 mg, 0.42 mmol) followed by 4-(4-amino-2-fluorophenoxy)pyridine-2-amine (Compound B of Example 24, 65 mg, 0.30 mmol), and the reaction mixture was stirred for 20 h at rt.

Purification of the reaction mixture by preparative HPLC afforded the desired product (70 mg, 49 %) as a beige-colored solid (TFA salt). ^{1}H NMR (CD_3OD) δ 8.59 (dd, 1H, J = 7.1, 2.2 Hz), 8.03 (dd, 1H, J = 12.6, 2.2 Hz), 7.83 (d, 1H, J = 7.7 Hz), 7.75 (dd, 1H, J = 6.6, 2.2 Hz), 7.44 (d, 1H, J = 8.8 Hz), 7.32 (t, 1H, J = 8.8 Hz), 6.67 (m, 2H), 6.21 (d, 1H, J = 2.2 Hz); MS(ESI$^+$) m/z 341.2 $(M + H)^+$.

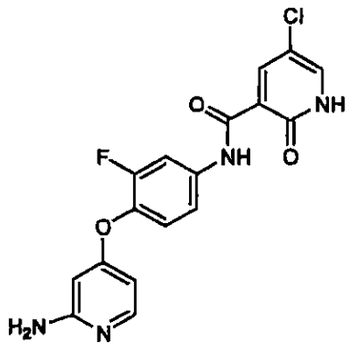
Example 52



***N*-(4-(2-Aminopyridin-4-yloxy)-3-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide, trifluroacetic acid salt**

[00239] To a solution of 2-hydroxy-6-methylnicotinic acid (Lancaster, 72 mg, 0.47 mmol) and HOBt (50 mg) in DMF (5 mL) at rt was added EDCI HCl (130 mg, 0.68 mmol) followed by 4-(4-amino-2-fluorophenoxy)pyridine-2-amine (Compound B of Example 24, 110 mg, 0.50 mmol), and the reaction mixture was stirred at rt over 72 h. Purification of the reaction mixture by preparative HPLC afforded the desired product (125 mg, 55 %) as a beige-colored solid (TFA salt). ^{1}H NMR (CD_3OD) δ 8.46 (d, 1H, J = 7.9 Hz), 8.03 (dd, 1H, J = 12.7, 2.8 Hz), 7.83 (d, 1H, J = 7.1Hz), 7.44 (dd, 1H, J = 8.8, 2.2 Hz), 7.33 (t, 1H, J = 8.8 Hz), 6.67 (dd, 1H, J = 7.7, 2.7 Hz), 6.45 (d, 1H, J = 7.7 Hz), 6.21 (d, 1H, J = 2.8 Hz), 2.40 (s, 3H); MS(ESI$^+$) m/z 355.2 $(M + H)^+$.

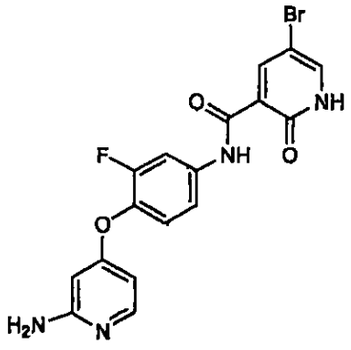
Example 53



***N*-(4-(2-Aminopyridin-4-yloxy)-3-fluorophenyl)-5-chloro-2-oxo-1,2-dihydropyridine-3-carboxamide, trifluroacetic acid salt**

[00240] To a solution of 2-hydroxy-5-chloronicotinic acid (Avocado, 87 mg, 0.50 mmol) and HOBt (40 mg) in DMF (4 mL) at rt was added EDCI.HCl (130 mg, 0.68 mmol) followed by 4-(4-amino-2-fluorophenoxy)pyridine-2-amine (Compound B of Example 24, 110 mg, 0.50 mmol), and the reaction mixture was stirred for 72 h. Purification of the reaction mixture by preparative HPLC afforded the desired product (115 mg, 45 %) as a beige-colored solid (TFA salt). ^{1}H NMR (CD_3OD) δ 8.50 (d, 1H, J = 3.3 Hz), 8.03 (dd, 1H, J = 12.6, 2.1 Hz), 7.84 (m, 2H), 7.46 (d, 1H, J = 8.8 Hz), 7.34 (t, 1H, J = 8.8 Hz), 6.67 (dd, 1H, J = 7.2, 2.2 Hz), 6.21 (d, 1H, J = 2.2 Hz); MS(ESI$^+$) m/z 375.1, 377.1 $(M + H)^+$.

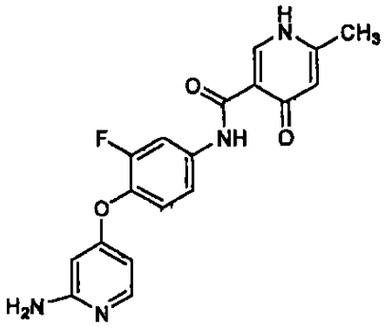
Example 54



***N*-(4-(2-Aminopyridin-4-yloxy)-3-fluorophenyl)-5-bromo-2-oxo-1,2-dihydropyridine-3-carboxamide, trifluoroacetic acid salt**

[00241] To a solution of 2-hydroxy-5-bromo-nicotinic acid (147 mg, 0.67 mmol, *Syn Comm.*, 1989, *19*, 553-559) and HOBt (30 mg) in DMF (4 mL) at rt was added EDCI.HCl (160 mg, 0.83 mmol) followed by 4-(4-amino-2-fluorophenoxy)pyridine-2-amine (Compound B of Example 24, 147 mg, 0.67 mmol), and the reaction mixture was stirred at rt overnight. Purification of the reaction mixture by preparative HPLC afforded the title compound (120 mg, 33 %) as a beige-colored solid (TFA salt). ^{1}H NMR (DMSO-d_6) δ 13.22 (s, 1H), 12.23 (s, 1H), 8.40 (d, 1H, J = 2.8 Hz), 8.14 (d, 1H, J = 2.8 Hz), 8.12-7.46 (m, 5H), 6.68 (dd, 1H, J = 7.2, 2.2 Hz), 6.14 (d, 1H, J = 2.2 Hz); MS(ESI$^+$) m/z 419 / 421 $(M+H)^+$.

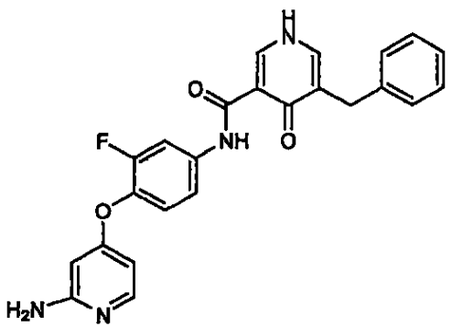
Example 55



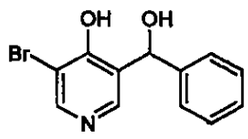
***N*-(4-(2-Aminopyridin-4-yloxy)-3-fluorophenyl)-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxamide, trifluoroacetic acid salt**

[00242] To a solution of 4-hydroxy-6-methyl-nicotinic acid (Wako, 77 mg, 0.50 mmol) and HOBt (50 mg) in DMF (5 mL) at rt was added EDCI.HCl (130 mg, 0.68 mmol) followed by 4-(4-amino-2-fluorophenoxy)pyridine-2-amine (Compound B of Example 24, 110 mg, 0.50 mmol), and the reaction mixture was stirred at rt overnight, and then heated at 75 °C for 1.5 h. After cooling the reaction mixture to rt purification by preparative HPLC afforded the title compound (70 mg, 29 %) as a white solid (TFA salt). ^{1}H NMR (DMSO-d_6) δ 13.22 (br s, 1H), 12.53 (s, 1H), 8.47 (d, 1H, J = 5.5 Hz), 8.04 (d, 1H, J = 2.2 Hz), 7.95 (d, 1H, J = 8.2 Hz), 7.82 (s, 2H), 7.46-7.42 (m, 2H), 6.70 (dd, 1H, J = 7.7, 2.7 Hz), 6.39 (s, 1H), 6.14 (d, 1H, J = 2.2 Hz); MS(ESI$^+$) m/z 355.3 $(M+H)^+$.

Example 56

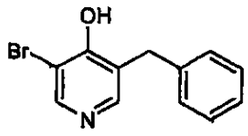


***N*-(4-(2-Aminopyridin-4-yloxy)-3-fluorophenyl)-5-benzyl-4-oxo-1,4-dihydropyridine-3-carboxamide, trifluoroacetic acid salt**



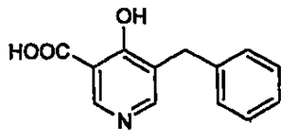
A) 3-Bromo-5-(hydroxy(phenyl)methyl)pyridin-4-ol

[00243] To a heterogeneous mixture of 3,5-dibromo-4-hydroxypyridine (2.53 g, 10 mmol, prepared following the procedure in *Synthesis*, **2001**, *14*, 2175-2179) in anhydrous THF (20 mL) at -78 °C under Ar-atm was added phenylmagnesium bromide solution (11 mL of 1 M solution in THF, 11 mmol). After stirring for 15 min. was added *n*-BuLi solution (5.5 mL of 2 M solution in cyclohexane), and the reaction mixture was stirred for 15 min at -78 °C under Ar-atm. To this mixture benzaldehyde (2.15 mL) was added and the reaction mixture was stirred for 2 h -78°C under Ar-atm. The reaction mixture was quenched by adding HOAc (3 mL) and TFA (3 mL), concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc/MeOH // 750:250:50 followed by hexane/EtOAc/MeOH/Et_3N // 460:460:50:10 to afford the desired product (2 85 g, 91 %) as a white solid. ^1H NMR (CD_3OD) δ 8.13 (s, 1H), 8.04 (s, 1H), 7.41-7.20 (m, 5H), 5.94 (s, 1H); MS(ESI$^+$) m/z 280, 282 $(M + H)^+$.



B) 3-Benzyl-5-bromopyridin-4-ol

[00244] A mixture of 3-bromo-5-(hydroxy(phenyl)methyl)pyridin-4-ol (2.55g, 91 mmol), TFA (16 mL) and Et_3SiH in CH_2Cl_2 (30 mL) was stirred at rt for 10 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc/MeOH // 600:300:50 followed by hexane/EtOAc/MeOH // 400:400:50:10 to afford an impure product which was triturated with a small amount of MeOH and Et_2O to obtain the desired product (255 mg, 10 %) as a white solid. ^1H NMR (DMSO-d_6) δ 11.75 (br s, 1H), 8.13 (s, 1H), 7.54 (s, 1H), 7.26-7.14 (m, 5H), 2.49 (s, 2H).



C) 5-Benzyl-4-hydroxynicotinic acid

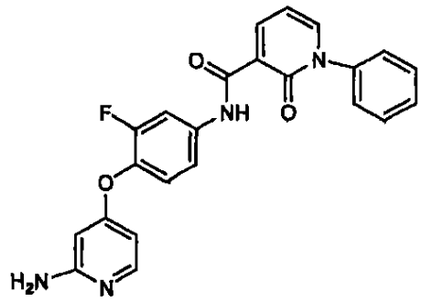
[00245] To a solution of 3-benzyl-5-bromopyridin-4-ol (220 mg, 0.83 mmol) in anhydrous THF (8 mL) at -78 °C under Ar-atm was added MeLi solution (0.61 mL of 1.5 M solution in THF, 0.92 mmol). After stirring for 5 min. *n*-BuLi solution (0.5 mL of 2 M solution in cyclohexane, 1.0 mmol) was added and the mixture was stirred for 15 min at -78 °C under Ar-atm. Carbon dioxide was bubbled through the reaction mixture for 20 min at -78 °C. The reaction mixture was then quenched by adding HOAc (2 mL), concentrated *in vacuo* and the residue was purified by by preparative HPLC to afford the desired product (100 mg, 35 %) as a white solid (TFA salt). ^1H NMR (DMF-d_7) δ 12.99 (br s, 1H), 8.69 (s, 1H), 8.28 (s, 1H), 7.35-7.19 (m, 5H), 3.90 (s, 2H); MS(ESI$^+$) m/z 230.1 $(M + H)^+$.

D) *N*-(4-(2-Aminopyridin-4-yloxy)-3-fluorophenyl)-5-benzyl-4-oxo-1,4-dihydropyridine-3-carboxamide, trifluoroacetic acid salt

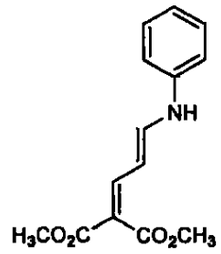
[00246] To a solution of 4-hydroxy-5-benzylnicotinic acid (35 mg, 0.15 mmol) and HOBt (30 mg) in DMF (2.5 mL) at rt was added EDCI.HCl (80 mg, 0.42 mmol) followed by 4-(4-amino-2-fluorophenoxy)pyridine-2-amine (Compound B of Example 24, 35 mg, 0.16 mmol), and the reaction mixture was stirred for 40 h at rt.

Purification of the reaction mixture by preparative HPLC afforded the desired product (35 mg, 43 %) as a white TFA solid salt. ^{1}H NMR (DMSO-d_6) δ 13.25 (br s, 1H), 12.44 (s, 1H), 8.59 (d, 1H, J = 4.9 Hz), 8.08 (dd, 1H, J = 13.2, 2.2 Hz), 7.97 (d, 1H, J = 7.1 Hz), 7.81 (d, 1H, J = 9.4 Hz), 7.52-7.19 (m, 7H), 6.72 (dd, 1H, J = 7.2, 2.2 Hz), 6.15 (d, 1H, J = 2.5 Hz), 3.81 (s, 2H), 3.51 (br s, 2H); MS(ESI$^+$) m/z 431.2 $(M + H)^+$.

Example 57

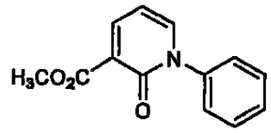


***N*-(4-(2-Aminopyridin-4-yloxy)-3-fluorophenyl)-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide, trifluoroacetic acid salt**



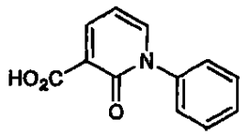
A) **(*E*)-Dimethyl 2-(3-(phenylamino)allylidene)malonate**

[00247] To a solution of 2-(3-methoxyallylidene)malonic acid dimethyl ester (Acros Organics, 200 mg, 1.0 mmol) in THF (2 mL) at rt was added aniline (300 mg, 3.2 mmol) and the reaction mixture was heated at 60 °C for 8.5 h. Purification of the reaction mixture by preparative HPLC provided the desired product (150 mg, 57 %) as a yellow solid. ^{1}H NMR (DMSO-d_6) δ 10.16 (d, 1H, J = 12.7 Hz), 8.06 (t, 1H, J = 12.7 Hz), 7.74 (d, 1H, J = 12.7 Hz), 7.30 (t, 2H, J = 8.7 Hz), 7.16 (d, 2H, J = 7.7 Hz), 6.98 (t, 1H, J = 7.7 Hz), 6.35 (t, 1H, J = 12.1 Hz), 3.69 (s, 3H), 3.65 (s, 3H).



B) Methyl 2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxylate

[00248] To a solution of the aniline adduct obtained above (130 mg, 0.50 mmol) in methanol (8 mL) at rt was added NaH (50 mg of the 60% NaH in oil, 1.2 mmol) and the mixture was stirred at rt for 3 h. Acetic acid (0.3 mL) was added to the mixture, concentrated to a volume of ~4 mL, and purification of the reaction mixture by preparative HPLC provided the desired product (105 mg, 92 %) as a yellow solid. ^{1}H NMR (CD_3OD) δ 8.30 (dd, 1H, J = 7.2, 2.2 Hz), 7.87 (dd, 1H, J = 6.6, 1.7 Hz), 7.57-7.38 (m, 5H), 6.53 (t, 1H, J = 7.0 Hz), 3.84 (s, 3H); MS(ESI$^+$) m/z 230.3 $(M + H)^+$.



C) 2-Oxo-1-phenyl-1,2-dihydropyridine-3-carboxylic acid

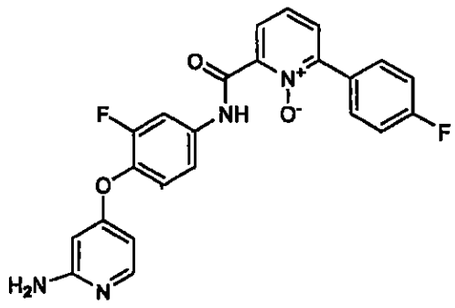
[00249] A mixture of methyl 2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxylate (70 mg, 0.31 mmol) and LiOH (40 mg) in methanol (6 mL) and water (1 mL) was stirred at rt overnight. To the reaction mixture were added EtOAc (50 mL) and 1 N aq HCl (15 mL). The EtOAc layer was separated, dried over $MgSO_4$, and concentrated *in vacuo* to afford the product (55 mg, 83 %) as a light yellow solid. ^{1}H NMR (DMF-d_7) δ 11.77 (br s, 1H), 8.57 (dd, 1H, J = 7.4, 2.0 Hz), 8.26 (dd, 1H, J = 6.6, 1.6 Hz), 7.64-7.55 (m, 5H), 6.88 (t, 1H, J = 7.0 Hz); MS(ESI$^+$) m/z 216.2 $(M + H)^+$.

D) *N*-(4-(2-Aminopyridin-4-yloxy)-3-fluorophenyl)-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide

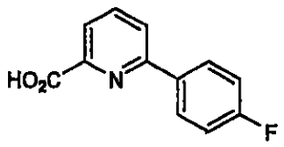
[00250] To a solution of 2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxylic acid (36 mg, 0.17 mmol) and HOBt (18 mg) in DMF (3 mL) at rt was added EDCI.HCl (45 mg, 0.23 mmol) followed by 4-(4-amino-2-fluorophenoxy)pyridine-2-amine (Compound B of Example 24, 36 mg, 0.17 mmol), and the reaction mixture was stirred at rt overnight. Purification of the reaction mixture by preparative HPLC

afforded the title compound (32 mg, 36 %) as a beige colored solid (TFA salt). ^{1}H NMR (DMSO-d_6) δ 13.35 (br s, 1H), 12.11 (s, 1H), 8.52 (dd, 1H, J = 7.3, 2.1 Hz), 8.08 (dd, 1H, J = 6.6, 2.1 Hz), 8.03 (d, 1H, J = 2.3 Hz), 7.89 (d, 1H, J = 7.2 Hz), 7.81 (s, 1H), 7.54-7.36 (m, 6H), 6.69-6.63 (m, 2H), 6.08 (d, 1H, J = 2.4 Hz), 3.55 (br s, 1H); MS(ESI$^+$) m/z 417.2 $(M+H)^+$.

Example 58



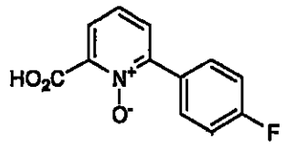
***N*-(4-(2-Aminopyridin-4-yloxy)-3-fluorophenyl)-6-(4-fluorophenyl)pyridyl-*N*-oxide-amide, trifluoroacetic acid salt**



A) 6-(4-Fluorophenyl)picolinic acid

[00251] A solution of 2-bromo-picolinic acid (Aldrich, 2.02 g, 10 mmol) in DME containing 4 mL of 10 % aq Na_2CO_3 was purged with Ar gas. To this mixture was added $Pd(PPh_3)_4$ followed by 2-(4-fluorophenyl)-5,5-dimethyl-1,3,2-dioxaborinane (Aldrich, 2.40 g, 11.5 mmol) and EtOH (20 mL), and the mixture was 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, and the filtrate solution was concentrated *in vacuo*. Purification of the resulting residue by flash column chromatography on silica gel eluting with EtOAc/MeOH // 900.100 followed by

EtOAc/MeOH/HOAc // 700:1500:50 provided 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

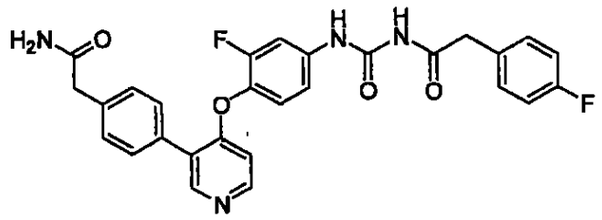
[00252] A mixture of picolinic acid derivative (1.0 g, 4.6 mmol), Na_2HPO_4 (1.2 g) and *m*-CPBA (1.1 g, ~70 % from Aldrich) in CH_2ClCH_2Cl (30 mL) was stirred at rt for 2 h. Additional Na_2HPO_4 (0.8 g) and *m*-CPBA (1.0 g) was added to the reaction mixture and it was stirred for 3 h at rt. Another Na_2HPO_4 (0.5 g) and *m*-CPBA (0.5 g) was 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 reation 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 // 700:240:60 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) *N*-(4-(2-Aminopyridin-4-yloxy)-3-fluorophenyl)-6-(4-fluorophenyl)pyridyl-*N*-oxide-amide, trifluoroaacetic acid salt

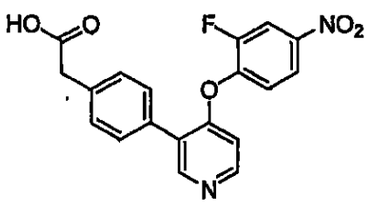
[00253] To a solution of 6-(4-fluorophenyl)picolinic acid-*N*-oxide (23 mg, 0.1 mmol) and HOBt (10 mg) in DMF (2 mL) at rt was added EDCI.HCl (30 mg, 0.16 mmol) followed by 4-(4-amino-2-fluorophenoxy)pyridine-2-amine (Compound B of Example 24, 22 mg, 0.1 mmol), and the reaction mixture was stirred at rt overnight. Purification of the reaction mixture by preparative HPLC afforded the title compound (25 mg, 46 %) as a white solid (TFA salt). ^{1}H NMR (DMF-d_7) δ 14.00 (s, 1H), 8.43 (dd, 1H, J= 8.0, 2.2 Hz), 8.15 (dd, 1H, J= 12.8, 2.4 Hz), 8.08 (d, 1H, J= 7.1 Hz),

7.99-7.37 (m, 9H), 6.72 (dd, 1H, J = 7.0, 2.4 Hz), 6.32 (d, 1H, J = 2.3 Hz), 3.7 (br s, 2H); MS(ESI$^+$) m/z 417.2 $(M+H)^+$.

Example 59

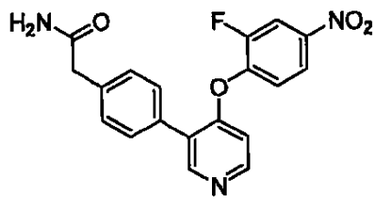


1-(4-(3-(4-(2-Amino-2-oxoethyl)phenyl)pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, hydrochloride salt



A) 2-(4-(4-(2-Fluoro-4-nitrophenoxy)pyridin-3-yl)phenyl)acetic acid

[00254] A 25 mL round bottom flask was charged with 4-(2-fluoro-4-nitrophenoxy)-3-iodopyridine (Compound A of Example 33, 120 mg, 0 33 mmol), 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetic acid (Frontier Scientific, 131 mg, 0.50 mmol), tetrakis(triphenylphosphine)palladium(0) (Strem Chemicals, 38 mg, 0.033 mmol), and sodium carbonate (245 mg, 2.3 mmol). The flask was flushed with nitrogen and then charged with dioxane and water (1 mL each). After stirring at 80 °C for 10 h, the mixture was cooled to room temperature and then concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (30% MeOH / EtOAc) to give the title compound (120 mg, 99%) as a white solid. ^{1}H NMR (CD_3OD) δ 8.61 (s, 1H), 8.48 (d, 1H, J = 5.6 Hz), 8.22 (dd, 1H, J = 10.4, 2.8 Hz), 8.14-8.11 (m, 1H), 7.54 (d, 2H, J = 8.1 Hz), 7.41 (d, 2H, J = 8.0 Hz), 7.40 (m, 1H), 7.05 (d, 1H, J = 5.7 Hz), 3.56 (s, 2H); MS(ESI$^+$) m/z 369.16 $(M+H)^+$.



B) 2-(4-(4-(2-Fluoro-4-nitrophenoxy)pyridin-3-yl)phenyl)acetamide

[00255] A 25 mL round bottom flask was charged with 2-(4-(4-(2-fluoro-4-nitrophenoxy)pyridin-3-yl)phenyl)acetic acid (50 mg, 0.136 mmol), HOBT (46 mg, 0.34 mmol), and EDCI (65 mg, 0.34 mmol). The flask was flushed with nitrogen and then DMF was added (1 mL). After stirring at rt for 1 h, the solution was cooled to 0°C and then charged with ammonium hydroxide (0.5 mL). The reaction was stirred at 0°C for 1 h and was then diluted with brine (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (20% MeOH / EtOAc) to give the title compound (33 mg, 66%) as a colorless oil. ^{1}H NMR (CD_3OD) δ 8.49 (s, 1H), 8.38 (d, 1H, J = 5.6 Hz), 8.10 (dd, 1H, J = 10.4, 2.4 Hz), 7.99 (m, 1H), 7.45 (d, 2H, J = 8.2 Hz), 7.30 (d, 2H, J = 8.2 Hz), 7.28 (m, 1H), 6.93 (d, 1H, J = 5.6 Hz), 3.44 (s, 2H); MS(ESI$^+$) m/z 368.18 $(M+H)^+$.

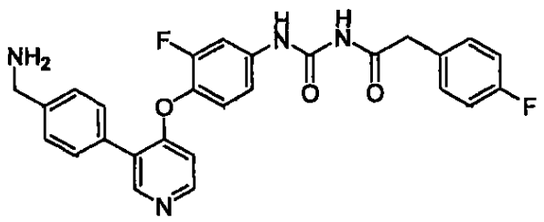
C) 1-(4-(3-(4-(2-Amino-2-oxoethyl)phenyl)pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea

[00256] A solution of 2-(4-(4-(2-flouro-4-nitrophenoxy)pyridin-3-yl)phenyl)acetamide (33 mg, 0.09 mmol) in THF (0.8 mL) and methanol (1.2 mL) was treated with Zn dust (59 mg, 0.9 mmol) followed by ammonium chloride (48 mg, 0.9 mmol). The mixture was stirred at rt for 4 h and was then filtered through a thin pad of Celite® with methanol. The filtrate was concentrated and the residue partitioned between EtOAc and saturated aqueous sodium bicarbonate solution. The EtOAc phase was dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give the crude product (25 mg, 82%) as a yellow oil which was sufficiently pure to use in the next step without further purification. ^{1}H NMR (CD_3OD) δ 8.33 (s, 1H), 8.19 (d, 1H, J = 5.6 Hz), 7.49 (d, 2H, J = 8.1 Hz), 7.32 (d, 2H, J = 8.2 Hz), 6.82 (t, 1H, J = 8.8 Hz),

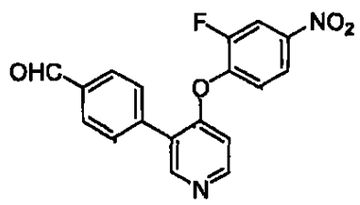
6.61 (d, 1H, J = 5.6 Hz), 6.44 (qd, 1H, J = 12.8, 2.8 Hz), 3.48 (s, 2H); MS(ESI$^+$) m/z 338.25 $(M + H)^+$.

[00257] The above amine was dissolved in THF (1 mL) and then charged with 2-(4-fluorophenyl)acetyl isocyanate (Compound D of Example 11, 250 uL, 0.074 mmol, 0.3 M in toluene). After stirring at rt for 1 h, the reaction was purified directly by flash chromatography on silica gel (10% MeOH / EtOAc) to give the title compound as a white solid. The solid was dissolved in dioxane (2 mL) and cooled to 0 °C. Anhydrous HCl (2 mL, 1 N in ether) was added. After stirring at 0 °C for 5 min, the solution was concentrated *in vacuo*. The resulting HCl salt was lyophilized from acetonitrile / water to give the title compound (23 mg, 57%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.02 (s, 1H), 10.59 (s, 1H), 8.83 (s, 1H), 8.58 (d, 1H, J = 6.4 Hz), 7.79 (dd, 1H, J = 12.8, 2.4 Hz), 7.60 (d, 2H, J = 8.4 Hz), 7.46-7.34 (m, 4H), 7.31-7.28 (m, 2H), 7.11 (t, 2H, J = 8.7 Hz), 6.88 (d, 1H, J = 5.6 Hz), 3.70 (s, 2H), 3.40 (s, 2H); MS(ESI$^+$) m/z 517.19 $(M + H)^+$.

Example 60



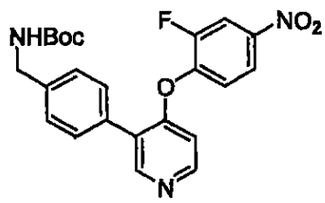
1-(4-(3-(4-(Aminomethyl)phenyl)pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, trifluoroacetic acid salt



A) 4-(4-(2-Fluoro4-nitrophenoxy)pyridin-3-yl)benzaldehyde

[00258] Prepared in a similar manner as Step A of Example 59 to give the title compound (86%) as a colorless oil. ^{1}H NMR (CD_3OD) δ 9.92 (s, 1H), 8.56 (s, 1H), 8.41 (d, 1H, J = 6 Hz), 8.12 (dd, 1H, J = 10.3, 2.6 Hz), 8.05-8.01 (m, 1H), 7.90 (d,

2H, J = 8.3 Hz), 7.73 (d, 2H, J = 8.2 Hz), 7.35 (t, 1H, J = 8.4 Hz), 6.95 (d, 1H, J = 6 Hz); MS(ESI$^+$) m/z 339.19 $(M + H)^+$.



B) *tert*-Butyl 4-(4-(2-fluoro-4-nitrophenoxy)pyridin-3-yl)benzylcarbamate

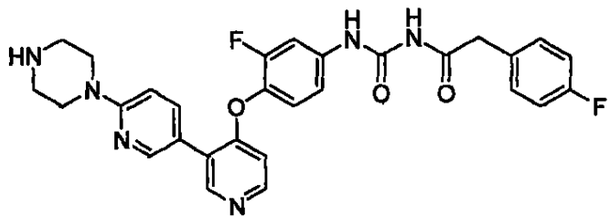
[00259] To 4-(4-(2-fluoro-4-nitrophenoxy)pyridin-3-yl)benzaldehyde (81 mg, 0.24 mmol) in methanol (2 mL) was added ammonium acetate (185 mg, 2.4 mmol) followed by sodium cyanoborohydride (16 mg, 0.24 mmol). The reaction was stirred at rt for 4 h and was then concentrated *in vacuo*. The residue was dissolved in water (5 mL) and extracted with EtOAc (2 × 5 mL). The combined organic extracts were washed with saturated aqueous sodium bicarbonate solution, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was dissolved in dichloromethane (2 mL) and then triethylamine (50 uL, 0.36 mmol), DMAP (spatula tip), and di-*tert*-butyl dicarbonate (Aldrich, 57 mg, 0.26 mmol) were added sequentially. The reaction was stirred at rt for 2 h and was then purified directly by flash column chromatography on silica gel (EtOAc) to give the title compound (13 mg, 12%) as a colorless oil. ^{1}H NMR (CD_3OD) δ 8.50 (s, 1H), 8.37 (d, 1H, J = 5.6 Hz), 8.09 (dd, 1H, J = 6.1, 2.6 Hz), 8.01-7 99 (m, 1H), 7.45 (d, 2H, J = 8 Hz), 7.26 (d, 2H, J = 8.2 Hz), 7.25 (m, 1H), 6.95 (d, 1H, J = 5.6 Hz), 4.16 (s, 2H), 1.35 (s, 9H); MS(ESI$^+$) m/z 440.19 $(M+H)^+$.

C) 1-(4-(3-(4-(Aminomethyl)phenyl)pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea

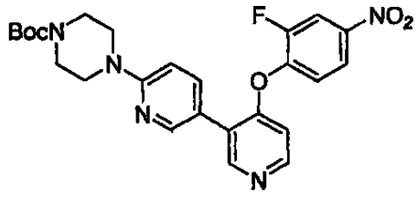
[00260] Prepared in a similar manner as Step C of Example 59. After acylurea formation, 4 N HCl in dioxane (5 mL) was added. After stirring at rt for 5 min, the reaction was concentrated *in vacuo*. The residue was suspended in EtOAc, washed with saturated aqueous sodium bicarbonate solution, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude material was purified by prep HPLC. The

appropriate fractions were concentrated *in vacuo* to remove methanol. Toluene was added and then concentrated (2 x 5 mL). The resulting solid was lyophilized from acetonitrile / water to give the TFA salt of the title compound (6 mg, 25%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.00 (s, 1H), 10.53 (s, 1H), 8.55 (s, 1H), 8.40 (d, 1H, J = 4 Hz), 7.73 (dd, 1H, J = 12, 4 Hz), 7.67 (d, 2H, J = 8 Hz), 7.51 (d, 2H, J = 8 Hz), 7.34-7.27 (m, 4H), 7.13-7.09 (m, 2H), 6.73 (d, 1H, J = 4 Hz), 4.03 (s, 2H), 3.68 (s, 2H); MS(ESI$^+$) m/z 489.18 $(M + H)^+$.

Example 61

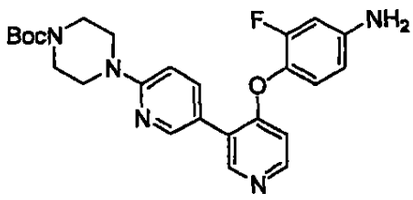


1-(3-Fluoro-4-(3-(6-(piperazin-1-yl)pyridin-3-yl)pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea, hydrochloride salt



A) *tert*-Butyl 4-(5-(4-(2-fluoro-4-nitrophenoxy)pyridin-3-yl)pyridin-2-yl)piperazine-1-carboxylate

[00261] Prepared in a similar manner as Step A of Example 59 to give the title compound (87%) as a colorless oil. ^{1}H NMR (CD_3OD) δ 8.62 (s, 1H), 8.46 (d, 1H, J = 6 Hz), 8.36 (d, 1H, J = 2.4 Hz), 8.24 (dd, 1H, J = 10.4, 2.8 Hz), 8.15-8.11 (m, 1H), 7.84 (dd, 1H, J = 8.8, 2.4 Hz), 7.41 (t, 1H, J = 8.4 Hz), 7.04 (d, 1H, J = 5.6 Hz), 6.92 (d, 1H, J = 8.8 Hz), 3.61-3.59 (m, 4H), 3.56-3.54 (m, 4H), 1.50 (s, 9H); MS(ESI$^+$) m/z 496.23 $(M + H)^+$.



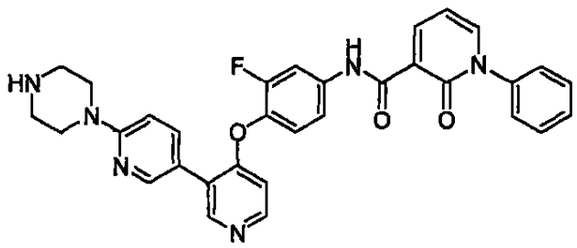
B) *tert*-Butyl 4-(5-(4-(4-amino-2-fluorophenoxy)pyridin-3-yl)pyridin-2-yl)piperazine-1-carboxylate

[00262] Prepared in a similar manner as Step C of Example 59 to give the title compound (96%) as a colorless oil. ^{1}H NMR (CD_3OD) δ 8 34 (s, 1H), 8.29 (d, 1H, J = 2 Hz), 8.18 (d, 1H, J = 6 Hz), 7.78 (dd, 1H, J = 9.2, 2.8 Hz), 6.87-6.83 (m, 2H), 6.61 (d, 1H, J = 5.6 Hz), 6.48 (dd, 1H, J = 12.8, 2.8 Hz), 6.44-6.41 (m, 1H), 3.50-3.46 (m, 8H), 1.38 (s, 9H); MS(ESI$^+$) m/z 466.25 $(M+H)^+$.

C) 1-(3-Fluoro-4-(3-(6-(piperazin-1-yl)pyridin-3-yl)pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea

[00263] Prepared in a similar manner as Step C of Example 59 to give the title compound (28%) as the HCl salt. ^{1}H NMR (DMSO-d_6) δ 11.33 (s, 1H), 10.76 (s, 1H), 9.09 (s, 1H), 8.74 (d, 1H, J = 6.8 Hz), 8.57 (d, 1H, J = 2.4 Hz), 8.16 (dd, 1H, J = 8.8, 2 Hz), 7.91 (dd, 1H, J = 12.8, 2 Hz), 7.61 (t, 1H, J = 8.8 Hz), 7.55-7.50 (m, 1H), 7.42-7.38 (m, 2H), 7.28 (d, 1H, J = 6.5 Hz), 7.27-7.18 (m, 3H), 3.98 (m, 4H), 3.82 (s, 2H), 3.23 (m, 4H); MS(ESI$^+$) m/z 545.19 $(M+H)^+$.

Example 62

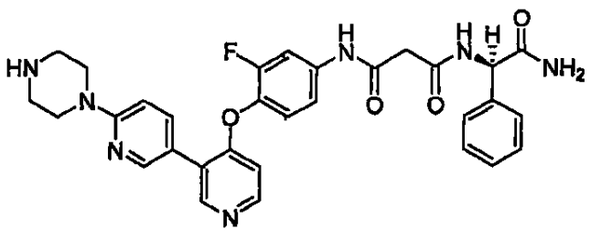


***N*-(3-Fluoro-4-(3-(6-(piperazin-1-yl)pyridin-3-yl)pyridin-4-yloxy)phenyl)-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide, hydrochloride salt**

[00264] To *tert*-butyl 4-(5-(4-(4-amino-2-fluorophenoxy)pyridin-3-yl)pyridin-2-yl)piperazine-1-carboxylate (Compound B of Example 61, 32 mg, 0.069 mmol) in

THF / DMF (1 mL each) was added 2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxylic acid (Compound C of Example 57, 15 mg, 0 069 mmol), DIPEA (60 uL, 0.35 mmol), then TBTU (Fluka, 33 mg, 0.10 mmol). After stirring at rt for 18 h, the reaction was diluted with EtOAc (5 mL), washed with 10% aqueous lithium chloride solution (2 × 5 mL) followed by saturated sodium bicarbonate solution (1 × 5 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was suspended in ether, cooled to 0 °C, and treated with 4 N HCl in dioxane (5 mL). The solution was allowed to warm to rt and then stirred at rt for 2 h. The solution was concentrated *in vacuo* and the resulting crude product was purified by prep HPLC. The appropriate fractions were concentrated to remove methanol and then made basic with saturated aqueous sodium bicarbonate solution. The aqueous solution was extracted with EtOAc (2 × 10 mL) and the pooled organic extracts were dried over anhydrous Na_2SO_4 and then concentrated *in vacuo*. The residue was dissolved in THF (2 mL), cooled to 0 °C, and treated with 1N HCl in ether (0.5 mL). After stirring at 0 °C for 5 min, the mixture was concentrated. The resulting white solid was lyophilized from acetonitrile / water to give the HCl salt of the title compound (26 mg, 56%) as a pale yellow solid. ^{1}H NMR (DMSO-d_6) δ 12.16 (s, 1H), 8.92 (s, 1H), 8.59 (d, 1H, J = 6.4 Hz), 8.53 (dd, 1H, J = 7.2, 2 Hz), 8.47 (d, 1H, J = 2.4 Hz), 8.10 (dd, 1H, J = 6.4, 2 Hz), 8.04 (d, 1H, J = 12 Hz), 7.99 (dd, 1H, J = 8.8, 2.4 Hz), 7.54-7.46 (m, 7H), 7.20 (d, 1H, J = 6.4 Hz), 7.97 (d, 1H, J = 9.2 Hz), 6.68 (t, 1H, J = 6.8 Hz), 3.82-3.80 (m, 4H), 3.12 (m, 4H); MS(ESI$^+$) m/z 545.19 $(M + H)^+$.

Example 63

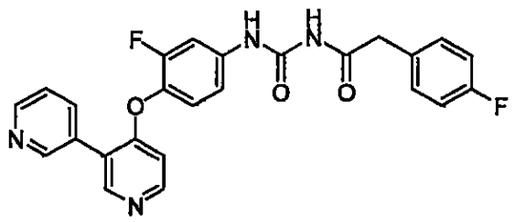


N^1-((*R*)-2-Amino-2-oxo-1-phenylethyl)-N^3-(3-fluoro-4-(3-(6-(piperazin-1-yl)pyridin-3-yl)pyridin-4-yloxy)phenyl)malonamide, hydrochloride salt

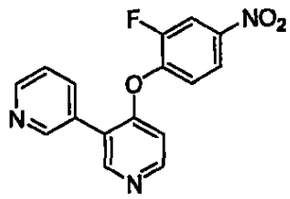
[00265] To *tert*-butyl 4-(5-(4-(4-amino-2-fluorophenoxy)pyridin-3-yl)pyridin-2-yl)piperazine-1-carboxylate (Compound B of Example 61, 32 mg, 0.069 mmol) in THF (1 mL) was added DIPEA (60 uL, 0.35 mmol) then ethyl 3-chloro-3-oxopropanoate (Aldrich, 10 uL, 0.076 mmol). After stirring at rt for 2 h, the reaction was diluted with EtOAc (5 mL), washed with saturated aqueous sodium bicarbonate solution (1 × 5 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The resulting yellow oil (65 mg) was dissolved in THF (2 mL) and then charged with 1 N aqueous sodium hydroxide solution (2 mL). The solution was stirred at rt for 6 h. The solution was concentrated to remove THF and then acidified to pH 4-5 with 1 N aqueous HCl solution. The solid was collected by vacuum filtration and washed with water to give the corresponding acid as a white solid (30 mg, 78% 2 steps). MS(ESI$^+$) m/z 552.21 $(M + H)^+$.

[00266] The above acid was coupled with *D*(-)-phenylglycinamide (Bachem) using TBTU as described above to give the HCl salt of the title compound (32%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 10.64 (s, 1H), 8.89 (s, 1H), 8.74 (d, 1H, J = 8 Hz), 8.56 (d, 1H, J = 5.6 Hz), 8.46 (d, 1H, J = 2.4 Hz), 7.96 (d, 1H, J = 8.8 Hz), 7.84 (d, 1H, J = 12 Hz), 7.74 (s, 1H), 7.46-7.37 (m, 4H), 7.31-7.22 (m, 5H), 7.06 (d, 1H, J = 9.2 Hz), 5.34 (d, 1H, J = 8 Hz), 3.81-3.78 (m, 4H), 3.40 (s, 2H), 3.12 (m, 4H); MS(ESI$^+$) m/z 584.25 $(M + H)^+$.

Example 64

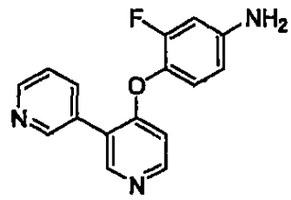


1-(3-Fluoro-4-(3-(pyridin-3-yl)pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea, hydrochloride salt



A) 3-(4-(2-Fluoro-4-nitrophenoxy)pyridin-3-yl)pyridine

[00267] Prepared in a similar manner as Step A of Example 59 give the title compound as a colorless oil. ^{1}H NMR (CD_3OD) δ 8.83 (d, 1H, J = 1.6 Hz), 8.69 (s, 1H), 8.61 (d, 1H, J = 5 Hz), 8.56 (d, 1H, J = 5.8 Hz), 8.27 (dd, 1H, J = 10.4, 2.8 Hz), 8.20-814 (m, 2H), 7.72-7.55 (m, 1H), 7.53 (t, 1H, J = 8.6 Hz), 7.08 (d, 1H, J = 6 Hz); MS(ESI$^+$) m/z 312.15 $(M+H)^+$.



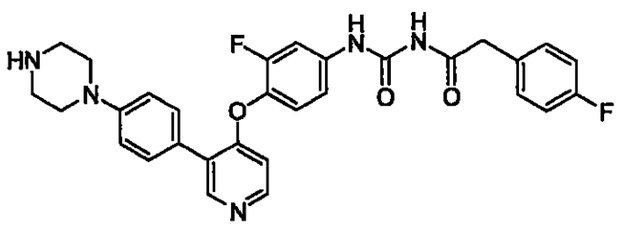
B) 3-Fluoro-4-(3-(pyridin-3-yl)pyridin-4-yloxy)benzenamine

[00268] Prepared in a similar manner as Step C of Example 59 give the title compound as a colorless oil. MS(ESI$^+$) m/z 282.12 $(M+H)^+$.

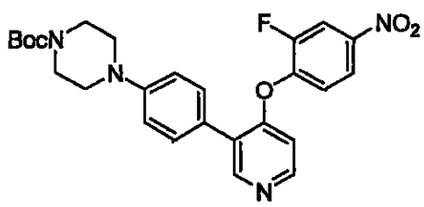
C) 1-(3-Fluoro-4-(3-(pyridin-3-yl)pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea

[00269] Prepared in a similar manner as Step C of Example 59 give to give the HCl salt of the title compound (47% combined yield for Steps B and C) as a yellow solid. ^{1}H NMR (DMSO-d_6) δ 11.14 (s, 1H), 10.73 (s, 1H), 9.16 (d, 1H, J = 1.6 Hz), 9.08 (s, 1H), 8.90 (dd, 1H, J = 5.2, 1.2 Hz), 8.78 (d, 1H, J = 6.4 Hz), 8.56 (d, 1H, J = 8 Hz), 7.95-7.90 (m, 2H), 7.60 (t, 1H, J = 8.8 Hz), 7.55-7.52 (m, 1H), 7.44-7.41 (m, 2H), 7.26-7.21 (m, 3H), 3.82 (s, 2H); MS(ESI$^+$) m/z 461.16 $(M+H)^+$.

Example 65

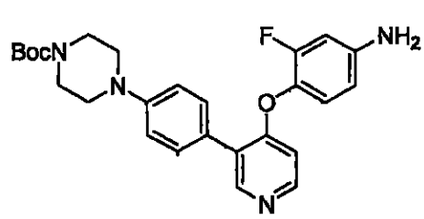


1-(3-Fluoro-4-(3-(4-(piperazin-1-yl)phenyl)pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea, trihydrochloride salt



A) *tert*-Butyl 4-(4-(4-(2-fluoro-4-nitrophenoxy)pyridin-3-yl)phenyl)piperazine-1-carboxylate

[00270] Prepared in a similar manner as Step A of Example 59 give the title compound as a colorless oil. ^{1}H NMR (CD_3OD) δ 8.48 (s, 1H), 8.32 (d, 1H, J = 5.6 Hz), 8.08 (dd, 1H, J = 12, 4 Hz), 7.97 (d, 1H, J = 8 Hz), 7.38 (d, 2H, J = 8.8 Hz), 7.21-7.18 (m, 1H), 6.95-6.92 (m, 3H), 3 46 (m, 4H), 3.09-3.06 (m, 4H), 1.10 (s, 9H); MS(ESI$^+$) m/z 495.23 $(M + H)^+$.



B) *tert*-Butyl 4-(4-(4-(4-amino-2-fluorophenoxy)pyridin-3-yl)phenyl)piperazine-1-carboxylate

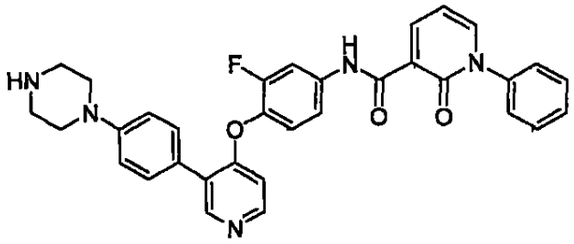
[00271] Prepared in a similar manner as Step C of Example 59 to give the title compound (94% combined yield for Steps A and B) as a colorless oil. ^{1}H NMR (CD_3OD) δ 8.30 (s, 1H), 8.14 (d, 1H, J = 5.6 Hz), 7.45 (d, 2H, J = 8.8 Hz), 6.98 (d, 2H, J = 8.8 Hz), 6.83 (t, 1H, J = 8.8 Hz), 6.58 (d, 1H, J = 5.6 Hz), 6.48 (dd, 1H, J =

12.8, 2.4 Hz), 6.43-6.41 (m, 1H), 3.49 (m, 4H), 3.11-3.09 (m, 4H), 1.16 (s, 9H); MS(ESI$^+$) m/z 465.24 $(M+H)^+$.

C) 1-(3-Fluoro-4-(3-(4-(piperazin-1-yl)phenyl)pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea

[00272] Prepared in a similar manner as Step C of Example 59 to give the HCl salt of the title compound (37%) as a pale yellow solid. ^{1}H NMR (DMSO-d_6) δ 11.01 (s, 1H), 10.60 (s, 1H), 8.77 (s, 1H), 8.51 (d, 1H, J = 6.4 Hz), 7.78 (d, 1H, J = 12 Hz), 7.59 (d, 2H, J = 8.4 Hz), 7.44-7.40 (m, 2H), 7.31-7.28 (m, 2H), 7.13-7.08 (m, 4H), 7.03 (d, 1H, J = 6.4 Hz), 3.70 (s, 2H), 3.42 (m, 4H), 3.15 (m, 4H); MS(ESI$^+$) m/z 544.26 $(M+H)^+$.

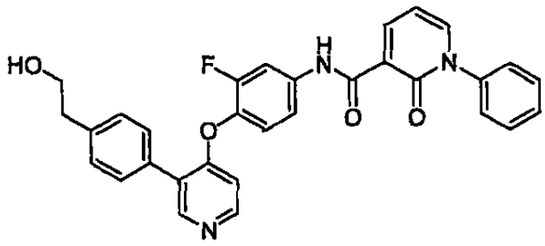
Example 66



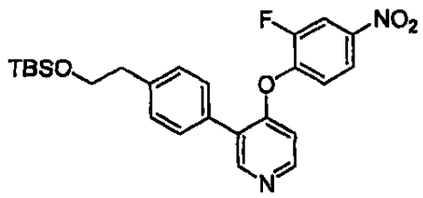
***N*-(3-Fluoro-4-(3-(4-(piperazin-1-yl)phenyl)pyridin-4-yloxy)phenyl)-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide, trihydrochloride salt**

[00273] Prepared in a manner similar to that of Example 62 to give the HCl salt of the title compound (43%) as a pale yellow solid. ^{1}H NMR (DMSO-d_6) δ 12.15 (s, 1H), 8.83 (s, 1H), 8.56-8.52 (m, 2H), 8.10 (dd, 1H, J = 6.8, 2.4 Hz), 8.04 (dd, 1H, J = 11.6, 2 Hz), 7.61 (d, 2H, J = 8.8 Hz), 7.55-7.45 (m, 7H), 7.15 (d, 1H, J = 6.8 Hz), 7.09 (d, 2H, J = 8.8 Hz), 6.61 (t, 1H, J = 6.8 Hz), 3.44 (m, 4H), 3.15 (m, 4H); MS(ESI$^+$) m/z 562.36 $(M+H)^+$.

Example 67

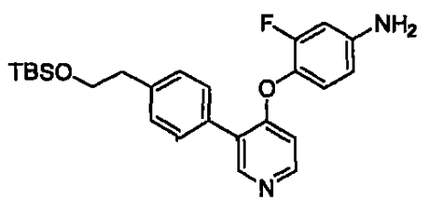


***N*-(3-Fluoro-4-(3-(4-(2-hydroxyethyl)phenyl)pyridin-4-yloxy)phenyl)-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide**



A) 3-(4-(2-(*tert*-Butyldimethylsilyloxy)ethyl)phenyl)-4-(2-fluoro-4-nitrophenoxy)pyridine

[00274] Prepared in a similar manner as Step A of Example 59 to give the title compound (77%) as a colorless oil. ^{1}H NMR (CD_3OD) δ 8.67 (s, 1H), 8.56 (d, 1H, J = 8 Hz), 8.27 (dd, 1H, J = 12, 4 Hz), 8.16 (d, 1H, J = 8 Hz), 7.58 (d, 2H, J = 8 Hz), 7.39 (d, 2H, J = 8 Hz), 7.36 (m, 1H), 7.15 (d, 1H, J = 4 Hz), 3.91 (t, 2H, J = 8 Hz), 2.90 (t, 2H, J = 8 Hz), 0.90 (s, 9H), 0 00 (s, 6H); MS(ESI$^+$) m/z 469.25 $(M + H)^+$.



B) 3-(4-(2-(*tert*-Butyldimethylsilyloxy)ethyl)phenyl)-4-(2-fluoro-4-nitrophenoxy)pyridine

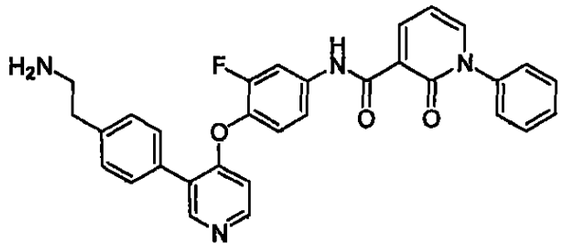
[00275] Prepared in a similar manner as Step C of Example 59 to give the title compound (76%) as a pale yellow oil. ^{1}H NMR (CD_3OD) δ 8.44 (s, 1H), 8.32 (d, 1H, J = 4 Hz), 7.57 (d, 2H, J = 8 Hz), 7.36 (d, 2H, J = 8.4 Hz), 6.95 (t, 1H, J = 8 Hz), 6.75 (d, 1H, J = 4 Hz), 6.61 (d, 1H, J = 8 Hz), 6.55 (d, 1H, J = 4 Hz), 3.90 (t, 2H, J = 6.8

Hz), 2.89 (t, 2H, J = 6.4 Hz), 0.87 (s, 9H), 0.00 (s, 6H), MS(ESI$^+$) m/z 439.26 (M+H)$^+$.

C) ***N*-(3-Fluoro-4-(3-(4-(2-hydroxyethyl)phenyl)pyridin-4-yloxy)phenyl)-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide**

[00276] Prepared in a similar manner as Step C of Example 62. After amide formation, the resulting yellow oil was dissolved in THF (2 mL) and then treated with TBAF (Aldrich, 180 uL, 1 M in THF) at rt for 1 h. The reaction was diluted with EtOAc (10 mL), washed successively with water and brine (5 mL each), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (10% methanol / EtOAc) to give the title compound (72%) as a pale yellow solid. ^{1}H NMR (CD_3OD) δ 8.59 (dd, 1H, J = 7.6, 2.0 Hz), 8.41 (s, 1H), 8.26 (d, 1H, J = 5.6 Hz), 7.91-7.85 (m, 2H), 7.55-7.46 (m, 5H), 7.41 (d, 2H, J = 6.7 Hz), 7.29 (d, 2H, J = 8.1 Hz), 7.26 (m, 1H), 7.13 (t, 1H, J = 8.7 Hz), 6.69 (d, 1H, J = 6 Hz), 6.64 (t, 1H, J = 7.2 Hz), 3.73 (t, 2H, J = 7.2 Hz), 2.82 (t, 2H, J = 6.8 Hz); MS(ESI$^+$) m/z 522.27 (M + H)$^+$.

Example 68

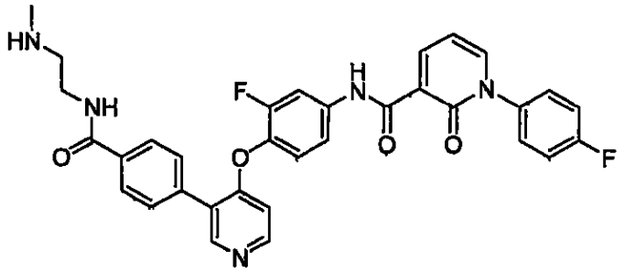


***N*-(4-(3-(4-(2-Aminoethyl)phenyl)pyridin-4-yloxy)-3-fluorophenyl)-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide, dihydrochloride salt**

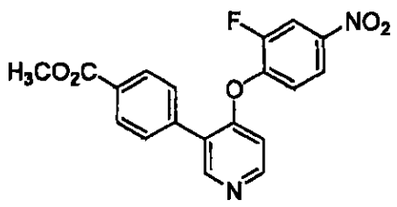
[00277] To *N*-(3-fluoro-4-(3-(4-(2-hydroxyethyl)phenyl)pyridin-4-yloxy)phenyl)-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide (Compound C of Example 67, 40 mg, 0.077 mmol) in THF (1 mL) was added DIPEA (27 uL, 0.154 mmol) followed by methanesulfonyl chloride (Aldrich, 7 uL, 0.092 mmol). After stirring at rt for 30 min, the reaction was concentrated *in vacuo*. The residue was dissolved in 3 mL of ethanol and transferred to a pressure tube. Ammonium hydroxide (7 mL) was added and the

tube was sealed and heated at 50 °C for 8 h. After cooling to rt, the reaction was diluted with EtOAc (10 mL), washed with water (2 x 10 mL) then brine (1 x 10 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by prep HPLC. The appropriate fractions were concentrated to remove methanol and basified with saturated sodium bicarbonate solution. The aqueous layer was extracted with EtOAc (2 × 20 mL) and the pooled organic extracts were washed with brine (1 × 10 mL), dried over anhydrous Na_2SO_4, and concentrated. The residue was dissolved in dioxane (2 mL) and charged with 1N HCl in ether (1 mL). The solution was concentrated and the resulting solid was lyophilized from acetonitrile / water to give the HCl salt of the title compound (24 mg, 53%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 12.13 (s, 1H), 8.74 (s, 1H), 8.55-8.51 (m, 2H), 8.09 (dd, 1H, J= 6.4, 2 Hz), 8.03 (m, 1H), 7.64 (d, 2H, J= 6 Hz), 7.63 (m, 1H), 7 54-7.41 (m, 6H), 7.38 (d, 2H, J= 8.4 Hz), 7.04 (d, 1H, J= 6 Hz), 6.68 (t, 1H, J= 6.8 Hz), 3.02 (m, 2H), 2.89 (m, 2H); MS(ESI$^+$) m/z 521.27 $(M+H)^+$.

Example 69

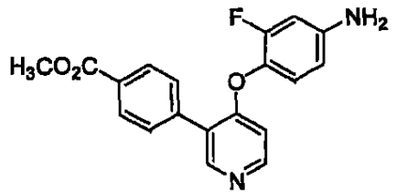


***N*-(4-(3-(4-((2-(Methylamino)ethyl)carbamoyl)phenyl)pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, dihydrochloride salt**



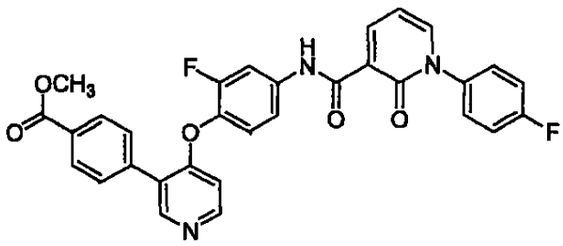
A) Methyl 4-(4-(2-fluoro-4-nitrophenoxy)pyridin-3-yl)benzoate

[00278] Prepared in a similar manner as Step A of Example 59 to give the title compound (77%) as a colorless oil. ^{1}H NMR (CD_3OD) δ 8.66 (s, 1H), 8.52 (d, 1H, J = 6 Hz), 8.22 (dd, 1H, J = 10.4, 2.8 Hz), 8.16-8.13 (m, 1H), 8.10 (d, 2H, J = 8.4 Hz), 7.97 (d, 2H, J = 8 Hz), 7.44 (t, 1H, J = 8.5 Hz), 7.06 (d, 1H, J = 6 Hz), 3.93 (s, 3H); MS(ESI$^+$) m/z 369.22 $(M + H)^+$.



B) Methyl 4-(4-(4-amino-2-fluorophenoxy)pyridin-3-yl)benzoate

[00279] Prepared in a similar manner as Step C of Example 59 to give the title compound (99%) as a yellow oil. ^{1}H NMR (CD_3OD) δ 8.38 (s, 1H), 8.24 (d, 1H, J = 6 Hz), 8.01 (d, 2H, J = 8.4 Hz), 7.66 (d, 2H, J = 8.4 Hz), 6.85 (t, 1H, J = 9.2 Hz), 6.65 (d, 1H, J = 6 Hz), 6.48 (dd, 1H, J = 12.8, 2.4 Hz), 6.43 (d, 1H, J = 2.8 Hz), 3.82 (s, 3H); MS(ESI$^+$) m/z 339.28 $(M + H)^+$.



C) Methyl 4-(4-(2-fluoro-4-(1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamido)phenoxy)pyridin-3-yl)benzoate

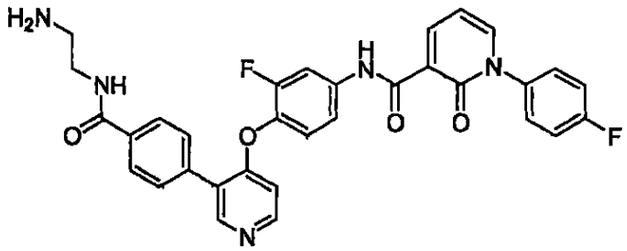
[00280] Prepared in a similar manner as Step C of Example 62 to give the title compound (81%) as a yellow oil. ^{1}H NMR (CD_3OD) δ 8.66 (dd, 1H, J = 7.2, 2 Hz), 8.56 (s, 1H), 8.40 (d, 1H, J = 6 Hz), 8.13 (d, 2H, J = 8.4 Hz), 7.97-7.95 (m, 2H), 7.78 (d, 2H, J = 8.4 Hz), 7.55-7.52 (m, 2H), 7.38-7.31 (m, 3H), 7.26 (t, 1H, J = 7.2 Hz), 6.82 (d, 1H, J = 5.6 Hz), 6.72 (t, 1H, J = 6.7 Hz), 3.94 (s, 3H); MS(ESI$^+$) m/z 554.21 $(M + H)^+$.

D) *N*-(4-(3-(4-((2-(Methylamino)ethyl)carbamoyl)phenyl)pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide

[00281] To the above ester (159 mg, 0.29 mmol) in THF (5 mL) was added 1 N aqueous NaOH (5 mL). After stirring at rt for 20 h, the reaction was concentrated to remove THF. The aqueous solution was acidified to pH 4 with 1 N aqueous HCl. The acid was collected by filtration and washed with water to give the desired product (144 mg, 92%) as a tan solid. MS(ESI$^+$) m/z 540.21 $(M + H)^+$.

[00282] The amide was prepared as described above using TBTU to give the HCl salt of the title compound (62%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 12.21 (s, 1H), 8.93-8.90 (m, 2H), 8.68-8.64 (m, 2H), 8.21 (dd, 1H, J = 6.4, 2 Hz), 8.16 (m, 1H), 8.11 (d, 2H, J = 8 Hz), 7.90 (d, 2H, J = 8.4 Hz), 7.69-7.65 (m, 2H), 7.60-7.47 (m, 4H), 7.16 (d, 1H, J = 5.6 Hz), 6.80 (t, 1H, J = 7 Hz), 3.64 (t, 2H, J = 5.2 Hz), 3.17 (t, 2H, J = 5.2 Hz), 2.65 (s, 3H); MS(ESI$^+$) m/z 596.37 $(M + H)^+$.

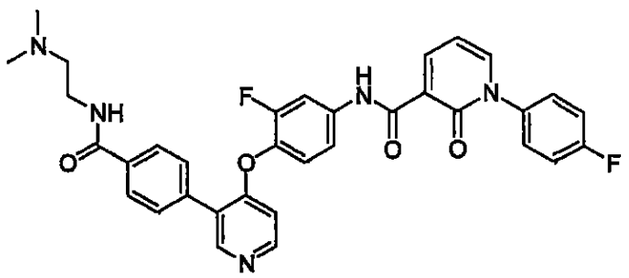
Example 70



***N*-(4-(3-(4-((2-Aminoethyl)carbamoyl)phenyl)pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, dihydrochloride salt**

[00283] Prepared in a similar manner as Example 69 to give the HCl salt of the title compound as an off-white solid. ^{1}H NMR (DMSO-d_6) δ 12.17 (s, 1H), 8.87-8.85 (m, 2H), 8.64 (d, 1H, J = 6.4 Hz), 8.59 (dd, 1H, J = 7.6, 2.4 Hz), 8.16 (dd, 1H, J = 6.8, 2.4 Hz), 8.10 (m, 1H), 8.06 (d, 2H, J = 8.4 Hz), 8.00 (br s, 2H), 7.85 (d, 2H, J = 8.4 Hz), 7.64-7.60 (m, 2H), 7.55-7.42 (m, 4H), 7.13 (d, 1H, J = 6 Hz), 6.75 (t, 1H, J = 7.2 Hz), 3.56-3.53 (m, 2H), 3.04-2.99 (m, 2H); MS(ESI$^+$) m/z 582.32 $(M + H)^+$.

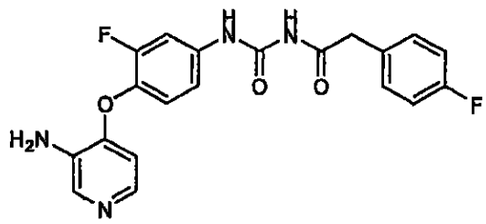
Example 71



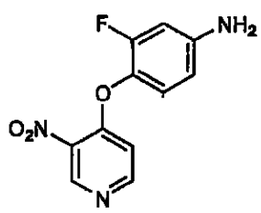
***N*-(4-(3-(4-((2-(Dimethylamino)ethyl)carbamoyl)phenyl)pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, dihydrochloride salt**

[00284] Prepared in a similar manner as Example 69 to give the HCl salt of the title compound (56%) as an off-white solid. ^{1}H NMR (DMSO-d_6) δ 12.08 (s, 1H), 8.87 (br s, 1H), 8.75 (s, 1H), 8.54-8.51 (m, 2H), 8.08 (dd, 1H, J = 6.8, 2.4 Hz), 8.02 (m, 1H), 7.99 (d, 2H, J = 8.4 Hz), 7.77 (d, 2H, J = 8.4 Hz), 7.56-7.53 (m, 2H), 7.47-7.34 (m, 4H), 6.99 (d, 1H, J = 5.6 Hz), 6.67 (t, 1H, J = 6.8 Hz), 3.61-3.57 (m, 2H), 3.23-3.21 (m, 2H), 2.77 (s, 3H), 2.76 (s, 3H); MS(ESI$^+$) m/z 610.30 $(M + H)^+$.

Example 72

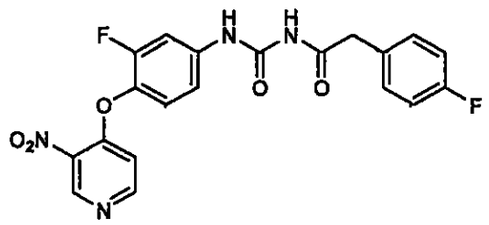


1-(4-(3-Aminopyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea



A) 3-Fluoro-4-(3-nitropyridin-4-yloxy)benzenamine

[00285] To 4-amino-2-fluorophenol (see Step A of Example 19, 127 mg, 1.0 mmol) in DMF (5 mL) at rt under nitrogen was added sodium hydride (80 mg, 2 mmol, 60%). After stirring at rt for 10 min, 4-chloro-3-nitropyridine hydrochloride (Lancaster, 195 mg, 1.0 mmol) was added. The mixture was stirred at rt for 1 h and was then diluted with EtOAc (50 mL) and washed with water, 10% aqueous lithium chloride solution, and then brine (1 × 30 mL each). The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel eluting with EtOAc to give the title compound (150 mg, 60%) as a yellow-orange solid. ^{1}H NMR (DMSO-d_6) δ 9.13 (s, 1H), 8.63 (d, 1H, J = 6 Hz), 7.09 (t, 1H, J = 9.2 Hz), 6.92 (d, 1H, J = 6 Hz), 6.55 (dd, 1H, J = 13.2, 2.4 Hz), 6.45 (dd, 1H, J = 9.2, 2.4 Hz), 5.61 (s, 2H); MS(ESI$^+$) m/z 250.18 $(M^+H)^+$.



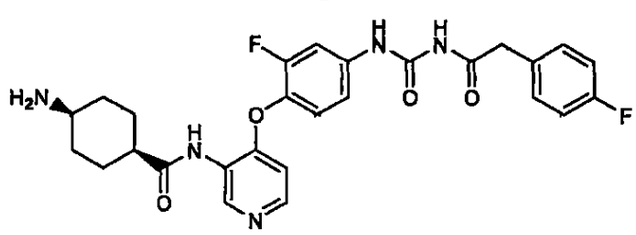
B) 1-(3-Fluoro-4-(3-nitropyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea

[00286] A solution of 3-fluoro-4-(3-nitropyridin-4-yloxy)benzenamine (158 mg, 0.63 mmol) in THF (3 mL) was treated with a solution of solution of 2-(4-fluorophenyl)acetyl isocyanate in toluene (Compound D of Example 11, 1.3 mmol) and stirred at room temperature for 2 h then at 50 °C for 5 min. The mixture was concentrated and the residue treated with DMF (15 mL) and SiO_2 (150 mg) and the mixture concentrated to dryness under vacuum and applied to a SiO_2 column. The column was eluted with 20 – 60 % EtOAc / hexanes to give the product, which was further purified by trituration with isopropyl ether to give a pale yellow solid (120 mg, 25%). ^{1}H NMR (DMSO-d_6) δ 11.07 (s, 1H), 10.63 (s, 1H), 9.19 (s, 1H), 8.67 (d, 1H, J = 5.6 Hz), 7.85 (d, 1H, J = 11.7 Hz), 7.46 – 7.45 (m, 2H), 7.39 – 7.35 (m, 2H), 7.18 (dd, 2H, J = 8.6, 8.6 Hz), 7.01 (d, 1H, J = 6.1 Hz), 3.76 (s, 2H).

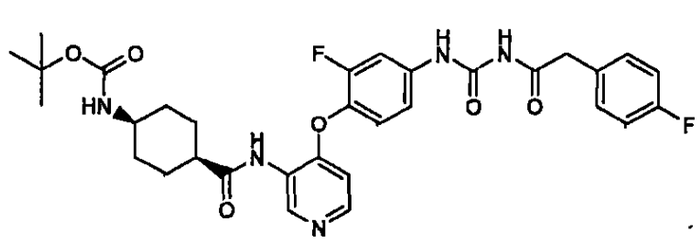
C) **1-(4-(3-Aminopyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea**

[00287] A suspension of 1-(3-fluoro-4-(3-nitropyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea (125 mg, 0.29 mmol) in 3:1 MeOH / THF (20 mL) was hydrogenated over Pt_2O (50 mg) using H_2 from a latex balloon for 6 h. The catalyst was filtered off with the aid of Celite® and the filtrate concentrated to give the title compound (85 mg, 74%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.03 (s, 1H), 10.55 (s, 1H), 8.03 (s, 1H), 7.75 (dd, 1H, J = 2.5, 13.2 Hz), 7.65 (d, 1H, J = 5.1 Hz), 7.38 – 7.35 (m, 3H), 7.23 – 7.16 (m, 3H), 6.42 (d, 1H, J = 5.1 Hz), 5.26 (s, 2H), 3.75 (s, 2H); MS(ESI$^+$): m/z 399.35 $(M + H)^+$.

Example 73



1-(4-(3-((1*S*,4*S*)-4-Aminocyclohexanecarboxamido)pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, trifluoroacetic acid salt



A) ***tert*-Butyl (1*S*,4*S*)-4-((4-(2-fluoro-4-(3-(2-(4-fluorophenyl)acetyl)ureido)phenoxy)pyridin-3-yl)carbamoyl)cyclohexylcarbamate**

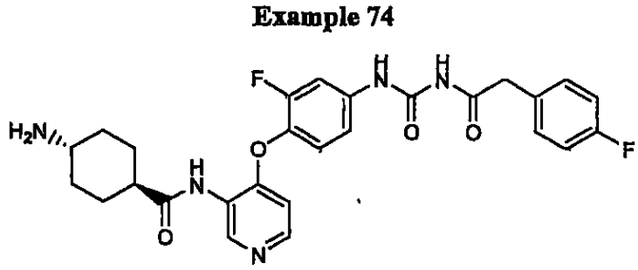
[00288] A solution of *N*-Boc-*cis*-1,4-diaminocyclohexane carboxylic acid (Chem-Imprex International, 24 mg, 0.10 mmol) in THF (1 mL) was cooled to 0 °C, and treated with Et_3N and then isobutylchloroformate. After 5 min, the mixture was

treated with a solution of 1-(4-(3-aminopyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea (Compound C of Example 72, 27 mg, 0.068 mmol) in THF (0.5 mL) and the stirring continued at 0 °C for 10 min and then at room temperature for 2 h. The mixture was partitioned between EtOAc and saturated aq. $NaHCO_3$ solution and the EtOAc phase separated, dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product. Purification of the residue by flash column chromatography on SiO_2 eluting with 50 -100 % EtOAc / hexanes gave the title compound (13 mg, 21%) as a white solid. MS(ESI$^+$): *m/z* 624.25 $(M + H)^+$.

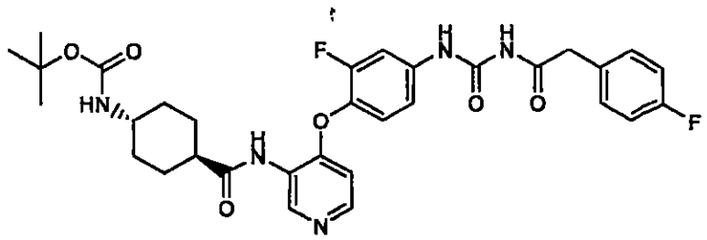
B) 1-(4-(3-((1*S*,4*S*)-4-Aminocyclohexanecarboxamido)pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, trifluoroacetic acid salt

[00289] A solution of tert-butyl (1*S*,4*S*)-4-((4-(2-fluoro-4-(3-(2-(4-fluorophenyl)acetyl)ureido)phenoxy)pyridin-3-yl)carbamoyl)cyclohexylcarbamate (10 mg, 0.016 mmol) in anhydrous MeOH (0.5 mL) was cooled to 0 °C and treated with 4 M HCl /1,4-dioxane (2 mL). The mixture was stirred at 0 °C for 1.5 h and then at room temperature for 20 min and finally concentrated *in vacuo* to give the crude product. Purification of the residue by preparative HPLC (Column A) gave the title compound (4 mg, 33%) as a yellow solid. ^{1}H NMR (DMSO-d_6) δ 11.07 (s, 1H), 10.64 (s, 1H), 9.28 (s, 1H), 8.40 – 8.37 (m, 1H), 7.94 (s, 1H), 7.83 (dd, 1H, J = 2.1, 12.7 Hz), 7.47 – 7.33 (m, 5H), 7.19 – 7.14 (m, 3H), 7.07 – 7.02 (m, 1H), 3.75 (s, 2H), 3.25 – 3.15 (m, 1H), 2.85 – 2.76 (m, 1H), 1.97 – 1.84 (m, 2H), 1.85 – 1.61 (m, 5H); MS(ESI$^+$): *m/z* 524.26 $(M + H)^+$.

Example 74



1-(4-(3-((1*R*,4*R*)-4-Aminocyclohexanecarboxamido)pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, bis-trifluoroacetic acid salt



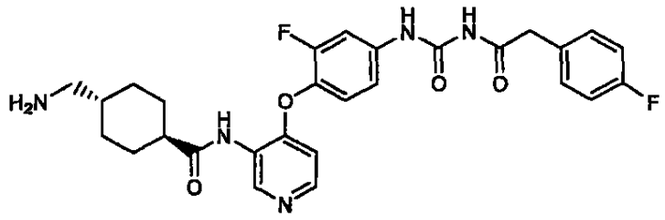
A) *tert*-Butyl (1*R*,4*R*)-4-((4-(2-fluoro-4-(3-(2-(4-fluorophenyl)acetyl)ureido)phenoxy)pyridin-3-yl)carbamoyl)cyclohexylcarbamate

[00290] The title compound was prepared from 1-(4-(3-aminopyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea (Compound C of Example 72, 57 mg, 0.14 mmol) and *N*-Boc-*trans*-4-aminocyclohexane-1-carboxylic acid (Anaspec Inc., 51 mg, 0.21 mmol) in a similar manner as described for Step A of Example 73 to give the title compound (32 mg, 66%) as white solid. MS(ESI$^+$): *m/z* 624.41 $(M + H)^+$.

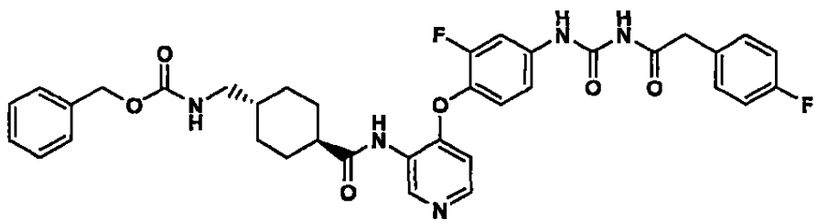
B) 1-(4-(3-((1*R*,4*R*)-4-Aminocyclohexanecarboxamido)pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, bis-trifluoroacetic acid salt

[00291] The title compound was prepared from *tert*-butyl (1*S*,4*S*)-4-((4-(2-fluoro-4-(3-(2-(4-fluorophenyl)acetyl)ureido)phenoxy)pyridin-3-yl)carbamoyl)cyclohexylcarbamate (25 mg) in a similar manner as described for Example 73. Purification of the reaction mixture by preparative HPLC (Column A) gave the title compound (7 mg, 23%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.06 (s, 1H), 10.61 (s, 1H), 9.94 (s, 1H), 9.19 (s, 1H), 8.28 (d, 1H, J = 5.6 Hz), 7.82 (dd, 1H, J = 2.0, 13.2 Hz), 7.79 – 7.76 (m, 3H), 7.43 (dd, 1H, J = 2.0, 8.6 Hz), 7.38 – 7.33 (m, 2H), 7.17 (dd, 2H, J = 9.2, 6.6 Hz), 6.86 (d, 1H, J = 5.6 Hz), 3.74 (s, 2H), 3.08 – 2.95 (m, 1H), 2.67 – 2.43 (m, 1H), 2.01 – 1.88 (m, 4H), 1.53 – 1.43 (m, 2H), 1.37 – 1.27 (m, 2H); MS(ESI$^+$): *m/z* 524.35 $(M + H)^+$.

Example 75



1-(4-(3-((1*R*,4*R*)-4-(Aminomethyl)cyclohexanecarboxamido)pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea



A) Benzyl ((1*R*,4*R*)-4-((4-(2-fluoro-4-(3-(2-(4-fluorophenyl)acetyl)ureido) phenoxy)pyridin-3-yl) carbamoyl)cyclohexyl)methylcarbamate

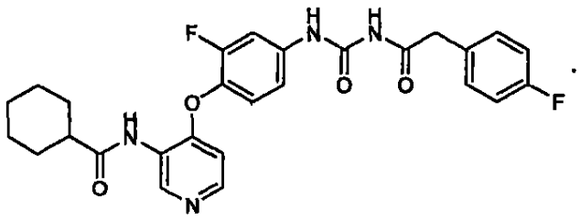
[00292] The title compound was prepared from 1-(4-(3-aminopyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea (Compound C of Example 72, 50 mg, 0.13 mmol) and *trans*-4-((benzyloxycarbonyl)methyl)cyclohexanecarboxylic acid (40 mg, 0.14 mmol, prepared according to the synthetic route described in Schaus, J. M. et al. *J. Med. Chem.* **1998**, *41*, 1943-1955) according to Step A of Example 73 to give the title compound (30 mg, 34%) as white solid. MS(ESI$^+$): *m/z* 672.34 $(M + H)^+$.

B) 1-(4-(3-((1*R*,4*R*)-4-(Aminomethyl)cyclohexanecarboxamido)pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea

[00293] A solution of benzyl ((1*R*,4*R*)-4-((4-(2-fluoro-4-(3-(2-(4-fluorophenyl) acetyl)ureido)phenoxy)pyridin-3-yl)carbamoyl)cyclohexyl)methylcarbamate (25 mg 0.037 mmol) in MeOH (1.5 mL) was hydrogenated over 10 % palladium-carbon (15 mg) for 4 h using H_2 form a rubber balloon. The catalyst was filtered off and the filtrate concentrated *in vacuo* to give the title compound (18 mg, 90%) as a yellow solid. ^{1}H NMR (DMSO-d_6) δ 10.62 (s, 1H), 9.64 (s, 1H), 9.01 (s, 1H), 8.17 (d, 1H, J = 5.6 Hz), 7.79 (dd, 1H, J = 2.5, 12.7 Hz), 7.42 – 7.35 (m, 4H), 7.30 (dd, 1H, J = 8.6,

9.2 Hz), 7.18 (m, 2H), 6.66 (d, 1H, J = 5.6 Hz), 3.75 (s, 2H), 2.39 (d, 2H, J = 6.6 Hz), 1.87 – 1 81 (m, 4H), 1.46 – 1.35 (m, 1H), 1.33 – 1.10 (m, 1H), 0.95 – 0.77 (m, 4H); MS(ESI$^+$): m/z 538.28$(M + H)^+$.

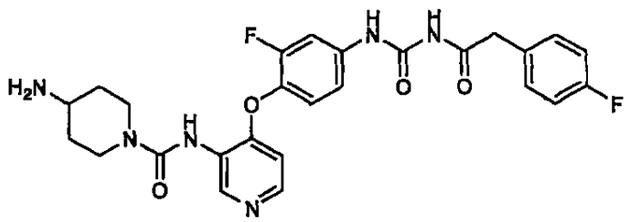
Example 76



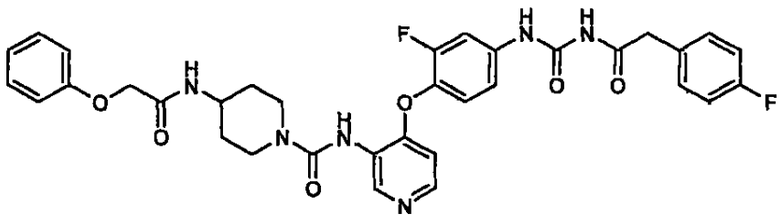
1-(4-(3-(Cyclohexanecarboxamido)pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea

[00294] A solution of 1-(4-(3-aminopyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea (Compound C of Example 72, 25 mg, 0.062 mmol) in CH_2Cl_2 (2 mL) was treated with Et_3N (10 μL, 0.074 mmol) and cyclohexanecarbonyl chloride (Aldrich, 11 mg, 0.074 mmol) and stirred at rt for 2 h. An additional portion of cyclohexanecarbonyl chloride (11 mg, 0.074 mmol) was added to the mixture and the reaction continued for 18 h. The mixture was diluted with CH_2Cl_2, washed with saturated aq. $NaHCO_3$ solution, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 eluting with 50 – 100 % EtOAc / hexanes to give the title compound (19 mg, 61%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.03 (s, 1H), 10.57 (m, 1H), 9.60 (m, 1H), 8.99 (s, 1H), 8.15 (d, 1H, J = 5.6 Hz), 7.76 (dd, 1H, J = 2.0, 13.2 Hz), 7.39 – 7.33 (m, 3H), 7.28 (dd, 1H, J = 8.6, 9.2 Hz), 7.18 – 7.14 (m, 2H), 6.65 (d, 1H, J = 5.1 Hz), 3.73 (s, 2H), 1.81 – 1.71 (m, 5H), 1.64 -1.61 (m, 1H), 1.43 – 1.34 (m, 2H), 1.29 – 1.14 (m, 3H), MS(ESI+): m/z 509.27 $(M + H)^+$.

Example 77



1-(4-(3-(4-Aminopiperidine-1-carboxamido)pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, bis-trifluoroacetic acid salt



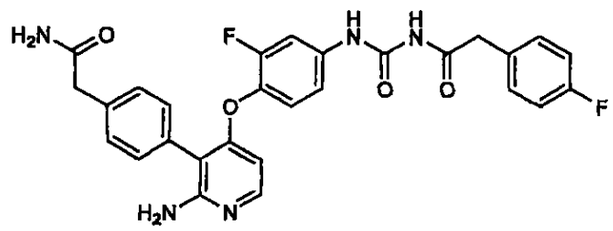
A) 1-(3-Fluoro-4-(3-(4-(2-phenoxyacetamido)piperidine-1-carboxamido)pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea

[00295] A solution of triphosgene (50 mg, 0.17 mmol), in CH_2Cl_2 (0.4 mL) was cooled to -10 °C and treated with a solution of 1-(4-(3-aminopyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea (Compound C of Example 72, 67 mg, 0.17 mmol) and DIPEA (65 µL, 0.37 mmol) in CH_2Cl_2 (0.4 mL). The mixture was stirred at -10 °C for 10 min and then treated with a solution of 4-((carbobenzyloxy)amido)piperidine (40 mg, 0.17 mmol, prepared using the procedure describe in Schaus, J. M. et al. *J. Med. Chem.* **1998,** *41,* 1943-1955) and DIPEA (65 µl, 0.37 mmol) in CH_2Cl_2 (0.4 mL). After stirring for 2 minutes, the mixture was warmed to room temperature then heated to 40 °C for 10 min. The mixture was diluted with EtOAc, washed with saturated aq. $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The product was purified by flash column chromatography on SiO_2 eluting with 0 –5 % MeOH / CH_2Cl_2 to give the title compound (50 mg, 45%) as yellow solid. MS(ESI+) *m/z* 659.29 $(M + H)^+$.

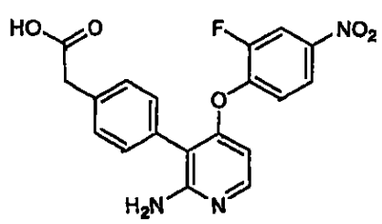
B) 1-(4-(3-(4-Aminopiperidine-1-carboxamido)pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, bis-trifluoroacetic acid salt

[00296] A solution of 1-(3-fluoro-4-(3-(4-(2-phenoxyacetamido)piperidine-1-carboxamido)pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea (45 mg, 0.068 mmol) in absolute MeOH (2.5 mL) was hydrogenated over 10 % palladium-carbon (15 mg) using H_2 from a rubber balloon for 2.5 h. The catalyst was filtered and the filtrate concentrated *in vacuo* and the residue was purified by preparative HPLC (Column A) to afford the title compound. ^{1}H NMR (DMSO-d_6) δ 10.57 (s, 1H), 8.55 (s, 1H), 8.27 (m, 1H), 8.14 (d, 1H, J = 5.6 Hz), 7.75 (dd, 1H, J = 2.0, 12.7 Hz), 7.37 – 7.33 (m, 3H), 7.23 – 7.14 (m, 3H), 6.65 (d, 1H, J = 5.1 Hz), 4.05 – 3.98 (m, 2H), 3.73 (s, 2H), 3.05 – 2.91 (m, 1H), 2.88 – 2.83 (m, 2H), 1.83 – 1.74 (m, 2H), 1.34 – 1.20 (m, 2H); MS(ESI+) *m/z* 525.35 $(M + H)^+$.

Example 78



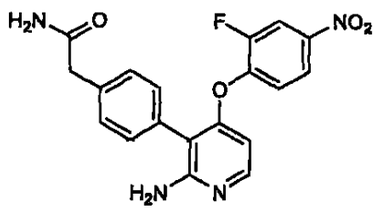
1-(4-(2-Amino-3-(4-(2-amino-2-oxoethyl)phenyl)pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, trifluoroacetic acid salt



A) 2-(4-(2-Amino-4-(2-fluoro-4-nitrophenoxy)pyridin-3-yl)phenyl)acetic acid

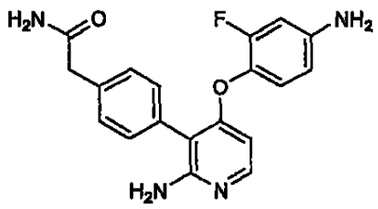
[00297] A mixture of 4-(2-fluoro-4-nitrophenoxy)-3-iodopyridin-2-amine (Compound C of Example 34, 88 mg, 0.23 mmol), 4-(dihydroxyborane)phenylacetic acid pinacol ester (Frontier Scientific Inc., 92 mg, 0.35 mmol), Na_2CO_3 (170 mg, 1.61

mmol), 1,4-dioxane (2 mL) and H_2O (2 mL) was degassed by vacuum / argon purge and treated with tetrakis(triphenylphosphine) palladium (27 mg, 0.023 mmol). After heating at 100 °C for 3 h, the pH of the mixture was adjusted to pH 6 using 1 N hydrochloric acid. The mixture was concentrated *in vacuo* and the residue partitioned between EtOAc and pH 7 phosphate buffer. The aqueous phase was extracted with EtOAc and the combined extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product. The product was triturated with 2:1 EtOAc/ MeOH to give the desired product (70 mg, 80%) as an orange-brown solid. ^{1}H NMR (DMSO-d_6) δ 12.34 (s, 1H), 8.23 (dd, 1H, J = 3.1, 10.5 Hz), 8.05 (d, 1H, J = 10.2 Hz), 7.94 (d, 1H, J = 6.1 Hz), 7.32 – 7.25 (m, 5H), 6.26 (d, 1H, J = 6.1 Hz), 5.62 (s, 2H), 3.57 (s, 2H); MS(ESI$^+$): *m/z* 384.16 $(M + H)^+$.



B) 2-(4-(2-Amino-4-(2-fluoro-4-nitrophenoxy)pyridin-3-yl)phenyl)acetamide

[00298] A solution of 2-(4-(2-amino-4-(2-fluoro-4-nitrophenoxy)pyridin-3-yl)phenyl)acetic acid (65 mg, 0.17 mmol) in anhydrous DMF (1.2 mL) was treated with PyBOP (125 mg, 0.24 mmol) and HOBt (32 mg, 0.24 mmol) followed by DIPEA (60 µL, 0.35 mmol) and NH_4Cl (19 mg, 0.35 mmol). After stirring at room temperature for 20 min, the mixture was concentrated under vacuum and the residue partitioned between EtOAc and saturated aq. $NaHCO_3$ solution. The EtOAc phase was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The product was purified by flash column chromatography on SiO_2 eluting with 0-8 % MeOH / CH_2Cl_2 to give the title compound (40 mg, 62%) as an amber colored oil. ^{1}H NMR (DMSO-d_6) δ 8.23 (dd, 1H, J = 10.7, 2.5 Hz), 8.05 (d, 1H, J = 9.2 Hz), 7.93 (d, 1H, J = 6.1 Hz), 7.42-7.32 (m, 2H), 7.33-7.25 (m, 4H), 6.92 (s, 1H), 6 25 (d, 1H, J = 5.6 Hz), 5.64 (s, 2H), 3.36 (s, 2H); MS(ESI$^+$): *m/z* 383.17 $(M + H)^+$.



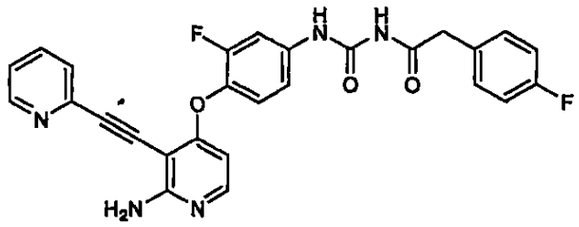
C) **2-(4-(2-Amino-4-(4-amino-2-fluorophenoxy)pyridin-3-yl)phenyl)acetamide**

[00299] A mixture of 2-(4-(2-amino-4-(2-fluoro-4-nitrophenoxy)pyridin-3-yl)phenyl)acetamide (32 mg, 0.086 mmol), DMF (1 mL), EtOH (1 mL) and H_2O (1mL) was treated with Fe powder (67 mg, 1.2 mmol), and NH_4Cl (128 mg, 2.4 mmol) and the mixture heated at 100 °C for 20 min. The mixture was filtered through Celite®, the pH of the filtrate adjusted to pH 7 using phosphate buffer and then the mixture was extracted with EtOAc. The organic extract was dried ($MgSO_4$) and concentrated to give the desired product (20 mg, 67%) as a yellow-brown solid. MS(ESI$^+$): *m/z* 353.32 $(M + H)^+$.

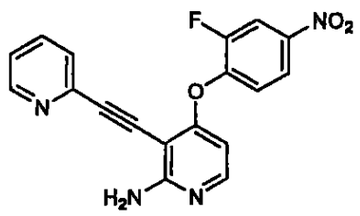
D) **1-(4-(2-Amino-3-(4-(2-amino-2-oxoethyl)phenyl)pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea trifluoroacetic acid salt**

[00300] The title compound was prepared form 2-(4-(2-amino-4-(4-amino-2-fluorophenoxy)pyridin-3-yl)phenyl)acetamide (19 mg, 0.054 mmol) and 0.3 M solution of 2-(4-fluorophenyl)acetyl isocyanate in toluene (Compound D of Example 11, 0.27 mL, 0.081 mmol) in a similar manner as that described for Step D of Example 33. Purification of the reaction mixture by preparative HPLC (Column A) gave the title compound (9 mg, 26%) as a white solid. ^{1}H NMR (DMSO-d_6): δ 11.03 (s, 1H), 10.57 (s, 1H), 7.93 (d, 1H, J = 7.1 Hz), 7.76 (dd, 1H, J = 2.0, 13.2 Hz), 7.44 - 7.42 (m, 3H), 7.37 – 7.29 (m, 6H), 7.16 (dd, 2H, J = 8.6, 8.8 Hz), 6.94 (s, 1H), 6.31 (d, 1H, J = 7.1 Hz), 3.72 (s, 2H), 3.43 (s, 2H); MS(ESI$^+$). *m/z* 532.24 $(M + H)^+$.

Example 79

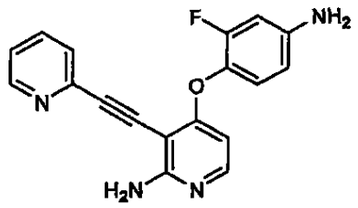


1-(4-(2-Amino-3-(2-(pyridin-2-yl)ethynyl)pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, dihydrochloride salt



A) 4-(2-Fluoro-4-nitrophenoxy)-3-(2-(pyridin-2-yl)ethynyl)pyridin-2-amine

[00301] A mixture of 4-(2-fluoro-4-nitrophenoxy)-3-iodopyridin-2-amine (Compound C of Example 34, 100 mg, 0.27 mmol) and 2-ethynylpyridine (Aldrich, 57 mg, 0.54 mmol), THF (2 mL) and Et_3N (2 mL) was degassed by vacuum / argon purge and treated in turn with CuI (6 mg, 0.032 mmol) and $(Ph_3P)_4Pd$ (20 mg, 0.017 mmol). The mixture was heated at 60 °C for 45 minutes, cooled, partitioned between EtOAc and saturated aq. sodium bicarbonate solution. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product. Purification of the residue by flash column chromatography on SiO_2 eluting with 0-1.5 % MeOH / CH_2Cl_2 gave the title compound (55 mg, 58%) as a brown solid. ^1H NMR (DMSO-d_6) δ 8.53 (d, 1H, J = 5.1 Hz), 8.39 (dd, 1H, J = 2.5, 10.7 Hz), 8.15 (dm, 1H, J = 8.1 Hz), 7.97 (d, 1H, J = 5.6 Hz), 7.81 (d, 1H, J = 8.1 Hz), 7.71 (d, 1H, J = 7.6 Hz), 7.52 (dd, 1H, J = 8.6, 8.6 Hz), 7.38 – 7.34 (m, 1H), 6.71 (s, 2H), 6.21 (d, 1H, J = 5.6 Hz); MS(ESI$^+$): *m/z* 351.25 $(M + H)^+$.



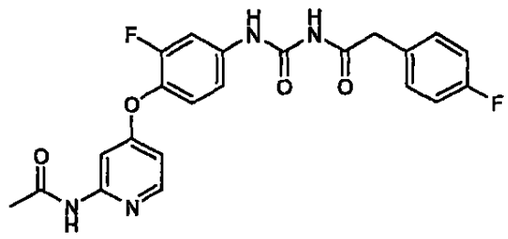
B) 4-(4-Amino-2-fluorophenoxy)-3-(2-(pyridin-2-yl)ethynyl)pyridin-2-amine

[00302] A mixture of 4-(2-fluoro-4-nitrophenoxy)-3-(2-(pyridin-2-yl)ethynyl)pyridin-2-amine (35 mg, 0.1 mmol), THF (1.5 mL) and MeOH (1.5 ml) was treated with zinc dust (65 mg, 1.0 mmol) and NH_4Cl (53 mg, 1.0 mmol) and heated at 60 °C for 45 min. The reaction mixture was cooled, filtered and concentrated under vacuum. The residue was partitioned between EtOAc and saturated aq. $NaHCO_3$ solution. The organic phase was separated, washed with brine, dried ($MgSO_4$) and concentrated to give the title compound (25 mg, 78%) as a brown solid. MS(ESI$^+$): *m/z* 321.2 $(M + H)^+$.

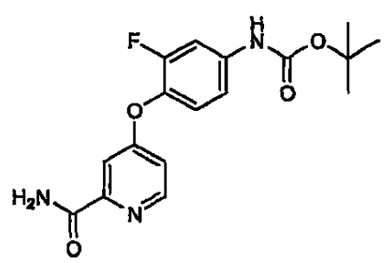
C) 1-(4-(2-Amino-3-(2-(pyridin-2-yl)ethynyl)pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, dihydrochloride salt

[00303] A solution of 4-(4-amino-2-fluorophenoxy)-3-(2-(pyridin-2-yl)ethynyl)pyridin-2-amine (25 mg, 0.078 mmol) in THF (2 mL) was cooled to 0 °C and treated with 0.3 M solution of 2-(4-fluorophenyl)acetyl isocyanate in toluene (Compound D of Example 11, 0.26 mL, 0.078 mmol). After 1 h, the mixture was warmed to room temperature and stirred for 15 min. The mixture was concentrated under vacuum and the residue purified by preparative HPLC (Column A) to give the title compound as a TFA salt. The TFA salt was dissolved in anhydrous MeOH and treated with 1 M HCl / Et_2O at 0 °C and stirred for 5 min. The mixture was then concentrated *in vacuo* to give the title compound (18 mg, 41%) as a brown solid. ^1H NMR (DMSO-d_6) δ 11.06 (s, 1H), 10.63 (s, 1H), 8.62 (d, 1H, J = 4.5 Hz), 8.22 (s, 2H), 7.99 (d, 1H, J = 7.1 Hz), 7.94 – 7.81 (m, 3H), 7.48 – 7.44 (m, 3H), 7.37 – 7.33 (m, 2H), 7.16 (dd, 2H, J = 6.2, 9.2 Hz), 6.30 (d, 1H, J = 7.1 Hz), 3.74 (s, 2H); MS(ESI$^+$): *m/z* 500.21 $(M + H)^+$.

Example 80

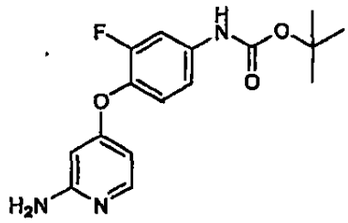


1-(4-(2-Acetamidopyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, hydrochloride salt



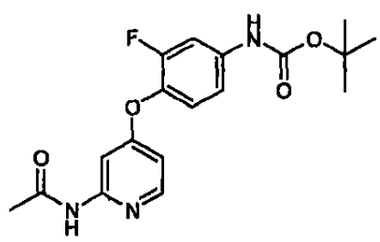
A) *tert*-Butyl 4-(2-carbamoylpyridin-4-yloxy)-3-fluorophenylcarbamate

[00304] A mixture of 4-(4-amino-2-fluorophenoxy)picolinamide (Compound B' of Example 24, 190 mg, 0.76 mmol), *tert*-butyl alcohol (2 mL), 1,4-dioxane (1 mL), DMF (1 mL) and Boc_2O (167 mg, 0.76 mmol) was heated at 65 °C for 16 h. Additional portions of Boc_2O (85 mg and 60 mg) were added after 16 h and 32 h, respectively and the mixture heated for a total of 40 h. The mixture was concentrated under vacuum and the residue partitioned between EtOAc and saturated aq. $NaHCO_3$ solution. The EtOAc phase was dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product. Purification of the residue by flash column chromatography on SiO_2 eluting with 30 – 60 % EtOAc / hexanes gave the title compound (180 mg, 68%) as a brown solid. ^1H NMR (DMSO-d_6) δ 9.74 (s, 1H), 8.52 (d, 1H, J = 5.6 Hz), 8.13 (s, 1H), 7.72 (s, 1H), 7.62 (d, 1H, J = 13.7 Hz), 7.35-7.31 (m, 3H), 7.18 (dd, 1H, J = 5.6, 2.5 Hz), 1.39 (s, 9H); MS(ESI$^+$): *m/z* 348.22 $(M + H)^+$.



B) *tert*-Butyl 4-(2-aminopyridin-4-yloxy)-3-fluorophenylcarbamate

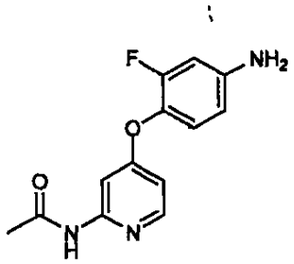
[00305] A solution of KOH (280 mg, 5.0 mmol) in H_2O (2 mL) was cooled to 0 – 5°C and treated dropwise with bromine (162 mg, 1.0 mmol) and the mixture stirred for 5 min. *tert*-Butyl 4-(2-carbamoylpyridin-4-yloxy)-3-fluorophenylcarbamate (347 mg, 1.0 mmol) was added to the mixture in one portion as a solid and then 1,4-dioxane (3 mL) was added to dissolve the solids. The reaction mixture was stirred at room temperature for 30 min then at 55 °C for 45 min. The mixture was then cooled to room temperature, treated with HOAc (0.5 mL) and stirred until the foaming subsided. The mixture was reheated to 55 °C for 20 min, cooled to room temperature, treated with KOH (350 mg) and extracted with CH_2Cl_2. The organic extract was dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by flash column chromatography on SiO_2 eluting with 30 – 70 % EtOAc / hexanes to give the title compound (265 mg, 83%). ^{1}H NMR (DMSO-d_6) δ 9.67 (s, 1H), 7.77 (d, 1H, J = 6.1 Hz), 7.56 (d, 1H, J = 11.7 Hz), 7.26 – 7.18 (m, 2H), 6.12 (dd, 1H, J = 2.0, 6.1 Hz), 5.93 (s, 2H), 5.74 (d, 1H, J = 2.5 Hz), 1.47 (s, 9H); MS(ESI$^+$): *m/z* 320.23 $(M + H)^+$.



C) *tert*-Butyl 4-(2-acetamidopyridin-4-yloxy)-3-fluorophenylcarbamate

[00306] A *tert*-butyl 4-(2-aminopyridin-4-yloxy)-3-fluorophenylcarbamate (150 mg, 0.47 mmol) in anhydrous pyridine (0.5 mL) was cooled to 10 °C and treated with acetyl chloride (33 μL, 0.47 mmol) and the mixture stirred for 45 min. An additional portion of acetyl chloride (16 μL, 0.24 mmol) was added to the reaction and stirring

continued for 25 min. The mixture was diluted with EtOAc (20 mL), washed with brine, dried ($MgSO_4$) and concentrated under vacuum to give the title compound (115 mg, 68%). ^{1}H NMR (DMSO-d_6) δ 10.55 (s, 1H), 9.71 (s, 1H), 8.16 (d, 1H, J = 5.5 Hz), 7.63-7.55 (m, 2H), 7.29-7.23 (m, 2H), 6.68-6.63 (m, 1H), 2.02 (s, 3H), 1.48 (s, 9H); MS(ESI$^+$): *m/z* 362.22 $(M+H)^+$.



D) *N*-(4-(4-Amino-2-fluorophenoxy)pyridin-2-yl)acetamide

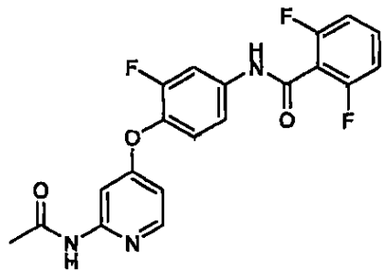
[00307] A solution of *tert*-butyl 4-(2-acetamidopyridin-4-yloxy)-3-fluorophenylcarbamate (110 mg, 0.30 mmol) in 4 M HCl / 1,4-dioxane (1.5 mL) was stirred at 0 °C for 20 min then at room temperature for 25 min. The mixture was diluted with EtOAc (25 mL) and saturated aq. $NaHCO_3$ solution (20 mL), and stirred vigorously for 5 min. The EtOAc phase was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound (69 mg, 87%) as a yellow solid. ^{1}H NMR (DMSO-d_6) δ 10.49 (s, 1H), 8.13 (d, 1H, J = 5.6 Hz), 7.60 (m, 1H), 6.95 (dd, 1H, J = 8.6, 9.2 Hz), 6.60 (dd, 1H, J = 2.5, 5.6 Hz), 6.48 (dd, 1H, J = 2.5, 13.2 Hz), 6.40 (dd, 1H, J = 2.0, 8.6 Hz), 5.44 (s, 2H), 2.02 (s, 3H).

E) 1-(4-(2-Acetamidopyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, hydrochloride salt

[00308] A solution of *N*-(4-(4-amino-2-fluorophenoxy)pyridin-2-yl)acetamide (20 mg, 0.077 mmol) in THF (1 mL) was treated with 0.3 M solution of 2-(4-fluorophenyl)acetyl isocyanate in toluene (Compound D of Example 11, 0.26 mL, 0.77 mmol) and the mixture was stirred at room temperature for 1 h. The mixture was concentrated under vacuum and the residue purified by preparative HPLC (Column A) to give the title compound as a TFA salt The TFA salt was dissolved in anhydrous MeOH and treated with 1 M HCl / Et_2O at 0 °C and stirred for 5 min. The mixture was then concentrated *in vacuo* to give the title compound (12 mg, 33%) as a white

solid. ^{1}H NMR (DMSO-d_6): δ 11.04 (s, 1H), 10.65 (s, 1H), 10.58 (s, 1H), 8.18 (d, 1H, J = 6.1 Hz), 7.77 (dd, 1H, J = 2.0, 12.7 Hz), 7.56 (m, 1H), 7.40 – 7.30 (m, 5H), 7.18 – 7.14 (m, 2H), 6.71 (dd, 1H, J = 2.5, 6.1 Hz), 3.74 (s, 2H), 2.03 (s, 3H); MS(ESI$^+$): m/z 441.18 $(M + H)^+$.

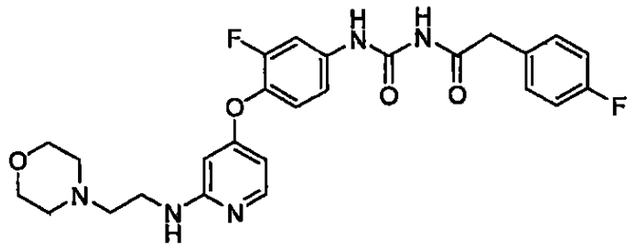
Example 81



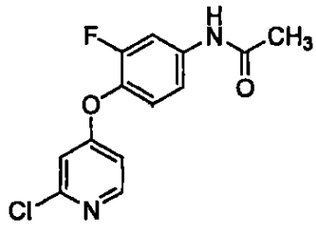
***N*-(4-(2-Acetamidopyridin-4-yloxy)-3-fluorophenyl)-2,6-difluorobenzamide, hydrochloride salt**

[00309] A solution of *N*-(4-(4-amino-2-fluorophenoxy)pyridin-2-yl)acetamide (Compound B' of Example 24, 15 mg, 0.057 mmol) in THF (0.5 mL) was treated with DIPEA (15 μL, 0.086 mmol) and 2-6-diflurobenzoyl chloride (10 mg, 0.057 mmol) and the mixture stirred at room temperature for 1.5 h. The mixture was concentrated under vacuum and the residue purified by preparative HPLC (Column A) to give the title compound as a TFA salt. The TFA salt was dissolved in anhydrous MeOH and treated with 1 M HCl / Et_2O at 0 °C and stirred for 5 min. The mixture was then concentrated *in vacuo* to give the title compound (15 mg, 60%) as a off-white solid. ^{1}H NMR (DMSO-d_6) δ 11.17 (s, 1H), 10.79 (s, 1H), 8.21 (d, 1H, J = 6.1 Hz), 7.89 (dd, 1H, J = 2.0, 12.7 Hz), 7.66 – 7.59 (m, 1H), 7.53 – 7.50 (m, 2H), 7.42 (dd, 1H, J = 8.6, 9.2 Hz), 7.28 (dd, 2H, J = 8.1, 8.1 Hz), 6.80 (dd, 1H, J = 2.0, 6.1 Hz), 2.06 (s, 3H); MS(ESI$^+$): m/z 402.13 $(M + H)^+$.

Example 82

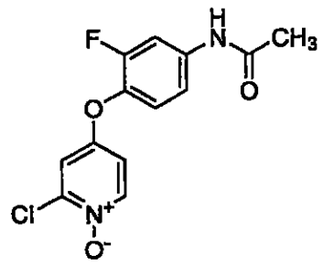


1-(3-Fluoro-4-(2-(2-morpholinoethylamino)pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea, dihydrochloride salt



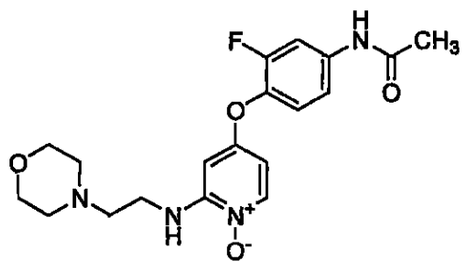
A) *N*-(4-(2-Chloropyridin-4-yloxy)-3-fluorophenyl)acetamide

[00310] A mixture of *N*-(3-fluoro-4-hydroxyphenyl)acetamide (Compound A of Example 13, 1.33 g, 7.87 mmol), 2-chloro-4-nitropyridine (Aldrich, 1.24 g, 7.87 mmol), K_2CO_3 (1.6 g, 11.8 mmol), and DMF (25 mL) was heated at 100 °C for 9 h. The mixture was concentrated *in vacuo* and the residue was partitioned between EtOAc and saturated aq. $NaHCO_3$ solution. The EtOAc phase was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 eluting with 30 -80 % EtOAc in hexanes to give the title compound (1.6 g, 73%) as a pale yellow solid. ^1H NMR (DMSO-d_6) δ 10.25 (s, 1H), 8.35 (d, 1H, J = 7 Hz), 7.80 (d, 1H, J = 14 Hz), 7.50 (d, 1H, J = 3 Hz), 7.33 (m, 2H), 7.02 (m, 1H), 2.06 (s, 3H); MS(ESI$^+$): *m/z* 281.16 $(M + H)^+$.



B) *N*-(4-(2-Chloropyridin-4-yloxy-1-oxide)-3-fluorophenyl)acetamide

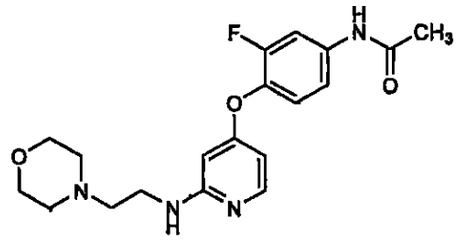
[00311] A mixture of *N*-(4-(2-chloropyridin-4-yloxy)-3-fluorophenyl)acetamide (0.98 g, 3.5 mmol), >90 %, *m*-chloroperoxybenzoic acid (1.3 g, 7.6 mmol), and $CHCl_3$ (50 mL) was stirred at rt for 60 h. The mixture was concentrated *in vacuo* and the residue triturated with Et_2O (2 × 100 mL) to give the title compound (0.89 g, 86%) as a pale yellow solid. ^{1}H NMR (DMSO-d_6) δ 10.25 (s, 1H), 8.35 (d, 1H, J = 7.3 Hz), 7.80 (d, 1H, J = 13 Hz), 7.33-7.32 (m, 3H), 7.02 (dd, 1H, J = 3.5, 7.5 Hz), 2.06 (s, 3H); MS(ESI): *m/z* 295.04 $(M + H)^+$.



C) *N*-(3-Fluoro-4-(2-(2-morpholinoethylamino)pyridin-4-yloxy-1-oxide)phenyl)acetamide

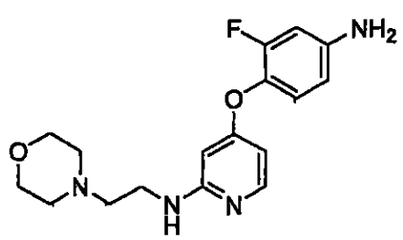
[00312] A mixture of *N*-(4-(2-chloropyridin-4-yloxy-1-oxide)-3-fluorophenyl)acetamide hydrochloride (205 mg, 0.62 mmol), 4-(2-aminoethyl)morpholine (Aldrich, 169 mg, 1.30 mmol), and absolute EtOH was heated at reflux 16 h. The reaction mixture was concentrated *in vacuo*, and the residue was treated with H_2O (3 mL) and applied to a 10 g Varian C-18 cartridge. The cartridge was eluted first with H_2O then with 30 % MeOH in H_2O. The eluent which contained the desired product was pooled, concentrated to 5 mL volume, and extracted 3 times with EtOAc. The combined extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound (100 mg, 40%). ^{1}H NMR (DMSO-

d_6) δ 10.22 (s, 1H), 7.84 (d, 1H, J = 6 Hz), 7.77 (dd, 1H, J = 2, 12 Hz), 7.31 (dd, 1H, J = 2, 9 Hz), 7.24 (dd, 1H, J = 9, 9 Hz), 6.41 (m, 1H), 6.13 (dd, 1H, J = 2, 6 Hz), 5.81 (d, 1H, J = 2.5 Hz), 3.56-3.48 (m, 2H), 3.31-3.19 (m, 4H), 2.38 (t, 2H, J = 7 Hz), 2.40-2.28 (m, 4H), 2.06 (s, 3H); MS(ESI$^+$): m/z 405.22 $(M + H)^+$.



D) *N*-(3-Fluoro-4-(2-(2-morpholinoethylamino)pyridin-4-yloxy)phenyl)acetamide, trifluoroacetic acid salt

[00313] A mixture of *N*-(3-fluoro-4-(2-(2-morpholinoethylamino)pyridin-4-yloxy-1-oxide)phenyl)acetamide (100 mg, 0.26 mmol), and triphenylphosphine polymer supported (1.4 -2.0 mmol/g) on polystyrene (500 mg) and DMF (2 mL) was stirred at 135 °C for 15 h. The mixture was filtered to remove the resin and the resin washed with DMF and EtOAc. The filtrate and washings were combined and concentrated. The crude product was purified by preparative HPLC (Column A) to give the title compound (45 mg, 24%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 10.33 (s, 1H), 8.02 (d, 1H, J = 7 Hz) 7.84 (dd, 1H, J = 2, 13 Hz), 7.39-7.31 (m, 2H), 6.52 (s, 1H), 6.10 (s, 1H), 3.83 (s, 4H), 3.60-3.48 (m, 2H), 3.32-3.18 (m, 6H), 2.08 (s, 3H); MS(ESI$^+$): m/z 375.12 $(M + H)^+$.



E) 4-(4-Amino-2-fluorophenoxy)-*N*-(2-morpholinoethyl)pyridin-2-amine, hydrochloride salt

[00314] A mixture of *N*-(3-fluoro-4-(2-(2-morpholinoethylamino)pyridin-4-yloxy)phenyl)acetamide trifluoroacetate (40 mg), MeOH (1 mL), and 6 M HCl (0.2

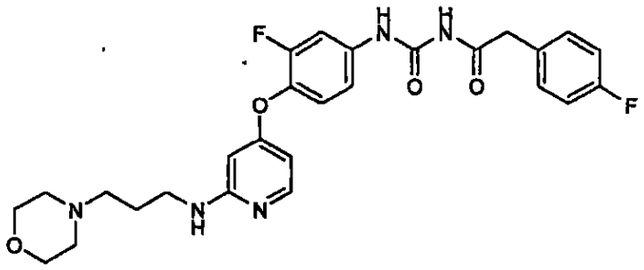
mL) was heated at reflux for 3 h. The mixture was concentrated on a rotary evaporator and the residue was lyophilized to give the title compound (30 mg) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.12 (s, 1H), 8.85 (s, 1H), 7.95 (d, 1H, J = 7 Hz), 7.08 (dd, 1H, J = 9, 9 Hz), 6.65-6.63 (m, 2H), 6.54 (d, 1H, J = 8 Hz), 6.31 (s, 1H), 3.90-3.75 (m 6H), 3.37-3.21 (m, 6H); MS(ESI): *m/z* 373.14 $(M + H)^+$.

F) 1-(3-Fluoro-4-(2-(2-morpholinoethylamino)pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea, dihydrochloride salt

[00315] A solution of 4-(4-amino-2-fluorophenoxy)-*N*-(2-morpholinoethyl)pyridin-2-amine hydrochloride (15 mg, 0.045 mmol) in MeOH (5 mL) was treated with Et_3N (2 mL) and the mixture stirred at room temperature for 5 min. The mixture was concentrated *in vacuo* to remove the MeOH, the residue suspended in THF (1 mL) and treated with a solution of 0.3 M solution of 2-(4-fluorophenyl)acetyl isocyanate in toluene (Compound D of Example 11, 180 mL, 0.054 mmol). After stirring, the mixture was concentrated *in vacuo* and the residue partitioned between EtOAc and saturated $NaHCO_3$. The EtOAc phase was separated, washed with brine, dried ($MgSO_4$) and concentrated. The mixture was concentrated under vacuum and the residue purified by preparative HPLC (Column A) to give the title compound as a TFA salt. The TFA salt was dissolved in anhydrous MeOH and treated with 1 N HCl / Et_2O at 0 °C and stirred for 5 min. The mixture was then concentrated *in vacuo* to give the title compound (10 mg, 43%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.05 (s, 1H), 10.61 (s, 1H), 7.98 (d, 1H, J = 7.1 Hz), 7.86-7.73 (m, 1H), 7.48-7.38 (m, 1H), 7.37-7.30 (m, 3H), 7.24-7.04 (m, 2H), 6.60 (s, 1H), 6.26 (s, 1H), 3.98-3.60 (m, 8H), 3.74 (s, 2H), 3.39-3.19 (m, 4H); MS(ESI$^+$): *m/z* 512.2 $(M + H)^+$.

[00316] Examples **83-85** were prepared in a similar manner as described for Example 82.

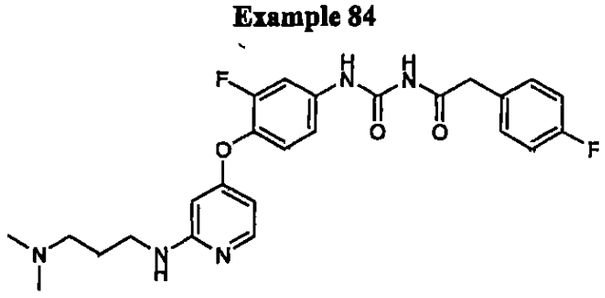
Example 83



1-(3-Fluoro-4-(2-(3-morpholinopropylamino)pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea, hydrochloride salt

[00317] ^{1}H NMR (DMSO-d_6) δ 11.06 (s, 1H), 10.62 (s, 1H), 7.93 (d, 1H, J = 7.1 Hz), 7.83 (d, 1H, J = 12.7 Hz), 7.45 – 7.33 (m, 4H), 7.16 (dd, 2H, J = 8.6, 9.2 Hz), 6.64 (s, 1H), 6.23 (s, 1H), 3.95 - 3.76 (m, 4H), 3.74 (s, 2H), 3.70 -3.48 (m, 4H), 3.48 – 3.35 (m, 2H), 3.20 – 3.-04 (m, 2H), 2.02 – 1.93 (m, 2H).

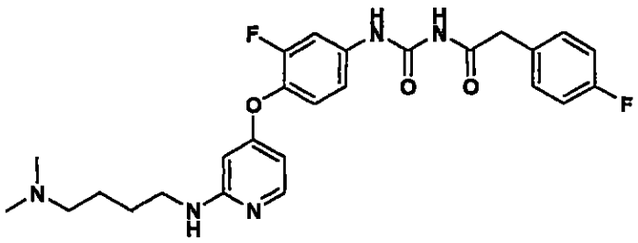
Example 84



1-(4-(2-(3-(Dimethylamino)propylamino)pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, hydrochloride salt

[00318] ^{1}H NMR (DMSO-d_6) δ 11.06 (s, 1H), 10.62 (s, 1H), 10.37 (s, 1H), 7.93 (d, 1H, J = 7.1 Hz), 7.82 (dd, 1H, J = 2.0, 12.7 Hz), 7.45 (dd, 1H, J = 2.6, 8.6 Hz), 7.40 (d, 1H, J = 8.6 Hz), 7.37 – 7.33 (m, 2H), 7 16 (dd, 2H, J = 8.7, 9.1 Hz), 6.65 (s, 1H), 6.24 (s, 1H), 3.75 (s, 2H), 3.45 – 3.36 (m, 2H), 3.13 – 3.03 (m, 2H), 2.73 (s, 3H), 2.72 (s, 3H), 1.94 – 1.90 (m, 2H).

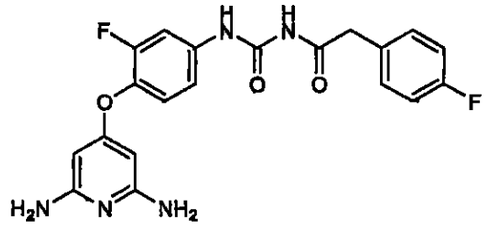
Example 85



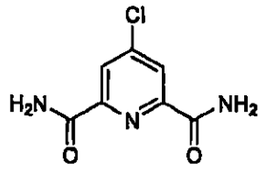
1-(4-(2-(4-(Dimethylamino)butylamino)pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, hydrochloride salt

[00319] MS(ESI$^+$): *m/z* 498 2 $(M+H)^+$.

Example 86



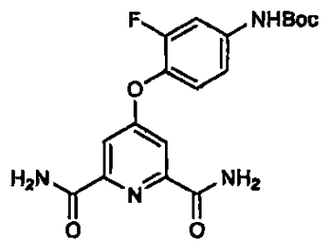
1-(4-(2,6-Diaminopyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, hydrochloride salt



A) 4-Chloropyridine-2,6-dicarboxamide

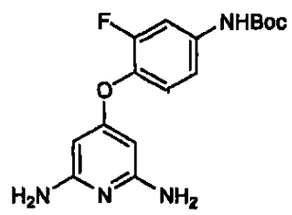
[00320] A mixture of chelidamic acid (3.19 g, 17.0 mmol), PCl_5 (2.1 g) and CCl_4 (30 mL) was refluxed for 6 h and then cooled to 65 °C and treated with MeOH (5 mL) under gentle reflux. The mixture was refluxed for 5 h and then concentrated *in vacuo*. The residue was treated with ice-water (50 mL) and the precipitated solid was collected by filtration and sucked dry on the funnel to give white needles of 2,6-biscarbomethoxy-4-chloropyridine (2.4 g). The product was treated with ~ 7 M NH_3 / MeOH and stirred at room temperature for 1 h. The mixture was filtered to collect the

title compound as a white solid (1.8 g, 53%). ^{1}H NMR (DMSO-d_6) δ 8.91 (s, 2H), 8.15 (s, 2H), 7.87 (s, 2H).



B) *tert*-Butyl 4-(2,6-dicarbamoylpyridin-4-yloxy)-3-fluorophenylcarbamate

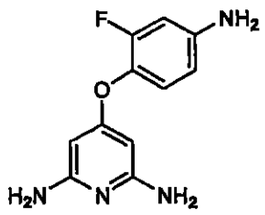
[00321] A solution of *N*-Boc-4-amino-2-fluorophenol (228 mg, 1.0 mmol) in DMF (2 mL) was treated with *t*-BuOK (124 mg, 1.1 mmol) and the mixture stirred at room temperature for 2 h. The mixture was treated with 4-chloropyridine-2,6-dicarboxamide (200 mg, 1.0 mmol) and K_2CO_3 (35 mg, 0.5 mmol) and heated at 80°C for 1.5 h. The mixture was concentrated *in vacuo*, treated with EtOAc (10 mL) and H_2O (10 mL) and filtered to remove the insoluble material. The EtOAc phase was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by flash column chromatography on SiO_2 eluting with 30 -100 % EtOAc / hexanes gave the title compound (170 mg, 44%) as a white solid containing 10 % of the starting chloropyridine. ^{1}H NMR (DMSO-d_6) δ 9.77 (s, 1H), 8.86 (s, 2H), 7.87 (s, 1H), 7.63 (d, 1H, J = 12.1 Hz), 7.55 (s, 2H), 7.38 – 7.31 (m, 2H), 1.48 (s, 9H).



C) *tert*-Butyl 4-(2,6-diaminopyridin-4-yloxy)-3-fluorophenylcarbamate

[00322] The title compound was prepared from *tert*-butyl 4-(2,6-dicarbamoylpyridin-4-yloxy)-3-fluorophenylcarbamate (110 mg, 0.28 mmol) using a similar procedure as described for Step B of Example 80. Flash chromatography on SiO_2 eluting with 0 - 2 % MeOH / EtOAc gave the title compound (60 mg, 63%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 9.60 (s, 1H), 7.50 (dd, 1H, J = 1.8, 13.6 Hz), 7.21

(dd, 1H, J = 2.2, 8.7 Hz), 7.13 (dd, 1H, J = 8.7, 9.2 Hz), 5.40 (s, 4H), 5.13 (s, 2H), 1.47 (s, 9H); MS(ESI$^+$): *m/z* 335.23 $(M + H)^+$.



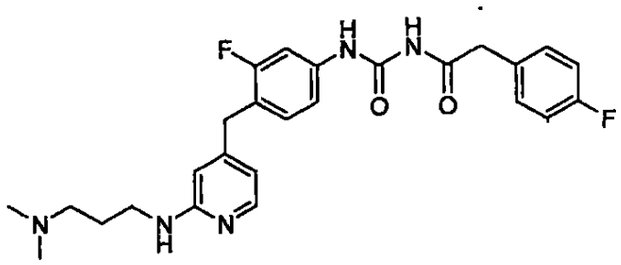
D) 4-(4-Amino-2-fluorophenoxy)pyridine-2,6-diamine

[00323] The title compound was prepared form *tert*-butyl 4-(2,6-diaminopyridin-4-yloxy)-3-fluorophenylcarbamate (30 mg, 0.089 mmol) in a manner similar to that is described in Step D of Example 80 to give a clear oil (20 mg, 100%). MS(ESI$^+$): *m/z* 235.22 $(M + H)^+$.

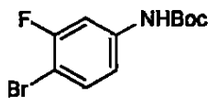
E) 1-(4-(2,6-Diaminopyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, hydrochloride salt

[00324] The title compound was prepared from 4-(4-amino-2-fluorophenoxy)pyridine-2,6-diamine (19 mg, 0.081 mmol) and a solution of 2-(4-fluorophenyl)acetyl isocyanate in toluene (0.3 M, Compound D of Example 11, 0.27 mL, 0.081 mmol) in a similar manner as Step D of Example 33. The reaction mixture was purified by preparative HPLC (Column A) to give the title compound as a TFA salt. The TFA salt was dissolved in anhydrous MeOH and treated with 1 M HCl / Et_2O at 0 °C and stirred for 5 min. The mixture was then concentrated *in vacuo* to give the title compound (8 mg, 24%) as a pale yellow solid. ^{1}H NMR (DMSO-d_6) δ 11.01 (s, 1H), 10.51 (s, 1H), 7.68 (dd, 1H, J = 2.6, 12.7 Hz), 7.36 – 7.30 (m, 3H), 7.22 – 7.14 (m, 3H), 5.52 (s, 4H), 5.15 (s, 2H), 3.73 (s, 2H); MS(ESI$^+$): *m/z* 414.09 $(M + H)^+$.

Example 87

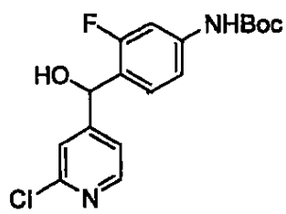


1-(4-((2-(3-(Dimethylamino)propylamino)pyridin-4-yl)methyl)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, dihydrochloride salt



A) *tert*-Butyl 4-bromo-3-fluorophenylcarbamate

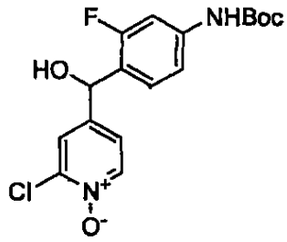
[00325] To a solution of 4-bromo-3-fluorobenzenamine (Lancaster, 7.05 g, 37.1 mmol) in anhydrous tetrahydrofuran (40 mL) at room temperature was added $(Boc)_2O$ (8.10 g, 37.1 mmol) and triethylamine (5.17 mL, 37.1 mmol). The reaction mixture was heated at reflux overnight. After cooling down, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on SiO_2 eluting with 20% dichloromethane in hexane, then 20% ethyl acetate in hexane to give *tert*-butyl 4-bromo-3-fluorophenylcarbamate (5.30 g, 49% yield). MS(ESI$^+$): *m/z* 290.2 $(M+H)^+$.



B) *tert*-Butyl 4-((2-chloropyridin-4-yl)(hydroxy)methyl)-3-fluorophenylcarbamate

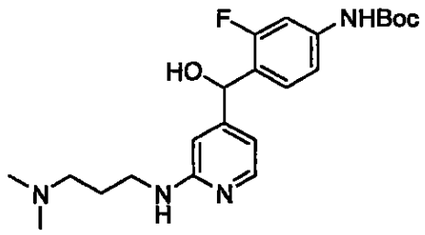
[00326] To a solution of *tert*-butyl 4-bromo-3-fluorophenylcarbamate (2.60 g, 9.0 mmol) in anhydrous THF (30 mL) at -78 °C was added MeMgBr (3.0 M in Et_2O, 3.1 mL, 9.3 mmol) via syringe. The solution was stirred for 10 min at that temperature,

and then warmed to 0 °C for 0.5 h. After the solution was cooled back to -78 °C, a solution of *t*-BuLi (1.7 M in hexane, 10.6 mL, 18.1 mmol) was added over 4 min. The resulting solution was allowed to stir for 5 min before a solution of 2-chloroisonicotinaldehyde (1.41 g, 10 mmol) (for preparation, see Frey, L. F. et al. *Tetrahedron Lett.* **2001**, *42*, 6815) in anhydrous THF (25 mL) was added in 3 min. The reaction mixture was stirred at -78 °C for 20 min and 2.0 mL of MeOH was added. The solution was then concentrated under reduced pressure and the residue was dissolved in 200 mL of EtOAc. It was subsequently washed with H_2O (2 × 50 mL), brine (2 × 50 mL) and dried over $MgSO_4$. After filtration and concentration, the residue was purified by flash chromatography on SiO_2 eluting with 0%-50% EtOAc in hexane to give *tert*-butyl 4-((2-chloropyridin-4-yl)(hydroxy)methyl)-3-fluorophenylcarbamate (1.30 g, 41% yield). MS(ESI$^+$): *m/z* 353.28 / 355.24 $(M + H)^+$.



C) ***tert*-Butyl 4-((2-chloropyridin-*N*-oxide-4-yl)(hydroxy)methyl)-3-fluorophenylcarbamate**

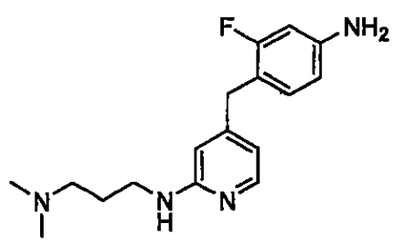
[00327] To a solution of *tert*-butyl 4-((2-chloropyridin-4-yl)(hydroxy)methyl)-3-fluorophenylcarbamate (1.20 g, 3.40 mmol) in a mixture of dichloromethane (100 mL) and ethyl acetate (10 mL) was added *m*-CPBA (70%, 2.34 g, 9.48 mmol). The reaction mixture was stirred at room temperature for 2 h, and then heated at reflux for 5 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on SiO_2 eluting with 50% EtOAc in hexane, 100% EtOAc and then 10 % MeOH in EtOAc, to give *tert*-butyl 4-((2-chloropyridin-*N*-oxide-4-yl)(hydroxy)methyl)-3-fluorophenylcarbamate (840 mg, 67% yield). MS(ESI$^+$): *m/z* 369.13 / 371.13 $(M + H)^+$.



D) *tert*-Butyl 4-((2-(3-(dimethylamino)propylamino)pyridine -4-yl)(hydroxy)methyl)-3-fluorophenylcarbamate

[00328] To a solution of *tert*-butyl 4-((2-chloropyridin-*N*-oxide-4-yl)(hydroxy)methyl)-3-fluorophenylcarbamate (80 mg, 0.22 mmol) in EtOH (2.0 mL) was added N^1,N^1-dimethylpropane-1,3-diamine (225 mg, 2.2 mmol). The reaction mixture was heated at 80 °C for 12 h and the solvent was removed to provide crude *tert*-butyl 4-((2-(3-(dimethylamino)propylamino)pyridine-*N*-oxide-4-yl)(hydroxy)methyl)-3-fluorophenylcarbamate, which was directly used in the next step. MS(ESI$^+$): *m/z* 435.37 $(M + H)^+$.

[00329] To a solution of *tert*-butyl 4-((2-(3-(dimethylamino)propylamino)pyridine-*N*-oxide-4-yl)(hydroxy)methyl)-3-fluorophenylcarbamate (~0.22 mmol) in MeOH (2.0 mL) was added zinc (114 mg, 1.75 mmol) and NH_4CO_2H (139 mg, 2.20 mmol). The suspension was refluxed overnight. More zinc (114 mg) and NH_4CO_2H (139 mg) were added and the suspension was refluxed for 2 h. After cooling down, the solution was filtered and the filtrate was concentrated under reduced pressure. The residue was then purified by flash chromatography on SiO_2 eluting with 10-30% MeOH in DCM to give *tert*-butyl 4-((2-(3-(dimethylamino)propylamino)pyridine- 4-yl)(hydroxy)methyl)-3-fluorophenylcarbamate (80 mg, 87% yield). MS(ESI$^+$): *m/z* 419.34 $(M + H)^+$.



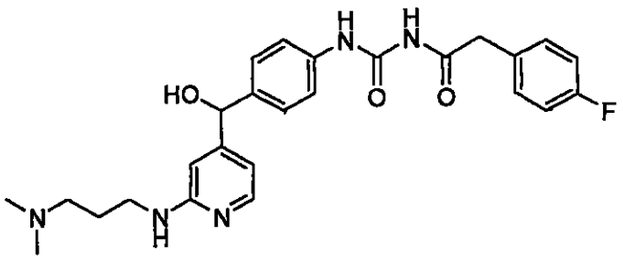
E) 4-(4-Amino-2-fluorobenzyl)-*N*-(3-(dimethylamino)propyl)pyridin-2-amine

[00330] To a solution of *tert*-butyl 4-((2-(3-(dimethylamino)propylamino)pyridine-4-yl)(hydroxy)methyl)-3-fluorophenylcarbamate (80 mg, 0.19 mmol) in MeOH (5.0 mL) was added 2 mL of conc. HCl and palladium on charcoal (10%, 200 mg). The suspension was heated at 75 °C under H_2 atmosphere for 24 h. The mixture was cooled down, filtered and concentrated *in vacuo*. The residue was dissolved in 1 mL of conc. NH_4OH and it was extracted with DCM (5 × 5 mL). The combined organic layer was dried over Na_2SO_4. After filtration, it was concentrated *in vacuo* to give 4-(4-amino-2-fluorobenzyl)-*N*-(3-(dimethylamino)propyl)pyridin-2-amine (31 mg, 40 % yield). MS(ESI$^+$): *m/z* 303.31 $(M + H)^+$.

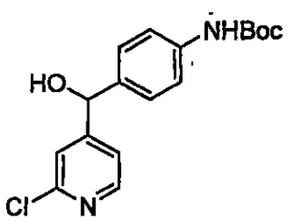
F) 1-(4-((2-(3-(Dimethylamino)propylamino)pyridin-4-yl)methyl)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, dihydrochloride salt

[00331] To a solution of 4-(4-amino-2-fluorobenzyl)-*N*-(3-(dimethylamino)propyl)pyridin-2-amine (30 mg, 0.1 mmol) in DCM (2 mL) was added a solution of 2-(4-fluorophenyl)acetyl isocyanate (Compound D of Example 11, 0.347 M in toluene, 0.25 mL). The mixture was stirred at room temperature for 0.5 h before it was quenched with MeOH. The solution was concentrated *in vacuo* and the residue was purified by prep. HPLC. The desired fractions were collected and concentrated *in vacuo*. The residue was dissolved in MeOH and polymer bound diethylene triamine (50 mg) was added to remove trifluoroacetic acid. After filtration and concentration, the residue was converted to a hydrochloride salt by the addition of 1 N HCl (0.5 mL) and lyophilized to give 1-(4-((2-(3-(dimethylamino)propylamino)pyridin-4-yl)methyl)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea hydrochloride (8.0 mg, 14% yield). MS(ESI$^+$): *m/z* 482.24 $(M + H)^+$.

Example 88

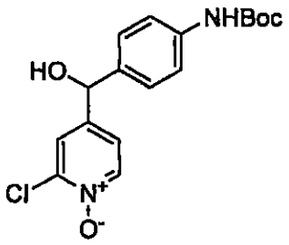


1-(4-((2-(3-(Dimethylamino)propylamino)pyridin-4-yl)(hydroxy)methyl)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea



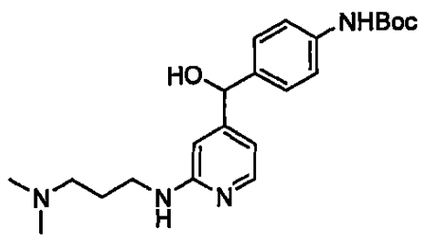
A) *tert*-Butyl 4-((2-chloropyridin-4-yl)(hydroxy)methyl)phenylcarbamate

[00332] Prepared in a manner similar to that which is described in Step B of Example 87. 2-Chloroisonicotinaldehyde (141mg, 1.0 mmol) was converted to *tert*-butyl 4-((2-chloropyridin-4-yl)(hydroxy)methyl)phenylcarbamate (190 mg, 57% yield). MS(ESI$^+$): *m/z* 335.27 / 337.27 $(M + H)^+$.



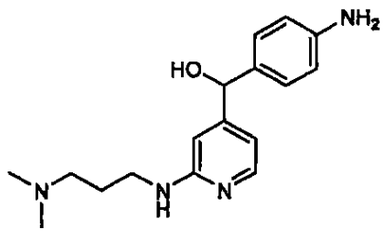
B) *tert*-Butyl 4-((2-chloropyridin-*N*-oxide-4-yl)(hydroxy)methyl) phenylcarbamate

[00333] Prepared in a manner similar to that which is described in Step C of Example 87. *tert*-Butyl 4-((2-chloropyridin-4-yl)(hydroxy)methyl)phenylcarbamate (78 mg, 0.23 mmol) was converted to *tert*-butyl 4-((2-chloropyridin-*N*-oxide-4-yl)(hydroxy)methyl) phenylcarbamate (36 mg, 44% yield). MS(ESI$^+$): *m/z* 351.28 / 353.27 $(M + H)^+$.



C) *tert*-Butyl 4-((2-(3-(dimethylamino)propylamino)pyridin-4-yl)(hydroxy)methyl)phenylcarbamate

[00334] Prepared in a manner similar to that which is described in Step D of Example 87. *tert*-Butyl 4-((2-chloropyridin-*N*-oxide-4-yl)(hydroxy)methyl) phenylcarbamate (36 mg, 0.1 mmol) was converted to *tert*-butyl 4-((2-(3-(dimethylamino)propylamino)pyridin-4-yl)(hydroxy)methyl)phenylcarbamate (16 mg, 40% yield). MS(ESI$^+$): *m/z* 401.38 $(M + H)^+$.



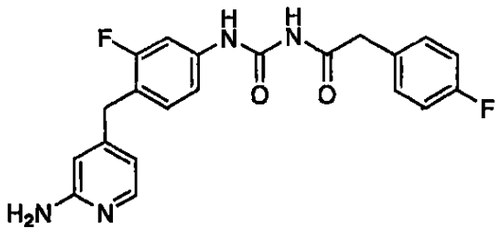
D) (4-Aminophenyl)(2-(3-(dimethylamino)propylamino)pyridin-4-yl)methanol

[00335] To a solution of *tert*-butyl 4-((2-(3-(dimethylamino)propylamino)pyridin-4-yl)(hydroxy)methyl)phenylcarbamate (16 mg, 0.04 mmol) in 1 mL of DCM were added Et_3SiH (0.1 mL)/TFA in DCM (10%, 0.2 mL). The mixture was stirred for ½ hr and no reaction was detected by LC-MS. Another 0.1 mL of Et_3SiH and 0.8 mL of TFA in DCM (10%) were added and the mixture was stirred for 2 h. The solvent was removed and was purified by solid extraction (Waters Oasis®MCX extraction cartridge) to give (4-aminophenyl)(2-(3-(dimethylamino)propylamino)pyridin-4-yl)methanol (6.0 mg, 50% yield). MS(ESI$^+$): *m/z* 301.40 $(M + H)^+$.

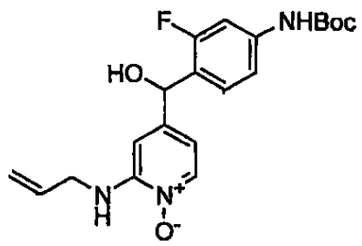
E) 1-(4-((2-(3-(Dimethylamino)propylamino)pyridin-4-yl)(hydroxy)methyl)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea

[00336] Prepared in a manner similar to that which is described in Step F of Example 87. 4-Aminophenyl-(2-(3-(dimethylamino)propylamino)pyridin-4-yl)methanol (6.0 mg, 0.02 mmol) was converted to 1-(4-((2-(3-(dimethylamino)propylamino)pyridin-4-yl)(hydroxy)methyl)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea, bis-trifluoroacetic acid (6.1 mg, 43% yield). ^{1}H NMR (CD_3OD) δ 7.82 (d, 1H, J = 6.4 Hz), 7.50 (m, 2H), 7.36 (m, 4H), 7.07 (m, 3H), 6.75 (m, 1H), 5.68 (s, 1H), 3.71 (s, 2H), 3.21-3.49 (m, 4H), 2.90 (s, 6H), 2.08 (m, 2H); MS(ESI$^+$): m/z 480.31 $(M+H)^+$.

Example 89



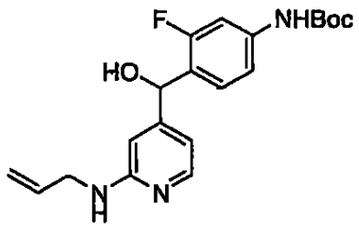
1-(4-((2-Aminopyridin-4-yl)methyl)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, trifluoroacetic acid salt



A) *tert*-Butyl 4-((2-(allylamino)pyridin-*N*-oxide-4-yl)(hydroxy)methyl)-3-fluorophenylcarbamate

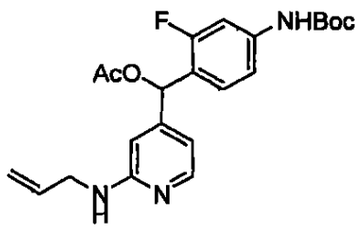
[00337] To a solution of *tert*-butyl 4-((2-chloropyridin-*N*-oxide-4-yl)(hydroxy)methyl)-3-fluorophenylcarbamate (Step C of Example 87, 500 mg, 1.36 mmol) in EtOH (14 mL) was added allylamine (1.0 mL, 13.6 mmol). The mixture was heated at 80 °C overnight. After cooling down, the solvent was removed and the

residue was purified by flash chromatography on SiO_2 eluting with 0%-15% MeOH in DCM to give *tert*-butyl 4-((2-(allylamino)pyridin-*N*-oxide-4-yl)(hydroxy)methyl)-3-fluorophenylcarbamate (440 mg, 83% yield). MS(ESI$^+$): *m/z* 390.19 $(M + H)^+$.



B) *tert*-Butyl 4-((2-(allylamino)pyridin-4-yl)(hydroxy)methyl)-3-fluorophenylcarbamate

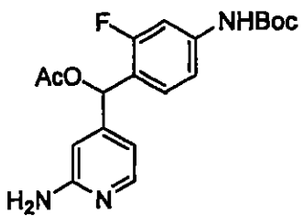
[00338] Prepared in a manner similar to that which is described in Step D of Example 87. *tert*-Butyl 4-((2-(allylamino)pyridin-*N*-oxide-4-yl)(hydroxy)methyl)-3-fluorophenylcarbamate (440 mg, 1.13 mmol) was converted to *tert*-butyl 4-((2-(allylamino)pyridin-4-yl)(hydroxy)methyl)-3-fluorophenylcarbamate (400 mg, 95% yield). MS(ESI$^+$): *m/z* 374.33 $(M + H)^+$.



C) (2-(Allylamino)pyridin-4-yl)(4-(*tert*-butoxycarbonyl)-2-fluorophenyl)methyl acetate

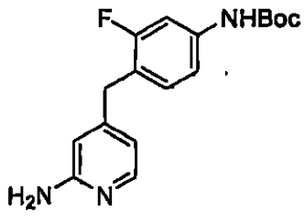
[00339] To a solution of *tert*-butyl 4-((2-(allylamino)pyridin-4-yl)(hydroxy)methyl)-3-fluorophenylcarbamate (400 mg, 1.1 mmol) in THF (10 mL) were added diisopropylethylamine (DIEA) (0.2 mL, 1.1 mmol), 4-dimethylaminopyridine (DMAP) (360 mg, 3.0 mmol) and Ac_2O (0.29 mL, 3.0 mmol). The mixture was stirred overnight and then heated at reflux for 1 h. After cooling down, the solvent was removed under reduced pressure and the residue was purified by flash chromatography on SiO_2 eluting with 0%-100% EtOAc in hexane to give (2-

(allylamino)pyridin-4-yl)(4-(*tert*-butoxycarbonyl)-2-fluorophenyl)methyl acetate (390 mg, 85% yield). MS(ESI$^+$). *m/z* 416.33 $(M + H)^+$.



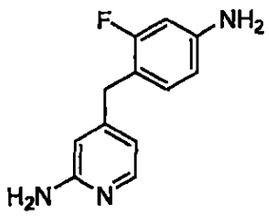
D) (2-Aminopyridin-4-yl)(4-(*tert*-butoxycarbonyl)-2-fluorophenyl)methyl acetate

[00340] A solution of (2-(allylamino)pyridin-4-yl)(4-(*tert*-butoxycarbonyl)-2-fluorophenyl)methyl acetate (380 mg, 0.91 mmol) in a mixture of EtOH/H_2O (10 :1, 40 mL) was degassed via bubbling N_2 into the solution for 1 h. To the mixture was added $Rh(PPh_3)_3Cl$ (80 mg, 0.09 mmol). The solution was refluxed to remove the solvent and the residue was purified by flash chromatography on SiO_2, followed by preparitve HPLC purification, to give (2-aminopyridin-4-yl)(4-(*tert*-butoxycarbonyl)-2-fluorophenyl)methyl acetate, trifluoroacetic acid salt (185 mg, 42% yield). MS(ESI$^+$): *m/z* 376.26 $(M + H)^+$.



E) *tert*-Butyl 4-((2-aminopyridin-4-yl)methyl)-3-fluorophenylcarbamate

[00341] To a solution of (2-aminopyridin-4-yl)(4-(*tert*-butoxycarbonyl)-2-fluorophenyl)methyl acetate as a TFA salt (180 mg, 0.37 mmol) in MeOH (10 mL) was added 10% Pd/C (90 mg). The suspension was stirred under H_2 atmosphere for 1 h. The catalyst was removed and the filtrate was concentrated *in vacuo*. The residue was then purified by flash chromatography on SiO_2 eluting with 3% MeOH in DCM, to give *tert*-butyl 4-((2-aminopyridin-4-yl)methyl)-3-fluorophenylcarbamate as a TFA salt (73 mg, 46% yield). MS(ESI$^+$): *m/z* 318.24 $(M + H)^+$.



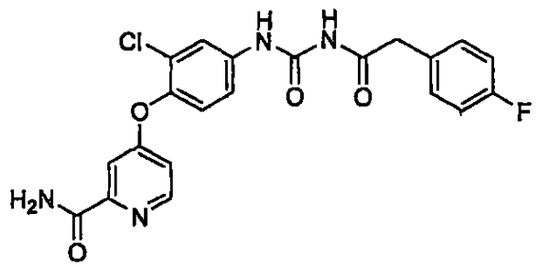
F) 4-(4-Amino-2-fluorobenzyl)pyridin-2-amine

[00342] To a solution of *tert*-butyl 4-((2-aminopyridin-4-yl)methyl)-3-fluorophenylcarbamate as a TFA salt (73 mg, 0.17 mmol) in DCM (4.0 mL) was added TFA (1.0 mL). The solution was stirred at room temperature for 2 h and the solvent was removed *in vacuo* to give 4-(4-amino-2-fluorobenzyl)pyridin-2-amine, bis-trifluoroacetic acid (70 mg, 93% yield). MS(ESI$^+$): *m/z* 218.12 $(M + H)^+$.

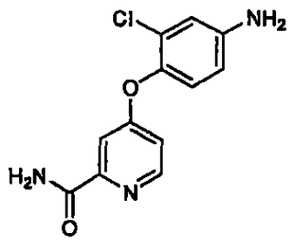
G) 1-(4-((2-Aminopyridin-4-yl)methyl)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, trifluoroacetic acid salt

[00343] Prepared in a manner similar to that which is described in Step F of Example 87. 4-(4-Amino-2-fluorobenzyl)pyridin-2-amine as 2 TFA salt (19 mg, 0.042 mmol) was converted to 1-(4-((2-aminopyridin-4-yl)methyl)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, trifluoroacetic acid salt (19 mg, 88% yield). ^{1}H NMR (DMSO-d_6) δ 10.94 (s, 1H), 10.47 (s, 1H), 7.76 (m, 3H), 7.50 (d, 1H, J = 11.5 Hz), 7.10-7.26 (m, 4H), 7.10 (m, 2H), 6.65 (d, 1H, J = 6.5 Hz), 6.55 (s, 1H), 3.89 (s, 2H), 3.65 (s, 2H); MS(ESI$^+$): *m/z* 397.26 $(M + H)^+$.

Example 90

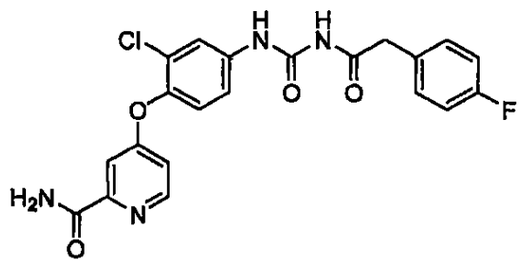


1-(4-(2-Carbamoylpyridin-4-yloxy)-3-chlorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea



A) 4-(4-Amino-2-chlorophenoxy)picolinamide

[00344] To a solution of 4-amino-2-chlorophenol (Aldrich, 430 mg, 3.0 mmol) in DMF (2.0 mL) at room temperature was added KO*t*-Bu (352 mg, 3.2 mmol). The mixture was allowed to stir at room temperature for 1 h. To the solution were then added 4-chloropicolinamide (468 mg, 3.0 mmol) and K_2CO_3 (221 mg, 1.6 mmol) The resulting suspension was heated at 90 °C overnight. After cooling down, the suspension was diluted with 100 mL of EtOAc and 50 mL of H_2O. The organic layer was separated and washed with brine (2 × 25 mL) and dried over $MgSO_4$. After filtration and concentration, the solid was triturated with 50 mL of DCM. The solid was then collected and washed with DCM (2 × 20 mL), EtOAc (5.0 mL) and dried to give 4-(4-amino-2-chlorophenoxy)picolinamide (320 mg, 40% yield). MS(ESI$^+$): *m/z* 264.12 / 266.07 $(M + H)^+$.

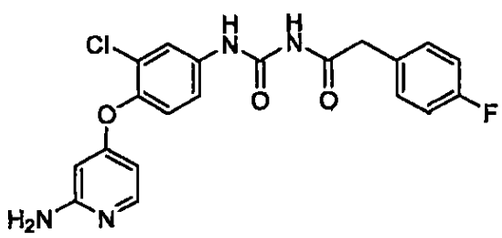


B) 1-(4-(2-Carbamoylpyridin-4-yloxy)-3-chlorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea

[00345] Prepared in a manner similar to that which is described in Step F of Example 87. 4-(4-Amino-2-chlorophenoxy)picolinamide (79 mg, 0.30 mmol) in DMF (1.0 mL) was converted to 1-(4-(2-carbamoylpyridin-4-yloxy)-3-chlorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea (65 mg, 49% yield). ^{1}H NMR (DMSO-d_6) δ 11.05 (s, 1H), 10.58 (s, 1H), 8.52 (d, 1H, J = 4.5 Hz), 8.15 (s, 1H), 7.98 (s, 1H), 7.70 (s,

1H), 7.55 (m, 1H), 7.39 (m, 3H), 7.27 (m, 1H), 7.16 (m, 3H), 3.73 (s, 2H); MS(ESI$^+$): *m/z* 443.17 $(M + H)^+$.

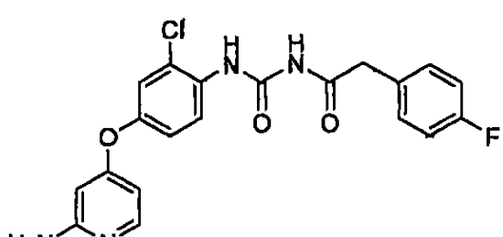
Example 91



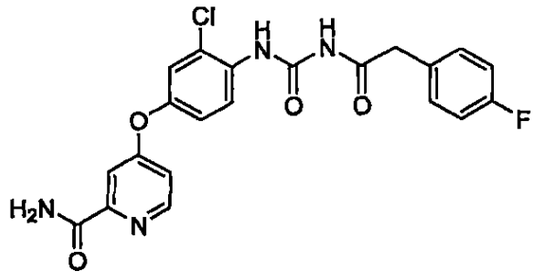
1-(4-(2-Aminopyridin-4-yloxy)-3-chlorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, hydrochloride salt

[00346] To a solution of 1-(4-(2-carbamoylpyridin-4-yloxy)-3-chlorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea (Example 90, 27 mg, 0.06 mmol) in DMF (1.0 mL) were added H_2O (2.2 mg, 0.12 mmol), pyridine (0.04 mL) and bis(trifluoroacetoxy)iodobenzene (Aldrich, 39 mg, 0.09 mmol) at room temperature. The solution was allowed to stir overnight and then it was purified on prep HPLC to give the desired product, which was further converted to 1-(4-(2-aminopyridin-4-yloxy)-3-chlorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea hydrochloride (19 mg, 70% yield) by the addition of 1N HCl solution (0.5 mL). ^{1}H NMR (DMSO-d_6) δ 13.50 (s, 1H), 11.02 (s, 1H), 10.57 (s, 1H), 7.80-7.95 (m, 4H), 7.55 (m, 1H), 7.37 (m, 1H), 7.30 (m, 2H), 7.11 (m, 2H), 6.60 (m, 1H), 6.00 (s, 1H), 3.70 (s, 2H); MS(ESI$^+$): *m/z* 415.16 $(M + H)^+$.

Example 92



1-(4-(2-Aminopyridin-4-yloxy)-2-chlorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea



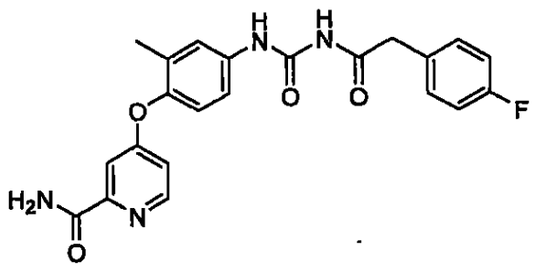
A) 1-(4-(2-Carbamoylpyridin-4-yloxy)-2-chlorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea

[00347] Prepared in a manner similar to that which is described in Step A of Example 90. 4-(4-Amino-3-chlorophenoxy)picolinamide (39 mg, 0.19 mmol) in DMF (1.0 mL) was converted to 1-(4-(2-carbamoylpyridin-4-yloxy)-2-chlorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea (18 mg, 41% yield) after prep HPLC purification. MS(ESI$^+$): *m/z* 443.13 / 445.14 $(M + H)^+$.

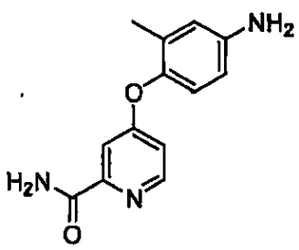
B) 1-(4-(2-Aminopyridin-4-yloxy)-2-chlorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea

[00348] Prepared in a manner similar to that which is described for Example 91. 1-(4-(2-Carbamoylpyridin-4-yloxy)-2-chlorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea (18 mg, 0.04 mmol) in DMF (1.0 mL) was converted to 1-(4-(2-aminopyridin-4-yloxy)-2-chlorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea (10 mg, 55% yield). ^{1}H NMR (DMSO-d_6) δ 13.47 (s, 1H), 11.26 (s, 1H), 11.08 (s, 1H), 8.37 (d, 1H, J = 8.5 Hz), 7.95 (d, 1H, J = 7.5 Hz), 7.88 (s, 2H), 7.62 (s, 1H), 7.35 (m, 3H), 7.17 (m, 2H), 6.64 (d, 1H, J = 7.5 Hz), 6.13 (s, 1H), 3.76 (s, 2H); MS(ESI$^+$): *m/z* 415.18 / 417.17 $(M + H)^+$.

Example 93



1-(4-(2-Carbamoylpyridin-4-yloxy)-3-methylphenyl)-3-(2-(4-fluorophenyl)acetyl)urea



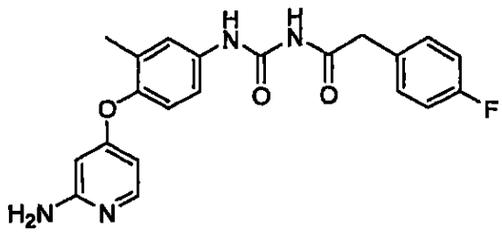
A) 4-(4-Amino-2-methylphenoxy)picolinamide

[00349] Prepared in a manner similar to that which is described in Step A of Example 90. 4-Amino-2-methylphenol (246 mg, 2.0 mmol) was converted to 4-(4-amino-2-methylphenoxy)picolinamide (230 mg, 47% yield). MS(ESI$^+$): *m/z* 244.15 $(M+H)^+$.

B) 1-(4-(2-Carbamoylpyridin-4-yloxy)-3-methylphenyl)-3-(2-(4-fluorophenyl)acetyl)urea

[00350] Prepared in a manner similar to that which is described in Step F of Example 87. 4-(4-Amino-2-methylphenoxy)picolinamide (48 mg, 0.2 mmol) in DMF (1.0 mL) was converted to 1-(4-(2-carbamoylpyridin-4-yloxy)-3-methylphenyl)-3-(2-(4-fluorophenyl)acetyl)urea (35 mg, 41% yield. ^{1}H NMR (DMSO-d_6) δ 10.92 (s, 1H), 10.44 (s, 1H), 8.44 (d, 1H, J = 5.5 Hz), 8.06 (s, 1H), 7.63 (s, 1H), 7.50 (s, 1H), 7.42 (m, 1H), 7.31 (m, 2H), 7.24 (d, 1H, J = 2.0 Hz), 7.06-7.12 (m, 4H), 3.69 (s, 2H), 2.02 (s, 3H);). MS(ESI$^+$): *m/z* 423.17 $(M+H)^+$.

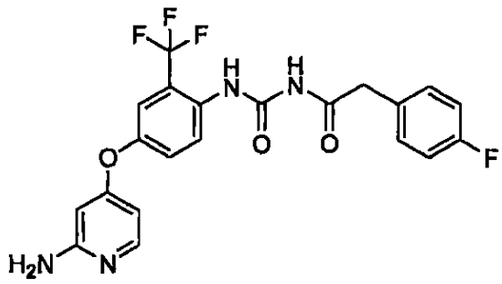
Example 94



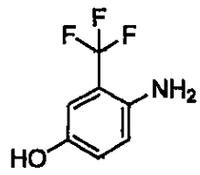
1-(4-(2-Aminopyridin-4-yloxy)-3-methylphenyl)-3-(2-(4-fluorophenyl)acetyl)urea, hydrochloride salt

[00351] Prepared in a manner similar to that which is described in Step A of Example 91. 1-(4-(2-Carbamoylpyridin-4-yloxy)-3-methylphenyl)-3-(2-(4-fluorophenyl)acetyl)urea (27 mg, 0.06 mmol) in DMF (1.0 mL) was converted to 1-(4-(2-aminopyridin-4-yloxy)-3-methylphenyl)-3-(2-(4-fluorophenyl)acetyl)urea, hydrochloride salt (24 mg, 88% yield) after HPLC purification. ^{1}H NMR (DMSO-d_6) δ 13.18 (s, 1H), 10.93 (s, 1H), 10.45 (s, 1H), 7.88 (d, 1H, J = 7.0 Hz), 7.73 (s, 2H), 7.50 (m, 2H), 7.29 (m, 2H), 7.10 (m, 3H), 6.56 (d, 1H, J = 7.0 Hz), 5.91 (d, 1H, J = 2.5 Hz), 3.68 (s, 2H), 2.02 (s, 3H); MS(ESI$^+$): *m/z* 395.20 $(M + H)^+$.

Example 95

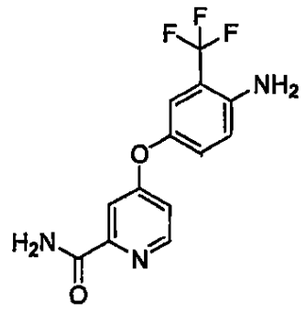


1-(4-(2-Aminopyridin-4-yloxy)-2-(trifluoromethyl)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea, hydrochloride salt



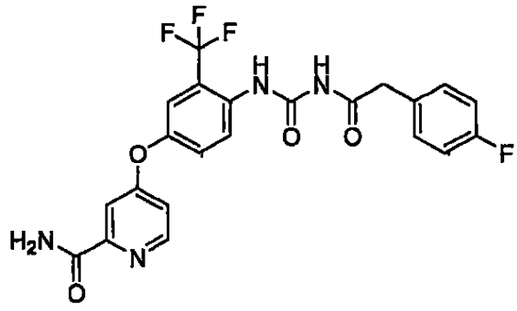
A) 4-Amino-3-(trifluoromethyl)phenol

[00352] A solution of 4-nitro-3-(trifluoromethyl)phenol (Aldrich, 414 mg, 2.0 mmol) in 10 mL of MeOH was added 10% Pd/C (100mg). The suspension was stirred under H_2 atmosphere for 12 h and it was then filtered and concentrated *in vacuo* to give 4-amino-3-(trifluoromethyl)phenol (350 mg, 95% yield), which was sufficiently pure to use in the next step. MS(ESI$^+$): *m/z* 178.02 $(M + H)^+$.



B) 4-(4-Amino-3-(trifluoromethyl)phenoxy)picolinamide

[00353] Prepared in a manner similar to that which is described in Step A of Example 90. 4-Amino-3-(trifluoromethyl)phenol (177 mg, 1.0 mmol) in DMF (2.0 mL) was converted to 4-(4-amino-3-(trifluoromethyl)phenoxy)picolinamide (180 mg, 61% yield). MS(ESI$^+$): *m/z* 298.20 $(M + H)^+$.



C) 1-(4-(2-Carbamoylpyridin-4-yloxy)-2-(trifluoromethyl)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea

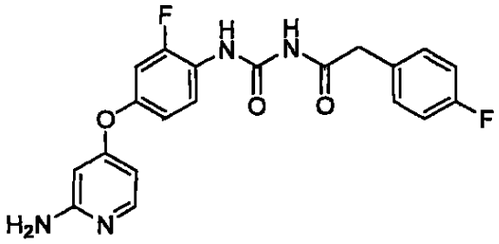
[00354] Prepared in a manner similar to that which is described in Step F of Example 87. 4-(4-Amino-3-(trifluoromethyl)phenoxy)picolinamide (30 mg, 0.1 mmol) in DMF (1.0 mL) was converted to 1-(4-(2-carbamoylpyridin-4-yloxy)-2-

(trifluoromethyl)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea (30 mg, 63% yield). MS(ESI$^+$): *m/z* 477.12 $(M + H)^+$.

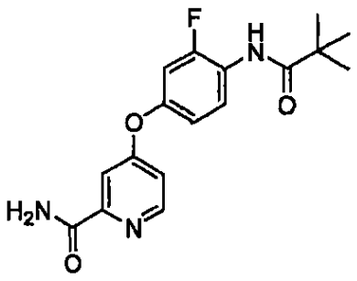
D) 1-(4-(2-Aminopyridin-4-yloxy)-2-(trifluoromethyl)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea

[00355] Prepared in a manner similar to that which is described in Step A of Example 91. 1-(4-(2-Carbamoylpyridin-4-yloxy)-2-(trifluoromethyl)phenyl)-3-(2-(4 fluorophenyl)acetyl)urea (26 mg, 0.055 mmol) in DMF (1.0 mL) was converted to 1-(4-(2-aminopyridin-4-yloxy)-2-(trifluoromethyl)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea hydrochloride (15 mg, 56% yield) after prep. HPLC purification. ^{1}H NMR (DMSO-d_6) δ 13.40 (s, 1H), 11.28 (s, 1H), 10.95 (s, 1H), 8.25 (d, 1H, J = 8.5 Hz), 7.97 (d, 1H, J = 7.0 Hz), 7.88 (s, 2H), 7.72 (d, 1H, J = 2.5 Hz), 7.65 (m, 1H), 7.35 (m, 2H), 7.19 (m, 2H), 6.66 (d, 1H, J = 2.5 Hz), 3.75 (s, 2H); MS(ESI$^+$): *m/z* 449.14 $(M + H)^+$.

Example 96



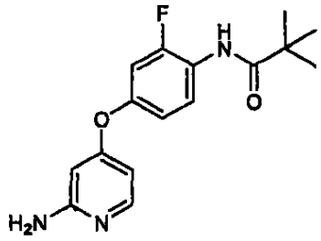
1-(4-(2-Aminopyridin-4-yloxy)-2-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, trifluoroacetic acid salt



A) 4-(3-Fluoro-4-pivalamidophenoxy)picolinamide

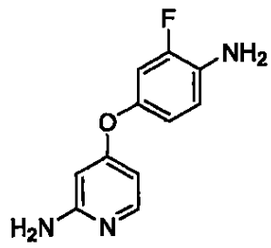
[00356] To a solution of 4-amino-3-fluorophenol (Oakwood Products Inc., 252 mg, 2.0 mmol) in NMP (4.0 mL) were added 4-chloropicolinamide (312 mg, 2.0 mmol) and DIEA (0.3 mL). The solution was heated at 250 °C in a microwave oven. After cooling down, the solution was diluted with H_2O and the solution was extracted with EtOAc (3 × 40 mL). The combined organic layers were washed with brine, dried over $MgSO_4$. After filtration and concentration, the residue was purified by flash chromatography on SiO_2 eluting with 0-30% MeOH in DCM to give a fraction containing 4-(4-amino-3-fluorophenoxy)picolinamide (50% pure, HPLC-UV detection). MS(ESI$^+$): *m/z* 248.12 $(M + H)^+$.

[00357] To a solution of 4-(4-amino-3-fluorophenoxy)picolinamide, obtained from previous step in THF (3.0 mL) and DCM (10.0 mL) were added 1 N NaOH (5.0 mL) and trimethylacetyl chloride (0.25 mL, 2 mmol) at room temperature. The solution was stirred for 2 h and was then extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$. After filtration and concentration, the residue was purified by flash chromatography on SiO_2 eluting with 0%-100% EtOAc in hexane to give 4-(3-fluoro-4-pivalamidophenoxy)picolinamide (110 mg, 17% yield for two steps). MS(ESI$^+$): *m/z* 332.18 $(M + H)^+$.



B) *N*-(4-(2-Aminopyridin-4-yloxy)-2-fluorophenyl)pivalamide

[00358] Prepared in a manner similar to that which is described in Step A of Example 91. 4-(3-Fluoro-4-pivalamidophenoxy)picolinamide (110 mg, 0.33 mmol) in acetonitrile (4 mL) was converted to *N*-(4-(2-aminopyridin-4-yloxy)-2-fluorophenyl)pivalamide (70 mg, 70% yield). MS(ESI$^+$): *m/z* 304.21 $(M + H)^+$.



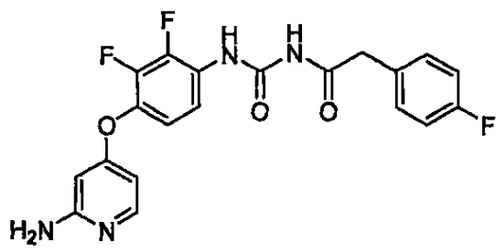
C) 4-(4-Amino-3-fluorophenoxy)pyridin-2-amine

[00359] A solution of *N*-(4-(2-aminopyridin-4-yloxy)-2-fluorophenyl)pivalamide (70 mg, 0.23 mmol) in 3 mL of MeOH was added 2 mL of 6 N HCl. The mixture was then heated at reflux for 48 h. After cooling down, the solvent was removed under reduced pressure and the residue was purified by solid extraction (Waters Oasis®MCX extraction cartridge) to give 4-(4-amino-3-fluorophenoxy)pyridin-2-amine (27 mg, 54% yield). MS(ESI$^+$): *m/z* 220.21 $(M + H)^+$.

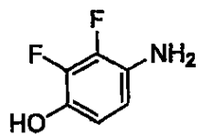
D) 1-(4-(2-Aminopyridin-4-yloxy)-2-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, trifluoroacetic acid salt

[00360] Prepared in a manner similar to that which is described in Step F of Example 87. 4-(4-Amino-3-fluorophenoxy)pyridin-2-amine (28 mg, 0.095 mmol) in THF (2.0 mL) was converted to 1-(4-(2-aminopyridin-4-yloxy)-2-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea trifluoroacetic acid (23 mg, 47% yield) after prep. HPLC purification. ^{1}H NMR (DMSO-d_6) δ 11.20 (s, 1H), 10.77 (s, 1H), 8.23 (m, 1H), 7.94 (d, 1H, J = 6.5 Hz), 7.70 (s, 2H), 7.45 (m, 1H), 7.35 (m, 2H), 7.16 (m, 3H), 6.64 (d, 1H, J = 2.5 Hz), 6.11 (s, 1H), 3.75 (s, 2H); MS(ESI$^+$): *m/z* 399.12 $(M + H)^+$.

Example 97



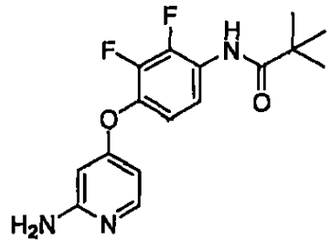
1-(4-(2-Aminopyridin-4-yloxy)-2,3-difluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, trifluoroacetic acid salt



A) 4-Amino-2,3-difluorophenol

[00361] To a solution of 1,2,3-trifluoro-4-nitrobenzene (Aldrich, 15.0 g, 84.7 mmol) in DMF (25.0 mL) were added K_2CO_3 (17.6 g, 127.8 mmol) and benzylalcohol (8.8 mL, 85.0 mmol). The suspension was stirred overnight. To the reaction mixture was then added H_2O (100 mL) and the solution was kept at 4 °C overnight. The precipitate was then collected and washed with H_2O to give a mixture of two isomers (22.4 g) [1-(benzyloxy)-2,3-difluoro-4-nitrobenzene and 2-(benzyloxy)-3,4-difluoro-1-nitrobenzene in a ratio of 1:1].

[00362] To a solution of [1-(benzyloxy)-2,3-difluoro-4-nitrobenzene and 2-(benzyloxy)-3,4-difluoro-1-nitrobenzene] (22.4 g, 84.5 mmol) in EtOAc (20.0 mL) and MeOH (100.0 mL) was added 10% Pd/C (1.0 g). The suspension was stirred under H_2 atmosphere for 12 h. The suspension was then filtered and concentrated *in vacuo* to give a mixture of two isomers (12.6 g) [4-amino-2,3-difluorophenol and 6-amino-2,3-difluorophenol in a ratio of 1:1]. MS(ESI$^+$): *m/z* 146.00 $(M + H)^+$.

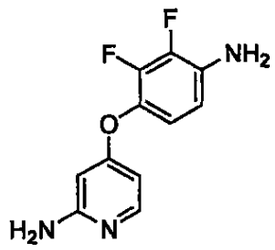


B) *N*-(4-(2-Aminopyridin-4-yloxy)-2,3-difluorophenyl)pivalamide

[00363] Prepared in a manner similar to that which is described in Step A of Example 90. A mixture of 4-amino-2,3-difluorophenol and 6-amino-2,3-difluorophenol (580 mg, 4.0 mmol) in DMF (3.0 mL) was converted to a mixture of 4-(4-amino-2,3-difluorophenoxy)picolinamide and 4-(6-amino-2,3-difluorophenoxy)picolinamide (300 mg). MS(ESI$^+$): *m/z* 266.13 $(M + H)^+$.

[00364] Prepared in a manner similar to that which is described in Step A of Example 96. A mixture of 4-(4-amino-2,3-difluorophenoxy)picolinamide and 4-(6-amino-2,3-difluorophenoxy)picolinamide (300 mg, 1.13 mmol) was converted to a mixture of 4-(2,3-difluoro-4-pivalamidophenoxy)picolinamide and 4-(2,3-difluoro-6-pivalamidophenoxy)picolinamide (406 mg). MS(ESI$^+$): *m/z* 350.20 $(M + H)^+$.

[00365] Prepared in a manner similar to that which is described in Step A of Example 91. A mixture of 4-(2,3-difluoro-4-pivalamidophenoxy)picolinamide and 4-(2,3-difluoro-6-pivalamidophenoxy)picolinamide (400 mg) was reacted with bis(trifluoroacetoxy)iodobenzene to give *N*-(4-(2-aminopyridin-4-yloxy)-2,3-difluorophenyl)pivalamide, trifluoroacetic acid salt (120 mg, 24% yield) after prep. HPLC purification. MS(ESI$^+$): *m/z* 322.23 $(M + H)^+$.



C) 4-(4-Amino-2,3-difluorophenoxy)pyridin-2-amine

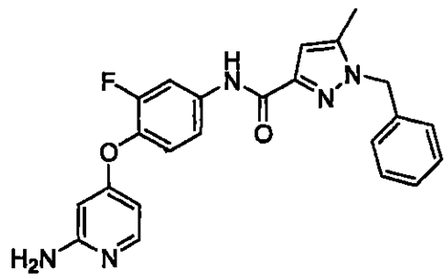
[00366] Prepared in a manner similar to that which is described in Step C of Example 96. *N*-(4-(2-Aminopyridin-4-yloxy)-2,3-difluorophenyl)pivalamide, trifluoroacetic acid salt (120 mg, 0.27 mmol) was converted to 4-(4-amino-2,3-difluorophenoxy)pyridin-2-amine (52 mg, 81% yield). MS(ESI$^+$): *m/z* 238.11 $(M + H)^+$.

D) 1-(4-(2-Aminopyridin-4-yloxy)-2,3-difluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, trifluoroacetic acid salt

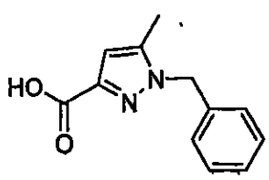
[00367] Prepared in a manner similar to that which is described in Step F of Example 87. 4-(4-Amino-2,3-difluorophenoxy)pyridin-2-amine (24 mg, 0.10 mmol) in THF (3.0 mL) was converted to 1-(4-(2-aminopyridin-4-yloxy)-2,3-difluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, trifluoroacetic acid (21 mg, 40% yield). ^{1}H NMR (DMSO-d_6) δ 11.27 (s, 1H), 10.84 (s, 1H), 8.02 (m, 1H), 7.96 (d, 1H,

J = 8.5 Hz), 7.73 (s, 2H), 7.34 (m, 3H), 7.17 (m, 2H), 6.70 (m, 1H), 6.20 (d,1H, J = 2.0 Hz), 3.75 (s, 2H); MS(ESI$^+$): *m/z* 417.10 $(M + H)^+$.

Example 98



N-(4-(2-Aminopyridin-4-yloxy)-3-fluorophenyl)-1-benzyl-5-methyl-1*H*-pyrazole-3-carboxamide, hydrochloride salt



A) **1-Benzyl-5-methyl-1*H*-pyrazole-3-carboxylic acid**

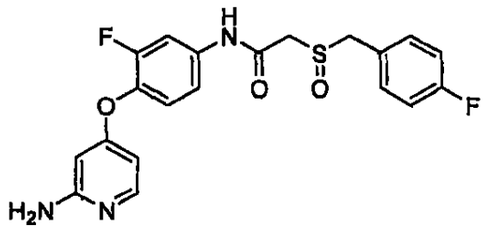
[00368] To a solution of 1-benzylhydrazine dihydrochloride (Aldrich, 0.98 g, 5.0 mmol) in EtOH (30 mL) were added DIEA (2.0 mL) and ethyl 2,4-dioxopentanoate (0.70 mL, 5.0 mmol). The mixture was stirred at room temperature for 12 h and was concentrated *in vacuo*. The residue was dissolved in 1 N NaOH (10 mL). The solution was heated at 60 °C for 1 h. After cooling down, the solution was extracted with DCM (3 × 50 mL). The aqueous layer was neutralized to pH 2.0 and then was extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$. It was filtered and concentrated to give 1-benzyl-5-methyl-1*H*-pyrazole-3-carboxylic acid (1.0 g, 92% yield). MS(ESI$^+$): *m/z* 217.12 $(M + H)^+$.

B) ***N*-(4-(2-Aminopyridin-4-yloxy)-3-fluorophenyl)-1-benzyl-5-methyl-1*H*-pyrazole-3-carboxamide, hydrochloride salt**

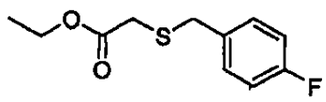
[00369] 4-(4-Amino-2-fluorophenoxy)pyridin-2-amine (Compound B of Example 24, 25 mg, 0.11 mmol) was coupled with 1-benzyl-5-methyl-1*H*-pyrazole-3-

carboxylic acid (25 mg, 0.11 mmol) in a manner similar to that which is described in Step C of Example 1 to give *N*-(4-(2-aminopyridin-4-yloxy)-3-fluorophenyl)-1-benzyl-5-methyl-1*H*-pyrazole-3-carboxamide hydrochloride (10 mg, 20% yield) after prep HPLC purification. ^{1}H NMR (DMSO-d_6) δ 10.64 (s, 1H), 7.8-7.98 (m, 3H), 7.00-7.65 (m, 9H), 6.71 (m, 1H), 6.15 (s, 1H), 5.65 (s, 2H), 2.24 (s, 3H); MS(ESI$^+$): *m/z* 418.21 $(M+H)^+$.

Example 99

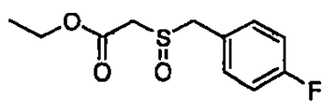


2-(4-Fluorobenzylsulfinyl)-*N*-(4-(2-aminopyridin-4-yloxy)-3-fluorophenyl)acetamide, hydrochloride salt



A) Ethyl 2-(4-fluorobenzylthio)acetate

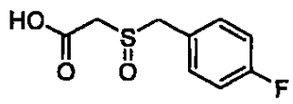
[00370] To a solution of ethyl 2-mercaptoacetate (Aldrich, 1.0 mL, 9.1 mmol) in acetonitrile (10.0 mL) were added K_2CO_3 (2.76 g, 20.0 mmol) and 1-(bromomethyl)-4-fluorobenzene (2.27 g, 12 0 mmol). The mixture was stirred at room temperature for 12 h. After filtration and concentration, the residue was purified by flash column chromatography on SiO_2 to give ethyl 2-(4-fluorobenzylthio)acetate (1.89 g, 91% yield). MS(ESI$^+$): *m/z* 251.08 $(M+H)^+$.



B) Ethyl 2-(4-fluorobenzylsulfinyl)acetate

[00371] To a solution of ethyl 2-(4-fluorobenzylthio)acetate (1.89 g, 8.29 mmol) in DCM (20.0 mL) at -40 °C was added a solution of *m*-CPBA (77%, 1.86 g, 8.29 mmol)

in DCM (20.0 mL) dropwise. The solution was stirred from -40 °C to room temperature overnight. The solution was then quenched with polymer bound diethylene triamine. After filtration and concentration, the residue was purified by flash chromatography on SiO_2 to give ethyl 2-(4-fluorobenzylsulfinyl)acetate (2.0 g, 98% yield). MS(ESI$^+$): *m/z* 267.09 $(M + H)^+$.



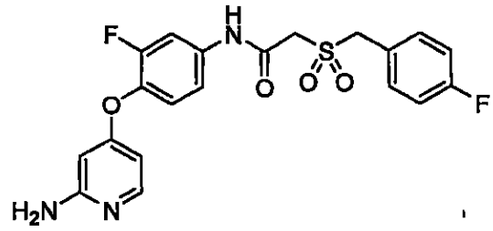
C) 2-(4-Fluorobenzylsulfinyl)acetic acid

[00372] To a solution of ethyl 2-(4-fluorobenzylsulfinyl)acetate (1.60 g, 6.55 mmol) in THF (10.0 mL) and MeOH (20.0 mL) was added 1 N NaOH (20.0 mmol). The mixture was stirred at room temperature for 2 h. After removal of organic solvent under reduced pressure, the remaining aqueous solution was neutralized with 1 N HCl (25.0 mL). It was extracted with EtOAc (3 × 100 mL) and the combined organic layer was dried over $MgSO_4$. The solution was then filtered and concentrated *in vacuo* to give 2-(4-fluorobenzylsulfinyl)acetic acid (1.25 g, 88% yield). MS(ESI$^+$): *m/z* 217.05 $(M + H)^+$.

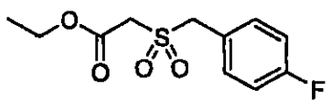
D) 2-(4-Fluorobenzylsulfinyl)-*N*-(4-(2-aminopyridin-4-yloxy)-3-fluorophenyl)acetamide, hydrochloride salt

[00373] 4-(4-Amino-2-fluorophenoxy)pyridin-2-amine dihydrochloride (Compound B of Example 24, 29 mg, 0.10 mmol) was coupled with 2-(4-fluorobenzylsulfinyl)acetic acid (22 mg, 0.1 mmol) in a manner similar to that which is described in Step C of Example 1 to give 2-(4-fluorobenzylsulfinyl)-*N*-(4-(2-aminopyridin-4-yloxy)-3-fluorophenyl)acetamide, hydrochloride salt (17 mg, 37% yield). ^{1}H NMR (DMSO-d_6) δ 10.94 (s, 1H), 7.97 (d, 1H, J = 7.5 Hz), 7.85 (m, 3H), 7.39-7.45 (m, 4H), 7.23 (t, 2H, J = 7.5 Hz), 6.70 (m, 1H), 6.13 (d, 1H, J = 2.5 Hz), 4.32 (d, 1H, J = 11.0 Hz), 4.11 (d, 1H, J = 11.0 Hz), 3.98 (d, 1H, J = 13.0 Hz), 3.65 (d, 1H, J = 13.0 Hz); MS(ESI$^+$): *m/z* 418.26 $(M + H)^+$.

Example 100

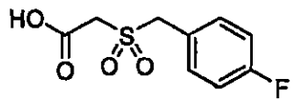


2-(4-Fluorobenzylsulfonyl)-*N*-(4-(2-aminopyridin-4-yloxy)-3-fluorophenyl)acetamide, hydrochloride salt



A) Ethyl 2-(4-fluorobenzylsulfonyl)acetate

[00374] To a solution of ethyl 2-(4-fluorobenzylsulfinyl)acetate (370 mg, 1.52 mmol) in DCM (5.0 mL) was added *m*-CPBA (77%, 450 mg, 2.0 mmol). The mixture was stirred at room temperature for 2 h and was then quenched with polymer bound diethylene triamine (1.5 g). The reaction mixture was filtered and concentrated *in vacuo* to give ethyl 2-(4-fluorobenzylsulfonyl)acetate (360 mg, 91% yield). MS(ESI$^+$): *m/z* 283.10 $(M + H)^+$



B) 2-(4-Fluorobenzylsulfonyl)acetic acid

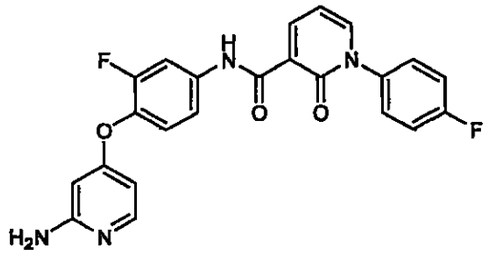
[00375] Prepared in a manner similar to that which is described in Step C of Example 99. Ethyl 2-(4-fluorobenzylsulfonyl)acetate (340 mg, 1.31 mmol) was converted to 2-(4-fluorobenzylsulfonyl)acetic acid (270 mg, 81% yield). MS(ESI$^+$): *m/z* 255.05 $(M + H)^+$.

C) 2-(4-Fluorobenzylsulfonyl)-*N*-(4-(2-aminopyridin-4-yloxy)-3-fluorophenyl)acetamide, hydrochloride salt

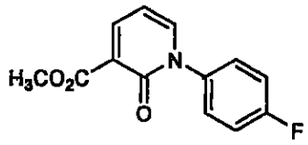
[00376] 4-(4-Amino-2-fluorophenoxy)pyridin-2-amine dihydrochloride (50 mg, 0.17 mmol) was coupled with 2-(4-fluorobenzylsulfonyl)acetic acid (33 mg, 0 14

mmol) in a manner similar to that which is described in Step C of Example 1 to give 2-(4-fluorobenzylsulfonyl)-*N*-(4-(2-aminopyridin-4-yloxy)-3-fluorophenyl)acetamide, hydrochloride salt (30 mg, 45% yield). ^{1}H NMR (DMSO-d_6) δ 13.40 (s, 1H), 11.15 (s, 1H), 7.97 (d, 1H, J = 7.0 Hz), 7.80-7.90 (m, 3H), 7.47 (m, 4H), 7.26 (t, 2H, J = 8.5 Hz), 6.72 (d, 1H, J = 7.0 Hz), 6.14 (d, 1H, J = 2.0 Hz), 4.69 (s, 2H), 4.27 (s, 2H); MS(ESI$^+$): *m/z* 434.15 $(M + H)^+$.

Example 101



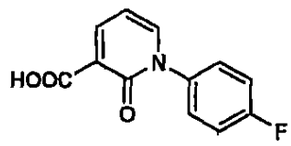
***N*-(4-(2-Aminopyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, hydrochloride salt**



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

[00377] To a solution of methyl 2-oxo-2*H*-pyran-3-carboxylate (Aldrich, 2.31 g, 15 mmol) 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 Solid precipitation was observed. To the 4-fluoroaniline adduct intermediate formed *via* Michael addition obtained *in situ* 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 1N 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 layer was dried over $MgSO_4$ and concentrated *in vacuo* to obtain a semi-solid material (~4.4 g). To this crude product were added ether (100 mL) and methanol (15 mL), stirred, and the solid was filtered to obtain the undesired solid product (870 mg). The filtrate

solution was concentrated to obtain a semi-solid crude desired product (2.95 g, crude 80 %) which was pure enough 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

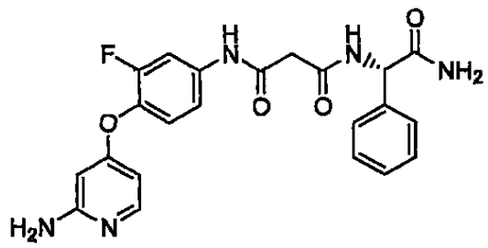
[00378] A mixture of methyl 1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (crude 2.45 g, 12 mmol) and 6 N aq NaOH (2.5 mL) in methanol (60 mL) was stirred at rt for 4 h. To the reaction mixture was added conc HCl (1 mL) slowly with stirring at rt, and the precipitated solid was filtered, washed with a small amount water and dried to obtain the desired acid product (2.1 g) as a yellow solid. The filtrate solution 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 the 2nd crop of product (195mg, 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-(2-Aminopyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, hydrochloride salt

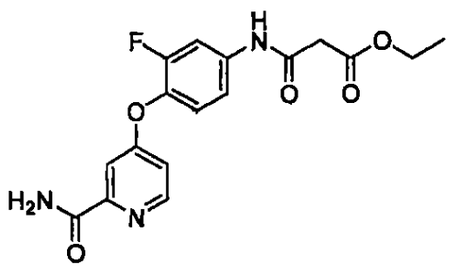
[00379] 4-(4-Amino-2-fluorophenoxy)pyridin-2-amine (Compound B of Example 24, 58 mg, 0.20 mmol) was coupled with 1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (47 mg, 0.20 mmol) in a manner similar to that which is described in Step C of Example 1 to give *N*-(4-(2-aminopyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, hydrochloride salt (22 mg, 23% yield). ^{1}H NMR (DMSO-d_6) δ 13.40 (s, 1H), 12.13 (s, 1H), 8.58 (d, 1H, J = 5.0 Hz), 8.13 (d, 1H, J = 5.0 Hz), 8.07 (d, 1H, J = 10.0 Hz),

7.98 (d, 1H, J = 7.5 Hz), 7.89 (s, 2H), 7.40-7.60 (m, 6H), 6.72 (m, 2H), 6.17 (d, 1H, J = 2.5 Hz); MS(ESI$^+$) m/z 435.18 $(M + H)^+$.

Example 102

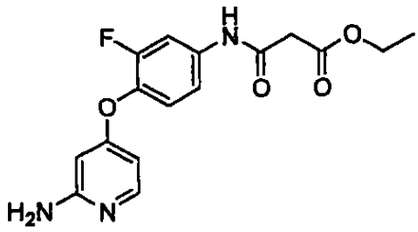


(*S*)-*N*^{1}-(2-Amino-2-oxo-1-phenylethyl)-*N*^{3}-(4-(2-aminopyridin-4-yloxy)-3-fluorophenyl)malonamide, hydrochloride salt



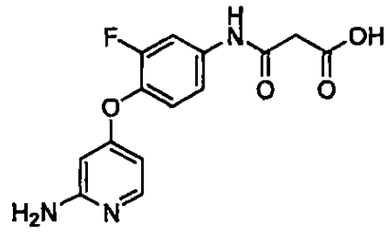
A) Ethyl 3-(4-(2-carbamoylpyridin-4-yloxy)-3-fluorophenylamino)-3-oxopropanoate

[00380] To a solution of 4-(4-amino-2-fluorophenoxy)picolinamide (Compound B' of Example 24, 1.0 g, 4.0 mmol) in DMF (10.0 mL) were added DIEA (2.0 mL) and ethyl 3-chloro-3-oxopropanoate (Aldrich, 0.75 mL, 6.0 mmol). The mixture was stirred at room temperature for 12 h and more ethyl 3-chloro-3-oxopropanoate (0.20 mL, 1.6 mmol) was added. The mixture was stirred for 2 h and was then diluted with EtOAc (200 mL). It was washed with H_2O and brine and then dried over $MgSO_4$. After filtration and concentration, the residue was triturated with DCM and filtered to give ethyl 3-(4-(2-carbamoylpyridin-4-yloxy)-3-fluorophenylamino)-3-oxopropanoate (900 mg, 62% yield). MS(ESI$^+$) m/z 362.28 $(M + H)^+$.



B) Ethyl 3-(4-(2-aminopyridin-4-yloxy)-3-fluorophenylamino)-3-oxopropanoate

[00381] Prepared in a manner similar to that which is described in Step A of Example 91. Ethyl 3-(4-(2-carbamoylpyridin-4-yloxy)-3-fluorophenylamino)-3-oxopropanoate (900 mg, 2.5 mmol) in DMF (10.0 mL) was converted to ethyl 3-(4-(2-aminopyridin-4-yloxy)-3-fluorophenylamino)-3-oxopropanoate (710 mg, 86% yield). MS(ESI$^+$) m/z 334.26 $(M + H)^+$.



C) 3-(4-(2-Aminopyridin-4-yloxy)-3-fluorophenylamino)-3-oxopropanoic acid

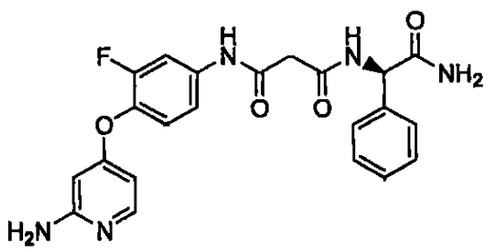
[00382] Prepared in a manner similar to that which is described in Step C of Example 99. Ethyl 3-(4-(2-aminopyridin-4-yloxy)-3-fluorophenylamino)-3-oxopropanoate (700 mg, 2.10 mmol) was converted to 3-(4-(2-aminopyridin-4-yloxy)-3-fluorophenylamino)-3-oxopropanoic acid (630 mg, 98% yield). MS(ESI$^+$) m/z 306.20 $(M + H)^+$.

D) (S)-N^1-(2-Amino-2-oxo-1-phenylethyl)-N^3-(4-(2-aminopyridin-4-yloxy)-3-fluorophenyl)malonamide, hydrochloride salt

[00383] 3-(4-(2-Aminopyridin-4-yloxy)-3-fluorophenylamino)-3-oxopropanoic acid (30 mg, 0.10 mmol) was coupled with (*S*)-2-amino-2-phenylacetamide hydrochloride (Acros, 28 mg, 0.15 mmol) in a manner similar to that which is described in Step C of Example 1 to give (*S*)-N^1-(2-amino-2-oxo-1-phenylethyl)-N^3-

(4-(2-aminopyridin-4-yloxy)-3-fluorophenyl)malonamide, hydrochloride salt (25 mg, 53% yield). ^{1}H NMR (DMSO-d_6) δ 10.68 (s, 1H), 8.80 (d, 1H, J = 8.0 Hz), 7.96 (d, 1H, J = 7.5 Hz), 7.77-7.90 (m, 4H), 7.20-7.45 (m, 8H), 6.70 (m, 1H), 6.12 (s, 1H), 5.39 (d, 1H, J = 7.5 Hz), 3.48 (d, 1H, J = 15.0 Hz), 3.41 (d, 1H, J = 15.0 Hz); MS(ESI$^+$) m/z 438.26 $(M + H)^+$.

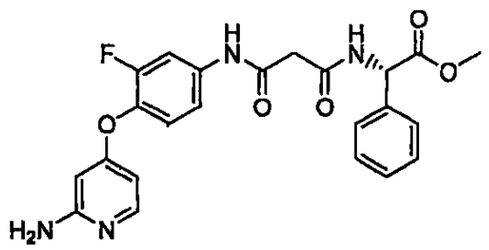
Example 103



(R)-N^1-(2-Amino-2-oxo-1-phenylethyl)-N^3-(4-(2-aminopyridin-4-yloxy)-3-fluorophenyl)malonamide, hydrochloride salt

[00384] 3-(4-(2-Aminopyridin-4-yloxy)-3-fluorophenylamino)-3-oxopropanoic acid (Compound C of Example 102, 30 mg, 0.10 mmol) was coupled with (R)-2-amino-2-phenylacetamide hydrochloride (Bachem, 28 mg, 0 15 mmol) in a manner similar to that which is described in Step C of Example 1 to give (R)-N^1-(2-amino-2-oxo-1-phenylethyl)-N^3-(4-(2-aminopyridin-4-yloxy)-3-fluorophenyl)malonamide, hydrochloride salt (14 mg, 30% yield). ^{1}H NMR (DMSO-d_6) δ 10.65 (s, 1H), 8.76 (d, 1H, J = 8.0 Hz), 7.92 (d, 1H, J = 7.0 Hz), 7.75-7.88 (m, 4H), 7.20-7.43 (m, 8H), 6.66 (m, 1H), 6.09 (s, 1H), 5.35 (d, 1H, J = 8.0 Hz), 3.45 (d, 1H, J = 15.0 Hz), 3.37 (d, 1H, J = 15 0 Hz); MS(ESI$^+$) m/z 438.23 $(M + H)^+$

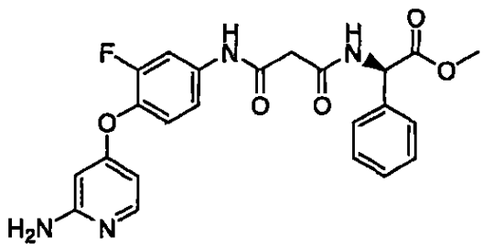
Example 104



(*S*)-Methyl 2-(3-(4-(2-aminopyridin-4-yloxy)-3-fluorophenylamino)-3-oxopropanamido)-2-phenylacetate, hydrochloride salt

[00385] 3-(4-(2-Aminopyridin-4-yloxy)-3-fluorophenylamino)-3-oxopropanoic acid (Compound C of Example 102, 30 mg, 0.10 mmol) was coupled with (*S*)-methyl 2-amino-2-phenylacetate hydrochloride (Aldrich, 30 mg, 0.10 mmol) in a manner similar to that which is described in Step C of Example 1 to give (*S*)-methyl 2-(3-(4-(2-aminopyridin-4-yloxy)-3-fluorophenylamino)-3-oxopropanamido)-2-phenylacetate, hydrochloride salt (21 mg, 43% yield). ^{1}H NMR (DMSO-d_6) δ 10.58 (s, 1H), 9.04 (d, 1H, J = 7.0 Hz), 7.97 (d, 1H, J = 7.0 Hz), 7.75-7.88 (m, 3H), 7.42 (m, 7H), 6.72 (d, 1H, J = 7.0 Hz), 6.12 (s, 1H), 5.45 (d, 1H, J = 7.0 Hz), 3.63 (s, 3H), 3.43-3.38 (m, 2H); MS(ESI$^+$) m/z 453.26 $(M + H)^+$.

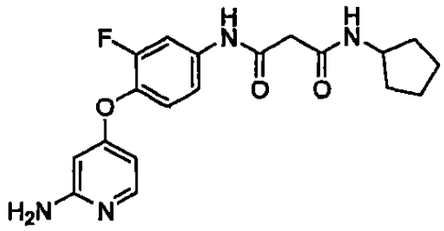
Example 105



(*R*)-Methyl 2-(3-(4-(2-aminopyridin-4-yloxy)-3-fluorophenylamino)-3-oxopropanamido)-2-phenylacetate, hydrochloride salt

[00386] 3-(4-(2-Aminopyridin-4-yloxy)-3-fluorophenylamino)-3-oxopropanoic acid (Compound C of Example 102, 30 mg, 0.10 mmol) was coupled with (*R*)-methyl 2-amino-2-phenylacetate, hydrochloride salt (Aldrich, 30 mg, 0.10 mmol) in a manner similar to that which is described in Step C of Example 1 to give (*R*)-methyl 2-(3-(4-(2-aminopyridin-4-yloxy)-3-fluorophenylamino)-3-oxopropanamido)-2-phenylacetate, hydrochloride salt (25 mg, 51% yield). ^{1}H NMR (DMSO-d_6) δ 10.58 (s, 1H), 9.03 (d, 1H, J = 7.0 Hz), 7.96 (d, 1H, J = 7.0 Hz), 7.77-7.88 (m, 3H), 7.42 (m, 7H), 6.71 (d, 1H, J = 7.5 Hz), 6.12 (s, 1H), 5.44 (d, 1H, J = 7.0 Hz), 3.63 (s, 3H), 3.44-3.38 (m, 2H); MS(ESI$^+$) m/z 453.29 $(M + H)^+$.

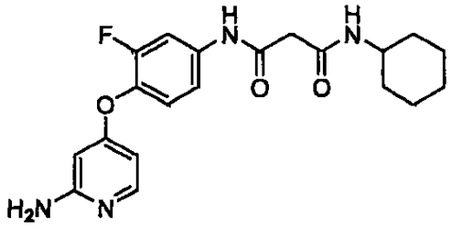
Example 106



N^1-(4-(2-Aminopyridin-4-yloxy)-3-fluorophenyl)-N^3-cyclopentylmalonamide, hydrochloride salt

[00387] 3-(4-(2-Aminopyridin-4-yloxy)-3-fluorophenylamino)-3-oxopropanoic acid (Compound C of Example 102, 30 mg, 0.10 mmol) was coupled with cyclopentanamine (Aldrich, 17 mg, 0.2 mmol) in a manner similar to that which is described in Step C of Example 1 to give N^1-(4-(2-aminopyridin-4-yloxy)-3-fluorophenyl)-N^3-cyclopentylmalonamide, hydrochloride salt (18 mg, 44% yield). ^{1}H NMR (DMSO-d_6) δ 13.34 (s, 1H), 10.66 (s, 1H), 8.15 (d, 1H, J = 7.0 Hz), 7.96 (d, 1H, J = 7.0 Hz), 7.77-7.88 (m, 3H), 7.42 (m, 2H), 6.70 (d, 1H, J = 7.5 Hz), 6.12 (s, 1H), 3.98 (m, 1H), 3.69 (s, 2H), 1.78 (m, 2H), 1.63 (m, 2H), 1.49 (m, 2H), 1.37 (m, 2H); MS(ESI$^+$) m/z 373.30 $(M + H)^+$.

Example 107

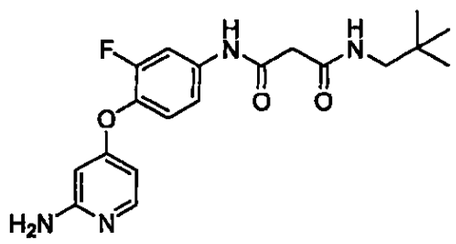


N^1-(4-(2-Aminopyridin-4-yloxy)-3-fluorophenyl)-N^3-cyclohexylmalonamide, hydrochloride salt

[00388] 3-(4-(2-Aminopyridin-4-yloxy)-3-fluorophenylamino)-3-oxopropanoic acid (Compound C of Example 102, 30 mg, 0.10 mmol) was coupled with cyclohexanamine (Aldrich, 20 mg, 0.2 mmol) in a manner similar to that which is described in Step C of Example 1 to give N^1-(4-(2-aminopyridin-4-yloxy)-3-fluorophenyl)-N^3-cyclohexylmalonamide, hydrochloride salt (22 mg, 52% yield). ^{1}H NMR (DMSO-d_6) δ 14.00 (s, 1H), 10.72 (s, 1H), 8.10 (d, 1H, J = 7.0 Hz), 7.97 (d,

1H, J = 7.0 Hz), 7.88 (m, 3H), 7.44 (m, 2H), 6.70 (m, 1H), 6.14 (d, 1H, J = 2.0 Hz), 3.54 (m, 1H), 3.27 (s, 2H), 1.66-1.75 (m, 4H), 1.52 (m, 1H), 1.15-1.25 (m, 5H); MS(ESI$^+$) m/z 387.32 $(M + H)^+$.

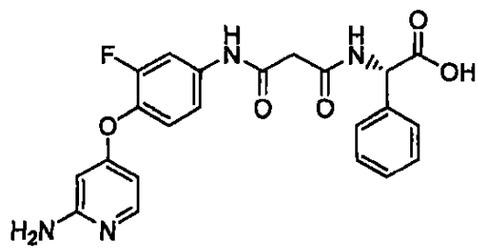
Example 108



N^1-(4-(2-Aminopyridin-4-yloxy)-3-fluorophenyl)-N^3-neopentylmalonamide, hydrochloride salt

[00389] 3-(4-(2-Aminopyridin-4-yloxy)-3-fluorophenylamino)-3-oxopropanoic acid (Compound C of Example 102, 30 mg, 0.10 mmol) was coupled with 2,2-dimethylpropan-1-amine (Aldrich, 12 mg, 0.2 mmol) in a manner similar to that which is described in Step C of Example 1 to give N^1-(4-(2-aminopyridin-4-yloxy)-3-fluorophenyl)-N^3-neopentylmalonamide, hydrochloride salt (13 mg, 32% yield). ^{1}H NMR (DMSO-d_6) δ 13.34 (s, 1H), 10.69 (s, 1H), 8.08 (m, 1H), 7.96 (d, 1H, J = 7.0 Hz), 7.87 (m, 3H), 7.44 (m, 2H), 6.70 (m, 1H), 6.13 (d, 1H, J = 2.0 Hz), 3.34 (s, 2H), 2.91 (d, 2H, J = 6.5 Hz), 0.84 (s, 9H); MS(ESI$^+$) m/z 375.32 $(M + H)^+$.

Example 109

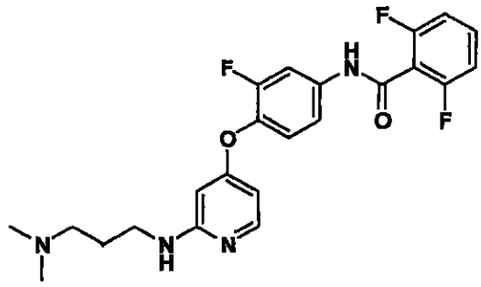


(*S*)-2-(3-(4-(2-Aminopyridin-4-yloxy)-3-fluorophenylamino)-3-oxopropanamido)-2-phenylacetic acid, hydrochloride salt

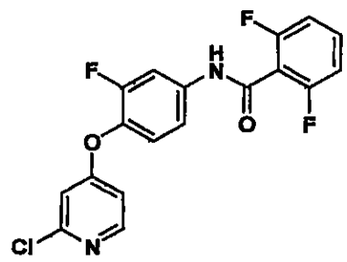
[00390] Following a procedure similar to that which is described in Step C of Example 99, (*S*)-methyl 2-(3-(4-(2-aminopyridin-4-yloxy)-3-fluorophenylamino)-3-

oxopropanamido)-2-phenylacetate hydrochloride (Compound D of Example 102, 14 mg, 0.028 mmol) was hydrolyzed to give (*S*)-2-(3-(4-(2-aminopyridin-4-yloxy)-3-fluorophenylamino)-3-oxopropanamido)-2-phenylacetic acid, hydrochloride salt (13 mg, 97% yield). ^{1}H NMR (DMSO-d_6) δ 13.20 (s, 1H), 10.57 (s, 1H), 8.92 (d, 1H, J= 7.0 Hz), 7.95 (d, 1H, J= 7.0 Hz), 7.87 (d, 1H, J= 11.0 Hz), 7.70 (s, 2H), 7.41 (m, 8H), 6.69 (d, 1H, J= 7.5 Hz), 6.12 (d, 1H, J= 2.0 Hz), 5.35 (d, 1H, J= 7.5 Hz), 3.42 (s, 2H); MS(ESI$^+$) m/z 439.27 $(M+H)^+$.

Example 110



***N*-(4-(2-(3-(Dimethylamino)propylamino)pyridin-4-yloxy)-3-fluorophenyl)-2,6-difluorobenzamide, hydrochloride salt**



A) *N*-(4-(2-Chloropyridin-4-yloxy)-3-fluorophenyl)-2,6-difluorobenzamide

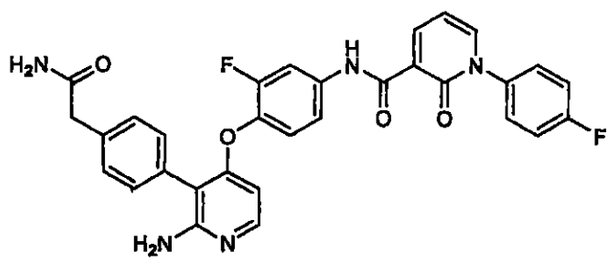
[00391] A solution 4-(2-chloropyridin-4-yloxy)-3-fluorobenzenamine (Compound B of Example 20, 64 mg, 0.27 mmol), THF (1 ml), Et_3N (100 μL) was treated dropwise with 2,6-difluorobenzoyl chloride (Aldrich, 33 μL, 0.27 mmol) and the mixture was stirred at rt for 30 min. The mixture was partitioned between EtOAc and saturated aq. $NaHCO_3$ and the EtOAc phase was separated, dried ($MgSO_4$) and

concentrated *in vacuo* to give the title compound (102 mg, 100 %) as white solid. MS(ESI$^+$): *m/z* 418.18 $(M + H)^+$.

B) *N*-(4-(2-(3-(Dimethylamino)propylamino)pyridin-4-yloxy)-3-fluorophenyl)-2,6-difluorobenzamide, hydrochloride salt

[00392] A mixture of *N*-(4-(2-chloropyridin-4-yloxy)-3-fluorophenyl)-2,6-difluorobenzamide (70 mg, 0.19 mmol), 3-(dimethylamino)propylamine (44 mL, 0.35 mmol), Cs_2CO_3 (85 mg, 0.26 mmol) and CuCl (17 mg, 0.17 mmol) in a screw capped vial was purged with N_2. NMP and 2,2,6,6,-tetramethyl-3,5-heptanedione (31 mg, 0.17 mmol) were added to the mixture which was then heated at 120 °C for 4 h. The mixture was cooled, partitioned between EtOAc and saturated aq. $NaHCO_3$ solution and the EtOAc phase was separated, dried ($MgSO_4$) and concentrated in vacuo to give the crude product. Purification of the residue by preparative HPLC (Column C) and conversion to the hydrochloride salt was carried out in a similar manner as Step D of Example 33 to give the title compound (7 mg, 7 %) as an off-white solid. MS(ESI$^+$): *m/z* 517.37 $(M + H)^+$.

Example 111

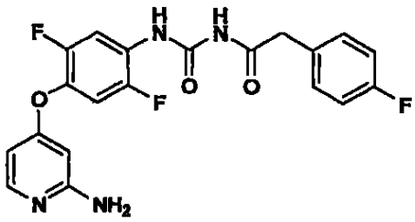


***N*-(4-(2-Amino-3-(4-(2-amino-2-oxoethyl)phenyl)pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, hydrochloride salt**

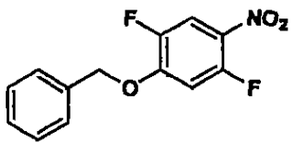
[00393] A solution of 2-(4-(2-amino-4-(4-amino-2-fluorophenoxy)pyridin-3-yl)phenyl)acetamide (Compound C of Example 78, 18 mg, 0.05 mmol) in DMF (1.5 mL) was treated with 1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (Compound B of Example 101, 11 mg, 0.05 mmol), DIPEA (10 μL, 0.06 mmol) and TBTU (19 mg, 0.06 mmol). The mixture was stirred at room temperature for 40 h.

The mixture was concentrated under vacuum and the residue was purified by preparative HPLC (Column A) to give the title compound as a TFA salt. The TFA salt was dissolved in anhydrous MeOH and treated with 1 M HCl / Et_2O at 0 °C and stirred for 5 min. The mixture was then concentrated *in vacuo* to give the title compound (15 mg, 47%) as a yellow solid. ^{1}H NMR (DMSO-d_6) δ 12.11 (s, 1H), 8.56 (dd, 1H, J = 2.2, 7.1 Hz), 8.13 (dd, 1H, J = 2.2, 6.7 Hz), 8.00 (dd, 1H, J = 2.2, 12.6 Hz), 7.96 (d, 1H, J = 7.7 Hz), 7.60 – 7.57 (m, 2H), 7.48 – 7.33 (m, 10H), 6.94 (s, 1H), 6.72 (dd, 1H, J = 7.2, 7.2 Hz), 6.38 (d, 1H, J = 7.2 Hz), 3.95 (s, 2H); MS(ESI$^+$): *m/z* 568.23 $(M + H)^+$.

Example 112

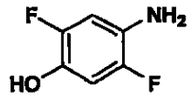


1-(4-(2-Aminopyridin-4-yloxy)-2,5-difluorophenyl)-3-(2-(4-fluorophenyl)-acetyl)urea, hydrochloric acid salt



A) 1-((2,5-Difluoro-4-nitrophenoxy)methyl)benzene

[00394] A mixture of 2,4,5-trifluoronitrobenzene (5.4 g, 30.8 mmol), benzylalcohol (3.2 mL, 30.8 mmol) and potassium carbonate (6.4 g, 46.1 mmol), in DMF (20 mL), was stirred at ambient temperature for 72 h. Water (60 mL) was added and the mixture was cooled at 4 °C for 24 h. The resultant precipitate was filtered, rinsed with water and dried *in vacuo* to afford the product (7.5 g, 92%) as a pale yellow solid. ^{1}H NMR ($CDCl_3$) δ 7.90-7.94 (m, 1H), 7.38-7.44 (m, 5H), 6.85-6.90 (m, 1H), 5.22 (s, 2H).



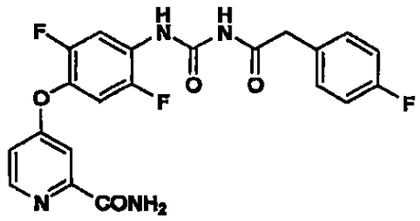
B) 4-Amino-2,5-difluorophenol

[00395] To a flask charged with 1-((2,5-difluoro-4-nitrophenoxy)methyl)benzene (4.1 g, 15.6 mmol), which was sequentially evacuated and then purged with nitrogen three times, was added 10% palladium on carbon (0.40 g). To the solids, under a nitrogen atmosphere, was added anhydrous methanol (100 mL). The mixture was then stirred under a hydrogen atmosphere for 16 h. Nitrogen was bubbled through the reaction mixture for thirty minutes, before the mixture was filtered through a pad of Celite®, which was then rinsed with methanol. The filtrate was concentrated *in vacuo*, then azeotroped with toluene to afford the title compound as a dark brown solid (2.2 g, 99%). ^{1}H NMR (DMSO-d_6) δ 9.05 (br s, 1H), 6.53-6.65 (m, 2H), 4.68 (s, 2H); MS(ESI$^+$) *m/z* 146 $(M+H)^+$.



C) 4-(4-Amino-2,5-difluorophenoxy)picolinamide

[00396] To a mixture of potassium hydride (30-35% dispersion in mineral oil, 1.9 g, 13.9 mmol) in DMF (30 mL) was added 4-amino-2,5-difluorophenol (1.7 g, 11.6 mmol) as a solution in DMF (5 mL). After one hour of stirring at ambient temperature, 4-chloropicolinamide (1.8 g, 11.6 mmol) was added and the reaction mixture was heated to 100 °C for 135 h. The mixture was cooled to room temperature, quenched with 10% aqueous lithium chloride and then extracted three times with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resultant solid was partitioned between chloroform and water. The organic layer was washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo* to a solid (3.0 g, 98%). ^{1}H NMR (DMSO-d_6) δ 8.51-8.57 (m, 1H), 8.14 (br s, 1H), 7.74 (br s, 1H), 7.37-7.38 (m, 1H), 7.17-7.30 (m, 2H), 6.74-6.80 (m, 1H), 5.62 (s, 2H); MS(ESI$^+$) *m/z* 266 $(M+H)^+$.



D) 1-(4-(2-Carbamoylpyridin-4-yloxy)-2,5-difluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea

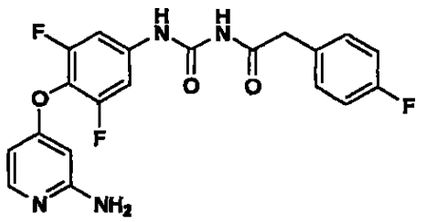
[00397] To a homogeneous mixture of 4-(4-amino-2,5-difluorophenoxy)picolinamide (0.15 g, 0.57 mmol) in THF (5 mL) was added diisopropylethylamine (0.10 mL, 0.57 mmol). The mixture was stirred for two minutes at ambient temperature before 2-(4-fluorophenyl)acetyl isocyanate (Compound D of Example 11, 0.36 M in toluene, 2.0 mL, 0.72 mmol) was added. After 3.5 hours, 2-(4-fluorophenyl)acetyl isocyanate (0.36 M in toluene, 2.0 mL, 0.72 mmol) was added to the reaction mixture. After an additional two hours, 2-(4-fluorophenyl)acetyl isocyanate (0.36 M in toluene, 2.0 mL, 0.72 mmol) was added to the reaction mixture. The mixture was then stirred for 16 hours before being concentrated *in vacuo*. The residue was treated with Et_2O and sonication and the resultant white solid was removed by filtration. The solid was treated with Et_2O and sonication two more times before vacuum filtration afforded a white solid (0.23 g, 91%). ^{1}H NMR (DMSO-d_6) δ 11.29 (s, 1H), 10.92 (s, 1H), 8.56 (d, 1H, J = 5.6 Hz), 8.21-8.26 (m, 1H), 8.16 (br s, 1H), 7.76 (br s, 1H), 7.66-7.71 (m, 1H), 7.12-7.44 (m, 6H), 3.77 (s, 2H); MS(ESI$^+$) *m/z* 445 $(M+H)^+$.

E) 1-(4-(2-Aminopyridin-4-yloxy)-2,5-difluorophenyl)-3-(2-(4-fluorophenyl)-acetyl)urea, hydrochloric acid salt

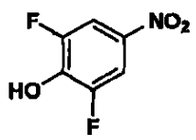
[00398] Bis(trifluoroacetoxy)iodobenzene (Aldrich, 0.18 g, 0.42 mmol) was added to a solution of 1-(4-(2-carbamoylpyridin-4-yloxy)-2,5-difluorophenyl)-3-(2-(4-fluorophenyl)-acetyl)urea (0.13 g, 0.30 mmol), water (0.01 mL, 0.60 mmol) and pyridine (0.05 mL, 0.66 mmol) in DMF (2 mL) at room temperature. After ten minutes, additional DMF (2 mL) was added. The reaction mixture was then stirred for 16 hours before being concentrated *in vacuo* to approximately one half of its

original volume. The resultant mixture was partitioned between 6 N HCl and Et_2O, the aqueous solution extracted with Et_2O and the combined organic layers discarded. The aqueous layer was neutralized with $NaHCO_3$(aq) and extracted with EtOAc. The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (eluting with 0-5% MeOH in $CHCl_3$) and the appropriate fractions were concentrated *in vacuo*. The residue was dissolved in THF (1 mL), cooled to 0 °C and treated with HCl (4 N in dioxane, 0.5 mL, 2.0 mmol). The reaction mixture was allowed to warm to room temperature and stirred for one hour, before being lyophilized to afford the title compound (73 mg, 53%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 13.54 (br s, 1H), 11.35 (s, 1H), 10.95 (s, 1H), 8.24-8.28 (m, 1H), 7.95-8.01 (m, 3H), 7.73-7.77 (m, 1H), 7.35-7.39 (m, 2H), 7.16-7.20 (m, 2H), 6.72-6.74 (m, 1H), 6.25 (s, 1H), 3.78 (s, 2H); HRMS(ESI$^+$): 417.1175 $(M+H)^+$ calcd., 417.1187 $(M+H)^+$ found.

Example 113

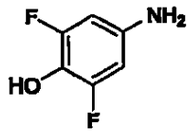


1-(4-(2-Aminopyridin-4-yloxy)-3,5-difluorophenyl)-3-(2-(4-fluorophenyl)-acetyl)urea, trifluoroacetic acid salt



A) 2,6-Difluoro-4-nitrophenol

[00399] 2,6-Difluorophenol (10.0 g, 76.9 mmol) was converted to the title compound (12.7 g, 94%) in a manner similar to the conditions described by Kirk et al. *J. Heterocyclic Chem.* **1976**, *13*, 1253. ^{1}H NMR ($CDCl_3$) δ 12.15 (br s, 1H), 8.01-8.10 (m, 2H).



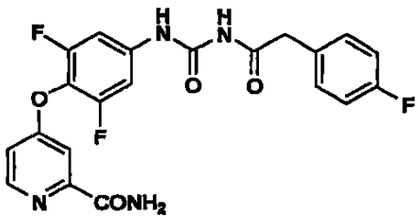
B) 4-Amino-2,6-difluorophenol

[00400] 2,6-Difluoro-4-nitrophenol (2.1 g, 12.1 mmol) was converted to the title compound (1.7 g, 99%) in a manner similar to that described by Demopoulos et al. *J. Med. Chem.* **2004**, *47*, 2706. MS(ESI$^+$) *m/z* 146 $(M+H)^+$.



C) 4-(4-Amino-2,6-difluorophenoxy)picolinamide

[00401] 4-Chloropicolinamide (0.47 g, 3.0 mmol) was converted to the title compound (0.23 g, 29%) in a manner similar to the preparation of Compound C of Example 112, except that 4-amino-2,6-difluorophenol (0.44 g, 3.0 mmol) was used instead of 4-amino-2,5-difluorophenol. ^{1}H NMR (DMSO-d_6) δ 8.60 (d, 1H, J = 5.6 Hz), 8.22 (br s, 1H), 7.83 (br s, 1H), 7.45-7.46 (m, 1H), 7.30-7.32 (m, 1H), 6.43-6.49 (m, 2H), 5.94 (s, 2H); MS(ESI$^+$) *m/z* 266 $(M+H)^+$.



D) 1-(4-(2-Carbamoylpyridin-4-yloxy)-3,5-difluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea

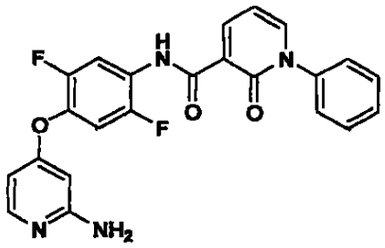
[00402] 4-(4-Amino-2,6-difluorophenoxy)picolinamide (104 mg, 0.39 mmol) was converted to the title compound (91 mg, 52%) in a manner similar to the preparation of Compound D of Example 112. ^{1}H NMR (DMSO-d_6) δ 11.07 (s, 1H), 10.62 (s, 1H), 8.50 (d, 1H, J = 5.6 Hz), 8.11 (br s, 1H), 7.72 (br s, 1H), 7.61 (m, 2H), 7.36-7.37

(d, 1H, J = 2.3 Hz), 7.23-7.31 (m, 3H), 7.11 (m, 2H), 3.69 (s, 2H); HRMS(ESI$^+$), 445.1124 $(M+H)^+$ calcd., 445.1117 $(M+H)^+$ found.

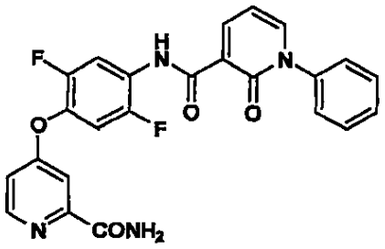
E) 1-(4-(2-Aminopyridin-4-yloxy)-3,5-difluorophenyl)-3-(2-(4-fluorophenyl)-acetyl)urea, trifluoroacetic acid salt

[00403] 1-(4-(2-Carbamoylpyridin-4-yloxy)-3,5-difluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea (87 mg, 0.20 mmol) was converted to the title compound in a manner similar to the preparation of Compound E of Example 112, except that the crude product 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 (23 mg, 22%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.09 (s, 1H), 10.63 (s, 1H), 7.92 (d, 1H, J = 7.2 Hz), 7.62-7.72 (m, 4H), 7.27-7.31 (m, 2H), 7.09-7.14 (m, 2H), 6.68-6.70 (m, 1H), 6.17-6.18 (m, 1H), 3.69 (s, 2H); MS(ESI$^+$) *m/z* 417 $(M+H)^+$.

Example 114



***N*-(4-(2-Aminopyridin-4-yloxy)-2,5-difluorophenyl)-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide, hydrochloric acid salt**



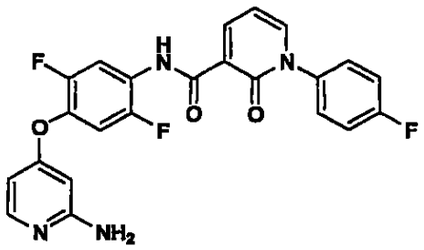
A) 4-(2,5-Difluoro-4-(2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamido)-phenoxy)picolinamide

[00404] To a homogeneous mixture of 2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxylic acid (Compound C of Example 57, 43 mg, 0.20 mmol) in DMF (4 mL) was added 1-hydroxy-benzotriazole hydrate (22 mg, 0.16 mmol). The mixture was stirred until homogeneous before 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (102 mg, 0.53 mmol) was added. After two minutes, 4-(4-amino-2,5-difluorophenoxy)picolinamide (Compound C of Example 112, 53 g, 0.20 mmol) was added and the reaction mixture stirred, at ambient temperature for 17 h. The reaction mixture was then warmed to 40 °C and stirred for an additional 143 h. After cooling to ambient temperature, the mixture was partitioned between EtOAc and 10% LiCl (aq). The organic layer was washed twice with 10% LiCl (aq), then concentrated *in vacuo*. The residue was purified by silica gel chromatography (eluting with 1:3 hexane / EtOAc) and the appropriate fractions were concentrated *in vacuo* to afford the title compound (45 mg, 49%) MS(ESI$^+$) *m/z* 463 $(M+H)^+$.

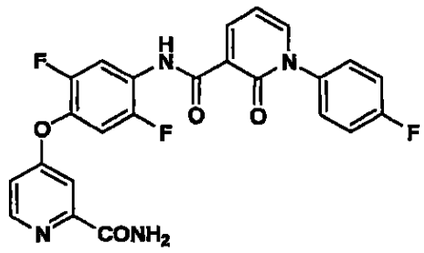
B) *N*-(4-(2-Aminopyridin-4-yloxy)-2,5-difluorophenyl)-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide, hydrochloric acid salt

[00405] 4-(2,5-Difluoro-4-(2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamido)-phenoxy)picolinamide (45 mg, 0.10 mmol) was converted to the title compound (19 mg, 40%) in a manner similar to the preparation of Compound E of Example 112. ^{1}H NMR (DMSO-d_6) δ 13.40 (br s, 1H), 12.47 (s, 1H), 8.53-8.57 (m, 2H), 8.12-8.13 (m, 1H), 7.92-7.93 (m, 1H), 7.83 (s, 2H), 7.66-7.71 (m, 1H), 7.46-7.53 (m, 5H), 6.66-6.72 (m, 2H), 6.19 (s, 1H); HRMS(ESI$^+$), 435.1269 $(M+H)^+$ calcd., 435.1258 $(M+H)^+$ found.

Example 115



***N*-(4-(2-Aminopyridin-4-yloxy)-2,5-difluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, hydrochloric acid salt**



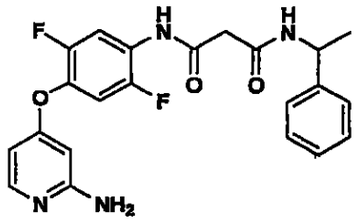
A) 4-(2,5-Difluoro-4-(1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamido)phenoxy)picolinamide

[00406] To a homogeneous mixture of 1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (Compound B of Example 101, 50 mg, 0.21 mmol) and 4-(4-amino-2,5-difluorophenoxy)picolinamide (Compound C of Example 112, 69 mg, 0 26 mmol) in DMF (3 mL) was added DIPEA (0.05 mL, 0.26 mmol) and *O*-benzotriazol-1-yl-*N,N,N',N'*-bis(tetramethylene)-uranium hexafluorophosphate (TBTU) (83 mg, 0.26 mmol). The resulting solution was stirred for 18 hours before being quenched with 10% LiCl (aq). The mixture was partitioned between EtOAc and 10% LiCl (aq), the layers separated, and the aqueous layer extracted with EtOAc. The combined organic layers were washed twice with 10% LiCl (aq), then concentrated *in vacuo*. The residue was purified by silica gel chromatography (eluting with 1:3 hexane / EtOAc) and the appropriate fractions were concentrated *in vacuo* to afford the title compound (22 mg, 22%). MS(ESI$^+$) *m/z* 481 $(M+H)^+$.

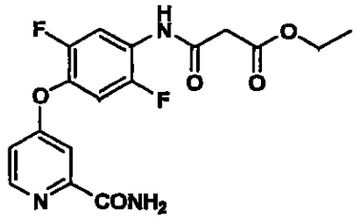
B) *N*-(4-(2-Aminopyridin-4-yloxy)-2,5-difluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, hydrochloric acid salt

[00407] 4-(2,5-Difluoro-4-(1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamido)phenoxy)picolinamide (22 mg, 0.04 mmol) was converted to the title compound (21 mg, 95%) in a manner similar to the preparation of Compound E of Example 112. ^{1}H NMR (DMSO-d_6) δ 13.71 (br s, 1H), 12.43 (s, 1H), 8.48-8.57 (m, 2H), 8.10-8.13 (m, 1H), 7.93-7.95 (m, 3H), 7.61-7.70 (m, 1H), 7.53-7.56 (m, 2H), 7.29-7.39 (m, 2H), 6.64-6.72 (m, 2H), 6.10 (s, 1H); HRMS(ESI$^+$), 453.1175 $(M+H)^+$ calcd., 453.1168 $(M+H)^+$ found.

Example 116

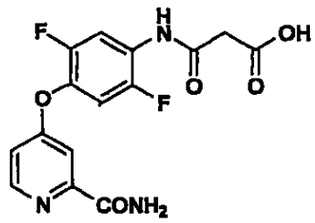


(±)-N^1-(4-(2-Aminopyridin-4-yloxy)-2,5-difluorophenyl)-N^3-(1-phenylethyl)malonamide, hydrochloric acid salt



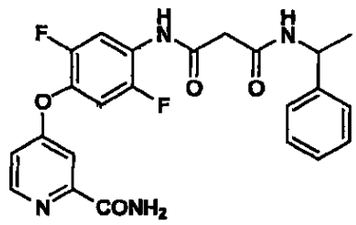
A) Ethyl 3-(4-(2-carbamoylpyridin-4-yloxy)-2,5-difluorophenylamino)-3-oxopropanoate

[00408] 4-(4-Amino-2,5-difluorophenoxy)picolinamide (Compound C of Example 112, 1.0 g, 3.9 mmol) was converted to the title compound (320 mg, 22%) in a manner similar to the preparation of Compound A of Example 102. ^{1}H NMR (DMSO-d_6) δ 10.32 (s, 1H), 8.54 (d, 1H, J = 5.5 Hz), 8.14-8.17 (m, 2H), 7.75 (br s, 1H), 7.61-7.65 (m, 1H), 7.42-7.43 (m, 1H), 7.24-7.25 (m, 1H), 4.12 (q, 2H, J = 7.2 Hz), 3.60 (s, 2H), 1.20 (t, 3H, J = 7.2 Hz); MS(ESI$^+$) m/z 380 $(M+H)^+$.



B) 3-(4-(2-Carbamoylpyridin-4-yloxy)-2,5-difluorophenylamino)-3-oxopropanoic acid

[00409] To a heterogeneous mixture of ethyl 3-(4-(2-carbamoylpyridin-4-yloxy)-2,5-difluorophenylamino)-3-oxopropanoate (305 mg, 0.80 mmol) in MeOH (8 mL) was added aqueous 1 M NaOH (1.70 mL, 1.70 mmol). After one hour of stirring, the mixture was acidified with aqueous 1N HCl (5 mL). The reaction was extracted with EtOAc before the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the title compound (317 mg) which was used without further purification. HRMS(ESI^+), 352.0745 $(M+H)^+$ calcd., 352.0752 $(M+H)^+$ found.



C) (±)-4-(2,5-Difluoro-4-(3-oxo-3-(1-phenylethylamino)propanamido)-phenoxy)picolinamide

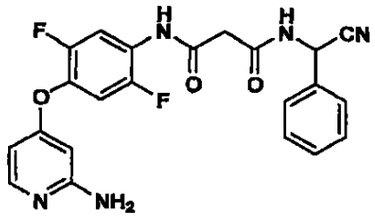
[00410] To a homogeneous mixture of 3-(4-(2-carbamoylpyridin-4-yloxy)-2,5-difluorophenylamino)-3-oxopropanoic acid (89 mg, 0.25 mmol) and (±)-1-phenyl-ethanamine (Aldrich, 0.05 mL, 0.38 mmol) in DMF (3 mL) was added DIPEA (0.07mL, 0.38mmol) and *O*-benzotriazol-1-yl-*N,N,N',N'*-bis(tetramethylene)uranium hexafluorophosphate (TBTU) (121 mg, 0.38 mmol). The resulting solution was stirred for 15 hours before being quenched with 10% LiCl (aq). The mixture was partitioned between EtOAc and 10% LiCl (aq), the layers separated, and the aqueous layer extracted with EtOAc. The combined organic layers were washed twice with 10% LiCl (aq), then concentrated *in vacuo*. The residue was purified by silica gel

chromatography (eluting with 1:3 hexane / EtOAc) and the appropriate fractions were concentrated *in vacuo* to afford the title compound (42 mg, 37%). HRMS(ESI$^+$), 455.1532 $(M+H)^+$ calcd , 455.1528 $(M+H)^+$ found.

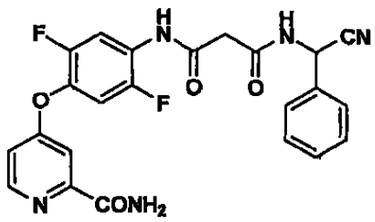
D) (±)-N^1-(4-(2-Aminopyridin-4-yloxy)-2,5-difluorophenyl)-N^3-(1-phenyl-ethyl)malonamide, hydrochloric acid salt

[00411] (±)-4-(2,5-Difluoro-4-(3-oxo-3-(1-phenylethylamino)propanamido)phenoxy)-picolinamide (41 mg, 0.09 mmol) was converted to the title compound (26 mg, 62%) in a manner similar to the preparation of Compound E of Example 112. ^{1}H NMR (DMSO-d_6) δ 10.46 (s, 1H), 8.70 (d, 1H, J = 7.8 Hz), 8.21-8.26 (m, 1H), 8.00 (d, 1H, J = 7.2 Hz), 7.89 (s, 2H), 7.67-7.72 (m, 1H), 7.22-7.36 (m, 5H), 6.73-6.76 (m, 1H), 6.21-6.22 (m, 1H), 4.93-4.96 (m, 1H), 3.57 (s, 2H), 1.35 (d, 3H, J = 7.0 Hz); HRMS(ESI$^+$), 427.1582 $(M+H)^+$ calcd., 427.1574 $(M+H)^+$ found.

Example 117



(±)-N^1-(4-(2-Aminopyridin-4-yloxy)-2,5-difluorophenyl)-N^3-(cyano(phenyl)-methyl)malonamide, trifluoroacetic acid salt



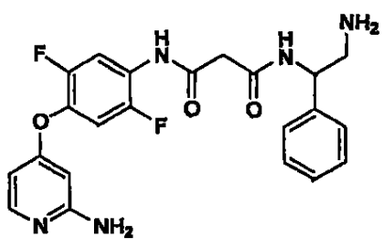
A) (±)-4-(4-(3-(Cyano(phenyl)methylamino)-3-oxopropanamido)-2,5-difluorophenoxy)picolinamide

[00412] 3-(4-(2-Carbamoylpyridin-4-yloxy)-2,5-difluorophenylamino)-3-oxopropanoic acid (Compound B of Example 116, 70 mg, 0.20 mmol) was converted to the title compound (67 mg, 72%) in a manner similar to the preparation of Compound C of Example 116, except that (±)-2-amino-2-phenylacetonitrile hydrochloride (Aldrich, 47 mg, 0.28 mmol) was used instead of (±)-1-phenylethanamine. MS(ESI$^+$) *m/z* 466 $(M+H)^+$.

B) (±)-*N*1-(4-(2-Aminopyridin-4-yloxy)-2,5-difluorophenyl)-*N*3-(cyano-(phenyl)methyl)malonamide, trifluoroacetic acid salt

[00413] (±)-4-(4-(3-(Cyano(phenyl)methylamino)-3-oxopropanamido)-2,5-difluoro-phenoxy)picolinamide (65 g, 0.14 mmol) was converted to the title compound in a manner similar to the preparation of Compound E of Example 112, except that the crude product was purified by preparative HPLC (YMC S10 ODS, 30 x 500mm, 30 minute gradient from 34% to 90% aqueous methanol with 0.1%TFA). The appropriate fractions were combined and lyophilized to afford the title compound (38 mg, 49%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 10 40 (s, 1H), 9.47 (d, 1H, J= 7.63 Hz), 8.21-8.26 (m, 1H), 7.99 (d, 1H, J= 7.2 Hz), 7.86 (br s, 2H), 7.68-7.73 (m, 1H), 7.43-7.54 (m, 5H), 6.74-6.77 (m, 1H), 6.20-6.22 (m, 2H), 3.55 (m, 2H); HRMS(ESI$^+$), 438.1378 $(M+H)^+$ calcd., 438.1374 $(M+H)^+$ found.

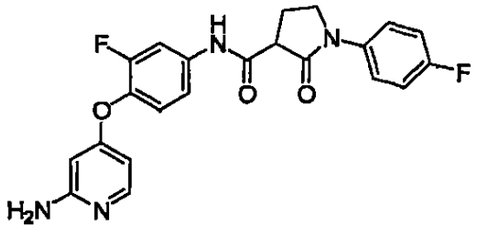
Example 118



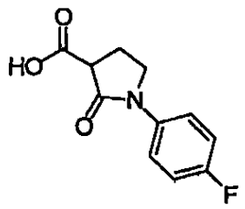
(±)-N^1-(2-Amino-1-phenylethyl)-N^3-(4-(2-aminopyridin-4-yloxy)-2,5-difluorophenyl)malonamide, bistrifluoroacetic acid salt

[00414] (±)-N^1-(4-(2-Aminopyridin-4-yloxy)-2,5-difluorophenyl)-N^3-(cyano(phenyl)-methyl)malonamide, trifluoroacetic acid salt (Compound B of Example 117, 21 mg, 0.04 mmol) was converted to the title compound in a manner similar to the conditions described by Campiani, et al. (*Tetrahedron* **2002**, *58*, 3689). The cobalt boride was purchased from Alfa Aesar. The crude product was purified by preparative HPLC (YMC S5 ODS, 10 x 250mm, 30 minute gradient from 10% to 90% aqueous methanol with 0.1%TFA). Appropriate fractions were combined and lyophilized to afford the title compound (5 mg, 21%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 10.39 (s, 1H), 8.72 (d, 1H, J = 8.5 Hz), 8.12-8.17 (m, 1H), 7.90-7.94 (m, 3H), 7.59-7.63 (m, 2H), 7.27-7.34 (m, 4H), 6.60-6.62 (m, 1H), 6.09-6.10 (m, 1H), 5.09-5.10 (m, 1H), 3.10-3-50 (m, 6H); HRMS(ESI$^+$), 442.1691 $(M+H)^+$ calcd., 442.1678 $(M+H)^+$ found.

Example 119



***N*-(4-(2-Aminopyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxopyrrolidine-3-carboxamide**



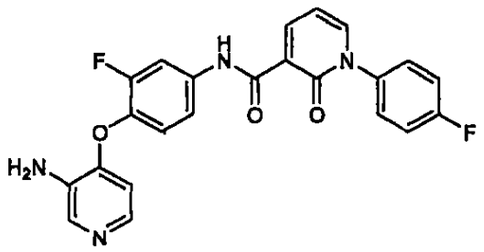
A) 1-(4-Fluorophenyl)-2-oxopyrrolidine-3-carboxylic acid

[00415] To a solution of 6,6-dimethyl-5,7-dioxaspiro[2.5]-octane-4,8-dione (Aldrich, 51 mg, 0.3 mmol) in DMF (0.5 mL) at room temperature was added 4-fluoroaniline (Aldrich, 33 mg, 0.3 mmol). The reaction mixture was heated at 90 °C for 2 h, cooled to room temperature, and used directly in the next step.

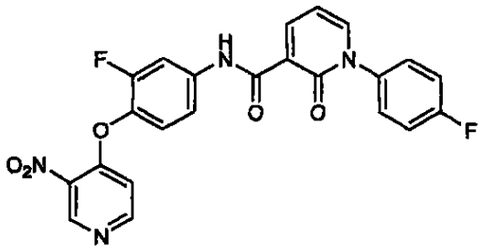
B) *N*-(4-(2-Aminopyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxopyrrolidine-3-carboxamide

[00416] To a mixture of 1-(4-fluorophenyl)-2-oxopyrrolidine-3-carboxylic acid (0.3 mol), 4-(4-amino-2-fluorophenoxy)pyridin-2-amine (Compound B of Example 24, 21.9 mg, 0.1 mmol) in DMF (0.5 ml), was added HATU (76 mg, 0.2 mmol) and followed by diisopropylethylamine (0.1 mL, 0.57 mmol). The reaction mixture was stirred at room temperature overnight and was then quenched with 2 mL of methanol. The reaction mixture was purified by prep HPLC. The desired fractions were combined, neutralized with sat. aq. $NaHCO_3$ solution, and concentrated *in vacuo* to afford the title compound (18 mg, 43%) as a white solid. ^1H NMR (DMSO-d_6) δ 10.76 (br s, 1H), 7.95 (d, 1H, J = 7.2 Hz), 7.91 (m, 1H), 7.68 (m, 2H), 7.50(m, 1H), 7.44 (t, 1H, J = 10.0 Hz), 7.24 (m, 2H), 6.70 (m, 1H), 6.11 (d, 1H, J = 2.8 Hz), 3.91 (m, 2H), 3.78 (t, 1H, J = 5.0 Hz), 2.41 (m, 2H); MS(ESI$^+$) *m/z* 425.15 $(M+H)^+$.

Example 120



***N*-(4-(3-Aminopyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide**



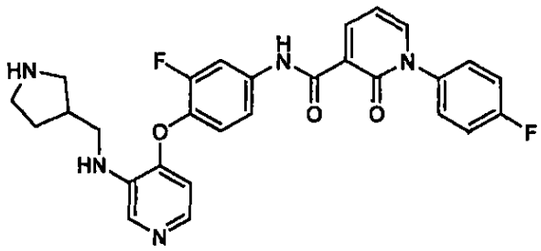
A) ***N*-(3-Fluoro-4-(3-nitropyridin-4-yloxy)phenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide**

[00417] Prepared from 3-fluoro-4-(3-nitropyridin-4-yloxy)benzenamine (Compound A of Example 72) in a manner similar to that of Example 62 to give the title compound (89%) as a tan solid. ^{1}H NMR (CD_3OD) δ 9.13 (s, 1H), 8.72 (dd, 1H, J = 8, 4 Hz), 8.60 (d, 1H, J = 6 Hz), 8.07 (d, 1H, J = 12 Hz), 8.01-7.99 (m, 1H), 7.58-7.55 (m, 2H), 7.45 (t, 1H, J = 8 Hz), 7.40-7.32 (m, 3H), 6.99 (d, 1H, J = 4 Hz), 6.76 (t, 1H, J = 8 Hz); MS(ESI$^+$) *m/z* 465.18 $(M + H)^+$.

B) ***N*-(4-(3-Aminopyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide**

[00418] Prepared in a similar manner as Step C of Example 59. The crude product was purified by flash chromatography on silica gel (10% MeOH / EtOAc) to give the HCl salt of the title compound (58%) as an off-white solid. ^{1}H NMR (DMSO-d_6) δ 12.07 (s, 1H), 8.59 (dd, 1H, J = 7.6, 2.4 Hz), 8.14 (dd, 1H, J = 6.4, 2 Hz), 8.04 (s, 1H), 7.99 (dd, 1H, J = 13.2, 2.4 Hz), 7.66 (d, 1H, J = 5.2 Hz), 7.63 – 7.60 (m, 2H), 7.46 – 7.41 (m, 3H), 7.22 (t, 1H, J = 9.2 Hz), 6.74 (t, 1H, J = 7.2 Hz), 6.46 (d, 1H, J = 5.2 Hz), 5 26 (br s, 2H); MS(ESI$^+$): *m/z* 435.26 $(M + H)^+$.

Example 121

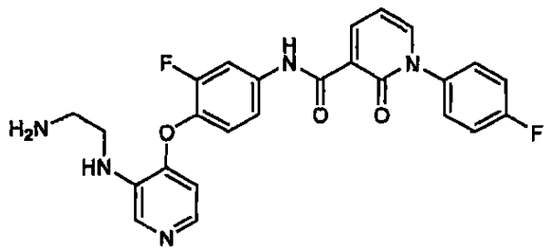


***N*-(3-Fluoro-4-(3-(pyrrolidin-3-ylmethylamino)pyridin-4-yloxy)phenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, hydrochloride salt**

[00419] To *N*-(4-(3-aminopyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (Example 120, 30 mg, 0.07 mmol) in DCE (1 mL) was added 3-formyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (CB Research and Development Inc., 28 mg, 0.14 mmol), acetic acid (5 uL, 0.084 mmol), then

sodium triacetoxyborohydride (23 mg, 0.104 mmol). After stirring at rt for 6 h, a second portion (23 mg) of sodium triacetoxyborohydride was added. After stirring at rt for 2 h, the reaction mixture was charged with 4N HCl in dioxane (5 mL) and stirred an additional 1 h at rt. The reaction was diluted with 10% MeOH / EtOAc (10 mL) and washed with saturated sodium bicarbonate solution (10 mL). The aqueous phase was back-extracted with 10 mL of 10% MeOH / EtOAc and the combined organic layers were dried over anhydrous Na_2SO_4 and then concentrated *in vacuo*. The resulting crude product was purified by prep HPLC. The appropriate fractions were concentrated to remove methanol and then made basic with saturated aqueous sodium bicarbonate solution. The aqueous solution was extracted with 10% MeOH / EtOAc (3 x 20 mL) and the pooled organic extracts were dried over anhydrous Na_2SO_4 and then concentrated *in vacuo*. The residue was lyophilized from acetonitrile (1 mL) / water (3 mL) / 1N aq HCl (0.2 mL) to give the HCl salt of the title compound (25 mg, 60%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 12.17 (s, 1H), 8.59 (dd, 1H, J = 7.6, 2 Hz), 8.30 (s, 1H), 8.16 (dd, 1H, J = 6.4, 2 Hz), 8.10 (dd, 1H, J = 12.8, 2 Hz), 8.00 (d, 1H, J = 6.4 Hz), 7.64-7.58 (m, 3H), 7.52 (t, 1H, J = 9.2 Hz), 7.46-7.42 (m, 2H), 7.00 (d, 1H, J = 6 Hz), 6.75 (t, 1H, J = 7.2 Hz), 3.72-3.64 (m, 3H), 3.37-3.26 (m, 1H), 3.17-3.10 (m, 1H), 2.97-2.92 (m, 1H), 2.74-2.66 (m, 1H), 2.10-2.03 (m, 1H), 1.75-1.68 (m, 1H); MS(ESI$^+$) *m/z* 518.29 $(M+H)^+$.

Example 122

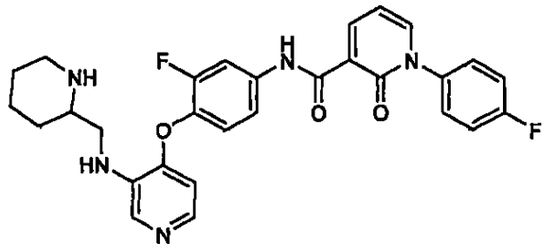


***N*-(4-(3-(2-Aminoethylamino)pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, hydrochloride salt**

[00420] Prepared in a similar manner as Example 121 to give the HCl salt of the title compound (52%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 12.10 (s, 1H), 8.52 (dd, 1H, J = 7.6, 2.4 Hz), 8.25 (s, 1H), 8.09 (dd, 1H, J = 6.8, 2.4 Hz), 8 06-8.02 (m,

1H), 7.96 (d, 1H, J = 6.4 Hz), 7.56-7.52 (m, 3H), 7.42-7.34 (m, 3H), 6.92 (d, 1H, J = 6 Hz), 6.68 (t, 1H, J = 6.8 Hz), 3.50-3.48 (m, 2H), 3.00-2.99 (m, 2H); MS(ESI$^+$) *m/z* 478.29 $(M + H)^+$.

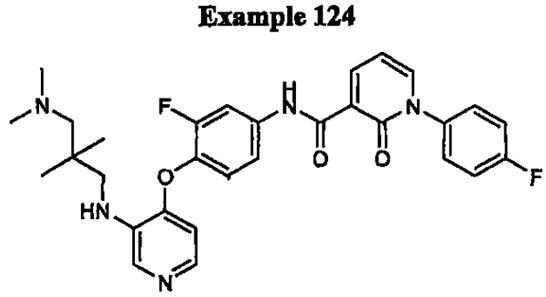
Example 123



***N*-(3-Fluoro-4-(3-(piperidin-2-ylmethylamino)pyridin-4-yloxy)phenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, hydrochloride salt**

[00421] Prepared in a similar manner as Example 121 to give the HCl salt of the title compound (71%) as a yellow solid. ^{1}H NMR (DMSO-d_6) δ 12.17 (s, 1H), 8.59 (dd, 1H, J = 7.2, 2 Hz), 8.51 (s, 1H), 8.16 (dd, 1H, J = 6.8, 2 Hz), 8.11 (dd, 1H, J = 13.2, 2.4 Hz), 8.02 (d, 1H, J = 6.4 Hz), 7.63-7.58 (m, 3H), 7.51 (t, 1H, J = 8.8 Hz), 7.46-7.41 (m, 2H), 7.01 (d, 1H, J = 6 Hz), 6.75 (t, 1H, J = 6.8 Hz), 3.70-3.63 (m, 1H), 3.52-3.45 (m, 1H), 3.30-3.27 (m, 2H), 2.86-2.84 (m, 1H), 1.95-1.93 (m, 1H), 1.80-1.62 (m, 3H), 1.58-1.44 (m, 2H); MS(ESI$^+$) *m/z* 532.31 $(M + H)^+$.

Example 124

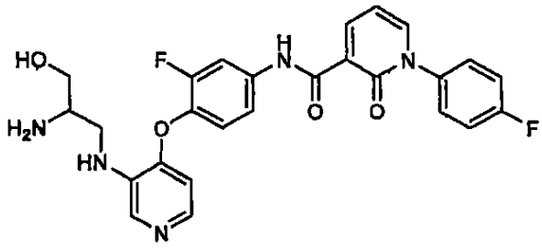


***N*-(4-(3-(3-(Dimethylamino)-2,2-dimethylpropylamino)pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, hydrochloride salt**

[00422] Prepared in a similar manner as Example 121 to give the HCl salt of the title compound (58%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 12.10 (s, 1H), 8.57 (s,

1H), 8.52 (dd, 1H, J = 7.6, 2 Hz), 8.09 (dd, 1H, J = 6.8, 2.4 Hz), 8.03 (dd, 1H, J = 13.2, 2.4 Hz), 7.90 (d, 1H, J = 6 4 Hz), 7.56-7.51 (m, 3H), 7.44 (t, 1H, J = 8.8 Hz), 7.39-7.35 (m, 2H), 6.92 (d, 1H, J = 6.4 Hz), 6.68 (t, 1H, J = 7.2 Hz), 3.33 (s, 2H), 3.10 (s, 2H), 2.77 (s, 3H), 2.76 (s, 3H), 1.07 (s, 6H); MS(ESI$^+$) m/z 548.34 $(M + H)^+$.

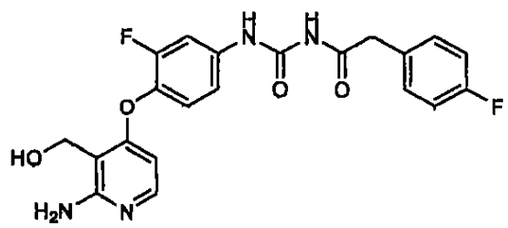
Example 125



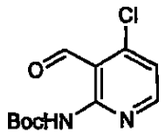
***N*-(4-(3-(2-Amino-3-hydroxypropylamino)pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, hydrochloride salt**

[00423] Prepared in a similar manner as Example 121 to give the HCl salt of the title compound (65%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 12.10 (s, 1H), 8.52 (dd, 1H, J = 7.2, 2 Hz), 8.30 (s, 1H), 8.09 (dd, 1H, J = 6.8, 2.4 Hz), 8 03 (dd, 1H, J = 12.8, 2 Hz), 7.96 (d, 1H, J = 6.4 Hz), 7.56-7.52 (m, 3H), 7.43-7.35 (m, 3H), 6.93 (d, 1H, J = 6 Hz), 6.68 (t, 1H, J = 7.2 Hz), 3.65-3.56 (m, 2H), 3.48-3.45 (m, 3H); MS(ESI$^+$) *m/z* 508.27 $(M + H)^+$.

Example 126

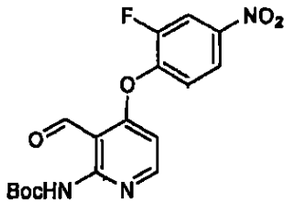


1-(4-(2-Amino-3-(hydroxymethyl)pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, hydrochloride salt



A) *tert*-Butyl 4-chloro-3-formylpyridin-2-ylcarbamate

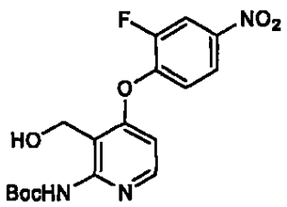
[00424] To (4-chloro-pyridin-2-yl)-carbamic acid *tert*-butyl ester (CB Research and Development Inc., 2.0 g, 8.75 mmol) in THF (18 mL) under nitrogen at –78 °C, was added *n*-BuLi (13.7 mL, 21.9 mmol, 1.6 M in hexanes) dropwise. After stirring at –78 °C for 45 min, a solution of DMF (1.93 mL) in THF (2 mL) was added dropwise. The reaction was stirred at –78 °C for 30 min and was then allowed to warm slowly to room temperature. The reaction was quenched with 1N aq HCl solution and then basified with saturated aqueous sodium bicarbonate solution (50 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (EtOAc) to afford the title compound (0.95 g, 42%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 10.44 (s, 1H), 10.13 (s, 1H), 8.47 (d, 1H, J = 5.2 Hz), 7.40 (d, 1H, J = 5.6 Hz), 1.48 (s, 9H).



B) *tert*-Butyl 4-(2-fluoro-4-nitrophenoxy)-3-formylpyridin-2-ylcarbamate

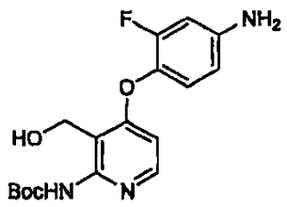
[00425] To 2-fluoro-nitrophenol (Aldrich, 700 mg, 4.44 mmol) in DMF (5 mL) was added sodium hydride (60%, 180 mg, 4.44 mmol). After stirring at rt for 5 min, a solution of *tert*-butyl 4-chloro-3-formylpyridin-2-ylcarbamate (0.95 g, 3.7 mmol) in 5 mL of DMF was added to the mixture. The reaction mixture was stirred at 60 °C for 20 h. After cooling to rt, the reaction was diluted with EtOAc (50 mL), washed with 10% aqueous lithium chloride solution (2 x 40 mL) followed by saturated aqueous sodium bicarbonate solution (40 mL), 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 (1.0 g, 72%) as a yellow oil. ^{1}H NMR

(CD_3OD) δ 10.59 (s, 1H), 8.37-8.25 (m, 2H), 7.67 (t, 1H, J = 7.6 Hz), 6.60 (d, 1H, J = 6 Hz), 1.59 (s, 9H).



C) ***tert*-Butyl 4-(2-fluoro-4-nitrophenoxy)-3-(hydroxymethyl)pyridin-2-ylcarbamate**

[00426] To *tert*-butyl 4-(2-fluoro-4-nitrophenoxy)-3-formylpyridin-2-ylcarbamate (75 mg, 0.2 mmol) in methanol (1 mL) at 0 °C was added sodium borohydride (7.6 mg, 0.20 mmol). After stirring at 0 °C for 30 min, the reaction was quenched with saturated aqueous ammonium chloride solution (1 mL). The reaction was diluted with EtOAc (5 mL) and the layers were separated. The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give the title compound (65 mg, 86%) as a white solid which was used without further purification. ^1H NMR (CD_3OD) δ 8.28 (dd, 1H, J = 10.4, 2.8 Hz), 8.22-8.18 (m, 2H), 7.45 (t, 1H, J = 8.4 Hz), 6.68 (d, 1H, J = 6 Hz), 4.81 (s, 2H), 1.57 (s, 9H); MS(ESI$^+$) *m/z* 380.27 $(M + H)^+$.



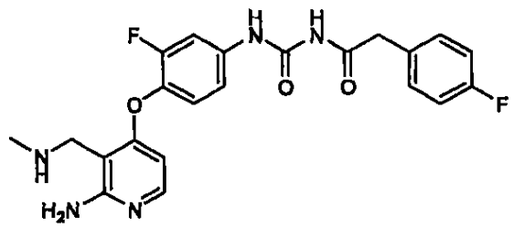
D) ***tert*-Butyl 4-(4-amino-2-fluorophenoxy)-3-(hydroxymethyl)pyridin-2-ylcarbamate**

[00427] Prepared in a similar manner as Step C of Example 59 to give the title compound as a white solid. ^1H NMR (CD_3OD) δ 8.14 (d, 1H, J = 6 Hz), 6.97 (t, 1H, J = 8.8 Hz), 6.62-6.54 (m, 2H), 6.46 (d, 1H, J = 6.4 Hz), 4.64 (s, 2H), 1.55 (s, 9H); MS(ESI$^+$) *m/z* 350.11 $(M + H)^+$.

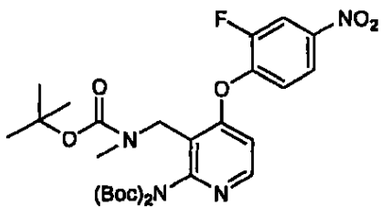
E) 1-(4-(2-Amino-3-(hydroxymethyl)pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, hydrochloride salt

[00428] Prepared in a similar manner as Step C of Example 59 to give the HCl salt of the title compound as a white solid. ^{1}H NMR (DMSO-d_6) δ 10.99 (s, 1H), 10.56 (s, 1H), 7.82 (d, 1H, J = 7.2 Hz), 7.74 (dd, 1H, J = 13.6, 2.8 Hz), 7.31-26 (m, 3H), 7.19-7.02 (m, 3H), 6.16 (d, 1H, J = 7.2 Hz), 4.57 (s, 2H), 3.69 (s, 2H); MS(ESI$^+$) m/z 429.16 $(M + H)^+$.

Example 127



1-(4-(2-Amino-3-((methylamino)methyl)pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, hydrochloride salt



A) *tert*-Butyl (2-bis-BOC-amino-4-(2-fluoro-4-nitrophenoxy)pyridin-3-yl)methyl(methyl)carbamate

[00429] To *tert*-butyl 4-(2-fluoro-4-nitrophenoxy)-3-formylpyridin-2-ylcarbamate (Compound B of Example 126, 75 mg, 0.2 mmol) in dichloroethane (1 mL) at 0 °C was added methylamine (240 μL, 0.24 mmol, 2M in THF), acetic acid (14 μL, 0.24 mmol), followed by sodium triacetoxyborohydride (400 mg, 1.89 mmol). After stirring at rt for 16 h, the reaction mixture was diluted with EtOAc (5 mL), washed with saturated aqueous sodium bicarbonate solution (5 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (20% MeOH / EtOAc) to give *tert*-butyl 4-(2-fluoro-4-

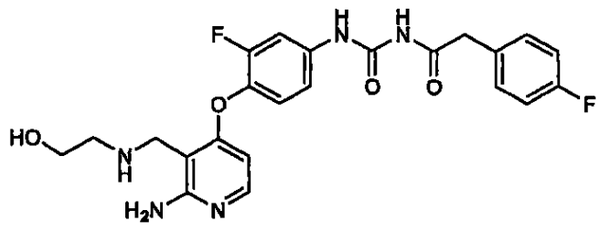
nitrophenoxy)-3-((methylamino)methyl)pyridin-2-ylcarbamate (37 mg, 47%) as a yellow oil.

[00430] To *tert*-butyl 4-(2-fluoro-4-nitrophenoxy)-3-((methylamino)methyl)pyridin-2-ylcarbamate (48 mg, 0.122 mmol) and DMAP (16 mg, 0.134 mmol) in dichloromethane (1 mL) was added di-*tert*-butyl dicarbonate (Aldrich, 32 mg, 0.15 mmol). After stirring at rt 30 min, a mixture of bis- and tris-BOC material (2:1) was observed. An additional portion of DMAP and di-*tert*-butyl dicarbonate was added. After stirring at rt for 30 min, the reaction was purified directly by flash column chromatography on silica gel (EtOAc) to give the title compound (44 mg, 61%) as a yellow oil. ^{1}H NMR (CD_3OD) δ 8.50 (d, 1H, J = 5.2 Hz), 8.15-7.97 (m, 2H), 7.43 (d, 1H, J = 5.6 Hz), 7.07 (t, 1H, J = 8.4 Hz), 4.64 (s, 2H), 2.83 (s, 3H), 1.44 (s, 27H); MS(ESI$^+$) *m/z* 593.34 $(M + H)^+$.

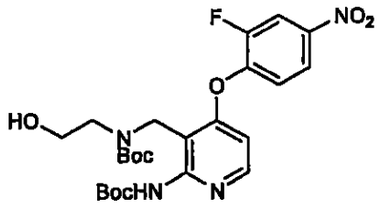
B) 1-(4-(2-Amino-3-((methylamino)methyl)pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, hydrochloride salt

[00431] Prepared in a similar manner as Step C of Example 59 to give the HCl salt of the title compound (60%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 10.88 (s, 1H), 10.35 (s, 1H), 7.45-7.42 (m, 1H), 7.30 (m, 3H), 7.11-7.07 (m, 4H), 6.52 (d, 1H, J = 7.2 Hz), 4.02 (s, 2H), 3.66 (s, 2H), 2.54 (s, 3H), MS(ESI$^+$) *m/z* 442.30 $(M + H)^+$.

Example 128



1-(4-(2-Amino-3-((2-hydroxyethylamino)methyl)pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, trifluoroacetic acid salt



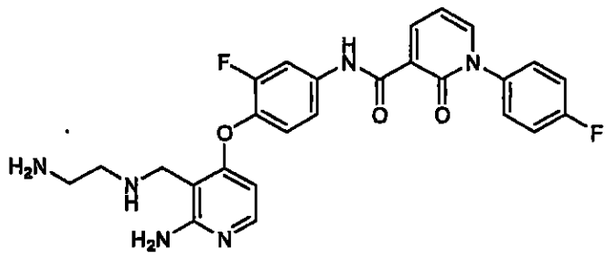
A) *tert*-Butyl (2-BOC-amino-4-(2-fluoro-4-nitrophenoxy)pyridin-3-yl)methyl(2-hydroxyethyl)carbamate

[00432] Prepared in a similar manner as Step A of Example 127 to give the title compound (14%) as a yellow oil. ^{1}H NMR (CD_3OD) δ 8.30 (dd, 1H, J = 10.4, 2.8 Hz), 8.23-8.20 (m, 2H), 7.52 (t, 1H, J = 8.4 Hz), 6.64 (d, 1H, J = 7.2 Hz), 4.71 (s, 2H), 3.65 (t, 2H, J = 6 Hz), 3.40 (m, 2H), 1.57 (s, 18H); MS(ESI$^+$) *m/z* 523.32 (M + H)$^+$.

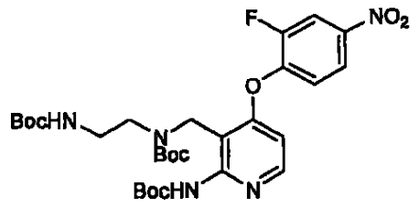
B) 1-(4-(2-Amino-3-((2-hydroxyethylamino)methyl)pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, trifluoroacetic acid salt

[00433] Prepared in a similar manner as Step C of Example 59 to give the TFA salt of the title compound (45%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.12 (s, 1H), 10.69 (s, 1H), 8.01 (d, 1H, J = 6.8 Hz), 7.87 (dd, 1H, J = 12.8, 2.4 Hz), 7.53-7.40 (m, 4H), 7.26-7.20 (m, 2H), 6.68 (d, 1H, J = 7.2 Hz), 4.34 (s, 2H), 3.81 (s, 2H), 3.75 (t, 2H, J = 7.2 Hz), 3.18 (m, 2H); MS(ESI$^+$) *m/z* 472.24 (M + H)$^+$.

Example 129



***N*-(4-(2-Amino-3-((2-aminoethylamino)methyl)pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, trifluoroacetic acid salt**



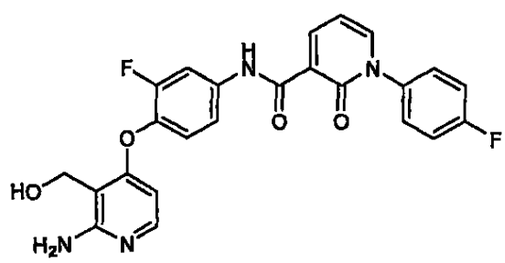
A) *tert*-Butyl (2-BOC-amino-4-(2-fluoro-4-nitrophenoxy)pyridin-3-yl)methyl(2-BOC-aminoethyl)carbamate

[00434] Prepared in a similar manner as Step A of Example 127 to give the title compound (19%) as a yellow oil. ^{1}H NMR (CD_3OD) δ 8.30 (dd, 1H, J = 10, 2.4 Hz), 8.23-8.20 (m, 2H), 7.52 (t, 1H, J = 8.4 Hz), 6.61 (d, 1H, J = 7.2 Hz), 4.65 (s, 2H), 3.39 (m, 2H), 3.25 (m, 2H), 1.61 (s, 27H); MS(ESI$^+$) *m/z* 622.47 $(M + H)^+$.

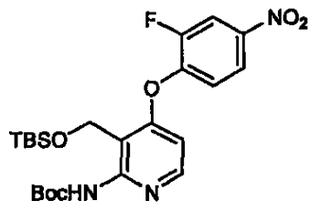
B) *N*-(4-(2-Amino-3-((2-aminoethylamino)methyl)pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, trifluoroacetic acid salt

[00435] The nitro group was reduced in a similar manner as Step C of Example 59 and then the amide was formed in a manner similar to Example 62 to give the TFA salt of the title compound (28%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 12.09 (s, 1H), 8.52 (dd, 1H, J = 7.2, 2 Hz), 8.09 (dd, 1H, J = 6.4, 2 Hz), 7.99 (dd, 1H, J = 12.8, 2.4 Hz), 7.89 (d, 1H, J = 6.4 Hz), 7.56-7.52 (m, 2H), 7.49-7.47 (m, 1H), 7.39-7.33 (m, 3H), 6.68 (t, 1H, J = 7.2 Hz), 6.07 (d, 1H, J = 7.2 Hz), 4 25 (s, 2H), 3.20 (m, 2H), 3.08 (m, 2H); MS(ESI$^+$) *m/z* 507.23 $(M + H)^+$.

Example 130

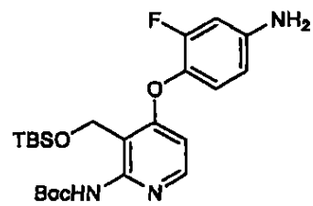


***N*-(4-(2-Amino-3-(hydroxymethyl)pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, trifluoroacetic acid salt**



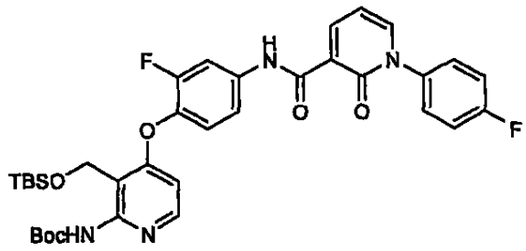
A) *tert*-Butyl 3-((tert-butyldimethylsilyloxy)methyl)-4-(2-fluoro-4-nitrophenoxy)pyridin-2-ylcarbamate

[00436] To *tert*-butyl 4-(2-fluoro-4-nitrophenoxy)-3-(hydroxymethyl)pyridin-2-ylcarbamate (Compound C of Example 126, 100 mg, 0.26 mmol) in dichloromethane (3 mL) was added imidazole (21 mg, 0.31 mmol) followed by *tert*-butyldimethylsilyl chloride (40 mg, 0.26 mmol). After stirring at rt for 1 h, a second equivalent of *tert*-butyldimethylsilyl chloride (40 mg, 0.26 mmol) was added. The reaction was stirred at rt for 3 h and was then diluted with dichloromethane (10 mL), washed with water (10 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (50% EtOAc / hexanes) to give the title compound (102 mg, 79%) as a white solid. ^{1}H NMR (CD_3OD) δ 8.16 (dd, 1H, J = 10.4, 2 8 Hz), 8.09-8.05 (m, 2H), 7.29 (t, 1H, J = 8.4 Hz), 6.53 (d, 1H, J = 5.6 Hz), 4.84 (s, 2H), 1.43 (s, 9H), 0.84 (s, 9H), 0.00 (s, 6H); MS(ESI$^+$) *m/z* 494.29 $(M+H)^+$.



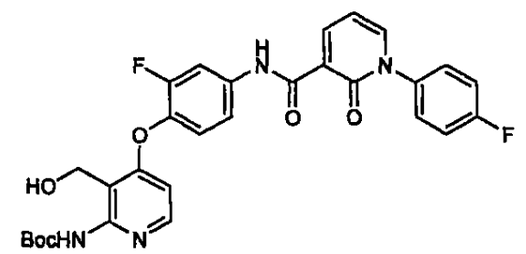
B) *tert*-Butyl 4-(4-amino-2-fluorophenoxy)-3-((tert-butyldimethylsilyloxy)-methyl)pyridin-2-ylcarbamate

[00437] Prepared in a similar manner as Step C of Example 59 give the title compound (95 mg, 98%) as a yellow oil. ^{1}H NMR (CD_3OD) δ 7.90 (d, 1H, J = 6 Hz), 6.76 (t, 1H, J = 8.8 Hz), 6.43 (dd, 1H, J = 12.8, 2.8 Hz), 6.39-6.37 (m, 1H), 6.21 (d, 1H, J = 5.6 Hz), 4.85 (s, 2H), 1.39 (s, 9H), 0.81 (s, 9H), 0.01 (s, 6H); MS(ESI$^+$) *m/z* 464.34 $(M+H)^+$.



C) ***tert*-Butyl 3-((tert-butyldimethylsilyloxy)methyl)-4-(2-fluoro-4-(1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamido)phenoxy)pyridin-2-ylcarbamate**

[00438] Prepared in a manner similar to that of Example 62 to give the title compound (86%) as a colorless oil. ^{1}H NMR (CD_3OD) δ 8.51 (dd, 1H, J = 7.6, 2.4 Hz), 7.93 (d, 1H, J = 6 Hz), 7.84-7.80 (m, 2H), 7.40-7.37 (m, 2H), 7.21-7.15 (m, 3H), 7.06 (t, 1H, J = 8.8 Hz), 6.57 (t, 1H, J = 6.8 Hz), 6.26 (d, 1H, J = 5.6 Hz), 4.86 (s, 2H), 1.40 (s, 9H), 0.82 (s, 9H), 0.00 (s, 6H); MS(ESI$^+$) *m/z* 679.34 $(M + H)^+$.



D) ***tert*-Butyl 4-(2-fluoro-4-(1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamido)phenoxy)-3-(hydroxymethyl)pyridin-2-ylcarbamate**

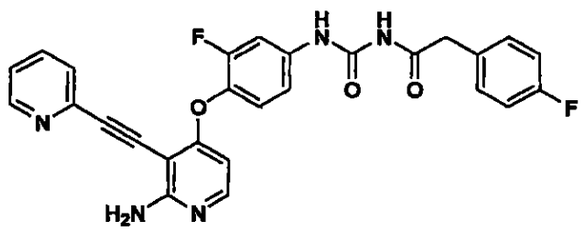
[00439] To *tert*-Butyl 3-((tert-butyldimethylsilyloxy)methyl)-4-(2-fluoro-4-(1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamido)phenoxy)pyridin-2-ylcarbamate (119 mg, 0.176 mmol) in THF (2 mL) at rt was added tetrabutylammonium flouride (260 μL, 0.264 mmol, 1 M in THF). After stirring at rt for 30 min, the reaction was diluted with ethyl acetate (20 mL), washed with water followed by brine (10 mL each), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (5% MeOH / EtOAc) to give the title compound (66 mg, 66%) as a yellow oil. ^{1}H NMR (CD_3OD) δ 8.62 (dd, 1H, J = 7.2, 2 Hz), 8.04 (d, 1H, J = 6 Hz), 7.94-7.90 (m, 2H), 7.50-7.46 (m, 2H), 7.33-7.25 (m, 3H), 7.20 (t, 1H, J = 8.8 Hz), 6.67 (t, 1H, J =

6.8 Hz), 6.40 (d, 1H, J = 5.2 Hz), 4.78 (s, 2H), 1.49 (s, 9H); MS(ESI$^+$) m/z 565.17 (M + H)$^+$.

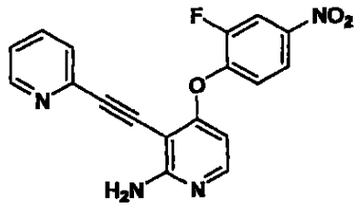
E) *N*-(4-(2-Amino-3-(hydroxymethyl)pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, trifluoroacetic acid salt

[00440] To *tert*-butyl 4-(2-fluoro-4-(1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamido)phenoxy)-3-(hydroxymethyl)pyridin-2-ylcarbamate (33 mg 0.058 mmol) in THF (2 mL) at rt was added 4N HCl in dioxane (10 mL). After stirring at rt for 8 h, the reaction was concentrated *in vacuo*. The resulting crude product was purified by prep HPLC. The appropriate fractions were concentrated and toluene was added (2 x 3 mL) and the resulting mixture was concentrated again. The residue was lyophilized from acetonitrile (1 mL) / water (3 mL) to give the TFA salt of the title compound (14 mg, 42%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 12.08 (s, 1H), 8.52 (dd, 1H, J = 7.2, 2 Hz), 8.09 (dd, 1H, J = 6.8, 2 Hz), 7.99 (dd, 1H, J = 12.8, 2.4 Hz), 7.81 (d, 1H, J = 7.2 Hz), 7.56-7.52 (m, 2H), 7.48-7.46 (m, 1H), 7.39-7.34 (m, 2H), 7.30 (t, 1H, J = 9.2 Hz), 6.67 (t, 1H, J = 7.2 Hz), 6.21 (d, 1H, J = 7.2 Hz), 4.58 (s, 2H); MS(ESI$^+$) m/z 465.17 (M + H)$^+$.

Example 131

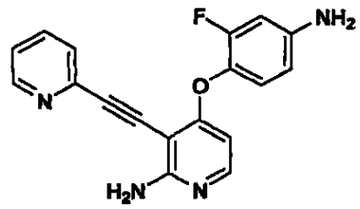


1-(4-(2-Amino-3-(2-(pyridin-2-yl)ethynyl)pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, dihydrochloride salt



A) 4-(2-Fluoro-4-nitrophenoxy)-3-(2-(pyridin-2-yl)ethynyl)pyridin-2-amine

[00441] A solution of 4-(2-fluoro-4-nitrophenoxy)-3-iodopyridin-2-amine (Compound C of Example 34, 100 mg, 0.27 mmol), 2-ethynylpyridine (Aldrich, 56 µL, 0.54 mmol), Et_3N (2 mL), and THF (2 mL) was degassed by vacuum / argon purge and then treated with CuI (6 mg, 0.032 mmol) and $(Ph_3P)_4Pd$ (20 mg, 0.017 mmol). The reaction mixture was heated at 60 °C for 45 min, cooled to RT and diluted with EtOAc. The mixture was washed with saturated aqueous $NaHCO_3$ solution, brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography on SiO_2 using 0-1.5 % MeOH / CH_2Cl_2 to give the title compound (55 mg, 57%) as an olive green solid. ^1H NMR (DMSO-d_6) δ 8.53 (d, 1H, J = 5.1 Hz), 8 42-8.37 (m, 1H), 8.19-8.12 (m, 1H), 7.96 (d, 1H, J = 5.6 Hz), 7.85-7.78 (m, 1H), 7.71 (d, 1H, J = 7.6 Hz), 7.52 (t, 1H, J = 8.6 Hz), 7.36 (ddd, 1H, J = 7.6, 5.1, 1.0 Hz), 6.71 (s, 2H), 6.21 (d, 1H, J = 5.6 Hz); MS(ESI$^+$): *m/z* 351.25 $(M+H)^+$.



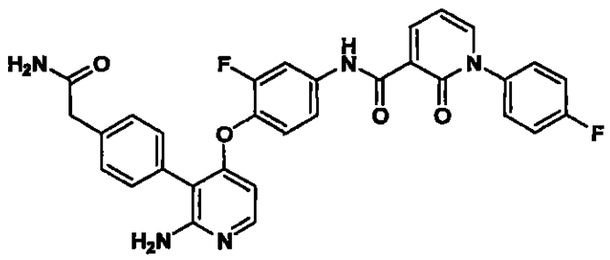
B) 4-(4-Amino-2-fluorophenoxy)-3-(2-(pyridin-2-yl)ethynyl)pyridin-2-amine

[00442] The title compound was prepared from the reduction of 4-(2-fluoro-4-nitrophenoxy)-3-(2-(pyridin-2-yl)ethynyl)pyridin-2-amine (35 mg, 0.10 mmol) using zinc dust (65 mg, 1.0 mmol) and NH_4Cl (53 mg, 1.0 mmol) in the same manner as Step C of Example 11. This gave the title compound (25 mg, 78%) as brown oil. MS(ESI$^+$): *m/z* 321.25 $(M+H)^+$.

C) 1-(4-(2-Amino-3-(2-(pyridin-2-yl)ethynyl)pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, dihydrochloride salt

[00443] The title compound was prepared from 4-(4-amino-2-fluorophenoxy)-3-(2-(pyridin-2-yl)ethynyl)pyridin-2-amine (25 mg, 0.078 mmol) and a 0.3 M solution of 2-(4-fluorophenyl)acetyl isocyanate in toluene (Compound D of Example 11, 0.26 mL, 0.078 mmol) in the same manner as Step E of Example 11. The crude product was prepared by preparative HPLC (Column B). The TFA salt was converted to the hydrochloride in the same manner as in Step E of Example 36 to give the title compound (18 mg, 40 %) as a brown solid. ^{1}H NMR(DMSO-d_6) δ 11.06 (s, 1H), 10.63 (s, 1H), 8.62 (d, 1H, J = 4.6 Hz), 8.23 (s, 1H), 7.99 (d, 1H, J = 7.1 Hz), 7.94-7.84 (m, 3H), 7.87-7.76 (m, 1H), 7.51-7.42 (m, 3H), 7.39-7.32 (m, 2H), 7.21-7.13 (m, 2H), 6.30 (d, 1H, J = 7.1 Hz), 3.74 (s, 2H) MS(ESI$^+$): m/z 498.11 $(M+H)^+$.

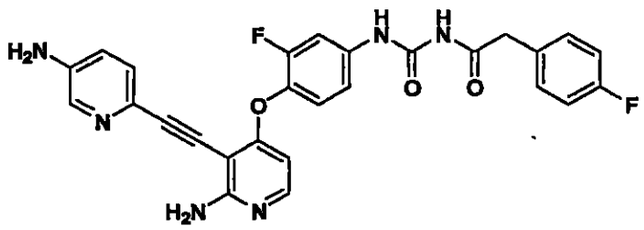
Example 132



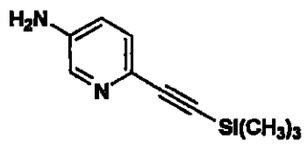
***N*-(4-(2-Amino-3-(4-(2-amino-2-oxoethyl)phenyl)pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, hydrochloride salt**

[00444] The title compound was prepared from 2-(4-(2-amino-4-(4-amino-2-fluorophenoxy)pyridin-3-yl)phenyl)acetamide (Compound C of Example 78, 18 mg, 0.05 mmol) and 1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (Compound B of Example 101, 11 mg, 0.05 mmol) in the same manner as Example 62. The crude product was prepared by preparative HPLC (Column B) followed by conversion of the TFA salt to the hydrochloride salt (15 mg, 50 %). ^{1}H NMR (DMSO-d_6) δ 12.11 (s, 1H), 8.58-8.54 (m, 1H), 8.13 (dd, 1H, J = 6.6, 2.2 Hz), 8.00 (dd, 1H, J = 12.6, 2.2 Hz), 7.96 (d, 1H, J = 7.7 Hz), 7.59 (dd, 2H, J = 8.8, 4.9 Hz), 7.47-7.41 (m, 6H), 7.40-7.35 (m, 3H), 6.94 (s, 1H), 6.72 (t, 1H, J = 7.1 Hz), 6.38 (d, 1H, J = 7.1 Hz), 3.44 (s, 2H); MS(ESI$^+$): m/z 568.23 $(M+H)^+$.

Example 133

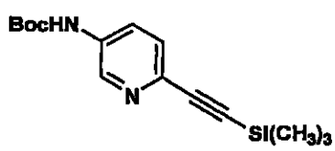


1-(4-(2-Amino-3-(2-(5-aminopyridin-2-yl)ethynyl)pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, dihydrochloride salt



A) 6-(2-(Trimethylsilyl)ethynyl)pyridin-3-amine

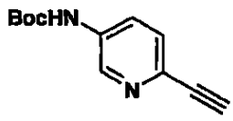
[00445] A mixture of 3-amino-6-bromopyridine (Alfa Aesar, 1.0 g, 5.8 mmol), ethynyl trimethylsilane (1.7 mL, 17.3 mmol), CH_3CN (3 mL), DMF (2 mL) and Et_3N (2 mL) was treated with CuI (60 mg, 0.32 mmol) and $(Ph_3P)_4Pd$ (114 mg, 0.10 mmol) and the mixture stirred at 45 °C for 1.5 h. More ethynyltrimethylsilane (1.7 mL, 17.3 mmol) was added to the reaction and the mixture was stirred for 2 h. The mixture was concentrated *in vacuo* and the residue partitioned between EtOAc and saturated aqueous $NaHCO_3$ solution. The EtOAc phase was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography on SiO_2 using 0-6 % EtOAc / hexanes to give the title compound (0.75 g, 68 %) as a brown solid. ^1H NMR (DMSO-d_6) δ 7.85 (s, 1H), 7.15 (d, 1H, J = 8.1 Hz), 6.81 (d, 1H, J = 8.1 Hz), 5.76 (s, 2H), 0.19 (s, 9H); MS(ESI$^+$): *m/z* 191.20 $(M+H)^+$.



B) *tert*-Butyl 6-(2-(trimethylsilyl)ethynyl)pyridin-3-ylcarbamate

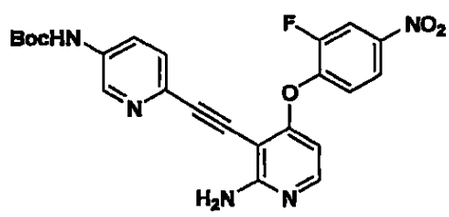
[00446] A solution 6-(2-(trimethylsilyl)ethynyl)pyridin-3-amine (0.5 g, 2.6 mmol) in THF was cooled to –50 °C and treated dropwise with 1.0 M NaHMDS in THF (5.3

mL, 5.5 mmol). The mixture was warmed to –20 °C, treated with BOC anhydride in one portion and allowed to warm to RT over 25 min. The mixture was partitioned between EtOAc and saturated aqueous $NaHCO_3$ solution and the EtOAc phase was separated and washed with brine. The EtOAc solution was dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography on SiO_2 using 0-25% EtOAc / hexanes to give the product (0.5 g, 67%) as a white solid. ^1H NMR (DMSO-d_6) δ 9.80 (s, 1H), 8.58 (d, 1H, J = 2.0 Hz), 7.86 (dd, J = 8.6, 2.5 Hz, 1 H), 7.44 (d, 1H, J = 8.6 Hz), 1.47 (s, 9H), 0.22 (s, 9H); MS(ESI$^+$): *m/z* 291.34 $(M+H)^+$.



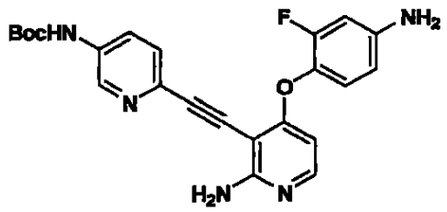
C) *tert*-Butyl 6-ethynylpyridin-3-ylcarbamate

[00447] A solution of *tert*-butyl 6-(2-(trimethylsilyl)ethynyl)pyridin-3-ylcarbamate (62 mg, 0.21 mmol) in THF (5 mL) was cooled to –15 °C and treated with 1.0 M tetrabutylammonium fluoride (Aldrich, 0.25 mL, 0.25 mmol) and stirred for 40 min. The mixture was concentrated *in vacuo* and partitioned between EtOAc and saturated aqueous $NaHCO_3$ solution. The EtOAc phase was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound (45 mg, 100%) as an off-white solid. ^1H NMR (DMSO-d_6) δ 9.78 (s, 1H), 8.58 (d, 1H, J = 2.5 Hz), 7.92-7.84 (m, 1H), 7.46 (d, 1H, J = 8.6 Hz), 4.17 (s, 1H), 1.47 (s, 9H); MS(ESI$^+$): *m/z* 219.20 $(M+H)^+$.



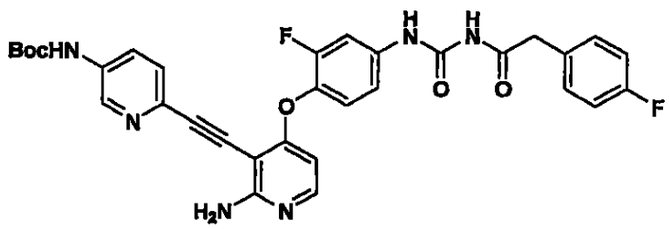
D) *tert*-Butyl 6-(2-(2-amino-4-(2-fluoro-4-nitrophenoxy)pyridin-3-yl)ethynyl)pyridin-3-ylcarbamate

[00448] The title compound was prepared from *tert*-butyl 6-ethynylpyridin-3-ylcarbamate and 4-(2-fluoro-4-nitrophenoxy)-3-iodopyridin-2-amine (Compound C of Example 34) in the same manner as Step A of Example 46 in 44% yield. ^{1}H NMR (DMSO-d_6) δ 9.77 (s, 1H), 8.56 (s, 1H), 8.40-8.36 (m, 1H), 8.14 (d, 1H, J = 8.8 Hz), 7.94 (d, 1H, J = 5.5 Hz), 7.89 (d, 1H, J = 8.2 Hz), 7.59 (d, 1H, J = 8.8 Hz), 7.53-7.47 (m, 1H), 6.63 (br s, 2H), 6.21 (d, 1H, J = 6.0 Hz), 1.47 (s, 9H); MS(ESI$^+$): *m/z* 466.22 $(M+H)^+$.



E) *tert*-Butyl 6-(2-(2-amino-4-(4-amino-2-fluorophenoxy)pyridin-3-yl)ethynyl)pyridin-3-ylcarbamate

[00449] The title compound was prepared from *tert*-butyl 6-(2-(2-amino-4-(2-fluoro-4-nitrophenoxy)pyridin-3-yl)ethynyl)pyridin-3-ylcarbamate in the same manner as Step C of Example 11 in quantitative yield. MS(ESI$^+$): *m/z* 436.29 $(M+H)^+$.



F) *tert*-Butyl 6-(2-(2-amino-4-(2-fluoro-4-(3-(2-(4-fluorophenyl)acetyl)ureido)phenoxy)pyridin-3-yl)ethynyl)pyridin-3-ylcarbamate

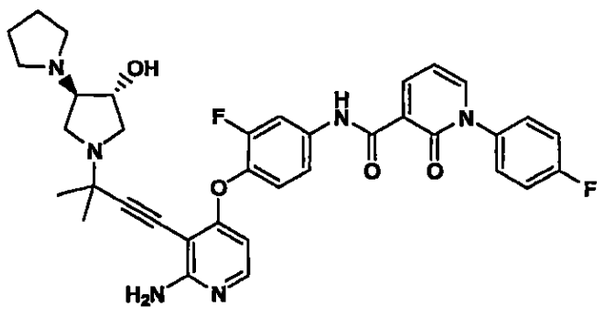
[00450] The title compound was prepared from *tert*-butyl 6-(2-(2-amino-4-(2-fluoro-4-nitrophenoxy)pyridin-3-yl)ethynyl)pyridin-3-ylcarbamate in the same manner as Step E of Example 11 in 80% yield. ^{1}H NMR (DMSO-d_6) δ 11.02 (s, 1H), 10.56 (s, 1H), 9.78 (s, 1H), 8.59 (d, 1H, J = 2.5 Hz), 7.91 (dd, 1H, J = 8.6, 2.5 Hz), 7.81 (d, 1H, J = 5.6 Hz), 7.75 (dd, 1H, J = 12.7, 2.5 Hz), 7.68 (d, 1H, J = 8.6 Hz,), 7.44-7.27

(m, 5H), 7.19-7.13 (m, 2H), 6.47 (s, 2H), 5.86-5.81 (m, 1H), 1.48 (s, 9H); MS(ESI$^+$): *m/z* 615.34 $(M+H)^+$.

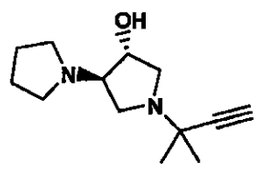
G) 1-(4-(2-Amino-3-(2-(5-aminopyridin-2-yl)ethynyl)pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, dihydrochloride salt

[00451] A solution of *tert*-butyl 6-(2-(2-amino-4-(2-fluoro-4-(3-(2-(4-fluorophenyl)acetyl)ureido)phenoxy)pyridin-3-yl)ethynyl)pyridin-3-ylcarbamate (23 mg, 0.037 mmol) in CH_2Cl_2 (2 mL) and treated with TFA (0.5 mL) and stirred at RT for 1 h. The mixture was concentrated *in vacuo* and the crude product purified by preparative HPLC (Column B) and converted to its hydrochloride salt (11 mg, 52%) in the same manner as Step E of Example 36. ^{1}H NMR (DMSO-d_6) δ 11.05 (s, 1H), 10.62 (s, 1H), 8.05 (s, 1H), 7.97 (d, 1H, J = 2.7 Hz), 7.94 (d, 1H, J = 7.1 Hz), 7.82 (d, 1H, J = 12.1 Hz), 7.66 (d, 1H, J = 8.8 Hz), 7.45-7.45 (m, 2H), 7.35 (dd, 2H, J = 8.2, 5.5 Hz), 7.20 (d, 1H, J = 6.6 Hz), 7.16 (t, 2H, J = 8.8 Hz), 6.24 (d, 1H, J = 6.6 Hz), 3.74 (s, 2H); MS(ESI$^+$): *m/z* 515.19 $(M+H)^+$.

Example 134

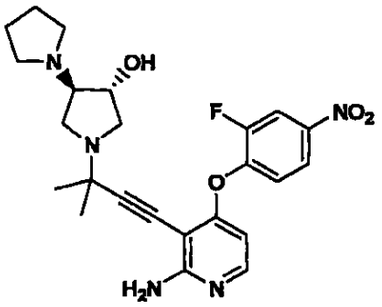


***N*-(4-(2-Amino-3-(3-((3*R*,4*R*)-3-hydroxy-4-(pyrrolidin-1-yl)pyrrolidin-1-yl)-3-methylbut-1-ynyl)pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, trihydrochloride salt**



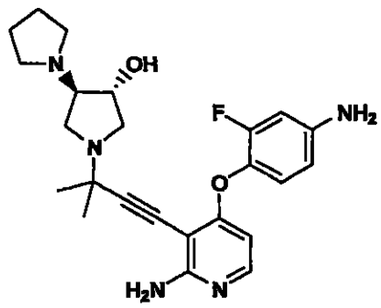
A) (3*R*,4*R*)-1-(2-Methylbut-3-yn-2-yl)-4-(pyrrolidin-1-yl)pyrrolidin-3-ol

[00452] A mixture of (3*R*,4*R*)-4-(pyrrolidin-1-yl)pyrrolidin-3-ol (Lexicon Pharma, 1.56 g, 10.0 mmol) and 3-chloro-3-methyl-1-butyne (GFS Chmeical, Inc., 1.36 g, 13.2 mmol), THF (15 mL) and Et_3N (13.3 mmol) was treated with CuI (77 mg, 0.78 mmol). An exothermic reaction ensued with concomitant formation of a precipitate. After stirring at RT for 15 h, the mixture was concentrated *in vacuo* and partitioned between EtOAc and saturated aqueous $NaHCO_3$ solution. The aqueous phase was extracted twice with EtOAc and the combined EtOAc phases were dried ($MgSO_4$) and concentrated to give a light brown solid (1.0 g, 45%). ^1H NMR ($CDCl_3$) δ 4.20 (br s, 1H), 3.13-3.04 (m, 1H), 2.95 (dd, 1H, *J* = 10.1, 6.6 Hz), 2.77 (dd, 1H, *J* = 10.1, 2.6 Hz), 2 64 (m, 3H), 2.61 (m, 2H), 2.55-2.46 (m, 1H), 2.26 (s, 1H), 1.85-1.74 (m, 4H), 1.38 (s, 3H), 1.36 (s, 3H); MS(ESI$^+$): *m/z* 223.29 $(M+H)^+$.



B) (3*R*,4*R*)-1-(4-(2-Amino-4-(2-fluoro-4-nitrophenoxy)pyridin-3-yl)-2-methylbut-3-yn-2-yl)-4-(pyrrolidin-1-yl)pyrrolidin-3-ol

[00453] The title compound was prepared from(3*R*,4*R*)-1-(2-methylbut-3-yn-2-yl)-4-(pyrrolidin-1-yl)pyrrolidin-3-ol and 4-(2-fluoro-4-nitrophenoxy)-3-iodopyridin-2-amine (Compound C of Example 34) in the same manner as Step D of Example 35 in 57% yield. ^1H NMR ($CDCl_3$) δ 8.10 (dd, 1H, *J* = 10.2, 2.5 Hz), 8.03 (d, 1H, *J* = 9.2 Hz), 7.99 (d, 1H, *J* = 5.6 Hz), 7.13-7.06 (m, 1H), 6.26 (d, 1H, *J* = 6.1 Hz), 5.18 (br s, 2H), 4.21 (m, 1H), 3.10-2.99 (m, 1H), 2.96 (s, 1H), 2.70 (dd, 2H, *J* = 9.7, 3.1 Hz), 2.66-1.15 (m, 2H), 1.87-1.76 (m, 5H), 133-1.32 (m, 2H), 1.32 (m, 3H); 1.34 (m, 3H); MS(ESI$^+$): *m/z* 470.20 $(M+H)^+$.



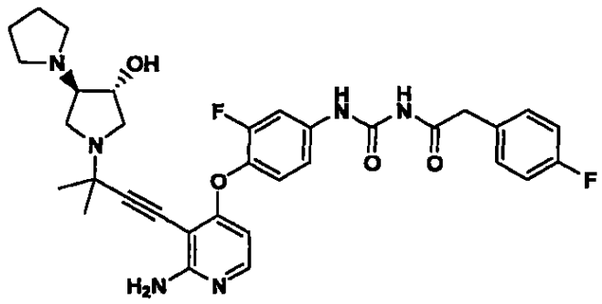
C) (3*R*,4*R*)-1-(4-(2-Amino-4-(4-amino-2-fluorophenoxy)pyridin-3-yl)-2-methylbut-3-yn-2-yl)-4-(pyrrolidin-1-yl)pyrrolidin-3-ol

[00454] The title compound was prepared from (3*R*,4*R*)-1-(4-(2-amino-4-(2-fluoro-4-nitrophenoxy)pyridin-3-yl)-2-methylbut-3-yn-2-yl)-4-(pyrrolidin-1-yl)pyrrolidin-3-ol in the same manner as Step C of Example 11 in 95% yield. MS(ESI$^+$): *m/z* 440.37 $(M+H)^+$.

D) *N*-(4-(2-Amino-3-(3-((3*R*,4*R*)-3-hydroxy-4-(pyrrolidin-1-yl)pyrrolidin-1-yl)-3-methylbut-1-ynyl)pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, trihydrochloride salt

[00455] The title compound was prepared from (3*R*,4*R*)-1-(4-(2-amino-4-(4-amino-2-fluorophenoxy)pyridin-3-yl)-2-methylbut-3-yn-2-yl)-4-(pyrrolidin-1-yl)pyrrolidin-3-ol and 1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (Compound B of Example 101) in the same manner as Example 62 in 50% yield. ^{1}H NMR (DMSO-d_6) δ 12.14 (s, 1H), 8.62-8.54 (m, 1H), 8.14 (dd, 3H, J = 6.6, 2.0 Hz), 8.05 (d, 1H, J = 13.2 Hz), 7.99 (d, 1H, J = 7.1 Hz), 7.62-7.51 (m, 5H), 7.42 (t, 2H, J = 8.6 Hz), 6.78-6.70 (m, 1H), 6.32 (d, 1H, J = 7.1 Hz), 4.65 (br s, 1H), 3.94-3.84 (m, 1H), 3.71 (d, 2H, J = 16.8 Hz), 3.60 (m, 2 H), 3.52 (m, 1H), 3.22-3.08 (m, 2H), 2.00-1.91 (m, 2H), 1.88-1.78 (m, 2H), 1.70 (s, 6H); MS(ESI$^+$): *m/z* 655.40 $(M+H)^+$.

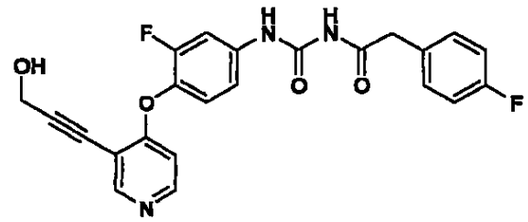
Example 135



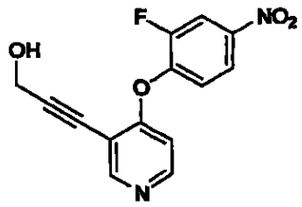
1-(4-(2-Amino-3-(3-((3*R*,4*R*)-3-hydroxy-4-(pyrrolidin-1-yl)pyrrolidin-1-yl)-3-methylbut-1-ynyl)pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, trihydrochloride salt

[00456] The title compound was prepared form (3*R*,4*R*)-1-(4-(2-amino-4-(4-amino-2-fluorophenoxy)pyridin-3-yl)-2-methylbut-3-yn-2-yl)-4-(pyrrolidin-1-yl)pyrrolidin-3-ol in 40% yield in the same manner as Step E of Example 11. ^{1}H NMR (DMSO-d_6) δ 11.06 (s, 1H), 10.62 (s, 1H), 7.97 (d, 2H, J = 6.6 Hz), 7.80 (d, 1H, J = 11 7 Hz), 7.51-7.40 (m, 2H), 7.38-7.32 (m, 2H), 7.16 (t, 2H, J = 8.6 Hz), 6.25 (d, 1H, J = 6.6 Hz), 4.63-4.53 (m, 1H), 3.79-3.68 (m, 1H), 3.74 (s, 2H), 3.68-3.56 (m, 2 H), 3.51-3.43 (m, 2H), 3.08-2.99 (m, 4H), 1.98-1.92 (m, 2H), 1.89-1.77 (m, 2H), 1.64 (s, 6H); MS(ESI$^+$): *m/z* 619.41 $(M+H)^+$.

Example 136

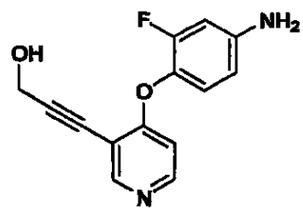


1-(3-Fluoro-4-(3-(3-hydroxyprop-1-ynyl)pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea, hydrochloride salt



A) 3-(4-(2-Fluoro-4-nitrophenoxy)pyridin-3-yl)prop-2-yn-1-ol

[00457] The title compound was prepared from 4-(2-fluoro-4-nitrophenoxy)-3-iodopyridine (Compound A of Example 33) and propargyl alcohol (Aldrich) in 77% yield in the same manner as Step A of Example 36. ^{1}H NMR (DMSO-d_6) δ 8.69 (s, 1H), 8.49 (d, 1H, J = 5.6 Hz), 8.43 (dd, 1H, J = 10.7, 2.5 Hz), 8.17 (d, 1H, J = 9.2 Hz), 7.57 (t, 1H, J = 8.6 Hz), 7.04 (d, 1H, J = 5.6 Hz), 5.40 (t, 1H, J = 6.1 Hz), 4.28 (d, 2H, J = 6.1 Hz); MS(ESI$^+$): *m/z* 289.15 $(M+H)^+$.



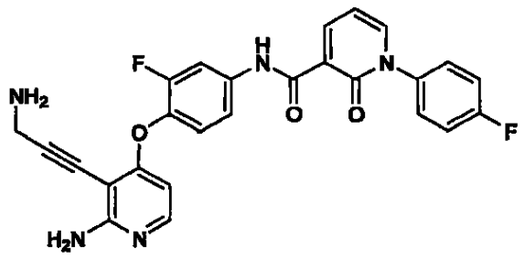
B) 3-(4-(4-Amino-2-fluorophenoxy)pyridin-3-yl)prop-2-yn-1-ol

[00458] The title compound was prepared in form 3-(4-(2-fluoro-4-nitrophenoxy)pyridin-3-yl)prop-2-yn-1-ol in 95% yield in the same manner as Step C of Example 11. MS(ESI$^+$): *m/z* 259.21 $(M+H)^+$.

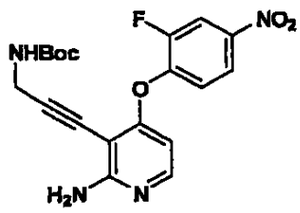
C) 1-(3-Fluoro-4-(3-(3-hydroxyprop-1-ynyl)pyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea, hydrochloride salt

[00459] The title compound was prepared from 3-(4-(4-amino-2-fluorophenoxy)pyridin-3-yl)prop-2-yn-1-ol in 36% yield in the same manner as Step E of Example 11. ^{1}H NMR (DMSO-d_6) δ 11.06 (s, 1H), 10.63 (s, 1H), 8.79 (s, 1H), 8.49 (d, 1H, J = 6.1 Hz), 7.82 (d, 1H, J = 12.2 Hz), 7.45-7.40 (m, 2H), 7.38-7.33 (m, 2H), 7.23-7.13 (m, 2H), 6.89 (d, 1H, J = 6.1 Hz), 4.37 (s, 2H), 3.74 (s, 2H); MS(ESI$^+$): *m/z* 438.23 $(M+H)^+$.

Example 137

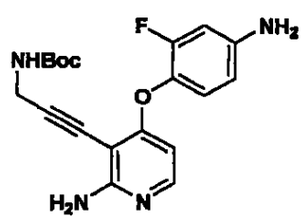


***N*-(4-(2-Amino-3-(3-aminoprop-1-ynyl)pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, dihydrochloride salt**



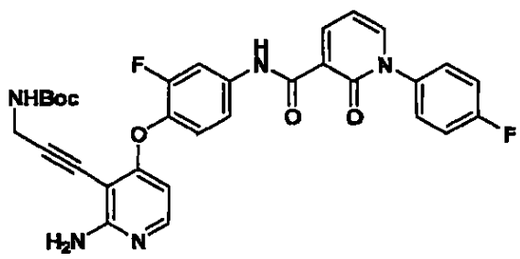
A) ***tert*-Butyl 3-(2-amino-4-(2-fluoro-4-nitrophenoxy)pyridin-3-yl)prop-2-ynylcarbamate**

[00460] The title compound was prepared from *N*-Boc propargylamine (Compound A of Example 42) and 4-(2-fluoro-4-nitrophenoxy)-3-iodopyridin-2-amine (Compound C of Example 34) in the same manner as Step A of Example 42 in 59% yield. ^{1}H NMR (DMSO-d_6) δ 8.35 (dd, 1H, J = 10.7, 2.5 Hz), 8.12 (d, 1H, J = 9.2 Hz), 7.88 (d, 1H, J = 5.6 Hz), 7.39 (t, 1H, J = 8.6 Hz), 7.31 (t, 1H, J = 5.1 Hz), 6.53 (s, 2H), 6.15 (d, 1H, J = 5.6 Hz), 3.92 (d, 2H, J = 5.6 Hz), 1.36 (s, 9H); MS(ESI$^+$): *m/z* 403.34 $(M+H)^+$.



B) *tert*-Butyl 3-(2-amino-4-(4-amino-2-fluorophenoxy)pyridin-3-yl)prop-2-ynylcarbamate

[00461] The title compound was prepared from *tert*-butyl 3-(2-amino-4-(2-fluoro-4-nitrophenoxy)pyridin-3-yl)prop-2-ynylcarbamate in quantitative yield in the same manner as Step C of Example 11. MS(ESI$^+$): *m/z* 373.35 $(M+H)^+$.



C) *tert*-Butyl 3-(2-amino-4-(2-fluoro-4-(1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamido)phenoxy)pyridin-3-yl)prop-2-ynylcarbamate

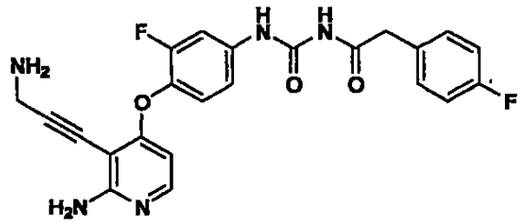
[00462] The title compound was prepared from *tert*-butyl 3-(2-amino-4-(4-amino-2-fluorophenoxy)pyridin-3-yl)prop-2-ynylcarbamate and 1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (Compound B of Example 101) in the same manner as Example 62 in 48% yield. ^{1}H NMR (DMSO-d_6) δ 12.07 (s, 1H), 8.57 (dd, 1H, J = 7.1, 2.0 Hz), 8.12 (dd, 1H, J = 6.6, 2.0 Hz), 8.00-7.93 (m, 1H), 7.75 (d, 1H, J = 6.1 Hz), 7.61 (d, 2H, J = 5.1 Hz), 7.59 (d, 1H, J = 4.6 Hz), 7.48-7.37 (m, 4 H), 7.30-7.25 (m, 1 H), 6.72 (t, 1H, J = 7.1 Hz), 6.37 (br s, 1H), 5.80 (d, 1H, J = 6.1 Hz), 4.00 (d, 2H, J = 5.1 Hz), 1.38 (s, 9H); MS(ESI$^+$): *m/z* 588.26 $(M+H)^+$.

D) *N*-(4-(2-Amino-3-(3-aminoprop-1-ynyl)pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, dihydrochloride salt

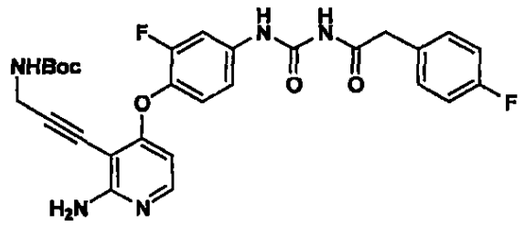
[00463] The title compound was prepared from *tert*-butyl 3-(2-amino-4-(2-fluoro-4-(1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamido)phenoxy)pyridin-3-yl)prop-2-ynylcarbamate in 80% yield in the same manner as Step E of Example 36. ^{1}H NMR (DMSO-d_6) δ 12.13 (s, 1H), 8.57 (dd, 1H, J = 7.1, 2.0 Hz), 8.51 (s, 2 H), 8.14 (dd, 1H, J = 6.6, 2.0 Hz), 8.11-8.02 (m, 1H), 7.98-7.90 (m, 1H), 7.60 (dd, 2H, J =

9.2, 5.1 Hz), 7.53 (d, 1H, J = 9.2 Hz), 7.46-7.37 (m, 3H), 6.76-6.71 (m, 1H), 6.20 (d, 1H, J = 6.6 Hz), 4.11-4.04 (m, 2H), MS(ESI$^+$): m/z 488.16 $(M+H)^+$.

Example 138



1-(4-(2-Amino-3-(3-aminoprop-1-ynyl)pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, dihydrochloride salt



A) *tert*-Butyl 3-(2-amino-4-(2-fluoro-4-(3-(2-(4-fluorophenyl)acetyl)ureido)phenoxy)pyridin-3-yl)prop-2-ynylcarbamate

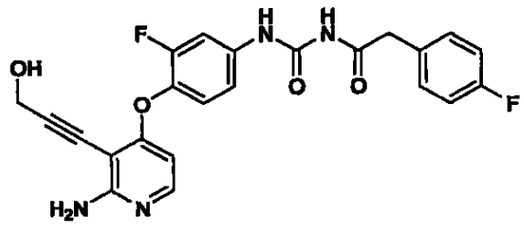
[00464] The title compound was prepared from *tert*-butyl 3-(2-amino-4-(4-amino-2-fluorophenoxy)pyridin-3-yl)prop-2-ynylcarbamate in 38% yield in the same manner as Step E of Example 11. ^{1}H NMR (DMSO-d_6) δ 11.02 (s, 1H), 10.55 (s, 1H), 7.80-7.73-7.69 (m, 2H), 7.38-7.29 (m, 3H), 7.33 (d, 1H, J = 5.1 Hz), 7.30-7.21 (m, 1H), 7.21-7.13 (m, 2H), 6.37 (br s, 1H), 5.76 (d, 1H, J = 6.1 Hz), 4.00 (s, 2H), 3.73 (s, 2H), 1.38 (s, 9H); MS(ESI$^+$): m/z 552.24 $(M+H)^+$.

B) 1-(4-(2-Amino-3-(3-aminoprop-1-ynyl)pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, dihydrochloride salt

[00465] The title compound was prepared from *tert*-butyl 3-(2-amino-4-(2-fluoro-4-(3-(2-(4-fluorophenyl)acetyl)ureido)phenoxy)pyridin-3-yl)prop-2-ynylcarbamate in 65% yield in the same manner as Step E of Example 11. ^{1}H NMR (DMSO-d_6) δ 11.05 (s, 1H), 10.61 (s, 1H), 8.48 (br s, 3H), 7.90 (d, 1H, J = 6.6 Hz), 7.84-7.76 (m,

2H), 7.45-7.39 (m, 1H), 7.39-7.32 (m, 3H), 7.20-7.13 (m, 2H), 6.11 (d, 1H, J = 6.1 Hz), 4.09-4.03 (m, 2H), 3.74 (s, 2H); MS(ESI$^+$): m/z 452.12 $(M+H)^+$.

Example 139

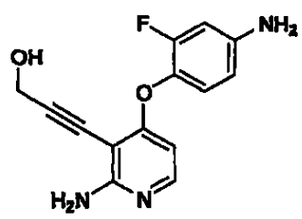


1-(4-(2-Amino-3-(3-hydroxyprop-1-ynyl)pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, hydrochloride salt



A) 3-(2-Amino-4-(2-fluoro-4-nitrophenoxy)pyridin-3-yl)prop-2-yn-1-ol

[00466] The title compound was prepared from propargyl alcohol (Aldrich) and 4-(2-fluoro-4-nitrophenoxy)-3-iodopyridin-2-amine (Compound C of Example 34) in 46% in the same manner as Step A of Example 36. ^{1}H NMR (DMSO-d_6) δ 8.40-8.34 (m, 1H), 8.13 (d, 1H, J = 8.6 Hz), 7.88 (d, 1H, J = 5.6 Hz), 7.42 (t, 1H, J = 8.6 Hz), 6.49 (s, 2H), 6.14 (d, 1H, J = 6 1 Hz), 5.26-5.20 (m, 1H), 4.26 (d, 2H, J = 6.1 Hz); MS(ESI$^+$): m/z 304.23 $(M+H)^+$.



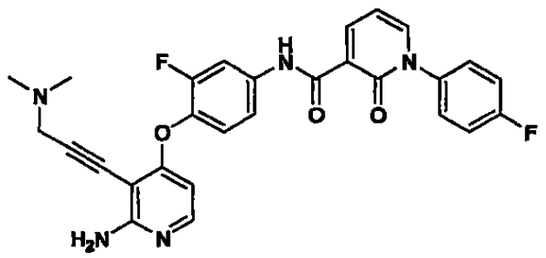
B) 3-(2-Amino-4-(4-amino-2-fluorophenoxy)pyridin-3-yl)prop-2-yn-1-ol

[00467] The title compound was prepared form 3-(2-amino-4-(2-fluoro-4-nitrophenoxy)pyridin-3-yl)prop-2-yn-1-ol in 65% yield. MS(ESI$^+$): *m/z* 274.21 $(M+H)^+$.

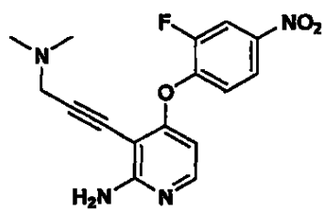
C) 1-(4-(2-Amino-3-(3-hydroxyprop-1-ynyl)pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, hydrochloride salt

[00468] The title compound was prepared from 3-(2-amino-4-(4-amino-2-fluorophenoxy)pyridin-3-yl)prop-2-yn-1-ol in 48% yield. ^{1}H NMR (DMSO-d_6) δ 11.05 (s, 1H), 10.60 (s, 1H), 7.86 (d, 1H, J = 7.1 Hz), 7.83-7.77 (m, 1H), 7.44-7.37 (m, 2H), 7.37-7.32 (m, 3 H), 7.20-7.13 (m, 2H), 6.14 (d, J = 6.6 Hz, 1H), 4.37 (s, 2H), 3.74 (s, 2H); MS(ESI$^+$): *m/z* 453.28 $(M+H)^+$.

Example 140



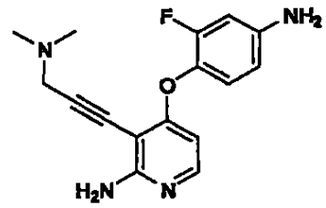
***N*-(4-(2-Amino-3-(3-(dimethylamino)prop-1-ynyl)pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, dihydrochloride salt**



A) 3-(3-(Dimethylamino)prop-1-ynyl)-4-(2-fluoro-4-nitrophenoxy)pyridin-2-amine

[00469] The title compound was prepared from 1-dimethylamin-2-propyne (Aldrich) and 4-(2-fluoro-4-nitrophenoxy)-3-iodopyridin-2-amine (Compound C of

Example 34) in 64% yield in the same manner as Step A of Example 42. ^{1}H NMR (DMSO-d_6) δ 8.36 (dd, 1H, J = 10.7, 2.5 Hz), 8.11 (d, 1H, J = 8.6 Hz), 7.93 (d, 1H, J = 5.6 Hz), 7.30 (t, 1H, J = 8.6 Hz), 6.43 (br s, 2H), 6.28 (d, 1H, J = 6.1 Hz), 3.41 (s, 2H), 2.05 (s, 6H); MS(ESI$^+$): m/z 331.28 $(M+H)^+$.



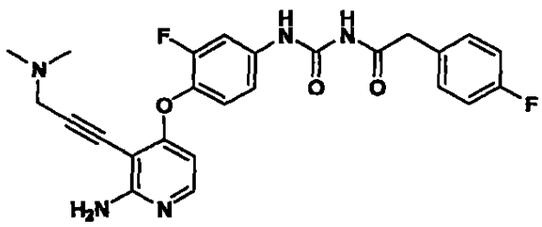
B) 4-(4-Amino-2-fluorophenoxy)-3-(3-(dimethylamino)prop-1-ynyl)pyridin-2-amine

[00470] The title compound was prepared from 3-(3-(dimethylamino)prop-1-ynyl)-4-(2-fluoro-4-nitrophenoxy)pyridin-2-amine in 77% yield in the same manner as Step C of Example 11. MS(ESI$^+$): m/z 301.30 $(M+H)^+$.

C) *N*-(4-(2-Amino-3-(3-(dimethylamino)prop-1-ynyl)pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, dihydrochloride salt

[00471] The title compound was prepared from 4-(4-amino-2-fluorophenoxy)-3-(3-(dimethylamino)prop-1-ynyl)pyridin-2-amine and 1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (Compound B of Example 101) in the same manner as Example 62 in 71% yield. ^{1}H NMR (DMSO-d_6) δ 12.14 (s, 1H), 11.39 (s, 1 H), 8.60-8.53 (m, 1H), 8.33 (s, 1H), 8.14 (dd, 1H, J = 6.6, 2.2 Hz), 8.05 (dd, 1H, J = 12.7, 2.2 Hz), 7.98 (d, 1H, J = 7.0 Hz), 7.61 (d, 1H, J = 5.3 Hz), 7.58 (d, 1H, J = 4.8 Hz), 7.56-7.50 (m, 1H), 7.37-7.47 (m, 3H), 6.76-6.69 (m, 1H), 6.30 (d, 1H, J = 7.0 Hz), 4.39 (s, 2H), 2.84 (s, 6H); MS(ESI$^+$): m/z 480.28 $(M+H)^+$.

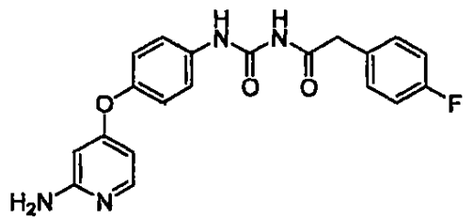
Example 141



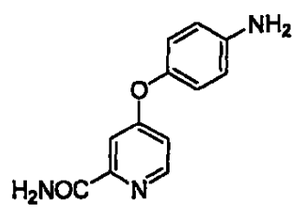
1-(4-(2-Amino-3-(3-(dimethylamino)prop-1-ynyl)pyridin-4-yloxy)-3-fluorophenyl)-3-(2-(4-fluorophenyl)acetyl)urea, dihydrochloride salt

[00472] The title compound was prepared from 4-(4-amino-2-fluorophenoxy)-3-(3-(dimethylamino)prop-1-ynyl)pyridin-2-amine in a similar manner as Step E of Example 11 in 70% yield. ^{1}H NMR (DMSO-d_6) δ 11.46 (br s, 1H), 11.07 (s, 1H), 10.64 (s, 1H), 8.37 br (s, 1H), 7.98 (t, 1H, J = 7.5 Hz), 7.81 (d, 1H, J = 13.6 Hz), 7.43-7.32 (m, 4H), 7.20-7.09 (m, 2H), 6.27 (d, 1H, J = 7.0 Hz), 4.38 (s, 2H), 3.75 (s, 2H), 2.84 (s, 6H); MS(ESI$^+$): m/z 516.31 $(M+H)^+$.

Example 142

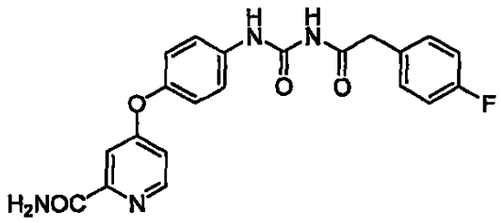


1-(4-(2-Aminopyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea, hydrochloride salt



A) 4-(4-Aminophenoxy)picolinamide

[00473] The title compound was prepared in a similar manner described in Step B' of Example 24, starting from 4-aminophenol. Yield. 85%. MS (ESI$^+$) m/z 230 $(M+H)^+$.



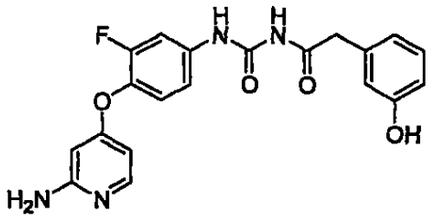
B) 1-(4-(2-Carbamoylpyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea

[00474] The title compound was prepared in a similar manner described in Step C' of Example 24. Yield: 95%. MS (ESI^+) *m/z* 409 $(M+H)^+$.

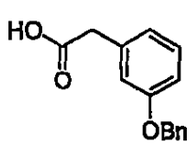
C) 1-(4-(2-Aminopyridin-4-yloxy)phenyl)-3-(2-(4-fluorophenyl)acetyl)urea, hydrochloride salt

[00475] The title compound was prepared in a similar manner described in Step D' of Example 24. Yield: 58%. ^1H NMR (DMSO-d_6) δ 12.86 (s, 1H), 10.97 (s, 1H), 10.51 (s, 1H), 7.91 (d, 1H, J = 6.0 Hz), 7.67 (d, 3H, J = 9.0 Hz), 7.34 (dd, 2H, J = 9.0, 5.0 Hz), 7.21 (d, 2H, J = 9.0 Hz), 7.16 (t, 2H, J = 9.0 Hz), 6.63 (dd, 1H, J = 9.5, 2.0 Hz), 6.05 (d, 1H, J = 2.0 Hz), 3.73 (s, 2H); MS (ESI^+) *m/z* 381 $(M+H)^+$.

Example 143



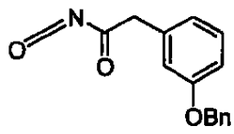
1-(4-(2-Aminopyridin-4-yloxy)-3-fluorophenyl)-3-(2-(3-hydroxyphenyl)acetyl)urea



A) 2-(3-(Benzyloxy)phenyl)acetic acid

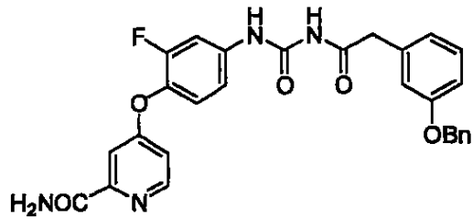
[00476] To a solution of 3-hydroxyphenylacetic acid (Acros, 3.04 g, 20 mmol) in 20 mL of DMF were added K_2CO_3 (6.90 g, 50 mmol) and benzyl bromide (4.75 mL, 40 mmol) at room temperature. The reaction mixture was stirred for 24 h. The suspension was filtered and washed with diethyl ether. The filtrate was then washed with brine and dried over $MgSO_4$. Filtration, followed by concentration, provided the crude benzyl 2-(3-(benzyloxy)phenyl)acetate which was used in the next step. MS (ESI^+) *m/z* 355 $(M+Na)^+$.

[00477] The crude benzyl 2-(3-(benzyloxy)phenyl)acetate was dissolved in a mixture of MeOH (20 mL) and THF (50 mL). To this solution was added 40 mL of 1N NaOH (40 mmol). The reaction mixture was stirred at room temperature for 2 h. The organic solvent was removed *in vacuo*. The remaining aqueous solution was extracted with diethyl ether (2 x 50 mL). The aqueous solution was then acidified with 1N HCl (50 mL) and the title compound precipitated. The solid was collected by filtration (4.35 g, 90% two steps). MS(ESI^+) *m/z* 265 $(M+Na)^+$.



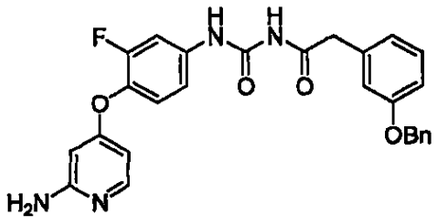
B) 2-(3-(Benzyloxy)phenyl)acetyl isocyanate

[00478] To a solution of 2-(3-(benzyloxy)phenyl)acetic acid (484 mg, 2 0 mmol) in DCM (10 mL) at room temperature was added 1 drop of DMF and thionyl chloride (0.30 mL, 4 mmol). The reaction mixture was stirred at room temperature for 1 h and then at 50 °C for 0.5 h. The mixture was cooled and the solvent was removed *in vacuo*. The residue was dissolved in 5 mL of toluene and AgOCN (600 mg, 4.0 mmol) was added. The suspension was stirred for 0.5 h and it was filtered to provide a solution of 2-(3-(benzyloxy)phenyl)acetyl isocyanate in toluene (0.40 M).



C) 1-(2-(3-(Benzyloxy)phenyl)acetyl)-3-(4-(2-carbamoylpyridin-4-yloxy)-3-fluorophenyl)urea

[00479] The title compound was prepared in a similar manner described in Step C' of Example 24, using the solution of Step B of this Example. Yield: 63%. MS(ESI$^+$) *m/z* 515 $(M+H)^+$.



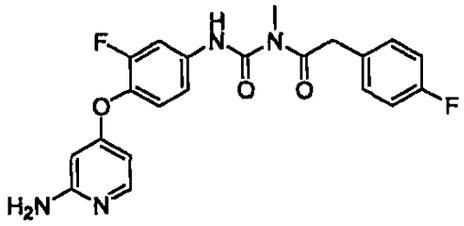
D) 1-(4-(2-Aminopyridin-4-yloxy)-3-fluorophenyl)-3-(2-(3-(benzyloxy)phenyl)acetyl)urea

[00480] The title compound was prepared in a similar manner described in Step D' of Example 24. Yield: 61%. MS(ESI$^+$) *m/z* 487 $(M+H)^+$.

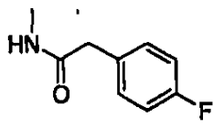
E) 1-(4-(2-Aminopyridin-4-yloxy)-3-fluorophenyl)-3-(2-(3-hydroxyphenyl)acetyl)urea

[00481] To a solution of 1-(4-(2-aminopyridin-4-yloxy)-3-fluorophenyl)-3-(2-(3-(benzyloxy)phenyl)acetyl)urea (150 mg, 0.31 mmol) in a mixture of 5 mL of EtOAc and 3 mL of MeOH was added 10% Pd/C (200 mg). The suspension was stirred under H_2 atmosphere for 1 h. Filtration, followed by concentration, provided the title compound (77 mg, 63%). ^{1}H NMR (DMSO-d_6) δ 10.95 (s, 1H), 10.54 (s, 1H), 9.35 (s, 1H), 7.74 (d, 1H, J = 6.0 Hz), 7.68 (dd, 1H, J = 13.0, 2.0 Hz), 7.30 (dd, 1H, J = 9.0, 1.1 Hz), 7.23 (t, 1H, J = 9.0 Hz), 7.07 (t, 1H, J = 8.0 Hz), 6.69 (s, 1H), 6.68 (d, 1H, J = 7.0 Hz), 6.62 (dd, 1H, J = 7.0, 2.0 Hz), 6.10 (dd, 1H, J = 6.0, 2.0 Hz), 5.90 (s, 2H), 5.73 (d, 1H, J = 2.0 Hz), 3.27 (s, 2H); MS(ESI$^+$) *m/z* 397 $(M+H)^+$.

Example 144

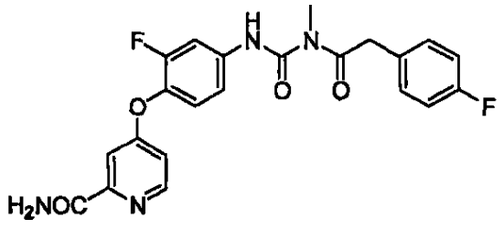


3-(4-(2-Aminopyridin-4-yloxy)-3-fluorophenyl)-1-(2-(4-fluorophenyl)acetyl)-1-methylurea, hydrochloride salt



A) 2-(4-Fluorophenyl)-*N*-methylacetamide

[00482] To a solution of methylamine in THF (2.0 M, 5 mL, 10 mmol) was added 4-fluorophenylacetyl chloride (518 mg, 3.0 mmol) at –78 °C. The reaction mixture was stirred from –78 °C to room temperature for 1 h. The solution was diluted with H_2O and extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$. Filtration, followed by concentration, provided the title compound (490 mg, 98%). MS(ESI$^+$) *m/z* 168 $(M+H)^+$.



B) 3-(4-(2-Carbamoylpyridin-4-yloxy)-3-fluorophenyl)-1-(2-(4-fluorophenyl)acetyl)-1-methylurea

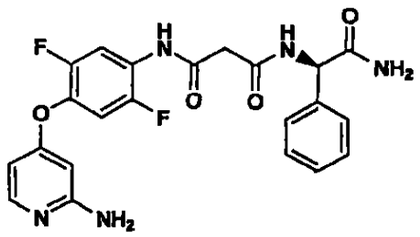
[00483] To a solution of 2-(4-fluorophenyl)-*N*-methylacetamide (89 mg, 0.53 mmol) in 2 mL of THF at –78 °C was added MeLi in Et_2O (1 6 M, 0.34 mL, 0.55 mmol). The solution was stirred at –78 °C for 5 min and then 20% phosgene in toluene (1.9 M, 0.29 mL, 0.55 mmol) was introduced quickly. After 2 min, 4-(4-

amino-2-fluorophenoxy)picolinamide (Compound B' of Example 24, 100 mg, 0.40 mmol) was added, followed by the addition of DMF (2 mL) and DIEA (0.4 mL). The reaction mixture was stirred at room temperature for 1 h and quenched with H_2O. The solution was then extracted with EtOAc and the organic layer was washed with brine, dried over $MgSO_4$. After filtration and concentration, the residue was purified by silica gel chromatography to give the title compound (77 mg, 33%). MS(ESI$^+$) *m/z* 441 $(M+H)^+$.

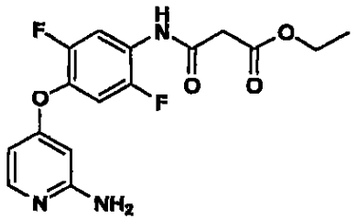
C) 3-(4-(2-Aminopyridin-4-yloxy)-3-fluorophenyl)-1-(2-(4-fluorophenyl)acetyl)-1-methylurea, hydrochloride salt

[00484] The title compound was prepared in a similar manner described in Step D' of Example 24. Yield: 24%. ^{1}H NMR (DMSO-d_6) δ 13.20 (s, 1H), 11.17 (s, 1H), 7.90 (d, 1H, J = 7.0 Hz), 7.78-7.74 (m, 3H), 7.39-7.34 (m, 2H), 7.23-7.21 (m, 2H), 7.10-7.05 (m, 2H), 6.63 (dd, 1H, J = 7.0, 2.0 Hz), 6.08 (d, 1H, J = 2.0 Hz), 4.00 (s, 2H), 3.24 (s, 3H); MS(ESI$^+$) *m/z* 413 $(M+H)^+$.

Example 145

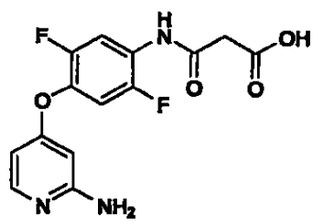


(*R*)-N^1-(2-Amino-2-oxo-1-phenylethyl)-N^3-(4-(2-aminopyridin-4-yloxy)-2,5-difluorophenyl)malonamide, trifluoroacetic acid salt



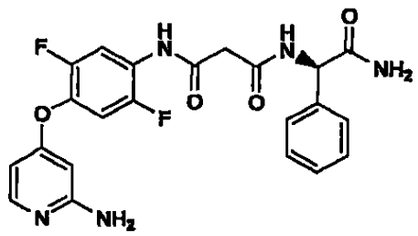
A) **Ethyl 3-(4-(2-aminopyridin-4-yloxy)-2,5-difluorophenylamino)-3-oxopropanoate**

[00485] Ethyl 3-(4-(2-carbamoylpyridin-4-yloxy)-2,5-difluorophenylamino)-3-oxopropanoate (Compound A of Example 116, 0.73 g, 1.9 mmol) was converted to the title compound (0.24 g, 35%) in a manner similar to the preparation of Compound E of Example 112. MS(ESI$^+$) *m/z* 352 $(M+H)^+$.



B) **3-(4-(2-Aminopyridin-4-yloxy)-2,5-difluorophenylamino)-3-oxopropanoic acid**

[00486] Ethyl 3-(4-(2-aminopyridin-4-yloxy)-2,5-difluorophenylamino)-3-oxopropanoate (0.24 g, 0.68 mmol) was converted to the title compound (0.039 mg, 18%) in a manner similar to the preparation of Compound B of Example 116. HRMS(ESI$^+$), Calcd.: 324.0796 $(M+H)^+$, found: 324.0795 $(M+H)^+$.

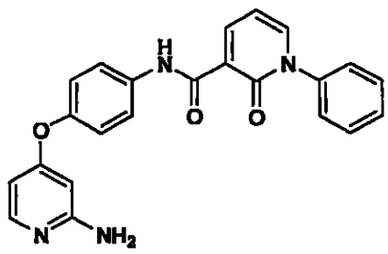


C) **(*R*)-N^1-(2-Amino-2-oxo-1-phenylethyl)-N^3-(4-(2-aminopyridin-4-yloxy)-2,5-difluorophenyl)malonamide trifluoroacetic acid salt**

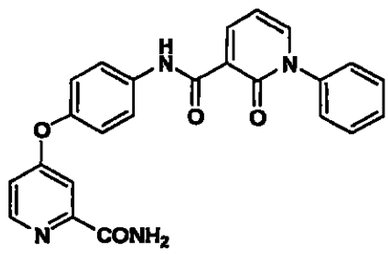
[00487] 3-(4-(2-Aminopyridin-4-yloxy)-2,5-difluorophenylamino)-3-oxopropanoic acid (0.039 g, 0.12 mmol) was coupled with (*R*)-2-amino-2-phenylacetamide hydrochloride (Bachem, 0.023 g, 0.12 mmol), in a manner similar to the preparation of Example 103, to afford the title compound (0.0048 g, 7%). ^{1}H NMR (DMSO-d_6) δ 10.33 (s, 1H), 8.77 (d, 1H, J = 7.8 Hz), 8.10-8.19 (m, 1H), 7.90 (d, 1H, J = 7.2 Hz),

7.60-7.75 (m, 4H), 7.17-7.39 (m, 6H), 6.66-6.69 (m, 1H), 6.11 (s, 1H), 5.35 (d, 1H, J = 7.8 Hz); HRMS(ESI$^+$), Calcd.: 456.1483 $(M+H)^+$, found: 456.1487 $(M+H)^+$.

Example 146

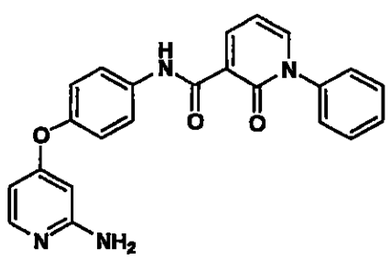


***N*-(4-(2-Aminopyridin-4-yloxy)phenyl)-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide, hydrochloride salt**



A) **4-(4-(2-Oxo-1-phenyl-1,2-dihydropyridine-3-carboxamido)phenoxy) picolinamide**

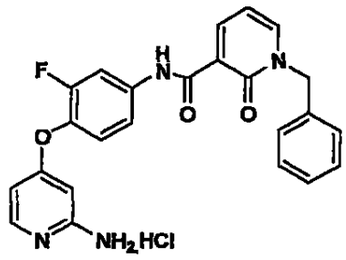
[00488] 4-(4-Aminophenoxy)picolinamide (Compound A of Example 142, 0.030 g, 0.13 mmol) was coupled with Compound C of Example 57 (0.028 g, 0.13 mmol), in a manner similar to the preparation of Compound A of Example 115, to afford the title compound (0.057 g, 100%) which was used without further purification. MS(ESI$^+$) m/z 427 $(M+H)^+$.



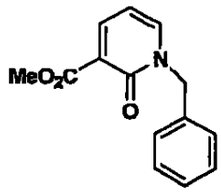
B) *N*-(4-(2-Aminopyridin-4-yloxy)phenyl)-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide, hydrochloride salt

[00489] 4-(4-(2-Oxo-1-phenyl-1,2-dihydropyridine-3-carboxamido)phenoxy) picolinamide (0.055, 0.13 mmol) was converted to the title compound (0.0093 g, 16%) in a manner similar to the preparation of Compound E of Example 112. ^{1}H NMR (CD_3OD) δ 12.10 (s, 1H), 8.59-8.61 (m, 1H), 7.88-7.90 (m, 1H), 7.69-7.76 (m, 3H), 7.39-7.53 (m, 5H), 7.10-7.13 (m, 2H), 6.66 (t, 1H, J = 6.9 Hz), 6.53-6.55 (m, 1H), 6.07-6.08 (m, 1H), 4.75 (br s, 2H); HRMS(ESI$^+$), Calcd.: 399.1457 $(M+H)^+$, found: 399.1453 $(M+H)^+$.

Example 147



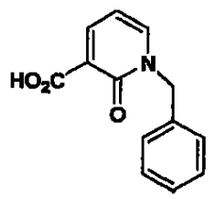
***N*-(4-(2-Aminopyridin-4-yloxy)-3-fluorophenyl)-1-benzyl-2-oxo-1,2-dihydropyridine-3-carboxamide, hydrochloride salt**



A) Methyl 1-benzyl-2-oxo-1,2-dihydropyridine-3-carboxylate

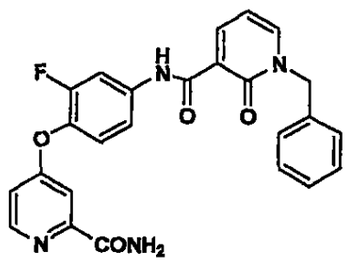
[00490] A heterogeneous mixture of methyl 2-oxo-2*H*-pyran-3-carboxylate (Aldrich, 2.0 g, 13 mmol, 1.0 eq) and 4-fluorobenzylamine (1.5 mL, 13 mmol, 1.0 eq) in DMF (10 ml) were stirred at room temperature for 3 h. The reaction mixture was treated with EDCI (3.4 g, 18 mmol, 1.4 eq) and DMAP (0.11 g, 9.91 mmol, 0.07 eq) at room temperature and the resulting solution was stirred for 12 h. The reaction mixture was quenched with 1N 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, that 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-Benzyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid

[00491] A solution of methyl 1-benzyl-2-oxo-1,2-dihydropyridine-3-carboxylate (2.4 g, 9.2 mmol, 1.0 eq) in MeOH (25 mL) was treated with 5N 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 then 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 was 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 used without further purification.. ^{1}H NMR (DMSO-d_6)
δ 8.39–8.44 (m, 2H), 7.42–7.46 (m, 2H), 7.18–7.24 (m, 2H), 6.78 (dd, 1H, J = 6.98 Hz), 5.31 (s, 2H); HRMS(ESI$^+$), Calcd.: 248.0723, found: 248.0718.



C) 4-(4-(1-Benzyl-2-oxo-1,2-dihydropyridine-3-carboxamido)-2-fluorophenoxy)picolinamide

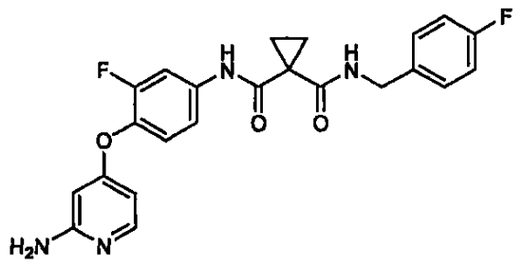
[00492] A homogeneous solution of 1-benzyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (0.10 g, 0.41 mmol, 1.0 eq), 4-(4-amino-2-fluorophenoxy)picolinamide (0.10 g, 0.41 mmol, 1.0 eq) and TBTU (0.17 g, 0.45 mmol, 1.1 eq) in DMF (2 mL) was treated with DIPEA (0.18 mL, 1.0 mmol, 2.5 eq) at room temperature and the reaction mixture was stirred for 12 h. The reaction mixture was quenched with 10% aqueous LiCl (15 mL) and 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 column chromatography (SiO_2, eluting with ethyl acetate) to afford the product (0.13 g, 67%) as a solid. ^1H NMR (DMSO-d_6) δ 12.26 (s, 1H), 8.49-8.56 (m, 2H), 8.33-8.36 (m, 1H), 8.15 (br m, 1H), 8.03-8.07 (m, 1H), 7.74-7.75 (m, 1H), 7.51-7.54 (m, 1H), 7.41-7.46 (m, 4H), 7.20-7.24 (m, 3H), 6.71 (dd, 1H, J = 6.89 Hz), 5.32 (s, 2H) HRMS(ESI$^+$), Calcd.: 477.1374, found: 477.1378.

D) *N*-(4-(2-aminopyridin-4-yloxy)-3-fluorophenyl)-1-benzyl-2-oxo-1,2-dihydropyridine-3-carboxamide, hydrochloride salt

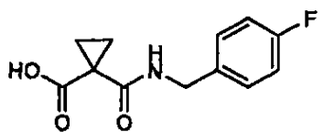
[00493] Bis (trifluoroacetoxy) iodobenzene (0.12 g, 0.28 mmol, 1.1 eq) was added to a solution of 4-(4-(1-benzyl-2-oxo-1,2-dihydropyridine-3-carboxamido)-2-fluorophenoxy)picolinamide (0.12 g, 0.26 mmol, 1.0 eq), and water (0.01 mL, 0.51 mmol, 2 0 eq) in DMF (1 mL) at room temperature. Pyridine (0.065 mL, 0.77 mmol, 3.0 eq) was added to the homogeneous mixture and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was quenched with 1N aqueous HCl (1 mL) and the resulting solution was extracted with diethyl ether (3 x 5 mL), discarding the organic layer. The aqueous fraction was neutralized with 1N aqueous NaOH and the resulting solution was extracted with 9/1 $CHCl_3$/MeOH (4 x 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, eluting 0-3% MeOH in $CHCl_3$) and the appropriate fractions were concentrated *in vacuo*. The free base was dissolved in THF, cooled to 0°C and the homogeneous

solution treated with anhydrous 4N HCl in dioxane. The reaction mixture was warmed to room temperature, concentrated *in vacuo* and the residue triturated with diethyl ether, discarding the filtrate. The solid was dried *in vacuo* to afford the title compound (0.082 g, 66%) as a HCl salt. ^{1}H NMR (DMSO-d_6) δ 13.66 (br s, 1H), 8.49-8.51 (m, 1H), 8.39-8.49 (m, 1H), 8.37-8.39 (m, 1H), 8.00-8.09 (m, 3H), 7.54-7.56 (m, 1H), 7.43-7.48 (m, 3H), 7.19-7.24 (m, 2H), 6.69-6.72 (m, 2H), 6.21-6.22 (m, 1H), 5.32 (s, 2H); HRMS(ESI$^+$), Calcd.: 449.1425, found: 449.1406.

Example 148

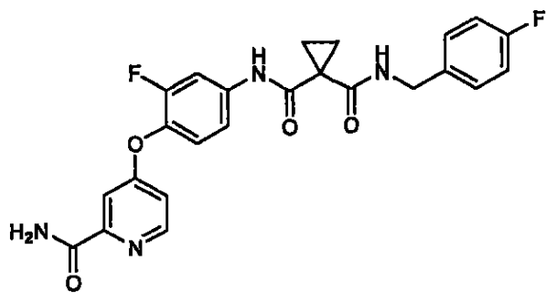


***N*-(4-Fluorobenzyl)-*N*-(4-(2-aminopyridin-4-yloxy)-3-fluorophenyl)cyclopropane-1,1-dicarboxamide**



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

[00494] To a solution of 1,1-cyclopropanecarboxylic acid (Aldrich, 390 mg, 3.0 mmol) in THF (5 mL) at 0 °C was added triethylamine (0.42 mL, 3.0 mmol). After stirring for 30 min at 0 °C, thionyl chloride (0.219 mL, 3.0 mmol) was added to the reaction mixture. The mixture was stirred at 0 °C for an additional 30 min and a solution of 4-fluorobenzylamine (Aldrich, 375 mg, 3.0 mmol) in THF (2 mL) was added. The reaction mixture was stirred at 0 °C for 2 h, diluted with ethyl acetate (100 mL) and extracted with 1 N NaOH (10 mL). The aqueous phase was acidified with 1 N HCl to pH 1-2. The solid which formed was collected by filtration (343 mg, 48%). MS(ESI$^+$) *m/z* 238.24 $(M+H)^+$.



B) *N*-(4-Fluorobenzyl)-*N*-(4-(2-carbamoylpyridin-4-yloxy)-3-fluorophenyl)cyclopropane-1,1-dicarboxamide

[00495] To a solution of 4-(4-amino-2-fluorophenoxy)picolinamide (Compound B' of Example 24, 49 mg, 0.2 mmol) in DMF (2 mL) at room temperature was added 1-((4-fluorobenzyl)carbamoyl)cyclopropanecarboxylic acid (47 mg, 0.2 mmol), HATU (Perseptive Biosystem, 114 mg, 0.3 mmol), and DIEA (0.2 mL, 1.1 mmol). The reaction mixture was stirred at rt for 2 h, and then quenched by adding 4 mL of methanol. The reaction mixture was purified by prep. HPLC. The desired fractions were combined, neutralized with aq. K_2HPO_4, and concentrated *in vacuo*. The solid which formed was collected by filtration (29 mg, 31%). ^{1}H NMR (DMSO-d_6) δ 10.78 (br s, 1H), 8.53 (d, 1H, J = 5.5 Hz), 8.47 (t, 1H, J = 5.5 Hz), 8.11 (s, 1H), 7.88 (dd, 1H, J = 13.2, 2.3 Hz), 7.70 (s, 1H), 7.47 (d, 1H, J = 9.2 Hz), 7.38 (t, 1H, J = 9.2 Hz), 7.34-7.29 (m, 3H), 7.22 (dd, 1H, J = 5.5, 2.8 Hz), 7.13 (t, 2H, J = 8.8 Hz), 4.30 (d, 2H, J = 5.5 Hz), 1.37 (d, 4H, J = 10.6 Hz); MS(ESI$^+$) *m/z* 467.12 $(M+H)^+$.

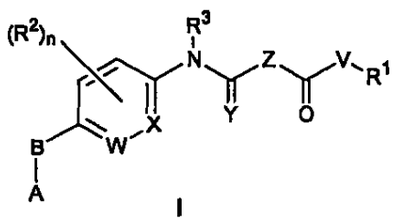
C) *N*-(4-Fluorobenzyl)-*N*-(4-(2-aminopyridin-4-yloxy)-3-fluorophenyl)cyclopropane-1,1-dicarboxamide

[00496] To a solution of *N*-(4-fluorobenzyl)-*N*-(4-(2-carbamoylpyridin-4-yloxy)-3-fluorophenyl)cyclopropane-1,1-dicarboxamide (25 mg, 0.05 mmol) in DMF (1 mL) at room temperature was added pyridine (0.2 mL), water (0.1 mL), and [bis(trifluoroacetoxyl)-iodo]benzene (Aldrich, 34 mg, 0.08 mmol). The reaction mixture was stirred at rt for 2 h, and then quenched by adding 2 mL of methanol. The reaction mixture was purified by prep. HPLC. The desired fractions were combined, neutralized with aq. K_2HPO_4, concentrated and extracted with ethyl acetate. The organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was

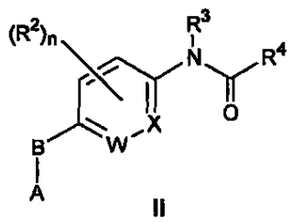
dissolved in a small amount of CH_3CN/H_2O and lyophillized to dryness to give the title comopound (21 mg, 90%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 10.87 (br s, 1H), 8.44 (t, 1H, J = 6.0 Hz), 7.91 (d, 1H, J = 6.6 Hz), 7.88 (d,1H, J = 13.2 Hz), 7.37-7.29 (m, 6H), 7.13 (t, 2H, J = 8.8 Hz), 4.29 (d, 2H, J = 6.1 Hz), 1.38 (d, 4H, J =2.2 Hz); MS(ESI$^+$) m/z 439.14 $(M+H)^+$.

WE CLAIM:

1. A compound having Formula I or II:



I



II

or an enantiomer, diastereomer, hydrate, solvate or pharmaceutically acceptable salt 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, NR^8CH_2, S, SO, SO_2, or CR^9R^{10};

V is NR^{11} or $-(CR^{37}R^{38})_p-$ provided that when VR^{11} is N, R^1 is an alkyl or cycloalkyl;

W and X are each independently C or N;

Y is selected from O, S, and NR^{12};

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

l is 0 to 2;

n is 0 to 4 if W and X are both C, 0 to 3 if one of X or W is N, and 0 to 2 if X and W are both N;

p is 1 to 4;

R^3, R^5, R^6, R^7, R^8, R^{11} and R^{15} are independently selected from H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl,

substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclo, substituted heterocyclo;

R^4 is selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, and substituted heterocycloalkyl, provided that

(a) if R^4 is phenyl

(i) R^4 is not substituted with both hydroxy and amido; and

(ii) R^4 is not substituted with $-NRSO_2R-$ wherein R is alkyl or aryl;

(b) if R^4 is pyridyl ,R^4 is not substituted with both hydroxy and methoxy; and

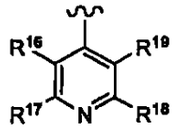
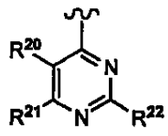
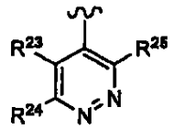
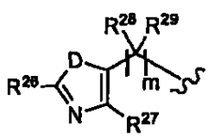
(c) if R^4 is pyrimidinyl, it is not substituted with =O;

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

R^{12} is selected from H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, CN, NO_2 or SO_2NH_2;

R^{13} and R^{14} are independently selected from H, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, substituted heterocycloalkyl or taken together to form a carbocyclic or heterocyclic ring of 3 to 8 atoms;

A is selected from one of the following:

wherein

D is S or O;

m is 0 to 6;

R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26} and R^{27} are independently selected from H, halogen, $NR^{30}R^{31}$, OR^{32}, CO_2R^{33}, $CONR^{34}R^{35}$, SO_2R^{36}, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl,

alkynyl, substituted alkynyl, -CN, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, or substituted heterocycloalkyl;

R^{28} and R^{29} are independently selected from H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, or taken together to form a carbocyclic or heterocyclic ring of 3 to 8 atoms;

R^{30}, R^{31}, R^{32}, R^{33}, R^{34}, R^{35}, and R^{36} are independently selected from H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, alkoxycarbonyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclo, substituted heterocyclo, heterocycloalkyl, or substituted heterocycloalkyl; and

$R^{37}$and R^{38} are each independently H, halogen, or alkyl.

2. The compound according to claim 1 wherein R^1 is a substituted or unsubstituted phenyl, a substituted or unsubstituted C_1 to C_4 alkyl, or a substituted or unsubstituted C_3 to C_8 cycloalkyl.

3. The compound according to claim 2 wherein R^1 is fluorophenyl, substituted methyl, cyclohexyl or cyclopentyl.

4. The compound according to claim 1 wherein R^2 is C_1 to C_4 alkyl, halogen, or haloalkyl.

5. The compound according to claim 1 wherein R^4 is optionally substituted phenyl, pyridinone, pyridyl, pyridyl-N-oxide, pyrazolyl, or pyrrolidyl.

6. The compound according to claim 5 wherein $R^4$is substituted with oxygen, phenyl, C_1 to C_4 alkyl, or halogen.

7. The compound according to claim 1 wherein B is O, $NHCH_2$, CH_2 or CH(OH); Y is O or S and Z is $-CR^{13}R^{14}$ or $-NR^{15}$ wherein R^{13}, R^{14}, and R^{15} are each H.

8. The compound according to claim 1 wherein A is an optionally substituted pyridine or pyrimidine.

9. The compound according to claim 8 wherein the substituent is alkyl, alkenyl, alkynyl, halogen, cycloalkyl, heterocycloalkyl, $-NR^{39}COR^{40}$, $-NR^{39}C(O)_2R^{40}$, $-NR^{41}R^{42}$, or $-C(O)NR^{43}R^{44}$, wherein R^{39}, R^{40}, R^{41}, R^{42}, R^{43}, and R^{44} are independently H, lower alkyl, substituted lower alkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, or $-NR^{43}R^{44}$ form a heterocycloalkyl.

10. The compound according to claim 7 wherein A is a pyridine substituted with $-NR^{41}R^{42}$, $-NR^{39}COR^{40}$, $-C(O)NR^{43}R^{44}$, halogen, C_1 to C_4 alkyl, $-C{=}C-R^{45}$, $-C{\equiv}C-R^{46}$, aryl, or heteroaryl wherein R^{45} and R^{46} are alkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, heterocycloalkyl, $-C(O)R^{47}$, $-NR^{39}COR^{40}$, aryl, or heteroaryl.

11. The compound according to claim 10 wherein said C_1 to C_4 alkyl is substituted with hydroxy, hydroxyalkylamino, alkylamino, aminoalkylamino, or heteroarylalkyl.

12. The compound according to claim 8 wherein R^{41} and R^{42} are each independently, H, methyl, ethyl, propyl, butyl, phenyl, or benzyl and R^{39} is H and R^{40} is methyl, cycloalkyl, or heterocycloalkyl.

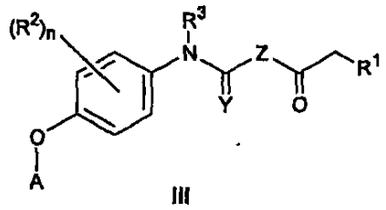
13. The compound according to claim 8 wherein R^{43} and R^{44} are H and R^{45} and R^{46} are each cyclohexene, azetidine, piperazine, piperidine, pyrrolidine, or pyridine, optionally substituted with C_1 to C_4 alkyl, $-CH_2NH_2$, $-NH_2$, or pyrrolidine.

14. The compound according to claim 8 wherein the pyridine is substituted with a phenyl group, optionally substituted with $CONH_2$, methyl, aminoethyl, hydroxyethyl, $-CONHCH_2CH_2NHCH_3$, or CH_2CONH_2; pyridine, or piperazine.

15. The compound according to claim 8 wherein A is pyrimidine substituted with $-NR^{41}R^{42}$, or $-NR^{39}CO_2R^{40}$.

16. The compound according to claim 15 wherein R^{41} and R^{42} are H or methyl and R^{39} and R^{40} are independently H or alkyl.

17. The compound according to claim 1 having the formula III:



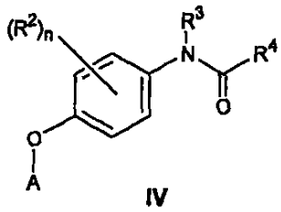
III

wherein

R^1 is optionally substituted phenyl or alkyl; Z is NH or NCH_3 ; R^2 is F, Cl, CH_3 or CF_3, R^3 is H; andY is O or S.

18. The compound according to claim 17 wherein $R^1$is C_3 to C_7 cycloalkyl, substituted or unsubstituted phenyl, or $-(CH_2)_n-R^{50}$ wherein n is 1 to 3, R^{50} is H, substituted or unsubstituted phenyl, amino, amido, CN, $-C(O)_2H$, or $-C(O)_2CH_3$.

19. The compound according to claim 1 having Formula IV:

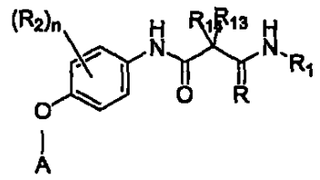


IV

wherein R^2 is halo or H; R^3 is H; R^4 is optionally substituted phenyl, optionally substituted pyrazole, or optionally substituted pyridyl; and A is optionally substituted pyridyl.

20. The compound according to claim 19 wherein R^4 is an optionally substituted pyridinone or a pyridine-N-oxide.

21. The compound according to claim 1 having formula V:



V

wherein R^1 is optionally alkyl or cycloalkyl; A is optionally substituted pyrimidine or pyridine; and R_2 is halo or H; and R^{13} and R^{14} are either H or together with the carbon to which they are attached for a cyclopropyl.

22. A compound according to claim 1 having an IC_{50} value of less than about 1.0 μM.

23. A method for treating cancer in a patient in need thereof comprising administering to the patient a therapeutically effective amount of a compound according to claim 1.

24. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to claim 1 and a pharmaceutically acceptable carrier.

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PCT/US 2005/014120

A. CLASIFICACION DEL TEMA

A61K 31/44 C07D 401/04 C07D 213/68 C07D 401/06 C07D 213/73
C07D 401/12 C07D 213/74 C07D 401/14 C07D 213/75 C07D 417/12
C07D 239/34 C07D 239/46 A61P 35/00

De acuerdo a la Clasificación de Patentes Internacional (IPC) o a la clasificación nacional y a la IPC

B. CAMPOS BUSCADOS

Documentación mínima buscada (sistema de clasificación seguido por los símbolos de clasificación):
C07D

Documentación buscada diferente a la documentación mínima, a la extensión que tales documentos están incluidos en los campos buscados:

Base de datos electrónicos consultados durante la búsqueda internacional (nombre de la base de datos y, en donde sea práctico, términos de búsqueda utilizados):
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEMS ABS Data,

C. DOCUMENTOS QUE SE CONSIDERA QUE SON RELEVANTES

Categoría	Cita del documento, con indicación, en donde sea apropiado, de los pasajes relevantes	Relevante para la Reiv No
X	DATABASE CROSSFIRE BEILSTEIN BEILSTEIN INSTITUT ZUR FOERDERUNG DER CHEMISCHEN WISSENSCHAFT, FRANKFURT AM MAIN, DE; XP002362294 Database accession no. BRN 667921 resumen ------- 	1 —
X	DATABASE CROSSFIRE BEILSTEIN BEILSTEIN INSTITUT ZUR FOERDERUNG DER CHEMISCHEN WISSENSCHAFT, FRANKFURT AM MAIN, DE; XP002362295 Database accession no. BRN 413351 resumen -------	1

[X] Documentos adicionales se enlistan en la continuación del bloque C [X] Véase familia de patentes anexa.

* Categorías especiales de los documentos citados
"A" documento que define el estado general de la técnica el cual no se considera ser de particular relevancia
"E" documento anterior publicado en o después de la fecha de presentación internacional
"L" documento el cual puede arrojar dudas sobre la(s) reivindicacion(es) de prioridad o el cual se cita para establecer la fecha de publicación de otra cita u otra razón especial (como se especifica)
"O" documento que se refiere a una descripción oral, uso, exhibición u otro medio
"P" documento publicado antes de la fecha de presentación internacional pero después de la fecha de prioridad reivindicada
"T" documento posterior publicado después de la fecha de presentación internacional o fecha de prioridad y no en conflicto con la solicitud, pero citado para entender el principio o teoria fundamental de la invención
"X" documento de relevancia particular, la invención reivindicada no puede ser considerada nueva o no se puede considerar que involucre una etapa inventiva cuando el documento es considerado de manera aislada
"Y" documento de particular relevancia, no se puede considerar que la invención involucre unz etapa inventiva cuando el documento es combinado con uno o más de tales documentos, tal combinación sería obvia para una persona experimentada en la técnica
"&" documento miembro de la misma familia de patentes

Fecha de la terminación real de la búsqueda internacional	Fecha de envío del reporte de búsqueda internacional
12 Enero 2005	25/01/2006
Nombre y dirección de correspondencia de la ISA European Patent Office ,PB. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel (+31-70)340-2040, Tx 31 551 epo nl Fax· (+31-70)340-3016	Funcionario Autorizado Bérillon, L

Forma PCT/ISA/210 (segunda hoja) (Enero 2004)

No. de solicitud internacional
PCT/US 2005/014120

C. DOCUMENTOS QUE SE CONSIDERA QUE SON RELEVANTES (Continuación)

Categoría	Cita del documento, con indicación, en donde sea apropiado, de los pasajes relevantes	Relevante para la Reiv No
X	DATABASE CROSSFIRE BEILSTEIN BEILSTEIN INSTITUT ZUR FOERDERUNG DER CHEMISCHEN WISSENSCHAFT, FRANKFURT AM MAIN, DE; XP002362296 Database accession no. BRN 450834 resumen ------- DATABASE CROSSFIRE BEILSTEIN BEILSTEIN INSTITUT ZUR FOERDERUNG DER CHEMISCHEN WISSENSCHAFT, FRANKFURT AM MAIN, DE; XP002362297 Database accession no. BRN 448780 resumen ------- WO 2005/005389 A (MERCK PATENT GMBH; BRUGE, DAVID; BUCHSTALLER, HANS-PETER; WIESNER, MAT) 20 Enero 2005 (2005-01-20) reivindicaciones 4,7 ------- EP 1 243 582 A (KIRIN BEER KABUSHIKI KAISHA) 25 Septiembre 2002 (2002-09-25) reivindicaciones 1,32 ------- EP 1 411 046 A (KIRIN BEER KABUSHIKI KAISHA) 21 Abril 2004 (2004-04-21) reivindicaciones 1,18 -------	1 1 1-24 1-24 1-24

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No de solicitud internacional
PCT/US 2005/014120

Bloque I Observaciones en donde ciertas reivindicaciones se encontraron inescrutables (Continuación del ítem 1 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·

1. [X] Reivindicaciones Nos..
debido a que se relacionan con temas que no requieren ser buscados por esta Autoridad, a saber·

Aunque la reivindicación 23 esta dirigida a un método de tratamiento del cuerpo humano/animal (Articulo 52(4) EPC),la búsqueda ha sido llevada a cabo y basada en los efectos alegados 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 2 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.:

4 [ ] 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

No De solicitud internacional
PCT/US 2005/014120

Documento de patente citado en el Reporte de Búsqueda	Fecha de publicación	Miembro(s) de la familia de patente(s)	Fecha de publicación
WO 2005005389 A	20-01-2005	NONE	
EP 1243582 A	25-09-2002	AU 2223201 A	09-07-2001
		WO 0147890 A1	05-07-2001
		US 2004132727 A1	08-07-2004
EP 1411046 A	21-04-2004	CA 2454538 A1	03-01-2003
		CN 1553899 A	08-12-2004
		WO 03000660 A1	03-01-2003
		US 2004242603 A1	02-12-2004

(12) SOLICITUD INTERNACIONAL PUBLICADA BAJO EL TRATADO DE COOPERACION EN MATERIA DE PATENTES (PCT)

(19)Organizacion Mundial de la Propiedad Intelectual
Oficina Internacional

(43) Fecha de publicación internacional
15 Diciembre 2005 (15 12 05)

PCT

(10) Número de publicación internacional:
WO 2005/117867 A3

(51) Clasificación de patente internacional[7]:
A61K 31/44 (2006.01) C07D 401/04 (2006.01)
C07D 213/68 (2006.01) C07D 401/06 (2006.01)
C07D 213/73 (2006 01) C07D 401/12 (2006.01)
C07D 213/74 (2006 01) C07D 401/14 (2006 01)
C07D 213/75 (2006 01) C07D 417/12 (2006 01)
C07D 239/34 (2006 01) A61P 35/00 (2006 01)
C07D 239/46 (2006.01)

(21) Número de solicitud internacional: PCT/US2005/014120

(22) Fecha de presentación internacional:
22 Abril 2005 (22.04 2005)

(25) Lenguaje de presentación: Inglés

(26) Lenguaje de publicación: Inglés

(30) Datos de prioridad:
60/564,842 23 Abril 2004 (23 04 2004) EU
60/639,178 23 Diciembre 2004 (23 12 2004) EU
11/111,144 21 Abril 2005 (21 04 2005) EU

(71) Solicitante (para todos los paises designados excepto EU): **BRISTOL-MYERS SQUIBB COMPANY [EU/EU]**; Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 (US).

(72) Inventores; y
(75) Inventores/Solicitantes (para EU solamente): **BORZILLERI, Robert M.** [US/US], 222 Riverwoods Drive, New Hope, PA 18938 (US) **CORNELIUS, Lyndon A. M.** [AG/US]; 29 Mill Pond Road, Jackson, NJ 08527 (US). **SCHMIDT, Robert J.** [US/US], 3 South Deer Place, Hainesport, New Jersey 08036 (US) **SCHROEDER, Gretchen M.** [US/US]; 82 Colleen Circle, Ewing, New Jersey 08638 (US). **KIM, Kyoung S.** [US/US], 252 Forest Lane, North Brunswick, New Jersey 08902 (US)

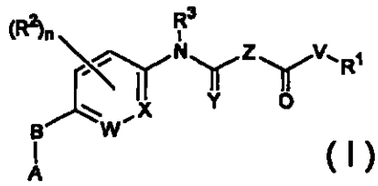
(74) Agente: **GIBBONS, Maureen, S.** et al ; Bristol-Myers Squibb Company, P O Box 4000, Princeton, New Jersey 08543-4000 (US)

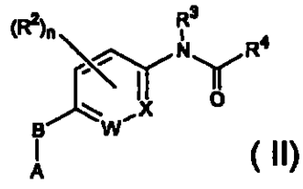
(81) Estados designados (Nacional)
AE,AG,AL,AM,AT,AU,AZ,BA,BB,BR,BG,BY,BZ,CA,CH,CN,CO,CR,CU,CZ,DE,DK,DM,DZ,EC,EE,ES,FI,GB,GD,GE,GH, GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KP,KR,KZ,LC,LK,LR,LS, LT,LU,LV,MA,MD,MG,MK,MN,MW,MX,MZ,NO,NZ,PH,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TN,TM,TR,TT,TZ,UA,UG,UZ, VN,YU,ZA,ZM,ZW

(84) Estados designados (Regional): Patente ARIPO (GH,GM,KE,LS,MW,MZ,SD,SL,SZ,TZ,UG,ZM,ZW) Patente Euroasiatica (AM,AZ,BY,KG,KZ,MD,RU,TJ,TM) Patente Europea (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR ,IE, IT, LU, MC, NL, PT ,SE, TR) Patente OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

(88) Fecha de publicación del reporte internacional de búsqueda:
30 Marzo 2006

(54) Título. HETEROCICLOS MONOCICLICOS COMO INHIBIDORES DE CINASA


(I)


(II)

(57) Extracto: La presente invención está dirigida a los compuestos que tienen la fórmula [I+II] y métodos para el uso de los mismos para el tratamiento del cáncer.

AS 102328

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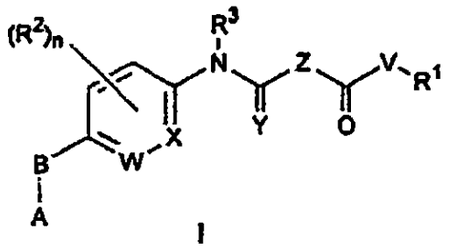
HETEROCICLOS MONOCICLICOS COMO INHIBIDORES DE CINASA

CAMPO DE LA INVENCION

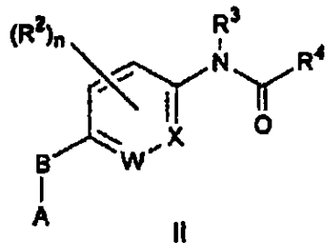
Esta invención se refiere a los compuestos que inhiben la actividad de la proteína tirosina-cinasa de los receptores del factor de crecimiento tales como c-Met, con lo cual son útiles como agentes anticancerosos. Las composiciones farmacéuticas que comprenden estos compuestos son también útiles en el tratamiento de enfermedades, diferentes del cáncer, que están asociadas con las vías de transducción de señales, que operan a través del factor de crecimiento y de los receptores anti-angiogénesis tales como c-Met.

BREVE DESCRIPCION DE LA INVENCION

La presente invención está dirigida a las composiciones que tienen las Fórmulas I y II como se describen más adelante, que son útiles en el tratamiento del cáncer.



I



II

o un enantiomero, diasteromero,hidrato,solvato, o una sal farmacéuticamente aceptable del mismo en donde:

R^1 es hidrógeno, alquilo substituido, cicloalquilo, cicloalquilo substituido, arilalquilo, arilalquilo

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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 hidrógeno, halogeno, 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, NR^8CH_2, S, SO, SO_2 o CR^9R^{10};

V es NR^{11} o $-(CR^{37}R^{38})p-$ con la condición de que cuando VR^{11} es N , R^1 es alquilo o cicloalquilo;

W y X es cada uno independientemente C o N;

Y es seleccionado de O, S, y NR^{12};

Z es $-CR^{13}R^{14}-$, o $-(CR^{13}R^{14})NR^{15}-$;

l es 0 a 2;

n es 0 a 4 si W y X son ambas C, 0 a 3 si uno de X ó W es N, y 0 a 2 si X y W son ambos N;

p es 1 a 4;

R^3, R^5, R^6, R^7, R^8, R^{11} y R^{15} son independientemente seleccionados de hidrógeno, alquilo, alquilo substituido,

alquenilo, alquenilo substituido, alquinilo, alquinilo substituido, cicloalquilo, cicloalquilo substituido, arilo, arilo substituido, heteroarilo, heteroarilo substituido, heterociclo, heterociclo substituido;

R^4 es seleccionado de arilo, arilo substituido, heteroarilo, heteroarilo substituido, heterocicloalquilo, y heterocicloalquilo substituido, con la condición de que

(a) si R^4 es fenilo

(i) R^4 no es substituido con ambos hidroxi y amido; y

(ii) R^4 no es substituido con - $NRSO_2R$ en donde R es alquilo o arilo;

(b) Si R^4 es piridilo, R^4 no es substituido con ambos hidroxi y metoxi y

(c) Si R^4 es pirimidinilo, no es substituido con =O;

R^9 y R^{10} son independientemente seleccionados de hidrógeno, halogeno, alquilo, alquilo substituido, cicloalquilo, cicloalquilo substituido, arilo, arilo substituido, heteroarilo, heteroarilo substituido, heterocicloalquil, hetrocicloalquil substituido;

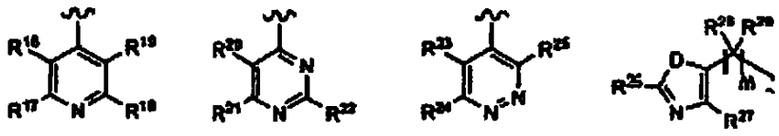
R^{12} es seleccionado de hidrógeno, alquilo, alquilo substituido, alquenilo, alquenilo substituido, alquinilo, alquilo substituido, CN, NO_2 o SO_2NH_2;

R^{13} y R^{14} son independientemente seleccionados de hidrógeno, halogeno, alquilo, alquilo substituido, alquenilo, alquenilo substituido,alquinilo, alquinilo substituido, ciclo

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alquilo, cicloalquilo substituido, arilo, arilo substituido, heteroarilo, heteroarilo substuido, heterocicloalquilo, heterocicloalquilo substituido o tomados juntos para formar un anillo carbociclico o heterociclico de 3 a 8 atomos;

A se selecciona de uno de los siguientes



en donde

D es S o O;

m es 0 a 6;

R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26} y R^{27} son independientemente seleccionados de hidrógeno, halogeno, $NR^{30}R^{31}$, OR^{32}, CO_2R^{33}, $CONR^{34}R^{35}$, SO_2R^{36}, alquilo, alquilo substituido, cicloalquilo, cicloalquilo substituido, alquenilo, alquenilo substituido, alquinilo, alquinilo substituido, -CN, arilo, arilo substituido, heteroarilo, heteroarilo substituido, heterocicloalquilo, o heterocicloalquilo substituido;

R^{28} y R^{29} es independientemente seleccionado de hidrógeno, alquilo, alquilo substituido, cicloalquilo, cicloalquilo substituido, arilo, arilo substituido, o tomados juntos para formar un anillo carbociclico o

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heterociclico de 3 a 8 átomos;

R^{30}, R^{31}, R^{32}, R^{33}, R^{34}, R^{35} y R^{36} son independientemente seleccionados de hidrógeno, alquilo, alquilo substituido, alquenilo, alquenilo substituido, alquinilo, alquinilo substituido, cicloalquilo, cicloalquilo substituido, alcoxicarbonilo, arilo, arilo substituido, heteroarilo, heteroarilo substituido, heterociclo, heterociclo substituido, heterocicloalquilo, o heterocicloalquilo substituido; y

R^{37} y R^{38} son cada uno independientemente hidrógeno, halogeno o alquilo.

DESCRIPCION DETALLADA DE LA INVENCION

La presente invención proporciona los compuestos de las Fórmulas I y II definidas anteriormente, las composiciones farmacéuticas que emplean tales compuestos y los métodos de uso de tales compuestos en el tratamiento del cáncer.

Ref. No.: 176521

El término "alquilo" en la presente solo o como parte de otro grupo más, se refiere a un radical derivado de alcano monovalente (hidrocarburo) que contiene de 1 a 12 átomos de carbono a no ser que se defina de otro modo. Los grupos alquilo preferidos son grupos alquilo inferiores que tienen de 1 a 6 átomos de carbono. Un grupo alquilo es un grupo hidrocarburo saturado, lineal, ramificado o cíclico, opcionalmente sustituido. Los grupos alquilo pueden estar sustituidos en cualquier punto disponible de enlace. Un grupo

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alquilo sustituido con otro grupo alquilo es también denominado como un "grupo alquilo ramificado". Los grupos alquilo ejemplares incluyen los grupos 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 similares. Los sustituyentes ejemplares incluyen, pero no están limitados a, uno o más de los siguientes grupos: alquilo, cicloalquilo, heterocicloalquilo, -CN, arilo, heteroarilo, halo (tal como flúor, cloro, bromo, yodo), haloalquilo (tal como CCl_3 o CF_3), hidroxilo, alcoxi, alquiltio, alquilamino, -COOH, -COOR, -C(O)R, -OCOR, amino, carbamoilo (-NHCOOR- o -OCONHR-), urea (-NHCONHR-) o tiol (-SH).

El término "alquenilo" en la presente, solo o como parte de otro grupo más, se refiere a un radical hidrocarburo lineal, ramificado o cíclico que contiene de 2 a 12 átomos de carbono y al menos un doble enlace carbono-carbono. Los grupos alquenilo pueden estar también sustituidos en cualquier punto de enlace disponible. Los sustituyentes ejemplares para los grupos alquenilo incluyen aquellos listados anteriormente para los grupos alquilo.

El término "alquinilo" en la presente solo o como parte de otro grupo más, se refiere a un radical hidrocarburo lineal, ramificado o cíclico que contiene de 2 a 12 átomos de

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carbono y al menos un triple enlace carbono-carbono. Los grupos alquinilo pueden también estar sustituidos en cualquier punto de enlace disponible. Los sustituyentes ejemplares para los grupos alquinilo incluyen aquellos listados anteriormente para los grupos alquilo.

Los números en el subíndice después del símbolo "C" definen el número de átomos de carbono que puede contener un grupo particular. Por ejemplo "alquilo C_{1-6}" (alquilo de 1 a 6 átomos de carbono) significa una cadena de carbono saturada lineal o ramificada 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 de 1 a 6 átomos de carbono" puede también referirse a alquileno de 1 a 6 átomos de carbono el cual une en puente dos grupos; los ejemplos incluyen propan-1,3-diilo, butan-1,4-diilo, 2-metil-butan-1,4-diilo, etc. "Alquenilo de 2 a 6 átomos de carbono" 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 de 2 a 6 átomos de carbono" puede también referirse a alquenodiilo de 2 a 6 átomos de carbono el cual une en puente dos grupos; los ejemplos incluyen

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etileno-1,2-diilo (vinileno), 2-metil-2-buten-1,4-diilo, 2-hexen-1,6-diilo, etc. "Alquinilo de 2 a 6 átomos de carbono" significa una cadena de carbono lineal o ramificada que tiene al menos un triple enlace carbono-carbono, y de dos a seis átomos de carbono; los ejemplos incluyen etinilo, propinilo, butinilo y hexinilo.

El término "cicloalquilo" en la presente, solo o como parte de otro grupo más, es una especie de alquilo .que contiene de 3 a 15 átomos de carbono, sin dobles enlaces alternados o resonantes entre los átomos de carbono. Este puede contener de 1 a 4 anillos. Los grupos ejemplares incluyen ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, adamantilo, etc. Los grupos cicloalquilo pueden estar sustituidos en cualquier punto disponible de enlace. Los sustituyentes ejemplares incluyen uno o más de los siguientes grupos: halógeno, tal como flúor, bromo o cloro, hidroxilo, alquilo, alcoxi, amino, nitro, ciano, tiol, alquiltio y cualquiera de los sustituyentes descritos anteriormente para los grupos alquilo.

Los términos "alcoxi" o "alquiltio" en la presente, solos o como parte de otro grupo más, denotan un grupo alquilo como se describe anteriormente enlazado a través de un enlace de oxígeno (-O-) o un enlace de azufre (-S-), respectivamente.

El término "alquiloxicarbonilo" en la presente, solo o

como parte de otro grupo más, denota un grupo alcoxi enlazado a través de un grupo carbonilo. Un radical alcoxicarbonilo es representado por la fórmula: -C(O)OR, donde el grupo R es un grupo alquilo de 1 a 6 átomos de carbono lineal o ramificado, cicloalquilo, arilo o heteroarilo.

El término "alquilcarbonilo" en la presente, solo o como parte de otro grupo más, se refiere a un grupo alquilo enlazado a través de un grupo carbonilo.

El término "alquilcarboniloxi" en la presente, solo o como parte de otro grupo más, denota un grupo alquilcarbonilo enlazado a través de un enlace de oxígeno.

El término "arilo" en la presente, solo o como parte de otro grupo mas, se refiere a los anillos aromáticos monocíclicos o bicíclicos, por ejemplo fenilo, fenilo sustituido y similares, así como los grupos que están fusionados, por ejemplo, naftilo, fenantrenilo y similares. Un grupo arilo contiene de este modo al menos un anillo que tiene al menos 6 átomos de carbono, con hasta cinco de tales anillos que están presentes, que contiene hasta 22 átomos en la presente, con dobles enlaces alternados (resonantes) entre los átomos de carbono adyacentes o los heteroátomos adecuados. Los grupos arilo pueden estar opcionalmente sustituidos con uno o más grupos que incluyen, pero no están limitados a halógeno, alquilo, alcoxi, hidroxilo, carboxilo, carbamoilo, alquiloxicarbonilo, nitro, alqueniloxi,

trifluorometilo, amino, cicloalquilo, arilo, heteroarilo, ciano, alquil-$S(O)_m$ (m=0, 1,2) o tiol.

El término "arilalquilo" o "aralquilo" en la presente, solo o como parte de otro grupo más, denota un grupo arilo como se describió anteriormente enlazado a través de un grupo alquilo, como se describió anteriormente. Un ejemplo de un grupo aralquilo es un grupo bencilo.

El término "amino" en la presente, solo o como parte de otro grupo más, se refiere a $-NH_2$. Un "amino" puede estar opcionalmente sustituido con uno o dos sustituyentes que pueden ser los mismos o diferentes, tales como los grupos alquilo, arilo, arilalquilo, alquenilo, alquinilo, heteroarilo, heteroarilalquilo, cicloheteroalquilo, cicloheteroalquilalquilo, cicloalquilo, cicloalquilalquilo, haloalquilo, hidroxialquilo, alcoxialquilo, tioalquilo, carbonilo o carboxilo. Estos sustituyentes pueden estar además sustituidos con un ácido carboxílico, cualquiera de los sustituyentes alquilo o arilo anteriormente descritos. En algunas modalidades, los grupos amino están sustituidos con carboxilo o carbonilo para formar los derivados de N-acilo o N-carbamoilo.

El término "heteroarilo" en la presente, solo o como parte de otro grupo más, se refiere a los grupos monociclicos de 5 o de 6 miembros, aromáticos, sustituidos y no sustituidos, los grupos bicíclicos de 9 ó 10 miembros, y los

grupos tricíclicos de 11 a 14 miembros que tienen al menos un heteroátomo (oxígeno, azufre o nitrógeno) 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 de uno a cuatro átomos de nitrógeno, con la condición de que el número total de heteroátomos en cada anillo sea cuatro o menos, y cada anillo tenga al menos un átomo de carbono. Los anillos fusionados que completan los grupos bicílicos y tricíclicos pueden contener únicamente átomos de carbono, y pueden estar saturados, parcialmente saturados, o insaturados. Los átomos de nitrógeno y azufre pueden estar opcionalmente oxidados, y los átomos de nitrógeno pueden estar opcionalmente cuaternizados. 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 puede estar enlazado en cualquier átomo de nitrógeno o carbono disponible de cualquier anillo. El sistema de anillo heteroarilo puede contener cero, uno, dos o tres sustituyentes seleccionados del grupo que consiste de halo, alquilo, alquilo sustituido, alquenilo, alquinilo, arilo, nitro, ciano, hidroxilo, alcoxi, tioalquilo, =O, $-CO_2H$, -C(=O)H, $-CO_2$-alquilo, -C(=O)alquilo, fenilo, bencilo, feniletilo, feniloxi, feniltio, cicloalquilo, cicloalquilo sustituido, heterociclo,

heteroarilo, -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" es independientemente seleccionado de hidrógeno, alquilo, alquilo sustituido, y cicloalquilo, o R' y R" juntos forman un anillo heterociclo o heteroarilo.

Los grupos heteroarilo monocíclicos ejemplares incluyen los grupos 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 los grupos indolilo, benzotiazolilo, benzodioxolilo, benzoxaxolilo, benzotienilo, quinolinilo, tetrahidroisoquinolinilo, isoquinolinilo, bencimidazolilo, benzopiranilo, indolizinilo, benzofuranilo, cromonilo, cumarinilo, benzopiranilo, cinolinilo, quinoxalinilo, indazolilo, pirrolopiridilo, furopiridinilo, dihidroisoindolilo, tetrahidroquinolinilo y similares.

Los grupos heteroarilo tricíclicos ejemplares incluyen los grupos carbazolilo, bencidolilo, fenantrolinilo, acridinilo, fenantridinilo, xantenilo y similares.

El término "anillo heterocíclico" en la presente, solo o como parte de otro grupo más, se refiere a un sistema de anillo monocíclico, estable, saturado o parcialmente

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insaturado que contiene 5 a 7 miembros en el anillo de átomos de carbono y otros átomos seleccionados de nitrógeno, azufre y/o oxígeno. Preferentemente, un anillo heterocíclico es un anillo monocíclico de 5 o de 6 miembros y contiene uno, dos o tres heteroátomos seleccionados de nitrógeno, oxígeno y/o azufre. El anillo heterocíclico puede estar opcionalmente sustituido, lo cual significa que el anillo heterocíclico puede estar sustituido en una o más posiciones de anillo sustituibles con uno o más grupos independientemente seleccionados de alquilo (preferentemente alquilo inferior), alcoxi (preferentemente alcoxi inferior), nitro, monoalquilamino (preferentemente un alquilamino inferior), dialquilamino (preferentemente un di[alquil inferior]amino), ciano, halo, haloalquilo (preferentemente trifluorometilo), alcanoilo, aminocarbonilo, monoalquilaminocarbonilo, dialquilaminocarbonilo, alquilamido (preferentemente [alquil inferior]amido), alcoxialquilo (preferentemente un alcoxi[alquilo inferior]), alcoxicarbonilo (preferentemente un alcoxicarbonilo inferior), alquilcarboniloxi (preferentemente un alquilcarboniloxi inferior) y arilo (preferentemente fenilo), el arilo está opcionalmente sustituido con los grupos halo, alquilo inferior y alcoxi inferior. Los ejemplos de tales anillos heterocíclicos son isoxazolilo, imidazolinilo, tiazolinilo, imidazolidinilo, pirrolilo, pirrolinilo, piranilo, pirazinilo, piperidilo,

morfolinilo y triazolilo. El anillo heterocíclico puede estar enlazado a la estructura progenitora a través de un átomo de carbono o a través de cualquier heteroátomo del heterociclilo, que de como resultado una estructura estable.

El término "heteroátomo" significa oxígeno, azufre o nitrógeno, seleccionado de una base independiente. Se debe notar que cualquier heteroátomo con valencias no satisfechas se asume que tiene el 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.

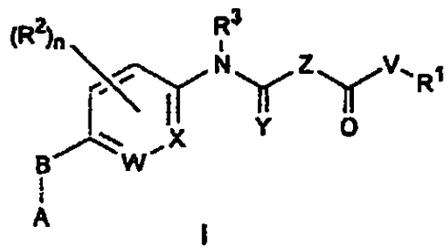
Cuando un grupo funcional es denominado "protegido", esto significa que el grupo está en forma modificada para excluir las reacciones colaterales no deseadas en el sitio protegido. Los grupos protectores adecuados para los compuestos de la presente invención serán reconocidos a partir de la presente solicitud tomando en cuenta el nivel de experiencia en la técnica, y con referencia a los libros de texto estándares, tales como Greene, T.W. et al., Protective Groups in Organic Synthesis, Wiley, N.Y. (1991).

Como se utiliza en la presente, el término "paciente" abarca todas las especies de mamíferos.

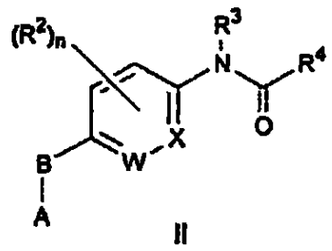
Los ejemplos adecuados de sales de los compuestos de acuerdo a la invención con ácidos inorgánicos u orgánicos son el clorhidrato, bromhidrato, sulfato, metansulfonato,

maleato, fumarato y fosfato. Las sales que no son adecuadas para uso farmacéutico, pero que pueden ser empleadas, por ejemplo, para el aislamiento o purificación de los compuestos I o II libres, sus sales farmacéuticamente aceptables, son también incluidos.

En general, la presente invención comprende, los compuestos que tienen la Fórmula I o II:



I



II

o un enantiómero, diastereoisómero, hidrato, solvato o sal farmacéuticamente aceptable de los mismos en donde:

R^1 es hidrógeno, alquilo, alquilo sustituido, cicloalquilo, cicloalquilo sustituido, arilalquilo, arilalquilo sustituido, arilo, arilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, heteroarilo, heteroarilo sustituido, heterociclo, heterociclo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, heterocicloalquilo o heterocicloalquilo sustituido:

Cada R^2 es independientemente hidrógeno, halógeno, ciano, NO_2, OR^5, NR^6R^7, alquilo, alquilo sustituido, cicloalquilo, cicloalquilo sustituido, arilo, arilo

(12) SOLICITUD INTERNACIONAL PUBLICADA BAJO EL TRATADO DE COOPERACION EN MATERIA DE PATENTES (PCT)

(19)Organizacion Mundial de la Propiedad Intelectual
Oficina Internacional

(43) Fecha de publicación internacional
15 Diciembre 2005 (15.12 .05)

PCT

(10) Número de publicación internacional:
WO 2005/117867 A3

(51) Clasificación de patente internacional[7]:
A61K 31/44 (2006.01) C07D 401/04 (2006 01)
C07D 213/68 (2006.01) C07D 401/06 (2006 01)
C07D 213/73 (2006.01) C07D 401/12 (2006 01)
C07D 213/74 (2006 01) C07D 401/14 (2006.01)
C07D 213/75 (2006 01) C07D 417/12 (2006.01)
C07D 239/34 (2006.01) A61P 35/00 (2006 01)
C07D 239/46 (2006 01)

(21) Número de solicitud internacional: PCT/US2005/014120

(22) Fecha de presentación internacional:
22 Abril 2005 (22 04 2005)

(25) Lenguaje de presentación: Inglés

(26) Lenguaje de publicación: Inglés

(30) Datos de prioridad:
60/564,842 23 Abril 2004 (23.04.2004) EU
60/639,178 23 Diciembre 2004 (23 12 2004) EU
11/111,144 21 Abril 2005 (21 04 2005) EU

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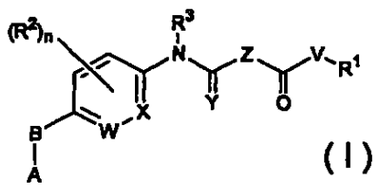
(74) Agente: **GIBBONS, Maureen, S.** et al ; Bristol-Myers Squibb Company, P.O. Box 4000, Princeton, New Jersey 08543-4000 (US).

(81) Estados designados (Nacional):
AE,AG,AL,AM,AT,AU,AZ,BA,BB,BR,BG,BY,BZ,CA,CH,CN,CO,CR,CU,CZ,DE,DK,DM,DZ,EC,EE,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KP,KR,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,MK,MN,MW,MX,MZ,NO,NZ,PH,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TN,TM,TR,TT,TZ,UA,UG,UZ,VN,YU,ZA,ZM,ZW

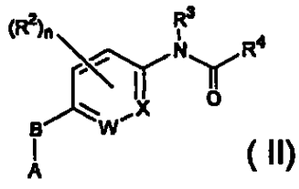
(84) Estados designados (Regional): Patente ARIPO (GH,GM,KE,LS,MW,MZ,SD,SL,SZ,TZ,UG,ZM,ZW) Patente Euroasiatica (AM,AZ,BY,KG,KZ,MD,RU,TJ,TM) Patente Europea (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR ,IE, IT, LU, MC, NL, PT ,SE, TR) Patente OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

(88) Fecha de publicación del reporte internacional de búsqueda:
30 Marzo 2006

(54) Título. HETEROCICLOS MONOCICLICOS COMO INHIBIDORES DE CINASA



(I)



(II)

(57) Extracto: La presente invención está dirigida a los compuestos que tienen la fórmula [I+II] y métodos para el uso de los mismos para el tratamiento del cáncer.

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Oficina Internacional

(43) Fecha de publicación internacional
15 Diciembre 2005 (15 12..05)

PCT

(10) Número de publicación internacional:
WO 2005/117867 A3

(51) Clasificación de patente internacional[7]:
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C07D 213/68 (2006.01) C07D 401/06 (2006 01)
C07D 213/73 (2006.01) C07D 401/12 (2006.01)
C07D 213/74 (2006.01) C07D 401/14 (2006.01)
C07D 213/75 (2006.01) C07D 417/12 (2006.01)
C07D 239/34 (2006.01) A61P 35/00 (2006 01)
C07D 239/46 (2006.01)

(21) Número de solicitud internacional: PCT/US2005/014120

(22) Fecha de presentación internacional:
22 Abril 2005 (22.04 2005)

(25) Lenguaje de presentación: Inglés

(26) Lenguaje de publicación: Inglés

(30) Datos de prioridad:
60/564,842 23 Abril 2004 (23.04.2004) EU
60/639,178 23 Diciembre 2004 (23.12.2004) EU
11/111,144 21 Abril 2005 (21 04 2005) EU

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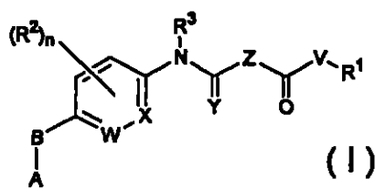
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(81) Estados designados (Nacional).
AE,AG,AL,AM,AT,AU,AZ,BA,BB,BR,BG,BY,BZ,CA,CH,CN,CO,CR,CU,CZ,DE,DK,DM,DZ,EC,EE,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KP,KR,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,MK,MN,MW,MX,MZ,NO,NZ,PH,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TN,TM,TR,TT,TZ,UA,UG,UZ,VN,YU,ZA,ZM,ZW

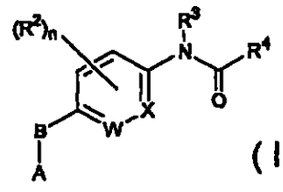
(84) Estados designados (Regional) Patente ARIPO (GH,GM,KE,LS,MW,MZ,SD,SL,SZ,TZ,UG,ZM,ZW) Patente Euroasiatica (AM,AZ,BY,KG,KZ,MD,RU,TJ,TM) Patente Europea (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR ,IE, IT, LU, MC, NL, PT ,SE, TR) Patente OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

(88) Fecha de publicación del reporte internacional de búsqueda:
30 Marzo 2006

(54) Título. HETEROCICLOS MONOCICLICOS COMO INHIBIDORES DE CINASA



(I)



(II)

(57) Extracto: La presente invención está dirigida a los compuestos que tienen la fórmula [I+II] y métodos para el uso de los mismos para el tratamiento del cáncer.

sustituido, heteroarilo, heteroarilo sustituido, heterociclo, heterociclo sustituido, arilalquilo, arilalquilo sustituido, heterocicloalquilo, o heterocicloalquilo sustituido;

B es O, NR^8, $NR^{8+}CH_2$, S, SO, SO_2 o CR^9R^{10};

V es NR^{11} o $-(CR^{37}R^{38})_p-$ con la condición de que cuando V sea nitrógeno, R^1 sea un alquilo o cicloalquilo;

W y X son cada uno independientemente carbono o nitrógeno;

Y se selecciona de oxígeno, azufre y NR^{12};

Z es $-CR^{13}R^{14}-$, o $-(CR^{13}R^{14})_1NR^{15}-$;

1 es 0 a 2;

n es 0 a 4 si W y X son ambos carbono, 0 a 3 si uno de X o W es nitrógeno, y 0 a 2 si X y W son ambos nitrógeno;

p es 1 a 4;

R^3, R^5, R^6, R^7, R^8, R^{11} y R^{15} son independientemente seleccionados de hidrógeno, alquilo, alquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, cicloalquilo, cicloalquilo sustituido, arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, heterociclo, heterociclo sustituido;

R^4 se selecciona de arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, heterocicloalquilo y heterocicloalquilo sustituido, con la condición de que:

(a) si R^4 es fenilo

(i) R^4 no está sustituido con hidroxilo y amido; y

(i) R^4 no está sustituido con $-NRSO_2R-$ en donde R es alquilo o arilo;

(b) si R^4 es piridilo, R^4 no está sustituido con hidroxilo y metoxi;

y

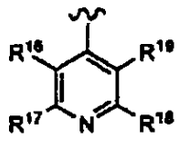
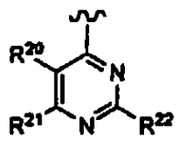
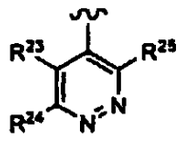
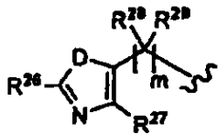
(c) si R^4 es pirimidinilo, éste no está sustituido con =O;

R^9 y R^{10} son independientemente seleccionados de hidrógeno, halógeno, alquilo, alquilo sustituido, cicloalquilo, cicloalquilo sustituido, arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, heterocicloalquilo o heterocicloalquilo sustituido;

R^{12} se selecciona de hidrógeno, alquilo, alquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, CN, NO_2 o SO_2NH_2;

R^{13} y R^{14} son independientemente seleccionados de hidrógeno, halógeno, alquilo, alquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, cicloalquilo, cicloalquilo sustituido, arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, heterocicloalquilo, heterocicloalquilo sustituido o tomados conjuntamente forman un anillo carbocíclico o heterocíclico de 3 a 8 átomos;

A se selecciona de uno de los siguientes:

en donde:

D es S u O;

m es 0 a 6;

R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26} y R^{27} son independientemente seleccionados de hidrógeno, halógeno, $NR^{30}R^{31}$, OR^{32}, CO_2R^{33}, $CONR^{34}R^{35}$, SO_2R^{36}, alquilo, alquilo sustituido, cicloalquilo, cicloalquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, -CN, arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, heterocicloalquilo, o heterocicloalquilo sustituido;

R^{28} y R^{29} son independientemente seleccionados de hidrógeno, alquilo, alquilo sustituido; cicloalquilo, cicloalquilo sustituido, arilo, arilo sustituido, o tomados conjuntamente forman un anillo carbocíclico o heterocíclico de 3 a 8 átomos;

R^{30}, R^{31}, R^{32}, R^{33}, R^{34}, R^{35} y R^{36} son independientemente seleccionados de hidrógeno, alquilo, alquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, cicloalquilo, cicloalquilo sustituido, alcoxicarbonilo, arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, heterociclo, heterociclo sustituido, heterocicloalquilo, o heterocicloalquilo sustituido; y

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R^{37} y R^{38} son cada uno independientemente hidrógeno, halógeno o alquilo.

En algunas modalidades de la presente invención, R^1 es un grupo fenilo sustituido o no sustituido, tal como fluorofenilo, un alquilo de 1 a 4 átomos de carbono sustituido o no sustituido, tal como metilo o un cicloalquilo de 3 a 8 átomos de carbono sustituido o no sustituido, tal como ciclohexilo o ciclopentilo.

En algunas modalidades de la presente invención, R^2 es alquilo de 1 a 4 átomos de carbono, halógeno o haloalquilo.

En algunas modalidades de la presente invención, R^4 es fenilo opcionalmente sustituido, o un grupo heteroarilo que contiene nitrógeno, de 5 ó 6 miembros, tal como piridilo, pirazolilo o pirrolidilo.

De acuerdo a una modalidad de la presente invención, B es O, $NHCH_2$, CH_2 o CH (OH); Y es O o S y Z es $-CR^{13}R^{14}$ o $-NR^{15}$ en donde R^{13}, R^{14} y R^{15} son cada uno hidrógeno.

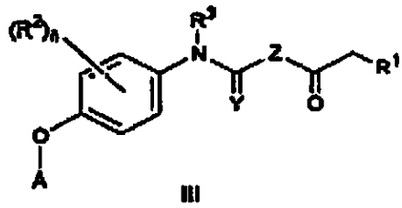
En algunas modalidades de la presente invención, A es una piridina o pirimidina opcionalmente sustituida, en donde el sustituyente es alquilo, alquenilo, alquinilo, halógeno, cicloalquilo, heterocicloalquilo, $-NR^{39}COR^{40}$, $-NR^{39}C(O)_2R^{40}$, $-NR^{41}R^{42}$ o $-C(O)NR^{43}R^{44}$, en donde $R^{39}R^{40}$, R^{41}, R^{42}, R^{43} y R^{44} son independientemente hidrógeno, alquilo inferior, alquilo inferior sustituido, hidroxialquilo, aminoalquilo, cicloalquilo, cicloalquilo sustituido, heterocicloalquilo,

heterocicloalquilo sustituido, cicloalquenilo, cicloalquenilo sustituido, arilo, arilo sustituido, heteroarilo, heteroarilo sustituido o $-NR^{43}R^{44}$ forman un heterocicloalquilo.

De acuerdo a algunas modalidades de la presente invención, A es una piridina sustituida con $-NR^{41}R^{42}$, $-NR^{39}COR^{40}$, $-C(O)NR^{43}R^{44}$, halógeno, alquilo de 1 a 4 átomos de carbono opcionalmente sustituido con hidroxi, hidroxialquilamino, alquilamino, aminoalquilamino, o heteroarilalquilo, o $-C=C-R^{45}$, $-C\equiv C-R^{46}$, en donde R^{45} y R^{46} son alquilo, hidroxialquilo, aminoalquilo, cicloalquilo, heterocicloalquilo, $-C(O)R^{47}$, $-NR^{39}COR^{40}$, arilo o heteroarilo; o la piridina está sustituida con arilo, tal como fenilo, que puede estar sustituida con $CONH_2$, metilo, aminoetilo, hidroxietilo, $-CONHCH_2CH_2NHCH_3$ o CH_2CONH_2, las piridinas pueden también estar sustituidas con los grupos piridilo o piperidilo.

De acuerdo a algunas modalidades de la presente invención, A es una pirimidina opcionalmente sustituida. Los sustituyentes preferidos incluyen-$NR^{41}R^{42}$, o $-NR^{39}CO_2R^{40}$, en donde R^{41} y R^2 son preferentemente hidrógeno o metilo y R^{39} y R^{40} son preferentemente, hidrógeno o alquilo.

En una modalidad de la presente invención, los compuestos tienen la siguiente formula III

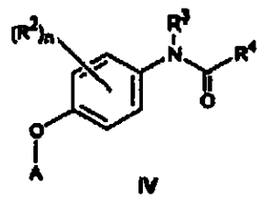


III

en donde

R^1 es fenilo o alquilo opcionalmente substituido; Z es NH o NCH_3; R^2 es F, Cl, CH_3, o CF_3, R^3 es hidrógeno; y Y es O o S. En algunas modalidades, R^1 es cicloalquilo C_3 -C_7, fenilo substituido o no substituido, o $-(CH_2)_n-R^{50}$ en donde n es de 1 a 3, R^{50} es hidrógeno, fenilo substituido o no substituido, amino, amido, CN, $-C(O)_2H$, o $-C(O)_2CH_3$.

En algunas modalidades de la presente invención , los compuestos tienen la siguiente formula IV

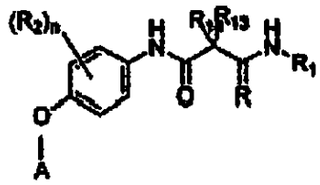


IV

en donde R^2 es halo o hidrógeno; R^3 es hidrógeno, R^4 es fenilo opcionalmente substituido, pirazolo opcionalmente substituido o piridilo opcionalmente substituido, piridinona, o piridina-N-oxido.

En una modalidad de la presente invención , los compuestos son aquellos de la formula V

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en donde R^1 es alquilo o cicloalquilo opcionalmente substituido; A es pirimidina opcionalmente substituida o piridina; y R_2 es halo o hidrógeno; y R^{13} y R^{14} es ya sea hidrógeno o junto con el carbono al cual esta unido forma un cicloalquilo tal como ciclopropilo.

La invención también proporciona los métodos para tratar una enfermedad proliferativa vía la modulación de la cinasa Met, mediante la administración a una especie de mamífero en necesidad de tal tratamiento, de una cantidad efectiva de un compuesto de las Fórmulas I o II, como se definieron anteriormente. En otra modalidad más, la invención proporciona un método para tratar una enfermedad proliferativa vía la modulación de la cinasa Met por administración a una especie de mamífero en necesidad de tal tratamiento, de una cantidad efectiva de un compuesto de las Fórmulas I o II, como se definieron anteriormente, en combinación (simultánea o secuencialmente) con al menos otro agente anticanceroso. En una modalidad preferida, la enfermedad proliferativa es el cáncer.

Ciertos compuestos de las Fórmulas I y II pueden ser preparados en general de acuerdo a los siguientes Esquemas

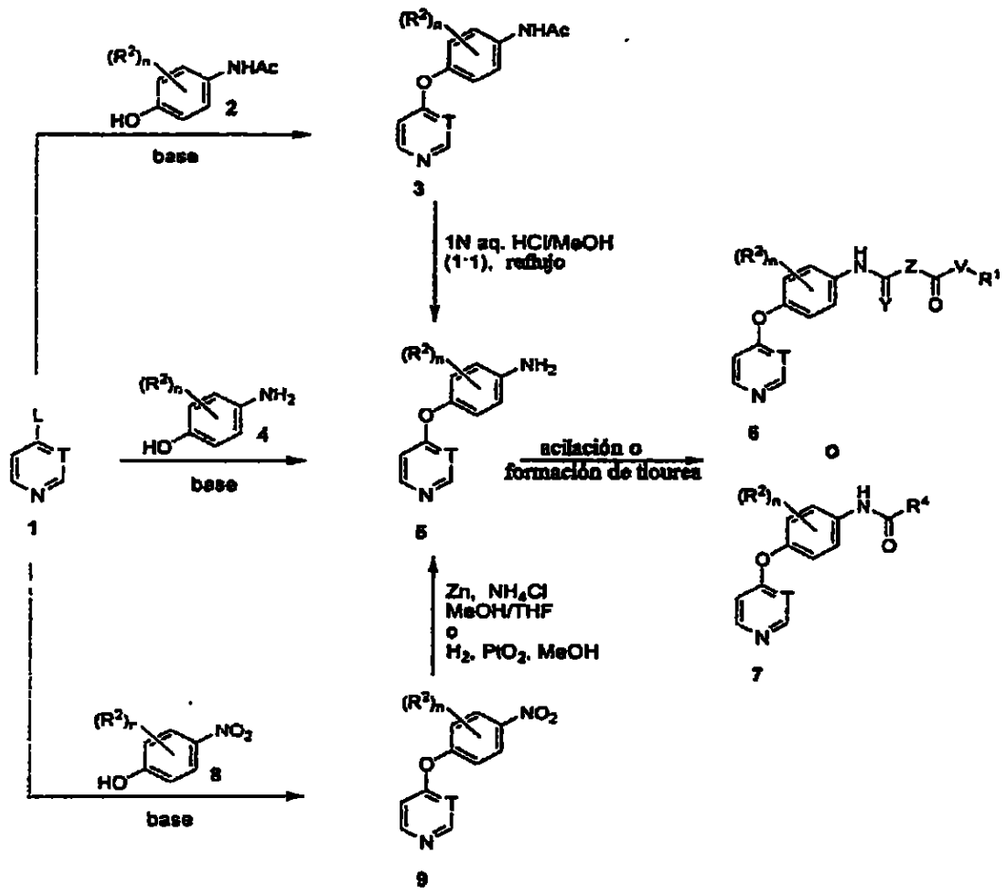
dee reacción 1-14. Los compuestos son sintetizados fácilmente utilizando métodos sintéticos conocidos por una persona de experiencia en la técnica. Los solvatos (por ejemplo, hidratos) de los compuestos de las Fórmulas I y II están también dentro del alcance de la presente invención. Los métodos de solvatación son en general conocidos en la técnica. En consecuencia, los compuestos de la presente invención pueden estar en la forma libre o de hidrato, y pueden ser obtenidos mediante los métodos ejemplificados por los siguientes Esquemas de Reacción.

Las rutas generales para los análogos de piridina y pirimidina descritos en la invención se ilustran en el Esquema de Reacción 1. Una piridina o pirimidina 1 apropiadamente sustituida puede ser tratada con los fenoles 2, 4 y 8 en presencia de una base, tal como hidruro de sodio, hidróxido de sodio, o carbonato de potasio, para proporcionar los éteres deseados 3, 5 y 9, respectivamente. La eliminación del grupo protector de acetamida del compuesto 3 con HCl acuoso en metanol, proporciona el intermediario clave 5.

Alternativamente, la anilina 5 puede ser obtenida a partir del compuesto 9 vía la reducción del grupo nitro ya sea con polvo de zinc y cloruro de amonio o catalizador de Adams (óxido de platino (IV)) bajo condiciones de hidrogenación. Los análogos 6 y 7 pueden ser entonces preparados mediante acilación de la anilina 5 con, por ejemplo isocianatos, cloruros de ácido o mediante tratamiento con un ácido

carboxílico y un reactivo de acoplamiento, tal como: hexafluorofosfato de benzotriazol-1-iloxitris(trimetilamino)fosfonio (reactivo BOP), hexafluorofosfato de bromotripirrolidinofosfonio (PyBroP), tetrafluoroborato de O-(1H-benzotriazol-1-il)-N,N,N',N'-tetrametiluronio (TBTU). La formación de la aciltiourea de 6 (Y=S, Z=NH) puede ser lograda mediante tratamiento de anilina 5 con un isotiocianato apropiadamente sustituido.

Esquema de Reacción 1

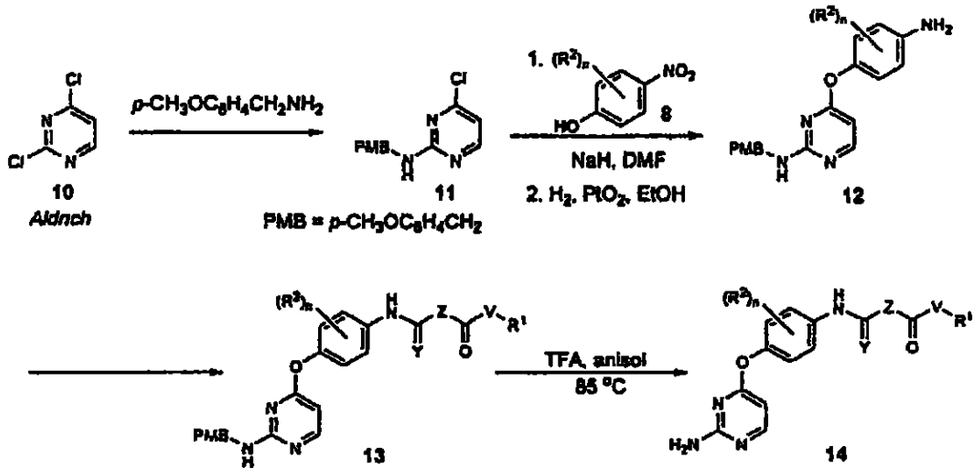


T=CR^{19} o N

L=grupo saliente, tal como un halógeno o NO2

Los dos diferentes análogos de aminopirimidina regioisoméricos 14 y 19 pueden ser preparados utilizando las rutas sintéticas descritas en los Esquemas de Reacción 2 y 3. La aminopirimidina 11 protegida con PMB, derivada de la 2,4-dicloropirimidina comercialmente disponible (10, Aldrich), puede ser convertida al éter 13 vía la anilina 12 utilizando la misma química descrita en el Esquema de Reacción 1. La eliminación del grupo PMB de 13 puede ser lograda con el ácido trifluoroacético y anisol para generar el compuesto 14.

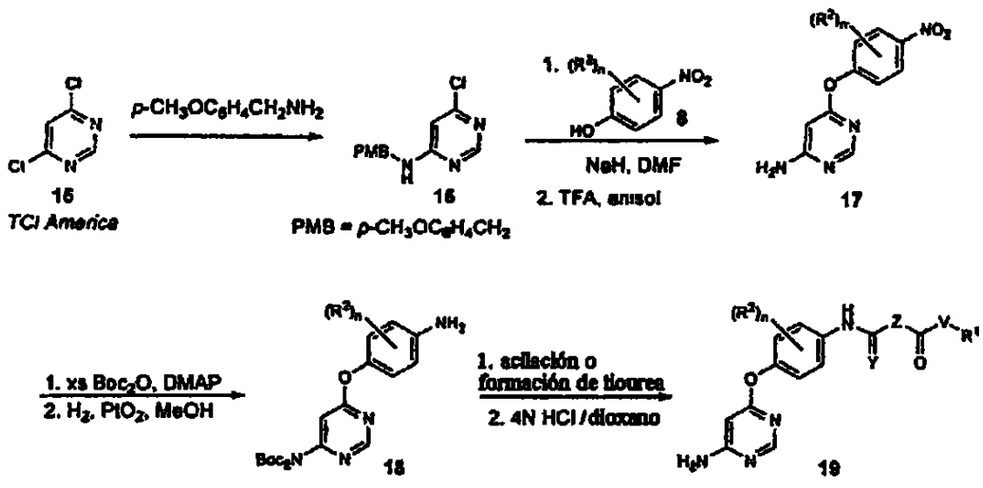
Esquema de Reacción 2



Similarmente, la aminopirimidina 16 protegida con PMB, derivada de la 4,6-dicloropirimidina comercialmente disponible (15, TCI America) puede ser convertida al éter 17 siguiendo el paso de desprotección de PMB (Esquema de Reacción 3). La protección con Bis-Boc(t-butoxicarbonilo) de la amina 17 con dicarbonato de di-ter-butilo en exceso,

seguido por hidrogenación con catalizador de Adams proporciona la anilina 18. La amina 19 puede ser obtenida a partir del compuesto 18 después de un paso de formación de tiourea o acilación y eliminación de los grupos protectores Boc bajo condiciones ácidas.

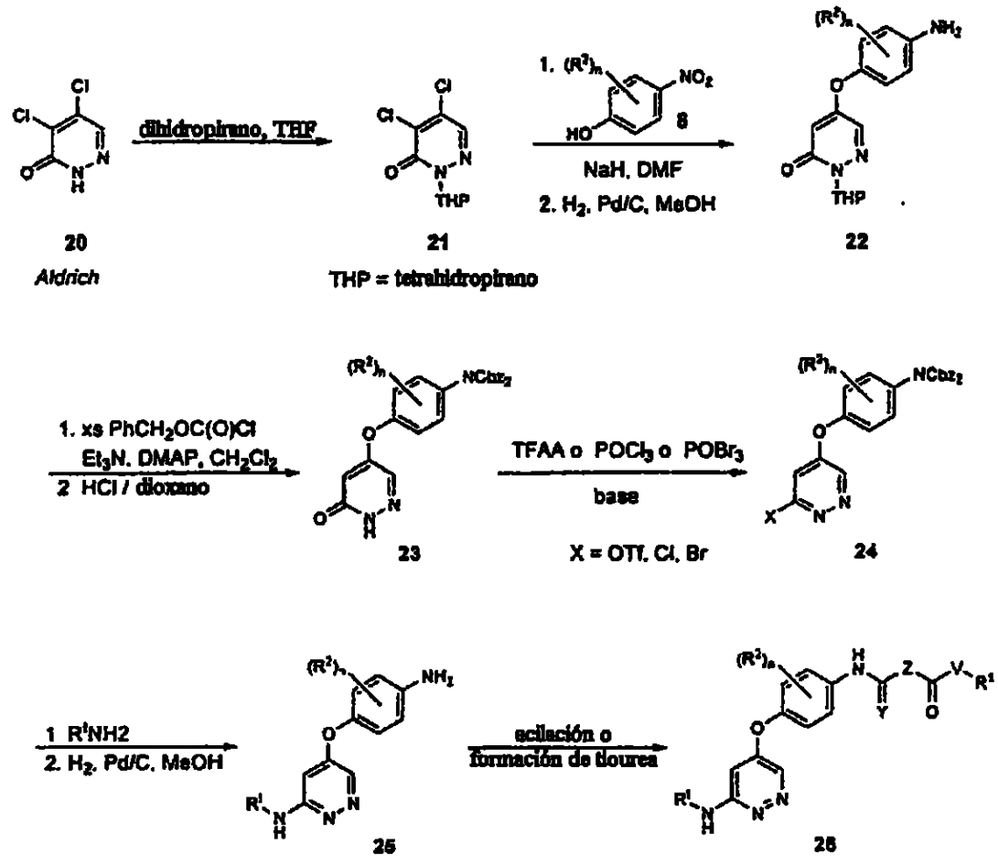
Esquema de Reacción 3



El derivado de aminopiridazina 26 puede ser preparado utilizando la ruta sintética descrita en el Esquema de Reacción 4, que está basada en una química similar citada en las siguientes referencias: Chung, H.-A. et al. J. Heterocyclic Chem. 1999, 36, 905-910 y Bryant R.D. et al. J. Heterocyclic Chem. 1995, 32, 1473-1476, las descripciones de las cuales se incorporan por referencia en la presente. La 4,5-dicloropiridazin-3(2H)-ona (20, Aldrich) puede ser protegida con, por ejemplo un grupo tetrahidropirano (THP) para dar el intermediario 21. El tratamiento del compuesto 21

con un fenol apropiadamente sustituido y una base (por ejemplo, hidruro de sodio) seguido por reducción del intermediario que contiene el grupo nitro bajo condiciones de hidrogenación catalítica, puede proporcionar la anilina 22. La protección del grupo anilina de 22 como un carbamato de bis-bencilo (Cbz) seguido por la eliminación del grupo THP bajo condiciones ácidas, puede proporcionar el compuesto 23. El tratamiento del compuesto 23 ya sea con anhídrido trifluoroacético (TFAA), oxicloruro de fósforo u oxibromuro de fósforo en presencia de una base, tal como trietilamina o diisopropiletilamina puede introducir el grupo saliente necesario en la posición 3 del compuesto 24. El desplazamiento del grupo saliente X del compuesto 24 con una amina apropiadamente sustituida, seguida por la eliminación de los grupos Cbz puede generar el intermediario 25. La anilina 25 puede ser convertida al análogo de 3-aminopiridazina 26, deseado, utilizando la química previamente descrita en los Esquemas de Reacción 1-3.

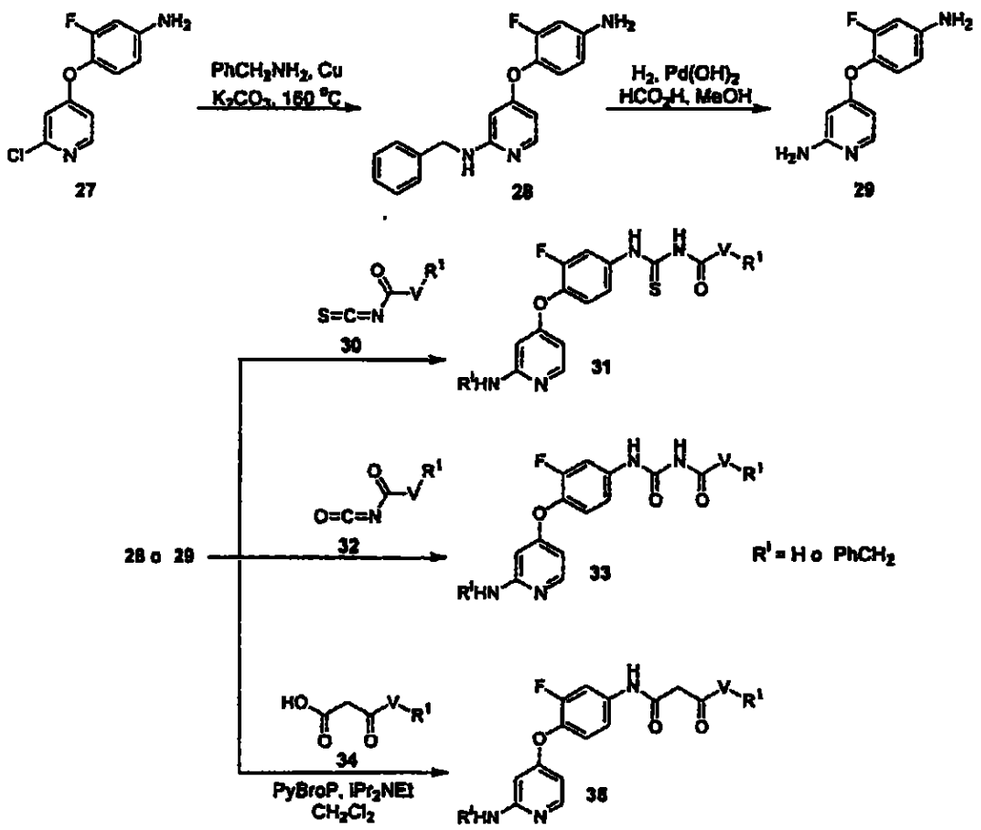
Esquema de Reacción 4



Los derivados de 2-aminopiridina pueden ser preparados utilizando las rutas sintéticas descritas en los Esquemas de Reacción 5 y 6. La anilina 27, derivada de la química descrita en el Esquema de Reacción 1 puede ser convertida al intermediario 28 después de calentamiento con polvo de cobre y carbonato de potasio en bencilamina (Esquema de Reacción 5). La eliminación del grupo protector de bencilo del compuesto 28 bajo condiciones de hidrogenación catalítica con

paladio o sobre carbono proporciona la aminopiridina 29. Los intermediarios 28 ó 29 pueden ser tratados con los isotiocianatos 30, isocianatos 32, y ácidos carboxílicos 34 en presencia de un reactivo de acoplamiento para proporcionar la aciltiourea 31, la acilurea 33, y la amida 35, respectivamente.

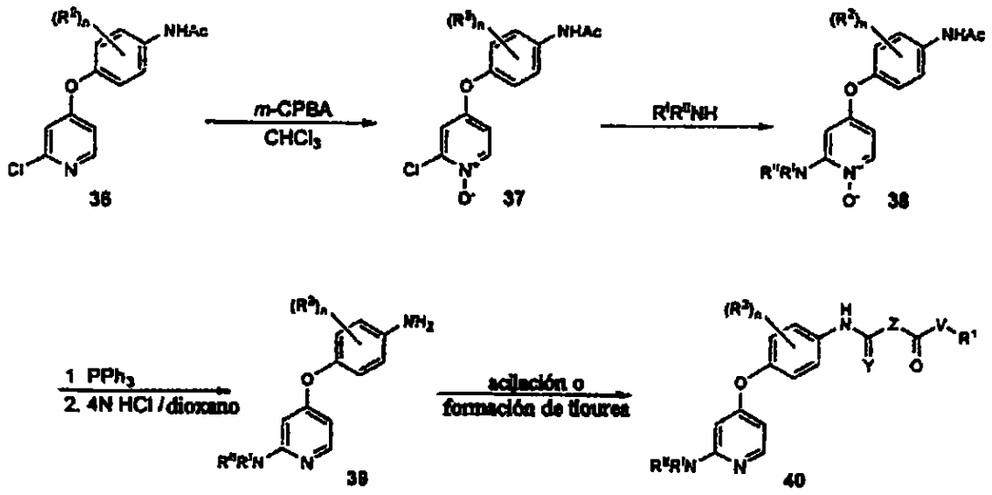
Esquema de Reacción 5



En un procedimiento relacionado, el intermediario 2-cloropiridina 36, obtenido utilizando la química descrita en el Esquema de Reacción 1, puede ser convertido al N-óxido 37

utilizando el ácido 3-cloroperoxibenzoico (m-CPBA) en cloroformo (ver, WO2004/002410) (Esquema de Reacción 6). El tratamiento del compuesto 37 con una amina apropiadamente sustituida puede proporcionar el intermediario 38. La reducción del N-óxido del compuesto 38 con, por ejemplo trifenilfosfina, seguido por la eliminación del grupo protector de acetamida bajo condiciones ácidas puede proporcionar anilina 39. La conversión de anilina 39 al análogo 40 deseado puede ser lograda utilizando la química previamente descrita en los Esquema de Reacción 1-5.

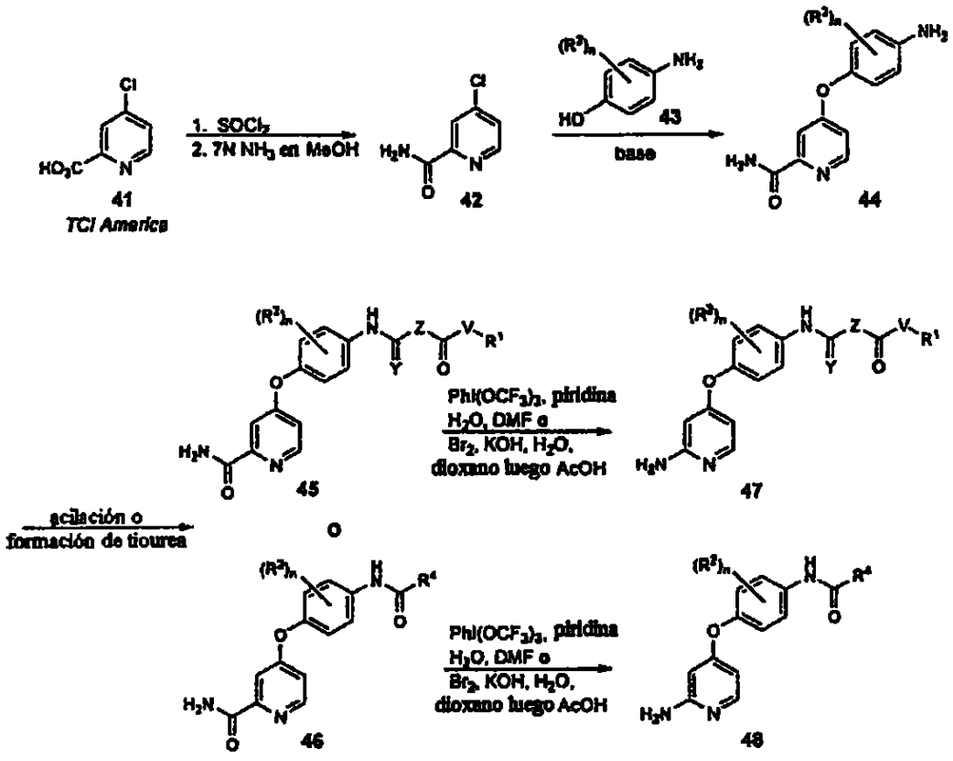
Esquema de Reacción 6



En un procedimiento alternativo a los compuestos relacionados a 40, los derivados de 2-aminopiridina 47 y 48 pueden ser preparados de acuerdo a la secuencia sintética ilustrada en el Esquema de Reacción 7. Para este fin, el

ácido 4-cloropicolínico (41, TCI America) puede ser convertido a la 4-cloropicolinamida (42) utilizando un procedimiento de dos pasos que involucra el cloruro de tionilo seguido por amoniaco en metanol. El acoplamiento del intermediario 42 con el derivado de 4-aminofenol 43, en presencia de una base, tal como t-butóxido de potasio puede proporcionar el derivado de picolinamida 44. La acilación o la formación de la acilurea del intermediario 44 puede proporcionar los intermediarios tales como 45 y 46. El tratamiento de los derivados de picolinamida 45 y 46 ya sea con bis-(trifluoroacetoxi)-yodobenceno, piridina y agua en DMF o bromo, hidróxido de potasio en agua, promueve un reacomodo de Hofmann para generar los derivados de 2-aminopiridina deseados, 47 y 48.

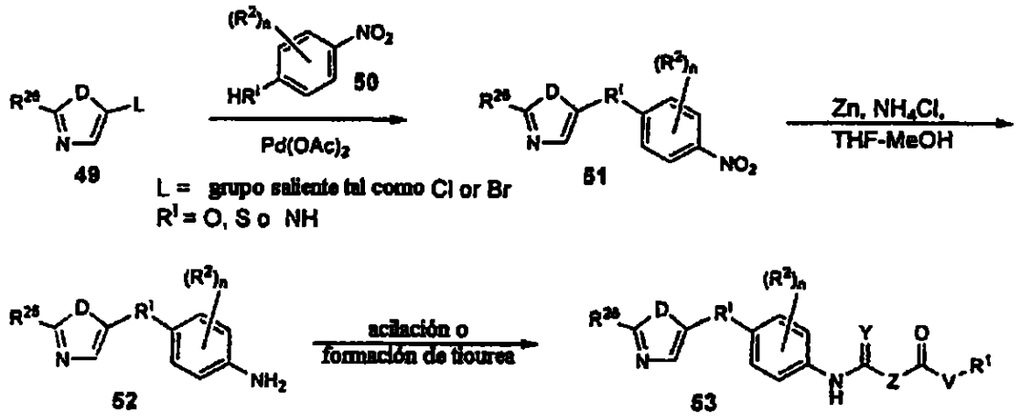
Esquema de Reacción 7



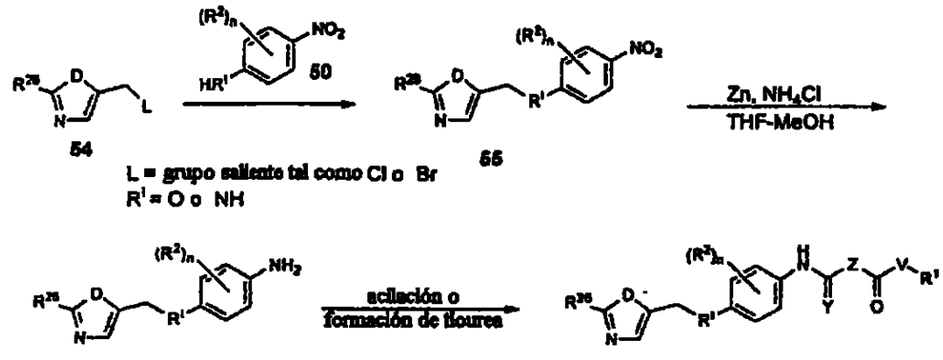
El tiazol que contiene los compuestos 53, 57 y 62 pueden ser preparados utilizando las rutas sintéticas descritas en los Esquemas de Reacción 8-10. El desplazamiento de los grupos salientes de 49 (Esquema de Reacción 8) o 54 (Esquema de Reacción 9) con una anilina/fenol 50 puede proporcionar los intermediarios 51 y 55, respectivamente. La reducción de los sustituyentes nitro de 51 y 55 con polvo de zinc y cloruro de amonio en una mezcla de THF-metanol debe generar las anilinas 52 y 56, respectivamente. La conversión de las anilinas 52 y 56 a los compuestos deseados 53 y 57 puede ser

lograda utilizando la química previamente descrita (ver arriba).

Esquema de Reacción 8



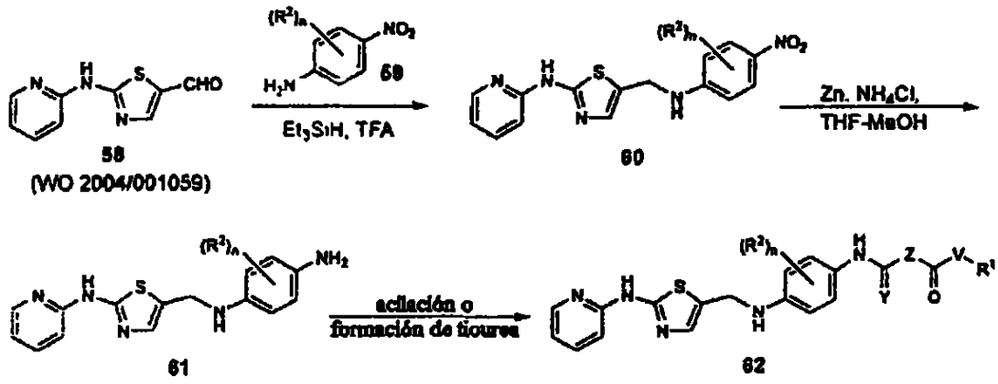
Esquema de Reacción 9



La aminación reductiva del aldehído 58 puede ser lograda utilizando los métodos descritos en WO2004/001059, incorporado por referencia en la presente en su totalidad, utilizando una anilina 59 apropiadamente sustituida, que

puede proporcionar el intermediario nitro 60 (Esquema de Reacción 10). El derivado de aminotiazol 62 deseado puede ser luego obtenido utilizando una química similar a aquélla que fue descrita en los Esquemas de Reacción 8 y 9.

Esquema de Reacción 10

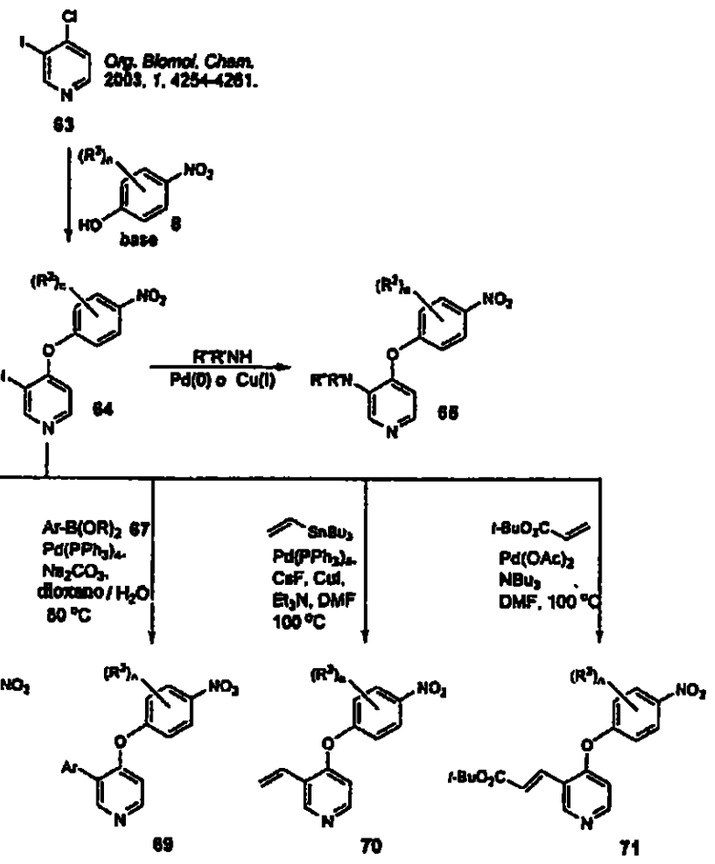


La incorporación de los diversos sustituyentes en la posición 3 del núcleo de piridina puede ser lograda utilizando la química descrita en el Esquema de Reacción 11. Para este fin, la 4-cloro-3-yodopiridina (63, Tabanella, S. et al. Org. Biomol. Chem. 2003, 1, 4254-4261) puede ser acoplada con el derivado de 4-nitrofenol 8 en presencia de una base, tal como diisopropiletilamina (base de Hunig) para proporcionar el intermediario de yoduro deseado 64. Una variedad de reacciones de acoplamiento mediadas por compuesto organometálico puede ser llevada a cabo con el derivado de yoduro 64, ejemplos de los cuales se ilustran en el Esquema de Reacción 11. El yoduro 64 puede ser tratado con las aminas

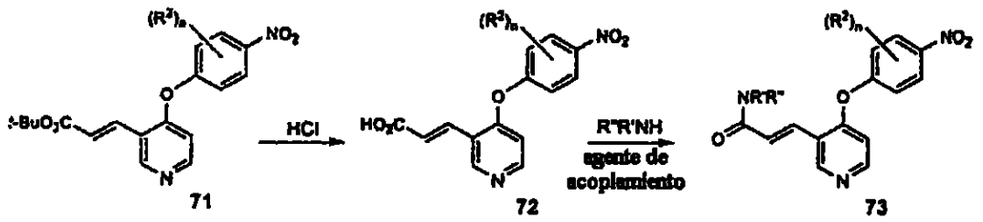
(R''R'NH), alquinos sustituidos 66, arilboronatos 67, vinilestananos, y ésteres α,β-insaturados en presencia de un catalizador de paladio o de cobre para proporcionar los intermediarios 65, 68-71, respectivamente. La porción nitro de los compuestos 65 y 68-71 puede ser reducida con, por ejemplo polvo de zinc y cloruro de amonio en una mezcla de THF-metanol, y los intermediarios de anilina resultantes pueden ser acilados utilizando la química previamente descrita en los Esquemas de Reacción 1-5.

El intermediario 71 puede ser entonces convertido a las amidas α,β-insaturadas 73 (Esquema de Reacción 12). El compuesto 72 derivado de la hidrólisis promovida por ácido del éster 71, puede ser acoplado con diversas aminas (R' R'NH) en presencia de un reactivo de acoplamiento tal como, pero no limitado a EDCI, TBTU, DCC, para proporcionar el intermediario de amida 73, deseado. La reducción de la porción nitro de 73 y la acilación subsiguiente del intermediario de anilina requerido, puede ser logrado utilizando la química previamente descrita en los Esquemas de Reacción 1-5.

Esquema de Reacción 11



Esquema de Reacción 12

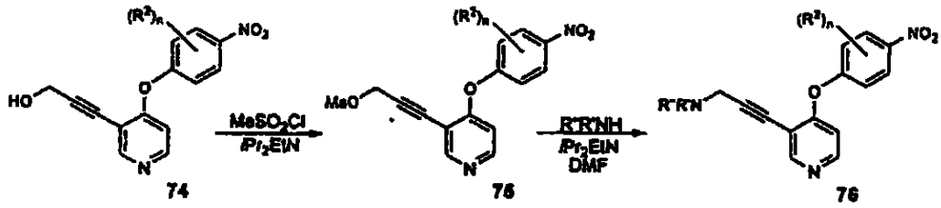


El intermediario 74 puede ser también modificado adicionalmente para preparar las aminas propargílicas 76 (Esquema de Reacción 13). La mesilación del alcohol

propargílico 74, puede ser lograda con cloruro de etansulfonilo en presencia de una base, tal como diisopropiletilamina (base de Hunig) para proporcionar el mesilato 75. El desplazamiento del grupo mesilato del compuesto 75 con diversas aminas (R"R'NH) puede proporcionar las aminas propargílicas 76.

La reducción de la porción nitro de 76 y la acilación subsecuente del intermediario de anilina requerido puede ser lograda utilizando la química previamente descrita en los Esquemas de Reacción 1-5.

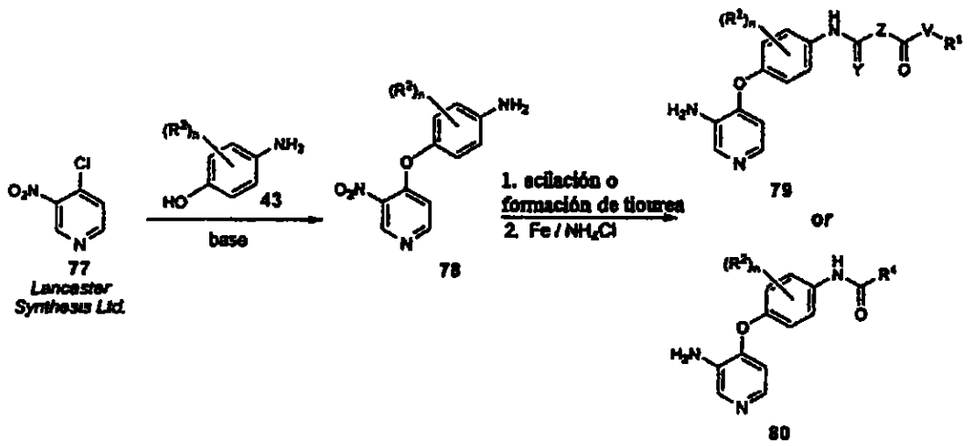
Esquema de Reacción 13



Los derivados de 3-aminopiridina 79 y 80 pueden ser preparados de acuerdo a la ruta sintética descrita en el Esquema de Reacción 14. Para este fin, la 4-cloro-3-nitropiridna (77, Lancaster Synthesis Ltd.) puede ser acoplada con el 4-aminofenol en presencia de una base, tal como hidruro de sodio en DMF para proporcionar el intermediario nitro 78. La química previamente descrita anteriormente puede ser utilizada para convertir el intermediario 78 a los compuestos deseados 79 y 80. El

sustituyente amino de 79 y 80 puede ser también adicionalmente modificado, por ejemplo vía la alquilación, acilación, arilación o sulfonilación.

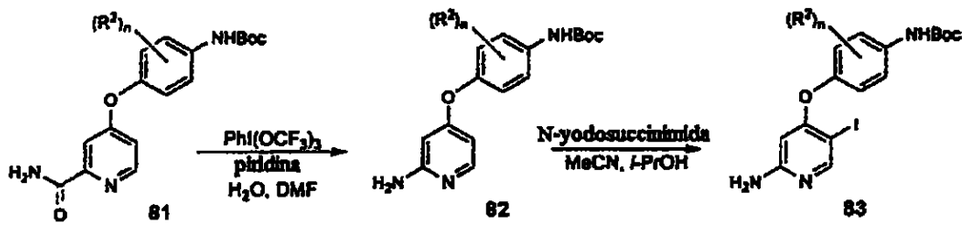
Esquema de Reacción 14



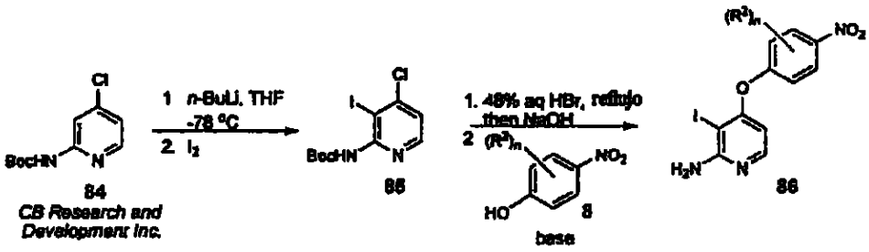
La incorporación de los sustituyentes ya sea en la posición 5 ó 3 del anillo de 2-aminopiridina puede ser lograda utilizando los intermediarios del yoduro 83 y 86, O respectivamente (Esquemas de Reacción 15 y 16). El derivado de 2-carboxamida 81 puede ser convertido al derivado de 2-aminopiridina 82 utilizando el protocolo de reacomodo de Hofmann previamente descrito en el Esquema de Reacción 7. La yodación de la posición 5 del compuesto 82 puede ser lograda con N-yodosuccinimida en una mezcla de acetonitrilo-isopropanol para proporcionar el intermediario de yoduro 83 deseado. Alternativamente, el 4-cloropiridin-2-ilcarbamato de t-butilo (84, CB Research and Development Inc.) puede ser

convertido al 4-cloro-3-yodopiridin-2-ilcarbamato de t-butilo (85) vía un proceso de dos pasos que involucra el n-butil-litio en THF a baja temperatura, seguido por la adición de yodo. La eliminación del grupo protector de N-Boc (t-butilcarbamato) de 85 con bromuro de hidrógeno acuoso a reflujo, seguido por el acoplamiento del intermediario de cloruro con el derivado de 4-nitrofenol 8 en presencia de diisopropilamina (base de Hunig) en N-metilpirrolidinona (NMP) a temperatura elevada, puede proporcionar el intermediario del yoduro 86. Los intermediarios de yoduro 83 y 86 pueden ser además procesados utilizando una química similar a aquella previamente descrita en el Esquema de Reacción 11.

Esquema de Reacción 15



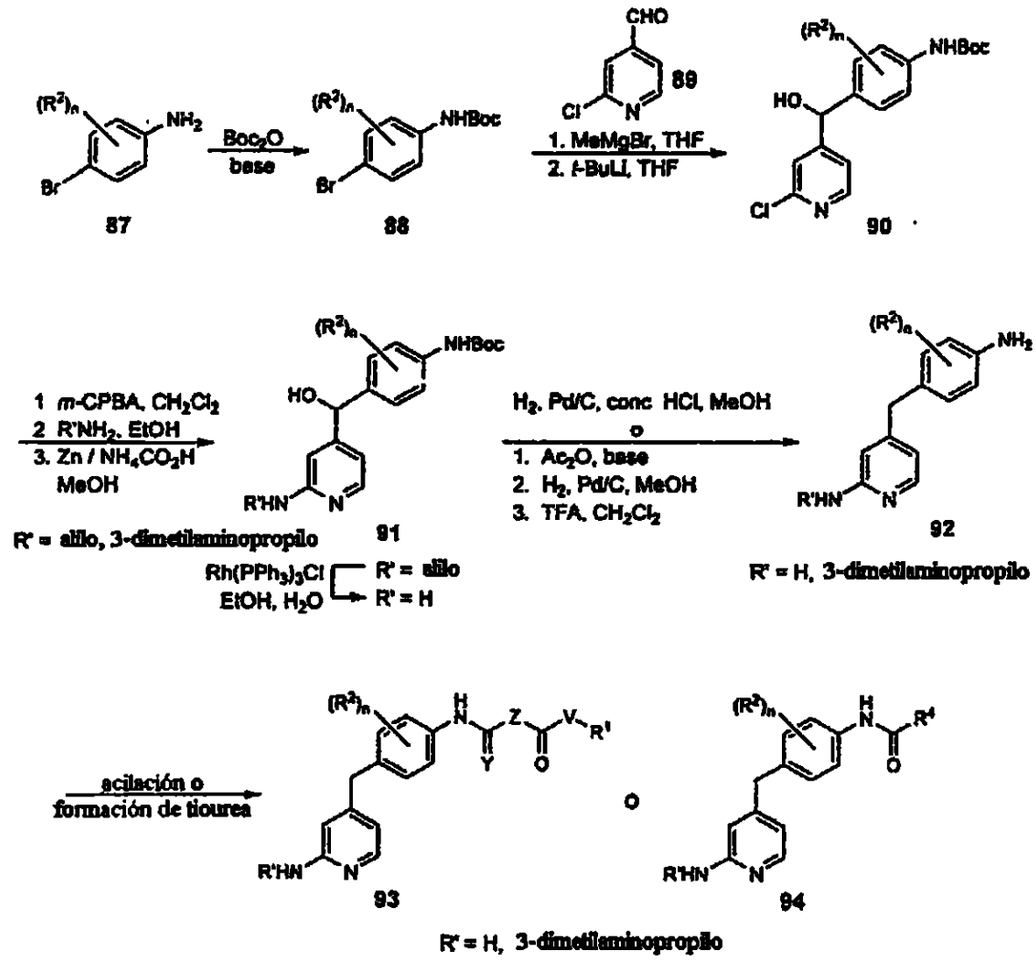
Esquema de Reacción 16



Los análogos 93 y 94 enlazados al metileno ($B=CH_2$) pueden ser preparados de acuerdo a la secuencia sintética descrita en el Esquema de Reacción 17. El compuesto 88, derivado de la protección con N-Boc del derivado de 4-bromoanilina 87, puede ser tratado con bromuro de metilmagnesio seguido por ter-butil-litio y 2-cloroisonicotinaldehído (Frey, L.F. et al. Tetrahedron Lett. 2001, 42, 6815-6818) a baja temperatura para proporcionar el intermediario 90. La oxidación del anillo de piridina de 90 con el ácido 3-cloroperoxibenzoico (m-CPBA), seguido por el desplazamiento del sustituyente cloro con una amina ($R'NH_2$) y la reducción subsecuente del intermediario de N-óxido con zinc y formiato de amonio en metanol, puede proporcionar el intermediario 91. Cuando se utiliza la alilamina como la amina nucleofílica ($R'NH_2$), el grupo alilo puede ser removido de la amina de 91 utilizando un catalizador de rodio en una mezcla de etanol-agua. La eliminación del grupo hidroxilo de 91 puede ser lograda mediante dos diferentes métodos. Por

ejemplo, la hidrogenólisis del compuesto 91 en presencia de un catalizador de paladio, seguido por la desprotección del grupo N-Boc sobre la anilina bajo condiciones ácidas (HCl en metanol) puede proporcionar el compuesto 92. Alternativamente, el compuesto 92 puede ser obtenido mediante acilación del alcohol de 91 y la hidrogenólisis subsecuente del intermediario en presencia de un catalizador de paladio y la eliminación del grupo protector de N-Boc bajo condiciones ácidas (ácido trifluoroacético en cloruro de metileno). El intermediario 92 puede ser luego acilado para proporcionar los compuestos deseados 93 y 94 utilizando la química previamente descrita en los Esquemas de Reacción 1-5.

Esquema de Reacción 17

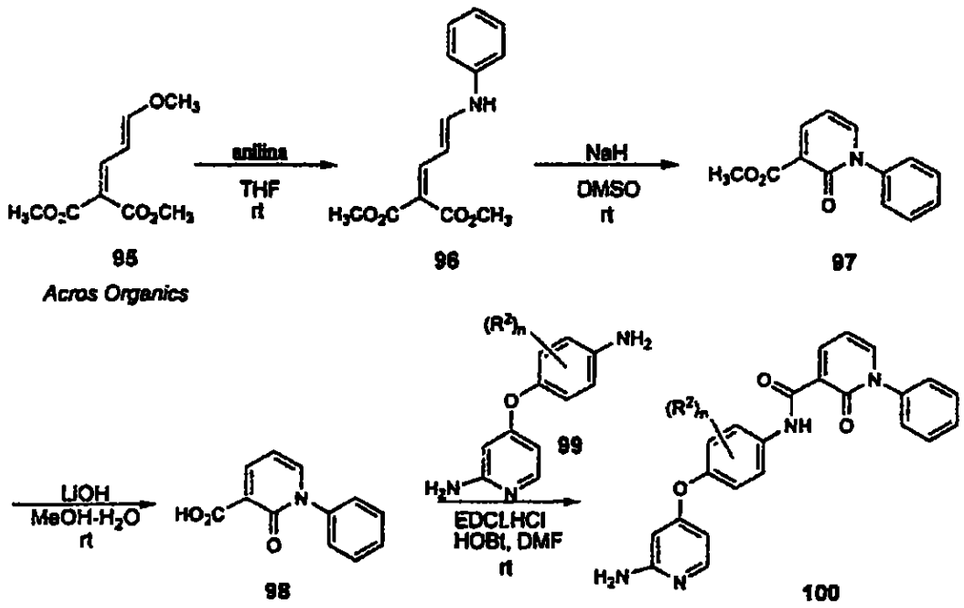


Los derivados de amida heterocíclica 100 y 105 pueden ser preparados de acuerdo a las rutas sintéticas descritas en los Esquemas de Reacción 18 y 19. Para est fin, el 2-oxo-1-fenil-1,2-dihidropiridn-3-carboxilato de metilo (97) puede ser obtenido en un proceso de dos pasos comenzando con el 2-(3-metoxialiliden)malonato de (E)-5 dimetilo (95) (Esquema de Reacción 18). De este modo, el tratamiento del compuesto 95

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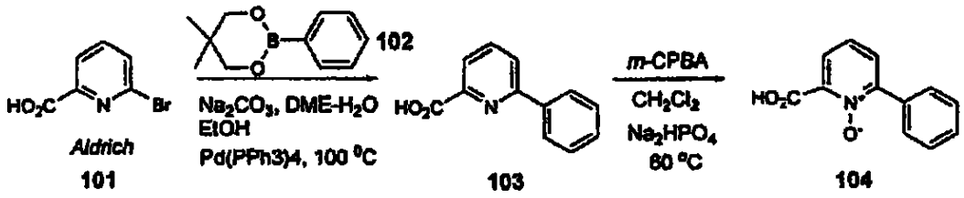
con anilina a temperatura ambiente puede proporcionar el intermediario 96, que puede ser luego ciclizado en presencia de una base, tal como hidruro de sodio en sulfóxido de dimetilo para generar el intermediario 97. La hidrólisis del intermediario 97 bajo condiciones básicas puede proporcionar el ácido 2-oxo-1-fenil-1,2-dihidropiridin-3-carboxílico (98). El ácido carboxílico 98 puede ser luego acoplado con el derivado de anilina 99 en presencia de un reactivo de acoplamiento, tal como el clorhidrato de 1-(dimetilaminopropil)-3-etilcarbodiimida (EDCI) e hidroxibenzotriazol (HOBt) en DMF para proporcionar el compuesto 100 deseado.

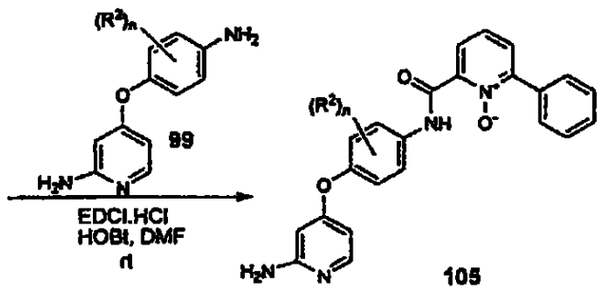
Esquema de Reacción 18



El intermediario de N-óxido de piridilo 104 (Esquema de Reacción 19) puede ser obtenido mediante un proceso de dos pasos en el cual el ácido.6-bromopicolínico (101) comercialmente disponible es acoplado con el fenil-1,3,2-dioxaborinano 102 (Aldrich) en presencia de un catalizador de paladio (0) y carbonato de sodio, seguido por la oxidación del intermediario requerido 103 a temperatura elevada. El acoplamiento del intermediario 104 con el derivado de anilina 99 puede proporcionar el compuesto 105 deseado.

Esquema de Reacción 19





Los compuestos de las Fórmulas I y II son útiles en el tratamiento de una variedad de cánceres, incluyendo, pero no limitados a, los siguientes:

(A) carcinoma, incluyendo aquel de vejiga, mama, colon,

riñón, hígado, pulmón, incluyendo el cáncer pulmonar de células pequeñas, esófago, vesícula biliar, ovario, páncreas, estómago, cérvix, tiroides, próstata y piel, incluyendo carcinoma de células escamosas;

(b) tumores hematopoyéticos de la línea linfoide, incluyendo leucemia, leucemia linfocítica aguda, leucemia linfoblástica aguda, linfoma de células B, linfoma de células T, linfoma de Hodgkin, linfoma no Hodgkin, linfoma de células pilosas y linfoma de Burkett;

(c) tumores hematopoyéticos de la línea mieloide, incluyendo leucemias mielogénicas 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 schwannomas; y

(f) otros tumores, incluyendo melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentoso, keratoxanthoma, cáncer folicular de tiroides y sarcoma de Kaposi.

Debido al papel clave de las cinasas proteicas en la regulación de la proliferación celular en general, los inhibidores podrían actuar como agentes citostáticos reversibles que pueden ser útiles en el tratamiento de

cualquier proceso de enfermedad que caracterice. La proliferación celular anormal, por ejemplo, hiperplasia prostática benigna, adenomatosis familiar, poliposis, neurofibromatosis, ateroesclerosis, fibrosis pulmonar, artritis, psoriasis, glomerulonefritis, restenosis después de la angioplasia o cirugía vascular, formación de cicatriz hipertrófica, enfermedad inflamatoria del intestino, rechazo de trasplante, choque endotóxico e infecciones por hongos.

Los compuestos de las Fórmulas I y II como moduladores de la apoptosis, serán útiles en el tratamiento del cáncer (incluyendo pero no limitados a aquellos tipos mencionados en la presente anteriormente), infecciones virales (incluyendo pero no limitadas a herpervirus, poxvirus, virus de Epstein-Barr, virus Sindbis y adenovirus), prevención del desarrollo de SIDA en individuos infectados con el VIH, enfermedades autoinmunes (incluyendo pero no limitadas a lupus eritematoso sistémico, glomerulonefritis mediada por procesos autoinmunes, artritis reumatoide, psoriasis, enfermedad inflamatoria del intestino, y diabetes mellitus autoinmune), trastornos neurodegenerativos (incluyendo pero no limitados a enfermedad de Alzheimer, demencia relacionada al SIDA, enfermedad de Parkinson, esclerosis lateral amiotrófica, retinitis pigmentosa, atrofia muscular espinal y degeneración cerebelar), síndromes mielodisplásticos, anemia aplástica, daño isquémico asociado con infartos del miocardio, apoplejía

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y daño por reperfusión, arritmia, ateroesclerosis, enfermedades hepáticas inducidas por toxinas o relacionadas al alcohol, enfermedades hematológicas (incluyendo pero no limitadas a anemia crónica y anemia aplástica), enfermedades degenerativas del sistema musculoesquelético (incluyendo pero no limitadas a osteoporosis y artritis) rinosinusitis sensible a la aspirina, fibrosis quística, esclerosis múltiple, enfermedades del riñón y dolor por cáncer.

Los compuestos de las Fórmulas I y II pueden modular el nivel de síntesis de ARN y ADN celular. Estos agentes podrían ser útiles por lo tanto en el tratamiento de infecciones virales (incluyendo pero no limitadas al VIH, virus de papiloma humano, herpesvirus, poxvirus, virus de Epstein-Barr, virus Sindbis y adenovirus).

Los compuestos de las Fórmulas I y II pueden ser útiles en la quimioprevención del cáncer. La quimioprevención es definida como la inhibición del desarrollo del cáncer invasor ya sea por el bloqueo del evento mutagénico iniciador o mediante el bloqueo de la progresión de las células pre-malignas que han sufrido ya un daño, o la inhibición de la recidiva tumoral.

Los compuestos de las Fórmulas I y II pueden también ser útiles en la inhibición de la angiogénesis tumoral y la metástasis.

El término agente "anticanceroso" incluye cualquier

agente que sea útil para el tratamiento del cáncer, incluyendo el 17α-etinilestradiol, dietilestibetrol, testosterona, prednisona, fluoximesterona, propionato de dromostanolona, testolactona, acetato de megestrol, metilprednisolona, metil-testosterona, prednisolona, triamcinolona, clorotrianiseno, hidroxiprogesterona, aminoglutetimida, estramustina, acetato de medroxiprogesterona, leuprolida, flutamida, toremifeno, zoladex, inhibidores de la metaloproteinasa de matriz, inhibidores de VEGF, incluyendo anticuerpos anti-VEGF tales como Avastin, y moléculas pequeñas tales como ZD6474 y SU6668, vatalanib, BAY-43-9006, SU11248, CP-547632, y CEP-7055 son también incluidos. Los anticuerpos anti-Her2 de Genentech (tal como Herceptin) puede ser también utilizado. Los inhibidores de EGFR adecuados incluyen gefitinib, erlotinib y cetuximab. Los inhibidores de Pan-Her incluyen canertinib, EKB-569 y GW-572016. Se incluyen también los inhibidores de Src así como Casodex® (bicalutamida, Astra Zeneca), Tamoxifeno, inhibidores de la cinasa MEK-1, inhibidores de la cinasa MAPK, inhibidores de PI3, e inhibidores de PDGF, tales como imatinib. También se incluyen agentes anti-angiogénicos y antivasculares los cuales, por interrupción del flujo sanguíneo a los tumores sólidos, hacen a las células cancerosas estar en reposo al privarlas de la nutrición. Puede ser también utilizada la castración, la cual

hace no profilerativos a los carcinomas dependientes de andrógenos. También se incluyen los inhibidores de IGF1R, inhibidores de las cinasas de tirosina de no receptor y de receptor, e inhibidores de la señalización de integrina. Los agentes anticancerosos adicionales incluyen agentes estabilizadores de los microtúbulos tales como paclitaxel (también conocido como Taxol®), docetaxel (también conocido como Taxotere®), 7-O-metiltiometilpaclitaxel (descrito en la Patente de los Estados Unidos No. 5,646,176), 4-desacetil-4-metilcarbonatopaclitaxel, 3'-ter-butil-3'-N-ter-butiloxicarbonil-4-desacetil-3'-defenil-3'-N-desbenzoil-4-O-metoxicarbonil-paclitaxel (descrito en USSN 09/712,352 presentado el 14 de noviembre del 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*,165*]]-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-diana (descrito en WO99/02514), [IS-[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 la Patente de los Estados Unidos No. 6,262,094) y derivados de los mismos; y los agentes perturbadores de los microtúbulos. También adecuados son los inhibidores de CDK, un inhibidor

antiproliferativo del ciclo celular, epidofilotoxina; una enzima antineoplásica; un inhibidor de toposiomerasa; procarbazina; mitoxantrona; complejos de coordinación de platino tales como cis-platino y carboplatino; modificadores de la respuesta biológica; inhibidores del crecimiento; agentes terapéuticos antihormonales; leucovorina; tegafur; y factores de crecimiento hematopoyético.

Los agentes citotóxicos adicionales incluyen, melfalan, hexametilmelamina, tiotepa, citarabina, idatrexato, trimetrexato, dacarbazina, L-asparaginasa, camptotecina, topotecan, bicalutamida, flutamida, leuprolida, derivados de piridobenzoindol, interferones e interleucinas.

Las composiciones farmacéuticas que contienen el ingrediente activo pueden estar en una forma adecuada para el uso oral, por ejemplo, como tabletas, trociscos, pastillas, suspensiones acuosas o aceitosas, polvos o gránulos dispersables, emulsiones, cápsulas de gelatina dura o suave, o jarabes o elixires. Las composiciones destinadas para el uso oral pueden ser preparadas de acuerdo a cualquier método conocido en la técnica para la fabricación de composiciones farmacéuticas, y tales composiciones pueden contener uno o más agentes seleccionados del grupo que consiste de agentes endulzantes, agentes saborizantes, agentes colorantes y agentes conservadores, con el fin de proporcionar preparaciones farmacéuticamente elegantes y gratas al

paladar. Las tabletas contienen el ingrediente activo en mezcla con excipientes no tóxicos farmacéuticamente aceptables 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 de desintegración, por ejemplo, celulosa microcristalina, croscarmelosa de sodio, almidón de maíz, o ácido algínico; agentes aglutinantes, por ejemplo almidón, gelatina, polivinil-pirrolidona o acacia, y agentes lubricantes, por ejemplo, estearato de magnesio, ácido esteárico o talco. Las tabletas pueden ser no recubiertas o éstas pueden ser recubiertas mediante técnicas conocidas para enmascarar el sabor no placentero del fármaco o retrasar la desintegración y la absorción en el tracto gastrointestinal y con esto proporcionar una acción sostenida en un periodo más prolongado. Por ejemplo, un material de enmascaramiento del sabor soluble en agua tal como hidroxipropil-metilcelulosa o hidroxipropil-celulosa, o un material de retraso en el tiempo tal como etilcelulosa, butirato de acetato de celulosa, puede ser también empleado.

Las composiciones farmacéuticas para el uso .oral pueden ser también presentadas como cápsulas de gelatina dura en donde el ingrediente activo es mezclado con un diluyente sólido inerte, por ejemplo, carbonato de calcio, fosfato de

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calcio o kaolin, o como cápsulas de gelatina suave en donde el ingrediente activo es mezclado con un portador soluble en agua tal como polietilenglicol o un medio aceitoso, por ejemplo aceite de cacahuate, parafina líquida, o aceite de oliva.

Las suspensiones acuosas contienen el material activo en mezcla con excipientes adecuados para la fabricación de suspensiones acuosas. Tales excipientes son agentes suspensores, por ejemplo carboximetilcelulosa de sodio, metilcelulosa, hidroxipropilmetil-celulosa, alginato de sodio, polivinilpirrolidona, goma de tragacanto y goma de acacia; los agentes dispersantes o humectantes pueden ser una fosfatida de origen natural, por ejemplo lecitina, o productos de condensación de un óxido de alquileno con ácidos grasos, por ejemplo estearato de polioxietileno o productos de condensación del 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-sorbitol, o productos de condensación del óxido de etileno con ésteres parciales derivados de ácidos grasos y anhídridos de hexitol, por ejemplo monooleato de polietilensorbitan. Las suspensiones acuosas pueden contener también uno o más conservadores, por ejemplo p-hidroxibenzoato de etilo, o de n-propilo, uno o más

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agentes colorantes, uno o más agentes saborizantes, y uno o más agentes endulzantes, tales como sucrosa, sacarina o aspartame.

Las suspensiones aceitosas pueden ser formuladas mediante la suspensión del ingrediente activo en aceite vegetal, por ejemplo aceite de cacahuate, aceite de oliva, aceite de ajonjolí o aceite de coco, o en aceite mineral tal como parafina líquida. Las suspensiones aceitosas pueden contener un agente espesante, por ejemplo cera de abejas, parafina dura o alcohol cetílico. Los agentes endulzantes tales como aquellos descritos anteriormente, y agentes saborizantes pueden ser agregados para proporcionar una preparación oral grata al paladar. Estas composiciones pueden ser conservadas mediante la adición de un anti-oxidante tal como hidroxianisol butilado o alfa-tocoferol.

Los polvos y gránulos dispersables, adecuados 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 suspensor y uno o más conservadores. Los agentes dispersantes o humectantes adecuados y los agentes suspensores son ejemplificados por aquellos ya mencionados anteriormente. Los excipientes adicionales, por ejemplo agentes endulzantes, saborizantes y colorantes pueden estar también presentes. Estas composiciones pueden ser preservadas por la adición de un

antioxidante tal como ácido ascórbico.

Las composiciones farmacéuticas de la invención pueden estar también en la forma de emulsiones aceite en agua. La fase aceitosa puede ser un aceite vegetal, por ejemplo aceite de oliva o aceite de cacahuate, o un aceite mineral, por ejemplo parafina líquida o mezclas de éstas. Los agentes emulsificantes adecuados pueden ser fosfatidas de origen natural, por ejemplo lecitina de frijol de soya, y ésteres o ésteres parciales derivados de ácidos grasos y anhídridos de hexitol, por ejemplo monooleato de sorbitan, y productos de condensación de los ésteres parciales con óxido de etileno, por ejemplo monooleato de polioxietilensorbitan. Las emulsiones pueden también contener agentes endulzantes, saborizantes, conservadores y antioxidantes.

Los jarabes y elixires pueden ser formulados con agentes endulzantes, por ejemplo glicerol, propilenglicol, sorbitol o sucrosa. Tales formulaciones pueden también contener un demulcente, un conservador, agentes saborizantes y colorantes y antioxidantes.

Las composiciones farmacéuticas pueden estar en la forma de soluciones acuosas inyectables estériles. Entre los vehículos y solventes aceptables que pueden ser empleados están el agua, la solución de Ringer y la solución isotónica de cloruro de sodio.

La preparación inyectable estéril puede también ser una

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microemulsión inyectable estéril aceite en agua, en donde el ingrediente activo es disuelto en la fase aceitosa. Por ejemplo, el ingrediente activo puede ser primeramente disuelto en una mezcla de aceite de soya y lecitina. La solución aceitosa es luego introducida en una mezcla de agua y glicerol y procesada para formar una microemulsión.

Las soluciones o microemulsiones inyectables pueden ser introducidas en una corriente sanguínea del paciente mediante inyección de bolo local. Alternativamente, puede ser ventajoso administrar la solución o microemulsión de una manera tal como para mantener una concentración constante en circulación del presente compuesto. Con el fin de mantener tal concentración constante, puede ser utilizado un dispositivo de administración intravenosa continua. Un ejemplo de tal dispositivo es la bomba intravenosa Deltec CADD-PLUS.TM modelo 5400.

Las composiciones farmacéuticas pueden estar en la forma de una suspensión acuosa u oleaginosa inyectable estéril para la administración intramuscular y subcutánea. Esta suspensión puede ser formulada de acuerdo a la técnica conocida utilizando aquellos agentes dispersantes o humectantes adecuados y agentes suspensores que han sido mencionados anteriormente. La preparación inyectable estéril puede también ser una solución inyectable estéril o suspensión en un diluyente o solvente no tóxico parenteralmente aceptable,

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por ejemplo como una solución en 1,3-butanodiol. Además, los aceites estériles fijos son convencionalmente empleados como un solvente o medio suspensor. Para este propósito, cualquier aceite fijo blando puede ser empleando mono- o di-glicéridos sintéticos. Además, los ácidos grasos tales como ácido oleico encuentran uso en la preparación de inyectables.

Los compuestos de las Fórmulas I y II pueden ser también administrados en la forma de supositorios para la administración rectal del fármaco. Estas composiciones pueden ser preparadas mediante el mezclado del fármaco con un excipiente no irritante, adecuado el cual es sólido a temperaturas ordinarias pero líquido a la temperatura rectal, y por lo tanto se fundirá 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 ácido graso de polietilenglicol.

Para el uso tópico, son empleadas cremas, ungüentos, jaleas, soluciones o suspensiones, etc., que contienen el compuesto de la Fórmula I. (Para fines de esta solicitud, la aplicación tópica incluirá lavados bucales y gárgaras).

Los compuestos de la presente invención pueden ser administrados en forma intranasal vía el uso tópico de los vehículos intranasales adecuados y dispositivo de administración, o por medio de las rutas transdérmicas,

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utilizando aquellas formas de parches para piel transdérmicos bien conocidos por aquellos expertos en la técnica. Para ser administrado en la forma de un sistema de administración transdérmica, la administración de la dosis, por supuesto, será continua en vez de intermitente a todo lo largo del régimen de dosificación. Los compuestos de la presente invención pueden ser también distribuidos como un supositorio empleando base tales como manteca de cacao, gelatina glicerinada, aceites vegetales hidrogenados, mezclas de polietilenglicoles de diversos pesos moleculares y ésteres de ácido graso de polietilenglicol.

Cuando un compuesto de acuerdo a esta invención es administrado a un sujeto humano, la dosis diaria normalmente será determinada por el médico que prescribe, con la dosis que varía en general de acuerdo a la edad, al peso, al sexo y a la respuesta del paciente individual, así como a la severidad de los síntomas del paciente.

Si se formulan como una dosis fija, tales productos en combinación emplean los compuestos de esta invención dentro del intervalo de dosis descrito anteriormente, y el otro agente farmacéuticamente activo o tratamiento dentro de su intervalo de dosis aprobado. Los compuestos de las Formulas I y II pueden ser también administrados secuencialmente con agentes anticancerosos o citotóxicos conocidos, cuando es inapropiada una formulación en combinación. La invención no

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está limitada en la secuencia de administración; los compuestos de las Fórmulas I y II pueden ser administrados ya sea antes de o después de la administración del o de los agentes anticancerosos o citotóxicos conocidos.

ENSAYOS

Las propiedades farmacológicas de los compuestos de esta invención pueden ser confirmadas por un número de ensayos farmacológicos. Los ensayos farmacológicos ejemplificados siguientes han sido llevados a cabo con los compuestos de acuerdo a la invención y las sales de los mismos.

Ensayo de Cinasa Met

Reactivos	Concentración Final de la Mezcla en sustratos
Solución de reserva	
Tris-HCl (1 M, pH 7.4)	20 mM
$MnCl_2$ (1 M)	1 mM
DTT (1 M)	1 mM
BSA (100 mg/ml)	0.1 mg/mi
$PoliGlu_4$/tyr (10 mg/mi)	0.1 mg/ml
ATP (1 mM)	1 µM
γ-ATP (10 µCi/µl)	0.2 µCi/ml

Amortiguador	Mezcla de enzimas
200 µl 1 M DTT	4 µl GST/enzima Met (3.2 mg/ml)=10 ng/rxn
200 µl 1 M Tris-HCl, pH 7.4	css 12 ml de amortiguador
20 µl 100 mg/ml de BSA	
Css 20 ml de agua	

Las mezclas de incubación empleadas para el ensayo de la cinasa Met contienen el sustrato sintético poliglu:Tyr, (4:1), ATP, ATPγ-^{33}P y el amortiguador que contiene Mn^{++} y/o Mg^{++}, DTT, BSA y amortiguador de Tris. Las reacciones fueron incubadas por 60 minutos a 27°C y detenidas por la adición de ácido tricloroacético (TCA) a una concentración final de 4%. Los precipitados de TCA fueron recolectados sobre placas de unifiltro GF/C (Packard Instrument Co., Meriden, CT) utilizando un cosechador universal Filtermate (Packard Instrument Co., Meriden, CT) y los filtros son cuantificados utilizando un contador de cintilación líquida de 96 pozos TopCount (Packard Instrument Co., Meriden, CT). Las curvas de dosis-respuesta fueron generadas para determinar la concentración requerida para inhibir 50% de la actividad de la cinasa (IC_{50}). Los compuestos fueron disueltos a 10 mM en sulfóxido de dimetilo (DMSO) y evaluados a seis concentraciones, cada una por cuadruplicado. La concentración final de DMSO en el ensayo es de 1%. Los valores de IC_{50} fueron derivados mediante análisis de regresión no lineal y

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tuvieron un coeficiente de varianza (SD/media, n=6)=16%.

Los compuestos preferidos de la invención inhiben la cinasa Met con valores de IC_{50} entre 0.01 a 100 µM. Los compuestos más preferidos tienen valores de IC_{50} menores de 0.5 µM.

La materia de interés adicional de la invención también incluye los productos farmacéuticos para el uso como se describió anteriormente incluyendo el control del cáncer, inflamación y artritis, que contienen al menos un compuesto de las Fórmulas I y II como se definieron anteriormente o al menos una de sus sales por adición de ácido farmacológicamente aceptables, y el uso de un compuesto de las Fórmulas I y II, como se definieron anteriormente para la preparación de un producto farmacéutico que tiene actividad contra las enfermedades proliferativas como se describieron previamente incluyendo contra el cáncer, la inflamación y/o artritis.

Los siguientes ejemplos y preparaciones describen la manera y el proceso de elaboración y uso de la invención, y son ilustrativos en vez de limitantes. Se debe entender que pueden existir otras modalidades que caigan dentro del espíritu y alcance de la invención como se define por las reivindicaciones anexas a la presente.

EJEMPLOS

La invención será ahora descrita adicionalmente por

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referencia a los siguientes ejemplos de trabajo, los cuales son modalidades preferidas de la invención. Todas las reacciones fueron llevadas a cabo con agitación magnética continua bajo una atmósfera de nitrógeno anhidro o argón. Todas las evaporaciones y concentraciones fueron llevadas a cabo sobre un operador rotatorio bajo presión reducida. Los reactivos comerciales fueron utilizados como se recibieron, sin purificación adicional. Los solventes fueron grados anhidros comerciales, y fueron utilizados sin secado o purificación adicionales. Se realizó la cromatografía instantánea utilizando gel de sílice (EMerck Kieselgel 60, 0.040-0.060 mm).

La Cromatografía Líquida de Alta Resolución de Fase Inversa (RP-HPLC) se realizó utilizando una columna Phenomenex Luna C18 S5 de 4.6 mm x 50 mm o una columna YMC S5 ODS de 4.6 x 50 mm. En cada caso, se utiliza un gradiente lineal de 4 minutos (de 100% de A:% de B hasta 0% de A:100% de B) con el siguiente sistema de fase móvil: A=90% de agua/MeOH+0.2% de H_3PO_4; B=90% de MeOH/H_2O0.2% de H_3PO_4 a velocidad de flujo=4 ml/minuto y detección a 220 nm.

La HPLC de Fase Inversa (RP) fue realizada con una elusión en gradiente lineal utilizando 10% de metanol, 90% de agua, 0.1% de TFA (solvente A y 90% de metanol, 10% de agua, 0.1% de TFA (solvente B) y detección a 220 nm sobre una de las siguientes columnas: A- una columna Shimadzu S5 ODS-VP 20

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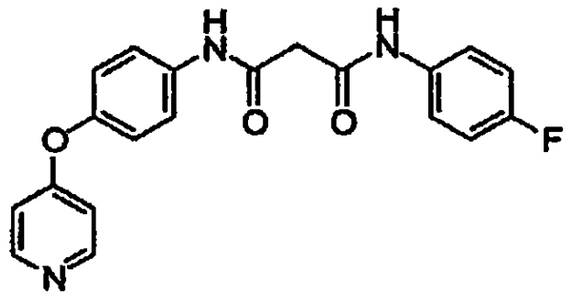
X 100 nm con una velocidad de flujo de 20 ml/minuto; B- una columna YMC S5 ODS 30 X 100 mm con una velocidad de flujo de 20 ml/minuto; C- una columna Phenomenex 30 x 250 mm-con una velocidad de flujo de 10 ml/minuto; D- una columna YMC S5 ODS 20 x 250 mm con una velocidad de flujo de 10 ml/minuto; E- una columna YMC S10 ODS 50 x 500 mm con una velocidad de flujo de 50 ml/minuto; o F- una columna YMC S10 ODS 30 x 500 mm con una velocidad de flujo de 20 ml/minuto.

Todos los productos finales fueron caracterizados por RMN ^{1}H, RP HPLC, ionización de electrorrocío (ESI MS) o espectrometría de masa de ionización de presión atmosférica (API MS). Los espectros de RMN $^{1}14$ fueron obtenidos ya sea sobre un JEOL a 500 MHz o un instrumento Bruker a 400 MHz. Los espectros de RMN ^{13}C fueron registrados a 100 ó 125 MHz. Las fuerzas de campo son expresadas en unidades de δ (partes por millón, ppm) con relación a los picos de solvente, y las multiplicidades pico son designadas como sigue: s, singulete; d, doblete; dd, doblete de dobletes; dm, doblete de multipletes; t, triplete; q, cuadruplete, br s, singulete amplio, m, multiplete.

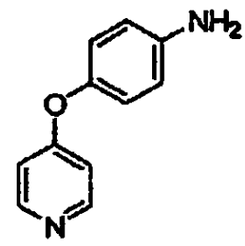
Se utilizan las siguientes abreviaturas para los reactivos comúnmente utilizados: Boc o BOC: carbamato de t-butilo; Fmoc: carbamato de 9H-fluorenilmetilo; TEA. Trietilamina; NMM: N-metilmorfolina; Ms: metansulfonilo; DIEA o DIPEA: diisopropiletilamina o base de Hunig; NMP: N-

metilpirrolidinona; reactivo BOP: hexafluorofosfato de benzotriazol-1-iloxitris(trimetilamino)fosfonio; DCC. 1,3-diciclohexilcarbodiimida; EDCI: clorhidrato de 1-(dimetilaminopropil)-3-etilcarbodiimida; RT o rt: temperatura ambiente; t_R: tiempo de retención; h: hora(s); min: minuto(s); PyBroP: hexafluorofosfato de bromotripirrolidinofosfonio; TBTU: tetrafluoroborato de O-(1H-benzotriazol-1-il)-N,N,N',N'-tetrametiluronio; DMAP: 4-N,N-dimetilaminopiridina; HOBt u HOBT: hidroxibenzotriazol; $Na(OAc)_3BH$: triacetoxiborohidruro de sodio; HOAc: ácido acético; TFA: ácido trifluoroacético; LiHMDS: bis(trimetilsilil)amida de litio; DMSO: sulfóxido de dimetilo; MeCN: acetonitrilo; MeOH: metanol; EtOAc: acetato de etilo; DMF: dimetilformamida; THF: tetrahidrofurano; DCE: 1,2-dicloroetano; Et_2O: éter dietílico; DCM: diclorometano o cloruro de metileno; m-CPBA: ácido 4-cloroperoxibenzoico.

Ejemplo 1

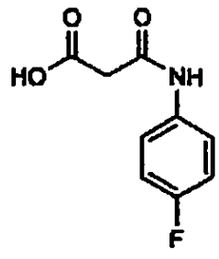


N-(4-Fluorofenil)-N-(4-(piridin-4-iloxi)fenil)malonamida



A) 4-(4-Aminofenoxi)piridina

Una solución de clorhidrato de 4-cloropiridina (Aldrich. 3.0 g, 20.0 mmol) en sulfóxido de dimetilo (40 mL) se trató con 4-aminofenol (Aldrich, 2.1 g, 20.0 mmol) y granulos de hidróxido de sodio (2.0 g, 50.0 mmol) y la mezcla se calentó a 100 °C por 18 h. La mezcla se enfrió a temperatura ambiente. Se vació sobre una mezcla de hielo-agua (300 g) y se extrajo con Et_2O (3 x 150 mL). Los extractos combinados se lavaron con salmuera, se secaron (sulfato de magnesio) y se concentró para dar la 4-(4-aminofenoxi)anilina como un sólido amarillo pálido (3.5 g, 94%). RMN-^{1}H (DMSO-d_6) δ 8.38 (dd, 2H, J = 5.5, 1.5 Hz), 6.83-6.79 (m, 4H), 6.63-6.59 (m, 2H), 5.13 (br s, 2H); MS (ESI^+) m/z 187.2 $(M + H)^+$.



B) ácido 3-(4-fluorofenilamino)-3-oxopropanoico

A una solución de etil 3-cloro-3-oxopropanoato (Aldrich, 5.0 mL. 40 mmol) en cloruro de metileno (100 mL) a 0°C se agregó diisopropiletilamina (8.4 mL. 48 mmol) seguido por 4-fluoroanilina (Aldrich, 3.6 mL, 38 mmol). La mezcla de reacción se agitó a temperatura ambiente toda la noche y se apagó luego con 100 mL de solución saturada de $NaHCO_3$. La capa acuosa se extrajo con cloroformo (3 x 100 mL). Los extractos orgánicos combinados se secaron sobre $NaSO_4$ (sulfato de sodio) anhidro y se concentró a vacío para dar el producto crudo como un aceite amarillo que solidificó con el reposo (10 g). RMN-^{1}H ($CDCl_3$) 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 226.11 $(M+H)^+$.

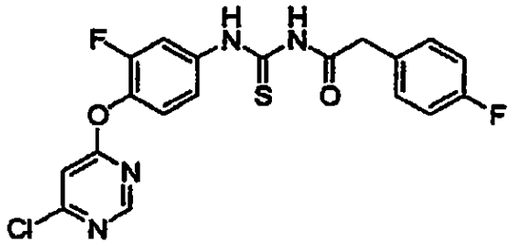
El éster anterior se disolvió en 100 mL de etanol y se enfrió a 0°C. se agregó solución acuosa de NaOH iN (100 mL) y la reacción se agitó a 0°C por 1 h. La reacción se concentró a vacío para remover el etanol. La solución acuosa se extrajo con EtOAc (50 mL) y luego se acidificó con solución acuosa de HCl. La solución acuosa se extrajo con EtOAc (5 x 100 mL). Los extractos orgánicos combinados se secaron sobre sulfato de sodio anhidro y se concentró a vacío para dar el producto crudo como un sólido amarillo (6.31 g, 84%) que se utilizó sin purificación adicional. RMN-^{1}H (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 198.43 $(M + H)^+$.

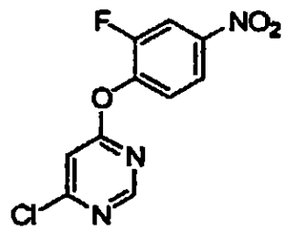
C) N-(4-Fluorofenil)-N-(4-(piridin-4-iloxi)fenil)malonamida

Una solución de 4-(4-aminofenoxi)piridina (93 mg, 0.50 mmol) en DMF se trató con ácido 3-(4-fluorofenilamino)-3-oxopropanoico (99 mg , 0.50 mmol), DIPEA (113 µL, 0.65 mmol) y TBTU (209 mg, 0.65 mmol) y la mezcla se agitó a temperatura ambiente por 2 h. La mezcla se concentró para remover la dimetilformamida y el residuo se dividió entre EtOAc y solución saturada de carbonato ácido de sodio. La fase de EtOAc se lavó con solución saturada de carbonato ácido de sodio, con salmuera, se secó ($MgSO_4$) y se concentró para dar el compuesto del título como una espuma blanquecina (140 mg, 76%). RMN-^{1}H (DMSO-d_6) δ 10.30 (s, 1H), 10.24 (s, 1H). 8.43 (dd, 2H , J = 5.5. 1.5 Hz), 7.70 (d, 2H, J = 9.1 Hz), 7.63-7.60 (m, 2H), 7.17-7.14 (m, 4H), 6.89 (dd, 2H, J = 5.5, 1.5 Hz), 3.46 (s, 2H); MS (ESI^+) m/z 365.9 $(M + H)^+$.

Ejemplo 2

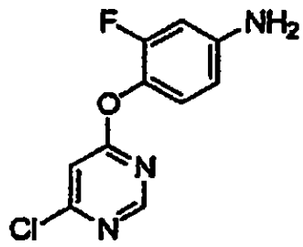


1-4-(6-Cloropirimidin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)tiourea



A) 4-Cloro-6-(2-fluoro-4-nitrofenoxi)pirimidina

Una mezcla de 4,6-dicloropirimidina (Aldrich, 0.74 g, 5.0 mmol), 2-fluoro-4-nitrofenol (Aldrich, 0.79 g, 5.0 mmol) y DMF (10 ml) se trató con carbonato de potasio (0.72 g, 5.2 mmol) y se calentó a 80°C por 3 h. La mezcla se enfrió, se diluyó con agua y se extrajo con acetato de etilo. El extracto de acetato de etilo se lavó con salmuera, se secó (sulfato de magnesio), y se concentró para dar el producto crudo como un sólido amarillo. El producto crudo se trituró con éter isopropílico para dar la 4-cloro-6-(2-fluoro-4-nitrofenoxi)pirimidina como un sólido amarillo (1.3 g. 94%). RMN-^{1}H (DMSO-d_6) δ 8.80 (s, 1H), 8.51 (dd, 1H, J = 8. 6, 2.5 Hz), 8.31 (d, 1H, J = 9.1 Hz). 7.87 (d, 1H, J = 9.1 Hz). 7.84 (s, 1H).



B) 4-Cloro-6-(2-amino-2-fluorofenoxi)pirimidina

Una solución de 4-cloro-6-(2-fluoro-4-nitrofenoxi)pirimidina (1.3 g, 4.8 mmol) en metanol (120 mL)

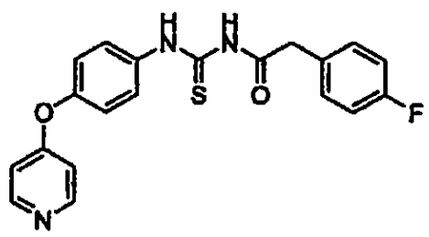
se trató con níquel de Raney (1.5 g, suspensión acuosa) y la mezcla de reacción se agitó bajo una atmósfera de hidrógeno (de un globo de látex) a temperatura ambiente por 3 h. El catalizador se filtró, el filtrado se concentró, y el residuo se dividió entre cloruro de metileno y agua. La fase de cloruro de metileno se separó, se secó (sulfato de magnesio) y se concentró. El producto crudo se purificó mediante cromatografía instantánea sobre gel de sílice utilizando 1-2% de MeOH en cloruro de metileno como el eluyente para dar 4-cloro-6-(2-amino-2-fluorofenoxi)pirimidina como un sólido blanco (600 mg, 52%). RMN-^{1}H (DMSO-d_6) δ 8.64 (s, 1H). 7.39 (s, 1H), 6.97 (dd, 1H, J = 8.8, 8.8 Hz), 6.46 (dd, 1H, J = 13.1, 2.5 Hz), 6.38 (dd, 1H, J = 8.6. 2.5 Hz), 5.44 (br s, 2H); MS (ESI$^+$) m/z 240.04 $(M + H)^+$.

C) 1-(4-(6-Cloropirimidin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)tiourea

Se agregó cloruro de 4-fluorofenilacetilo (Lancaster. 0.52 g, 3.0 mmol) a una mezcla de NaSCN (0.27 g, 3.3 mmol) y EtOAc (12 mL) y la mezcla resultante se agitó a temperatura ambiente por 30 min. Esta mezcla se agregó a una solución de 4-cloro-6-(2-amino-2-fluorofenoxi)pirimidina en 1:1 EtOAc/cloruro de metileno (5 ml) y la mezcla resultante se agitó a temperatura ambiente toda la noche. La mezcla se concentró y el residuo se dividió entre EtOAc/agua. La fase de EtOAc se separó, se lavó con salmuera, se secó (sulfato de

magnesio) y se concentró. El producto se purificó mediante cromatografía instantánea utilizando 10-35 % de EtOAc/hexanos como el eluyente para dar el compuesto del título como un sólido amarillo cristalino (0.85 g, 65%). RMN-^{1}H (DMSO-d_6) δ 12.40 (s, 1H), 11.81 (s, 1H), 8.67 (s, 1H), 7.90 (dd, 1H, J = 12.1, 2.0 Hz), 7.62 (s, 1H), 7.47-7.41 (m, 2H), 7.38-7.35 (m, 2H), 7.17 (t, 2H, J = 8.8 Hz), 3.81 (s, 2H); MS(ESI$^+$) m/z 434.98 $(M + H)^+$.

Ejemplo 3

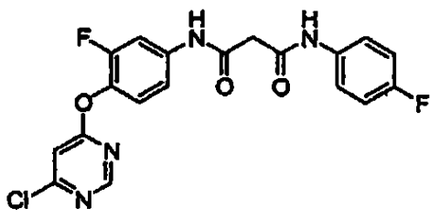


1-(2-(4-Fluorofenil)acetil)-3-(4-(piridin-4-iloxi)fenil)tiourea

El compuesto del título se preparó utilizando 4-(4-aminofenoxi)piridina (Compuesto A del Ejemplo 1) y un procedimiento similar descrito para la preparación del Compuesto C del Ejemplo 2.

Rendimiento: 10%. RMN-^{1}H ($CDCl_3$) δ 12.3 (s, 1H), 8.63 (s, 1H). 8.49.* (d, 2H, J = 6.2 Hz), 7.71 (d, 2H, J = 8.9 Hz), 7.31-7.27 (m, 2H), 7.14-7.09 (m, 4H). 6.90 (dd, 2H, J = 4.8, 1.4 Hz), 3.73 (s, 2H); MS(ESI$^+$) m/z 382.2 $(M + H)^+$.

Ejemplo 4

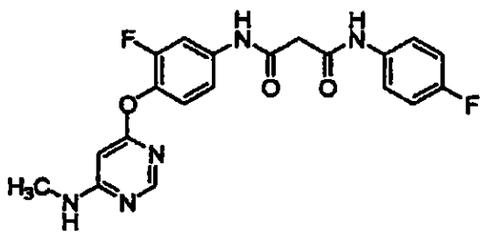


N^1-(4-(6-Cloropirimidin-4-iloxi)-3-fluorofenil)-N^3-(4-fluorofenil)malonamida

Una solución de 4-cloro-6-(2-amino-2-fluorofenoxi)pirimidina (29 mg, 0.12 mmol, Compuesto B del Ejemplo 2), ácido 3-(4-fluorofenilamino)-3-oxopropanoico (26 mg, 0.13 mmol, Compuesto B del Ejemplo 1) en DMF (1.5 mL) se trató con DIPEA (24 µl, 0.14 mmol) y TBTU (46 mg, 0.14 mmol). La mezcla de reacción se agitó a temperatura ambiente toda la noche. Se diluyó con EtOAc (25 mL), y la fase orgánica se lavó con salmuera (3 x 20 mL), se secó (sulfato de magnesio) y se concentró.

El producto se purificó mediante cromatografía instantánea utilizando 1-3% de MeOH en cloruro de metileno como el eluyente para dar el compuesto del título como un sólido blanco (35 mg, 78%). RMN-^{1}H (DMSO-d_6) δ 10.49 (s, 1H). 10.25 (s, 1H), 8.65 (s, 1H), 7.78 (d, 1H, J = 12.1 Hz), 7.63-7.57 (m, 3H), 7.40-7.34 (m, 2H), 7.16 (t, 2H, J = 8.8 Hz), 3.48 (s, 2H); MS (ESI$^+$) m/z 419.21 $(M + H)^+$.

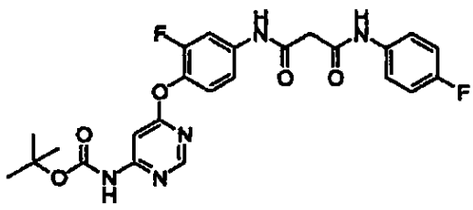
Ejemplo 5



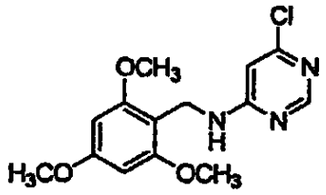
N^1-(3-Fluoro-4-(6-(metilamino)pirimidin-4-iloxi)fenil)-N^1-(4-fluorofenil) malonamida

Una solución de N^1-(4-(6-cloropirimidin-4-iloxi)-3-fluorofenil)-N^3-(4-fluorofenil)malonamida (100 mg, 0.42 mmol. Ejemplo 4) en n-BuOH (3 mL) se trató con 2 M metilamina/THF (0.2 mL) y se calentó en un frasco de tapón roscado a 80 °C por 12 h. La mezcla se concentró y el residuo se purificó mediante HPLC preparativa utilizando un gradiente de MeOH-agua que contenía 0.1 % de TFA. La fracción que contenía el producto se liofilizó para dar el compuesto del título como un sólido amarillo pálido (60 mg, 34%). RMN-^{1}H (DMSO-d_6) o 10.58 (s, 1H). 10.36 (br s, 2H), 8.19 (br s, 1H), 7.76 (d, 1H, J = 12.1 Hz), 7.64-7.62 (m, 2H). 7.36-7.27 (m, 2H), 7.15 (dd, 2H, J = 8.8, 8.8 Hz), 5.95 (br s. 1H), 3.49 (s, 2H), 2.80 (s, 3H); MS(ESI$^+$) m/z 414.16 (M +.H)$^+$.

Ejemplo 6



6-(2-fluoro-4-(3-(4-fluorofenilamino)-3-oxopropanamido)fenoxi)pirimidin-4-ilcarbamato de ter-butilo



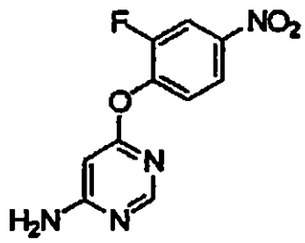
A) N-(2,4,6-Trimetoxibencil)-6-cloropirimidin-4-amina

Una mezcla de 4,6-dicloropirimidina (Aldrich, 1.48 g, 10.0 mmol), clorhidrato de 2,4,6-trimetoxibencilamina (2.33 g, 10.0 mmol), DIPEA (4.8 mL. 27.7 mmol). y n-BuOH (50 mL) se calentó a 100°C por 2 h.

La mezcla se enfrió, se diluyó con agua (200 mL) y el producto precipitado se recolectó mediante filtración a vacío sobre un embudo Buchner.

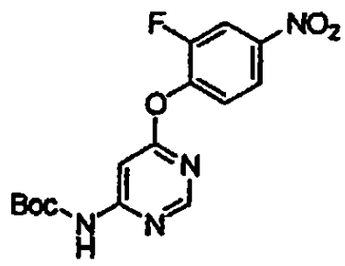
El producto se lavó con agua fría, éter y se secó a vacío para dar un sólido blanquecino (2.8 g, 90%). RMN-^{1}H (DMSO-d_6) δ 8.28 (s, 1H). 7.38 (s, 1H), 6.49 (s, 1H), 6.25 (s, 2H), 4.34 (s, 2H), 3.77 (s, 9H).

360



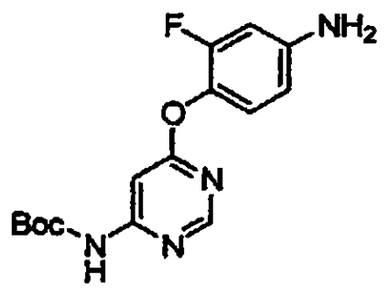
B) 6-(2-Fluoro-4-nitrofenoxi)pirimidin-4-amina

Una mezcla de N-(2,4,6-trimetoxibencil)-6-cloropirimidin-4-amina (2.2 g, 7.11 mmol), 2-fluoro-4-nitrofenol (1.1 g. 7.0 mmol), y 2-metoxietil-éter (50 mL) se calentó a 160 °C por 60 h. La mezcla de reacción se enfrió a temperatura ambiente; se vació en agua (200 mL). El sólido se recolectó, se lavó con Na_2CO_3 acuoso 2M y agua, y luego se secó a vacío sobre un embudo Buchner. El producto crudo se trató con TFA (20 mL) en dioxano (40 mL) y se agitó a temperatura ambiente por 4 h. La mezcla de reacción se concentró, el residuo se dividió entre EtOAc y solución saturada de carbonato ácido de sodio. La fase de EtOAc se separó, se secó (sulfato de magnesio), se concentró y el producto crudo se purificó mediante cromatografía instantánea utilizando 1-2 % de McOH en cloruro de metileno como el eluyente para dar 6-(2-fluoro-4-nitrofenoxi)pirimidin-4-amina (440 mg, 31%). RMN-^{1}H (DMSO-d_6) δ 8.31 (dd, 1H, J = 10.4, 2.5 Hz), 8.14 (dd J = 9.8, 2.0 Hz), 8.04 (s, 1H), 7.61 (dd, 1H, J = 8.3, 8.3 Hz), 7.07 (s, 2H), 6.02 (s, 1H); MS(ESI$^+$) m/z 251.15 $(M + H)^+$.



C) 6-(2-fluoro-4-nitrofenoxi)pirimidin-4-ilcarbamato de ter-butilo

Una mezcla de 6-(2-fluoro-4-nitrofenoxi)pirimidin-4-amina (439 mg, 1.2 mmol), BOC_2O (261 mg, 1.2 mmol), DMAP (10 mg), y THF (10 mL) se agitó a temperatura ambiente por 1 h luego se concentró a vacío para dar el producto crudo. El producto se purificó mediante cromatografía instantánea utilizando 1-2 de McOH en cloruro de metileno como el, eluyente para dar 6-(2-fluoro-4-nitrofenoxi)pirimidin-4-ilcarbamato de ter-butilo como un sólido blanco (110 mg, 26%). RMN-^{1}H (DMSO-d_6) δ 10.59(s, 1H), 8.39 (dd, 1H, J = 8.8, 1.1 Hz), 8.32 (dd, 1H, J = 10.3, 2.4 Hz), 8.15 (ddd, 1H, J = 9.1, 2.5, 1.0 Hz), 7.67 (dd, 1H, J = 8.8, 8.8 Hz). 7.45 (s, 1H), 1.44 (s, 9H); MS (ESI^+) m/z 349.08 (M - H).



D) 6-(4-amino-2-fluorofenoxi)pirimidin-4-ilcarbamato de ter-butilo

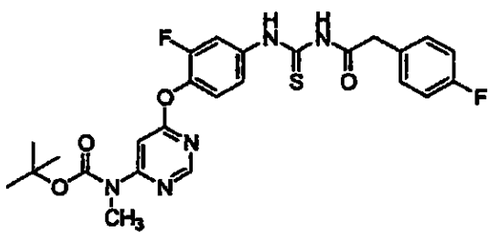
Una solución de 6-(2-fluoro-4- nitrofenoxi)pirimidin-4-ilcarbamato de ter-butilo (11 mg. 0.031 mmol) en McOH (2 mL) se trató con PtO_2 y la mezcla de reacción se agitó bajo una atmósfera de hidrógeno (de un globo de látex) por 2 h. El catalizador se filtró y el iltrado se concentró para dar 6-(4-amino-2- fluorofenoxi)pirimidin-4-ilcarbamato de ter-butilo (8 mg, 81%). RMN-^{1}H (DMSO-d_6) δ 10.62 (s, 1H), 8.43 (d, 1H, J = 2.5 Hz), 8.36 (dd, 1H, J = 9.8, 2.5 Hz), 8.36 (dd, 1H, J = 9.8, 2.5 Hz). 8.20-8.17 (m, 1H), 7.71 (dd, 1H, J = 8.8, 8.8 Hz), 7.49 (s, 1H), 1.48 (s, 9H).

E) 6-(2-fluoro-4-(3-(4-fluorofenilamino)-3-oxopropanamido)fenoxi)pirimidin-4-ilcarbamato de ter-butilo

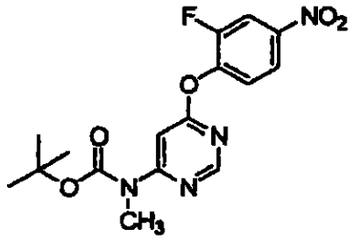
El compuesto del título se preparó a partir de 6-(4-amino-2-flúorofenoxi)pirimidin-4-ilcarbamato de ter-butilo (8 mg, 0.025 mmol) y ácido (4-fluorofenilamino)-3-oxopropanoico (6 mg, 0.031 mmol, Compuesto B del Ejemplo 1), TBTU (11 mg, 0.034 mmol), y DIPEA (6 µL. 0.030 mmol) utilizando un procedimiento similar descrito para la preparación del

Compuesto C, Ejemplo 1. Cromatografía instantánea utilizando 1-1.5 % de McOH en cloruro de metileno como el eluyente dio el compuesto del título como un sólido blanco (10 mg, 80%). RMN-^{1}H (DMSO-d_6) δ 10.48 (s, 1H), 10.46 (s, 1H). 10.25 (s, 1H), 8.39 (s, 1H), 7.74-7.77 (m, 1H), 7.62 (d, 1H, J = 5.5 Hz), 7.61 (d, 1H, J = 4.9 Hz), 7.36-7.30 (m, 2H), 7.17-7.13 (m, 2H), 3.48 (s, 2H), 1.46 (s, 9H); MS(ESI+) m/z 500.12 (M + H)$^+$.

Ejemplo 7



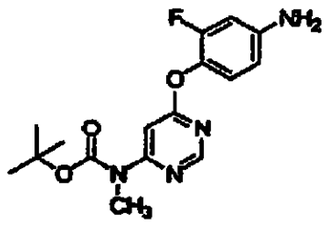
6-(2-fluoro-4-(3-(4-fluorofenilamino)-3-oxopropanamido)fenoxi)pirimidin-4-il(metil)carbamato de ter-butilo



A) 6-(2-fluoro-4-nitrofenoxi)pirimidin-4-il(metil)carbamato de ter-butilo

Una solución de 6-(2-fluoro-4-nitrofenoxi)pirimidin-4-

ilcarbamato de ter-butilo (Compuesto C del Ejemplo 6, 44 mg, 0.13 mmol) en DMF anhidra (1 mL) se enfrió en un baño de hielo y se trató con NaH al 60 % (44 mg. 0.16 mmol) y se agitó a la misma temperatura por 30 minutos. La mezcla de reacción se trató con yodometano (10 µl, 0.15 mmol) y se agitó a 0-5 °C por 10 min. La mezcla de reacción se dejó calentar a temperatura ambiente y se agitó por 30 min. La mezcla se diluyó con H_2O (10 mL) y se extrajo con EtOAc (2x10 mL). Los extractos combinados se secaron (sulfato de magnesio) y se concentró a vacío para dar el producto (35 mg, 74%) como un sólido amarillo pálido. RMN-^{1}H (DMSO-d_6) δ 8.57 (d, 1H, J = 1.1 Hz), 8.37 (dd, 1H, J = 9.8, 3.0 Hz), 8.19 (ddd, 1H, J = 9. 1, 2.5, 1.0 Hz), 7.71 (dd, 1H, J = 8. 8, 8.8 Hz), 7.66 (s, 1H), 3.38 (s, 3H), 1.51 (s, 9H).



B) 6-(4-amino-2-fluorofenoxi)pirimidin-4-il(metil)carbamato de ter-butilo

Una mezcla de 6-(2-fluoro-4-nitrofenoxi)pirimidin-4-il(metil)carbamato de ter-butilo en EtOH/MeOH 1:1 (2 mL) se trató con PtO_2 (10 mg) y la mezcla de reacción se agitó bajo una atmósfera de H2 (de un globo de látex) por 2 h. La mezcla

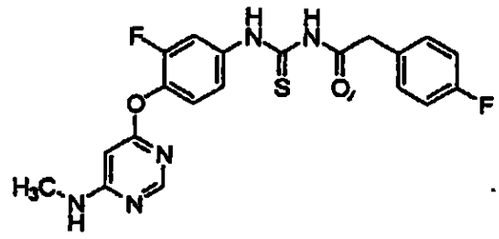
de reacción se filtró y se concentró para dar el producto deseado (30 mg, 75%) como un sólido café claro. MS (ESI^+) m/z 365.13 $(M + H)^+$.

C) 6-(2-fluoro-4-(3-(4-fluorofenilamino)-3-oxopropanamido)fenoxi)pirimidin-4-il(metil)carbamato de ter-butilo

El compuesto del título se preparó a partir de 6-(4-amino-2-fluorofenoxi)pirimidin-4-il(metil)carbamato de ter-butilo (30 mg, 0.068 mmol), cloruro de 4-fluorofenilacetilo (Lancaster, 15 mg, 0.088 mmol) y NaSCN (9 mg, 0.11 mmol) en EtOAc/cloruro de metileno utilizando un procedimiento similar descrito para la preparación del Compuesto C del Ejemplo 2. Cromatografía instantánea sobre $5\pm0_2$ utilizando EtOAc al 1-4% en hexanos como el eluyente dio el compuesto del título (30 mg, 83%) como un sólido blanco. RMN-^{1}H (DMSO-d_6) δ 12.40 (s, 1H), 11 .79 (s, 1H), 8.55 (s, 1H), 7.86 (dd, 1H, J = 12.1, 2.5 Hz), 7.54 (d, 1H, J = 1.1 Hz), 7.45-7.35 (m, 4H), 7.20-7.14 (ddd, 2H, J = 8. 8, 8. 8, 2.1 Hz), 3.81 (s, 2H), 3.36 (s, 3H), 1.49 (s, 9H); MS (ESI^+) m/z 530.09 $(M + H)^+$.

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Ejemplo 8

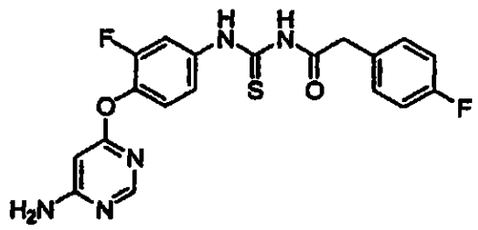


1-(3-Fluoro-4-(6-(metilamino)pirimidin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)tiourea

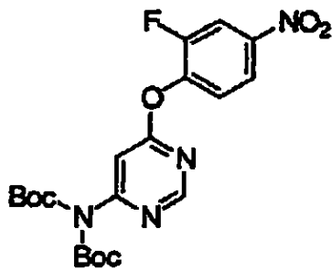
El 6-(2-fluoro-4-(3-(4-fluorofenilamino)-3-oxopropanamido)fenoxi)pirimidin-4-il(metil)carbamato de terbutilo (Ejemplo 7, 25 mg, 0.047 mmol) se trató con HCl 4M en 1,4-dioxano (3 mL), se agitó a temperatura ambiente por 4 h y se concentró a vacío. El residuo se dividió entre solución acuosa saturada de carbonato ácido de sodio y EtOAc. La fase de EtOAc se separó, se secó (sulfato de magnesio) y se concentró a vacío. Cromatografía instantánea sobre SiO2 utilizando 1 % de MeOH en cloruro de metileno como el eluyente dio el compuesto del título (10 mg, 50%) como un sólido blanco. RMN-^{1}H (DMSO-d_6) δ 12.37 (s, 1H), 11.77(s, 1H), 8.09 (s, 1H), 7.82 (d, 1H, J = 11.6 Hz), 7.41-7.35 (m, 5H), 7.32-7.28 (m, 1H), 7.19-7.14 (m, 2H), 3.81 (s, 2H), 2.78 (s, 3H); MS (ESI$^+$) m/z 430.07 $(M + H)^+$.

~~368~~ 367

Ejemplo 9



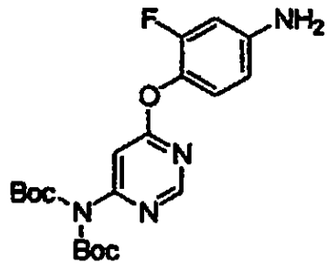
1-(4-(6-Aminopirimidin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)tiourea



A) 6-(N,N-di-ter-butiloxicarbonil)amino-4-(2-fluoro-4-nitrofenoxi)pirimidina

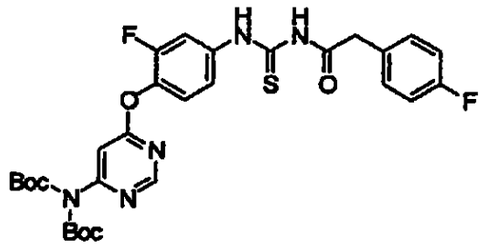
Una mezcla de 6-(2-fluoro-4-nitrofenoxi)pirimidin- 4-amina (Compuesto B del Ejemplo 6, 150 mg, 0.60 mmol), BOC_2O (275 mg, 1.26 mmol), DMAP (5 mg), y THF (20 mL) se agitó a temperatura ambiente por 2.5 h. La mezcla de reacción se concentró a vacío para dar el producto crudo. Cromatografía instantánea sobre SiO_2 utilizando 5-15% de EtOAc en hexanos como el eluyente dio el compuesto del título (180 mg, 67%) como un sólido blanco. RMN-^{1}H (DMSO-d_6) δ 8.62(d, 1H, J = 1.0

Hz), 8.42-8.39 (m, 1H), 8.21 (ddd, 1H, J = 9.1, 2.5. 1.0 Hz), 7.77 (dd, 1H, J = 8.8, 8.8 Hz), 7.49 (d, 1H, J = 1.1 Hz), 1.49 (s, 18H); MS(ESI^+) m/z 451.12 $(M + H)^+$.



B) 6-(N,N-di-ter-Butiloxicarbonil)amino-4-(4-amino-2-fluorofenoxi)pirimidina

Una mezcla de 6-(N,N-di-ter-butiloxicarbonil)amino-4-(2-fluoro-4-nitrofenoxi)pirimidina (175 mg, 0.38 mmol) en tolueno (5 mL) y McOH (3 mL) se trató con PtO_2 (35 mg) y la mezcla de reacción se agitó bajo una atmósfera de hidrógeno (de un globo de látex) por 15 h. El catalizador se filtró, el filtrado se concentró a vacío y el residuo se purificó mediante cromatografía instantánea sobre SiO_2 utilizando 1-10 de McOH en cloruro de metileno como el eluyente para dar el producto (110 mg, 68%) como un sólido blanco. RMN-^{1}H (DMSO-d_6) δ 8.56 (s, 1H), 7.17 (s, 1H), 6.97 (dd, 1H, J = 8.8, 8.8 Hz), 6.46 (dd, 1H, J = 12.6, 2.5 Hz), 6.38 (dd, 1H, J = 8.8, 2.5 Hz), 5.40 (s, 2H), 1.89 (s, 18H).



C) 1-(4-(N,N-di-ter-butiloxicarbonil-6-aminopirimidin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)tiourea

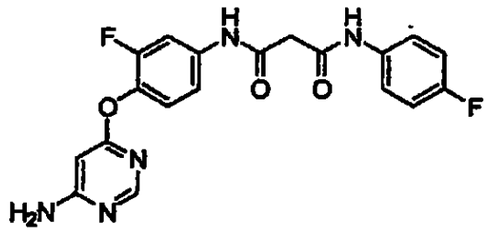
El compuesto del título se preparó a partir de 6-(N,N-di-tert-butiloxicarbonil)amino-4-(4-amino-2-fluorofenoxi)pirimidina (20 mg, 0.048 mmol), cloruro de 4-fluorofenilacetilo (Lancaster, 10 mg, 0.062 mmol). y NaSCN (95 mg, 0.062 mmol) en EtOAc/cloruro de metileno utilizando un procedimiento similar descrito para la preparación del Compuesto C del Ejemplo 2. Cromatografía instantánea sobre SiO_2 utilizando 10-20 de EtOAc en hexanos como el eluyente dio el compuesto del título (23 mg, 77%) como un sólido blanco. RMN-^{1}H (DMSO-d_6) δ 12.40 (s, 1H), 11.79 (s, 1H), 8.59 (s, 1H), 7.88 (dd, 1H, J = 12.5, 1.8 Hz), 7.46-7.41 (m, 2H), 7.38-7.35 (m, 3H), 7.17 (dd, 2H, J = 8.8, 8.8 Hz), 3.81 (s, 2H), 1.47 (s, 18H); MS (ESI$^+$) m/z 616.12 $(M + H)^+$.

D) 1-(4-(6-Aminopirimidin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil) acetil) tiourea

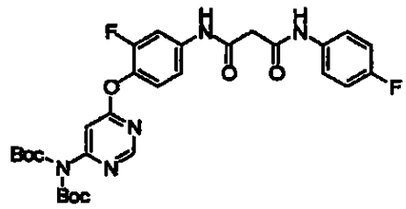
Una mezcla de 1-(4-(N,N-di-ter-butilcarbonil-6-aminopirimidin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)tiourea (18 mg, 0.029 mmol) y HCl1 4M en

dioxano (1.5 mL) se agitó a temperatura ambiente por 18 h y luego se concentró para dar el producto crudo. El producto crudo se dividió entre EtOAc y solución acuosa saturada de carbonato ácido de sodio. La fase de EtOAc se separó, se secó (sulfato de magnesio), se concentró a vacío y el residuo se purificó mediante cromatografía instantánea sobre SiO_2 utilizando 1-2% de MeOH en cloruro de metileno para dar el compuesto del título (12 mg, 99%) como un sólido blanco. RMN-^{1}H (DMSO-d_6) δ 12.38 (s, 1H), 11.77(s, 1H), 8.05 (s, 1H). 7.83 (dd, 1H, J = 12.3, 1.8 Hz), 7.41-7.35 (m, 3H), 7.31 (dd, 2H, J = 8.8, 8.8 Hz), 7.17 (t, 1H, J = 8.8 Hz), 7.02 (s, 2H), 5.89 (s, 1H), 3.81 (s, 2H); MS(ESI$^+$) m/z 416.06 $(M + H)^+$.

Ejemplo 10



N^1-1-(4-(6-Aminopirimidin-4-iloxi)-3-fluorofenil)-N^3-(4-fluorofenil)malonamida



A) N^1-(4-(N,N-di-ter-butilcarbonil-6-aminopirimidin-4-iloxi)-3-fluorofenil)-N^3-(4-fluorofenil)malonamida

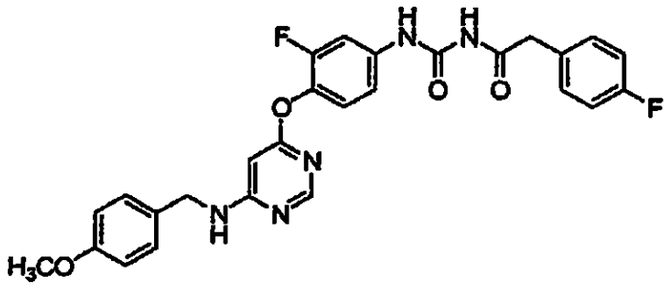
El compuesto del título se preparó a partir de una mezcla de 6-(N,N-di-ter-butiloxicarbonil)amino-4-(4-amino-2-fluorofenoxi)pirimidina (Compuesto B del Ejemplo 9, 20 mg, 0.048 mmol), ácido 3-(4-fluorofenilamino)-3-oxopropanoico (Compuesto B del Ejemplo 1, 14 mg, 0.072 mmol), DIPEA (12 µL, 0.069 mmol) en DMF utilizando un procedimiento similar descrito para la preparación del Compuesto C del Ejemplo 1. Cromatografía instantánea sobre gel de sílice utilizando 15-50 % de EtOAc en hexanos como el eluyente dio el compuesto del título (23 mg, 80%) como un sólido blanco. RMN-^{1}H (DMSO-d_6) δ 10.47 (s, 1H), 10.24 (s, 1H), 8.58 (d, 1H, J = 1 Hz), 7.77 (dd, 1H, J = 12.9, 1.8 Hz), 7.63-7.60 (m, 2H), 7.37-7.36 (m, 2H), 7.32 (s, 1H), 7.15 (t, 2H, J = 8.8 Hz), 1.47 (s, 18H); MS (ESI$^+$) m/z 600.17 $(M + H)^+$.

B) N^1-(4-(6-Aminopirimidin-4-iloxi)-3-fluorofenil)-N^3-(4-fluorofenil)malonamida

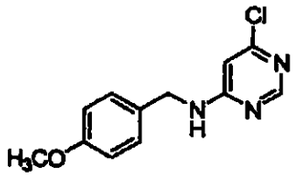
El compuesto del título se preparó a partir de N-1-(4-(N,N-di-ter-butilcarbonil-6-aminopirimidin-4-iloxi)-3-fluorofenil-N-3-(4-fluorofenil)malonamida (20 mg, 0.032 mmol) utilizando un procedimiento similar descrito para la preparación del Compuesto D del Ejemplo 9 para dar el compuesto del título (13 mg, 98%) como un sólido blanco. RMN-^{1}H (DMSO-d_6) δ 10.42 (s, 1H), 10.24 (s, 1H), 8.03 (s, 1H),

7.73 (d, 1H, J = 11.0 Hz), 7.61 (dd, 2H, J = 9.2, 4.9 Hz), 7.33-7.30 (m, 1H), 7.28-7.23 (m, 1H), 7.18-7.13 (m, 2H), 6.89 (s, 2H), 5.80 (s, 1H), 3.47 (s, 2H); MS (ESI^+) m/z 400.09 $(M + H)^+$.

Ejemplo 11



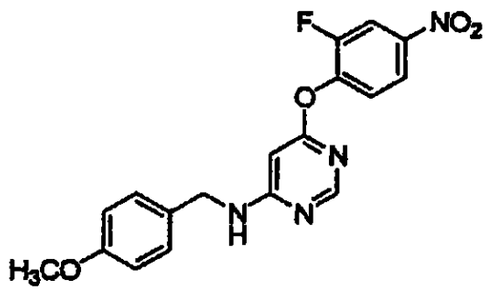
1-(4-(6-(4-Metoxibencilamino)pirimidin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea



A) N-(4-Metoxibencil)-6-cloropirimidin-4-amina

Una mezcla de 4,6-dicloropirimidina (Aldrich, 3.6 g, 24.2 mmol), 4-metoxibencilamina (2.7 g, 19.7 mmol), DIPEA (5 ml, 28.8 mmol), y n-BuOH se calentó a reflujo por 3 h. La mezcla se concentró y el residuo se trató con H_2O (150 mL) y EtOAc (175 mL). La fase de EtOAc se separó, se lavó con solución acuosa saturada de carbonato ácido de sodio y salmuera, se secó (sulfato de magnesio), y se concentró para

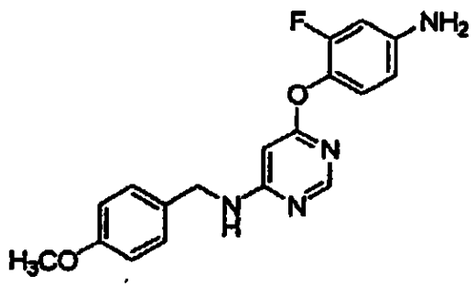
dar el compuesto del título (4.5 g) que se utilizó sin urificación adicional. RMN-^{1}H (DMSO-d_6) δ 8.29 (s, 1H), 8.13 (br s, 1H), 7.25 (d, 2H, J = 8.2 Hz), 6.90 (d, 2H, J = 8.2 Hz), 6.56 (s, 1H), 4.48 (s, 2H), 3.75 (s, 3H).



B) N-(4-Metoxibencil)-6-(2-fluoro-4-nitrofenoxi)pirimidin-4-amina

Una mezcla de N-(4-metoxibencil)-6-cloropirimidin-4-amina (2.3 g, 9.2 mmol), 2-fluoro-4-nitrofenol (1.45 g, 9.2 mmol), DIPEA (15 mL), y 2-metoxietil-éter (75 mL) se calentó a 160°C en una botella de presión sellada por 50 h. La mezcla se enfrió, se vació sobre hielo triturado (200 g), se trató con EtOAc (200 mL). Después de agitar vigorosamente por 10 min, el material insoluble se filtró. La fase de EtOAc se lavó con solución saturada de carbonato ácido de sodio (100 mL), salmuera (3 x 100 mL), se secó (sulfato de magnesio) y se concentró a vacío. El sólido gomoso obtenido se trituró con éter isopropílico para dar el compuesto del título (1.75 g, 76%) como un sólido café. RMN-^{1}H (DMSO-d_6) δ 8.32 (dd, 1H, J = 10.2, 2.0 Hz), 8.15 (d, 2H, J = 9.2 Hz), 8.05 (br s, 1H),

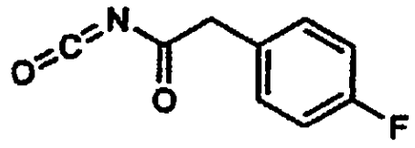
7.61 (dd, 1H, J = 8.4, 8.4 Hz), 7.26 (d, 2H, J = 8.5 Hz), 6.91 (d, 2H, J = 8.5 Hz), 6.14 (br s, 1H), 4.48 (br s, 2H), 3.74 (s, 3H).



C) N-(4-Metoxibencil)-6-(4-amino-2-fluorofenoxi)pirimidin-4-amina

Una solución de N-(4-metoxibencil)-6-(2-fluoro-4-nitrofenoxi)pirimidin-4-amina (150 mg, 0.41 mmol) en McOH/THF 1:1 (20 mL) se trató con cloruro de amonio (0.22 g, 4.1 mmol), y polvo de zinc (<20 micrómetros, 0.27 g, 4.2 mmol). La mezcla de reacción se agitó a temperatura ambiente por 1 h. Se agregó una porción adicional de polvo de zinc (150 mg) a la mezcla y la mezcla de reacción se agitó a temperatura ambiente por 1 h y se calentó a 70 °C por 20 min. La mezcla se filtró para remover los sólidos inorgánicos, se concentró a vacío, y el residuo se dividió entre EtOAc y salmuera. La fase de EtOAc se separó, se lavó con salmuera, se secó (sulfato de magnesio) y se concentró a vacío para dar el compuesto del título (145 mg, 99%). RMN-^{1}H (DMSO-d_6) δ 8.10 (br s. 1H), 7.76 (br s, 1H), 7.21 (d, 2H, J = 8.6 Hz), 6.88

(d, 3H, J = 8.6 Hz), 6.44 (dd, 1H, J = 12.7, 2.0 Hz), 6.36 (dd, 1H, J = 8.3, 2.3 Hz), 5.79 (s, 1H), 4.41 (br s, 2H), 3.73 (s, 3H); MS (ESI^+) m/z 341.18 $(M + H)^+$.



D) isocianato de 2-(4-fluorofenil)acetilo

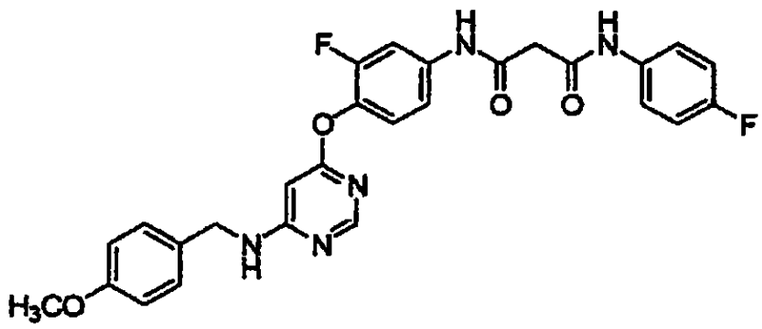
Se agregó cianato de plata (0.912 g, 6.08 mmol, 1.05 eq) a una solución de cloruro de 4-fluorofenilacetilo (Lancaster, 0.794 ml, 5.79 mmol, 1.0 eq) en tolueno (16 ml) a temperatura ambiente. La mezcla de reacción se protegió de la luz y se calentó a reflujo. Después de 60 minutos, La mezcla se enfrió a temperatura ambiente y se filtró (Acrodisc, PTFE 0.2 µM) para dar una solución 0.36 M de isocianato de 2-(4-fluorofenil)acetilo en tolueno, que se utilizó sin purificación.

E) 1-(4-(6-(4-Metoxibencilamino)pirimidin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea

Una solución de N-(4-metoxibencil)-6-(4-amino-2-fluorofenoxi)pirimidin-4-amina (88 mg, 0.26 mmol) en THE (2 mL) se trató con isocianato de 2-(4-fluorofenil)acetilo 0.36 M en tolueno (0.72 mL, 0.26 mmol) y la mezcla de reacción se agitó a temperatura ambiente por 1 h. La mezcla se concentró

a vacío y el sólido obtenido se trituró con éter isopropílico para dar el compuesto del título (125 mg, 93%) como un sólido blanquecino. RMN-^{1}H (DMSO-d_6) δ 11.00 (s, 1H), 10.50 (s, 1H). 8.09 (s, 1H), 7.85 (br s, 0.5 H), 7.66 (d, 1H, J = 12.6 Hz), 7.36-7.15 (m, 9.5 H), 6.88 (d, 1H, J = 8.1 Hz). 5.91 (s, 1H), 4.42 (br s, 2H), 3.72 (s, 2H), 3.71 (s, 3H); MS(ESI$^+$) m/z 520.14 $(M + H)^+$.

Ejemplo 12

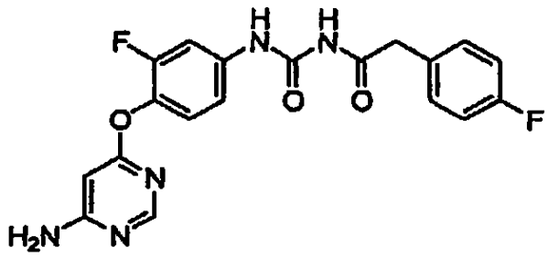


N^1-(4-(6-(4-Metoxibencilamino)pirimidin-4-iloxi)-3-fluorofenil)-N^3-(4-fluorofenil)malonamida

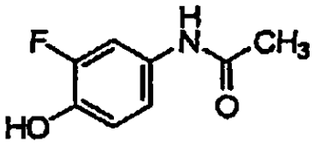
El compuesto del título se preparó a partir de N-(4-metoxibencil)-6-(4-amino-2-fluorofenoxi)pirimidin-4-amina (Compuesto C del Ejemplo 11, 200 mg, 0.59 mmol), ácido 3-(4-fluorofenilamino)-3-oxopropanoico (Compuesto B del Ejemplo 1, 128 mg. 0.65 mmol), TBTU (228 mg, 0.71 mmol), y DIPEA (123 µL, 0.71 mmol) en DMF utilizando un procedimiento similar descrito para la preparación del Compuesto C del Ejemplo 1. El producto crudo se purificó mediante trituración con éter

isopropílico para dar el compuesto del título (250 mg, 82% como un sólido blanquecino. RMN-^{1}H (DMSO-d_6) δ 10.43 (s, 1H), 10.25 (s, 1H), 8.09 (s, 1H), 7.85 (s, 1H), 7.72 (dd, 1H, J = 9.1, 5.0 Hz), 7.62 (dd, 2H. J = 8.8, 5.0 Hz), 7.31-7.21 (m, 4H), 7.15 (dd, 2H, J = 8.8, 8.8 Hz), 6.88 (m, 2H), 5.90 (s, 1H), 4.42 (br s, 2H), 3.71 (s, 3H), 3.46 (s, 2H); MS(ESI+) m/z 520.14$(M + H)^+$.

Ejemplo 13



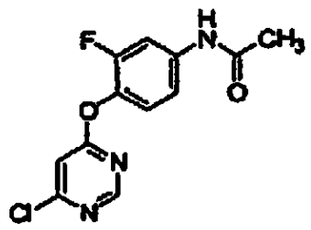
1-(4-(6-Aminopirimidin=4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea



A) N-(3-Fluoro-4-hidroxifenil)acetamida

El compuesto del título se preparó a partir del 2-fluoro-4-nitrofenol comercialmente disponible de acuerdo al procedimiento de Burckhalter, J. H. et al. (J. Am. Chem. Soc. 1948, 70. 1363). Nitrofenol (5.73 g, 36.5 mmol) y anhídrido

acético (3.72 g, 36.5 mmol) se disolvieron en ácido acético (20 mL) y se agregó luego PtO_2 (150 mg). La mezcla de reacción se agitó bajo atmósfera de hidrógeno 3.52 kg/cm2 (50 psi) a temperatura ambiente por 24 h. El precipitado que se formó se recolectó mediante filtración a vacío y el papel filtro se lavó con ácido acético (25 mL). El filtrado combinado y el lavado se concentraron a vacío para dar el compuesto del título (2.0 g). El sólido que permaneció sobre el papel filtro se trató con McOH para disolver el producto y el Pt_2O se filtró. El filtrado se concentró a vacío y el sólido obtenido se trituró con 1:1 EtOAc/hexanos (200 mL) para dar una segunda cosecha del compuesto del título (1.8 g. 62% en total). RMN-^{1}H (DMSO-d_6) δ 9.83 (s, 1H). 9.51 (s, 1H), 7.50 (dd, 1H, J = 13.6,2.5 Hz), 7.03 (d, 1H. J = 8.5 Hz), 6.84 (dd, 1H, J = 9.3. 9.3 Hz), 1.98 (s, 3H): MS(ESI$^+$) m/z 170.23 $(M + H)^+$.

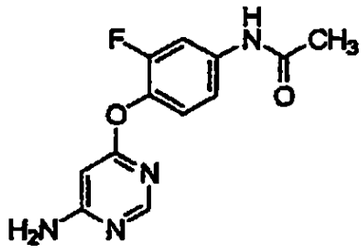


B) N-(4-(6-Cloropirimidin-4-iloxi)-3-fluorofenil)acetamida

Una mezcla de 4,6-dicloropirimidina (1.50 g, 10.0 mmol), N-(3-fluoro-4-hidroxifenil)acetamida (1.70 g, 10.0 mmol), K_2CO_3 (1.8 g. 13.0 mmol), y DMF (15 mL) se calentó a 70 °C por 1.5 h. La mezcla se concentró a la mitad de su volumen

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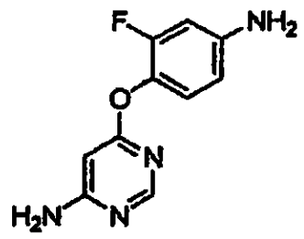
original y se enfrió en un baño de hielo. La mezcla se trató con H_2O (100 mL) para precipitar el producto que se recolectó mediante filtración a vacío. El producto se lavó con H_2O y se secó a vacío sobre el embudo toda la noche, para dar el compuesto del título (2.0 g, 71%) como un sólido gris. RMN-^{1}H (DMSO-d_6) δ 10. 26 (s, 1H), 8.67 (s, 1H), 7.78 (dd, 1H, J = 12.6, 2.0 Hz). 7.56 (s, 1H), 7.37-7.30 (m, 2H), 2.08 (s, 3H); MS (ESI$^+$) m/z 282.10 $(M + H)^+$.



C) N-(4-(6-Aminopirimidin-4-iloxi)-3-fluorofenil)acetamida

Una mezcla de N-(4-(6-aminopirimidin-4-iloxi)-3-fluorofenil)acetamida (1.0 g, 3.5 mmol) y NH_3 aproximadamente 7 M en NeOH (5 mL) se calentó a 100°C en una botella de presión sellada, por 2 h. La mezcla se concentró a vacío y el residuo se dividió entre EtOAc y solución acuosa saturada de carbonato ácido de sodio. La fase de EtOAc se separó, se lavó con salmuera, se secó (sulfato de magnesio) y se concentró. Cromatografía instantánea sobre SiO_2 utilizando primeramente

EtOAc al 50% en hexanos luego 5% de McOH en cloruro de metileno como eluyentes dio el compuesto del título (175 mg, 20%) como un sólido café. RMN-^{1}H (DMSO-d_6) δ 10.17 (s, 1H), 8.02 (s, 1H), 7.70 (dd, 1H, J = 13.2. 2.2 Hz), 7.26 (dd, 1H. J = 8.8. 2.2 Hz). 7.22 (dd, 1H, J = 8.8, 8.8 Hz), 6.89 (br s, 2H), 2.05 (s, 3H); MS (ESI$^+$) m/z 263.15 $(M + H)^+$.



D) 6-(4-Amino-2-fluorofenoxi)pirimidin-4-amina

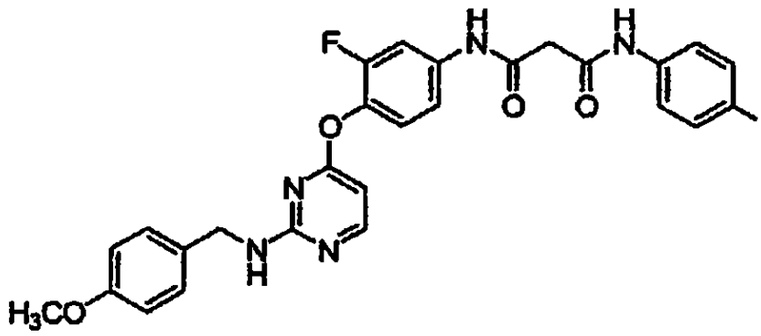
Una mezcla de N-(4-(6-aminopirimidin-4-iloxi)-3-fluorofenil)acetamida (175 mg, 0.67 mmol), HCl 1 M (6 mL), y McOH (2 mL) se calentó a reflujo por 3 h. La mezcla de reacción se enfrió, se alcalinizó (pH 8) solución acuosa de carbonato de sodio y se extrajo con EtOAc (2 x 25 mL). Los extractos combinados se secaron (sulfato de magnesio) y se concentró a vacío para dar el compuesto del título (140 mg, 96%) como un sólido café. RMN-1H (DMSO-d6) δ 8.02 (s, 1H), 6.89 (dd, 1H, J = 9.0, 9.0 Hz), 6.80 (br s, 2H), 6.43. (dd, 1H, J = 12 .7, 2.8 Hz), 6.35 (dd ,1H, J = 8. 8, 2.2 Hz), 5.67 (s, 1H), 5.34 (brs, 2H).

E) 1-(4-(6-Aminopirimidin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea

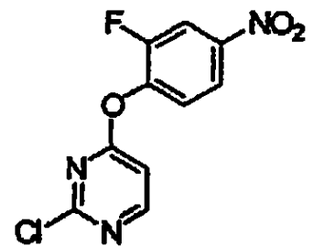
El compuesto del título se preparó a partir de 6-(4-

amino-2-fluorofenoxi)pirimidin-4-amina (92 mg, 0.42 nmol) y 0.36 M isocianato de 2-(4-fluorofenil)acetilo en tolueno (Compuesto D del Ejemplo 11, 1.3 mL, 0.45 mmol) en THF como se describió anteriormente para el Ejemplo 11. El producto crudo se purificó mediante trituración utilizando EtOH/agua 1:1 seguido por etanol absoluto. El producto se secó a vacío para dar el compuesto del título (100 mg, 60%). Una segunda cosecha ligeramente menos pura del producto (45 mg, 27%) se obtuvo mediante extracción de los filtrados combinados y lavando con EtOAc. RMN-^{1}H (DMSO-d_6) δ 10.99 (s, 1H), 10.50 (s, 1H), 8.01 (s, 1H), 7.65 (dd, 1H, J = 12.6, 2.1 Hz), 7.33 (dd, 2H, J = 8. 1, 6.0 Hz), 7.28 (dd, 1H, J = 8. 6, 2.0 Hz). 7.22 (dd, 1H, J = 8.8, 8.8 Hz), 7.17-7.12 (m, 2H), 6.89 (br s, 2H), 5.80 (s, 1H), 3.71 (s, 2H); MS (ESI$^+$) m/z 400.09(M + H)$^+$.

Ejemplo 14

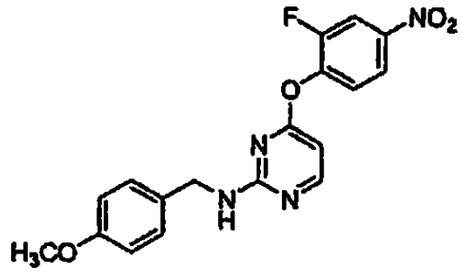


N^1-(4-(2-(4-Metoxibencilamino)pirimidin-4-iloxi)-3-fluorofenil)-N^3-(4-fluorofenil)malonamida



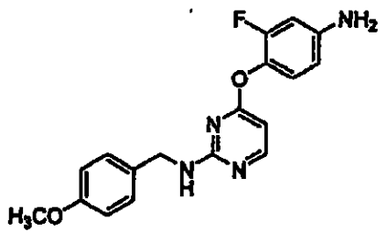
A) 2-Cloro-4-(2-fluoro-4-nitrofenoxi)pirimidina

Una mezcla de 2,4-dicloropirimidina (Aldrich, 0.74 g, 5.0 mmol), 2-fluoro-4-nitrofenol (Avacado, 0.79 g, 5.0 mmol), K_2CO_3 (0.76 g. 5.5 mmol), y DMF (50 mL) se calentó a 100 °C por 2 h. La mezcla se enfrió y se diluyó con solución acuosa saturada de carbonato ácido de sodio (100 mL) y se extrajo con EtOAc. El extracto de EtOAc se lavó con salmuera, se secó (sulfato de magnesio) y se concentró a vacío para dar una mezcla de los regioisómeros de 2-fenoxi- y 4-fenoxipirimidina como un sólido amarillo. Los regioisómeros se separaron mediante cromatografía instantánea utilizando 10-40 de EtOAc en hexanos como el eluyente para dar el compuesto del título (0.71 g, 53%) como un sólido blanco. RMN-^{1}H (DMSO-d_6) δ 8.76 (dd, 1H, J = 6. 0, 1.6 Hz), 8.43 (dt, 1H, J = 9.8, 2.2 Hz). 8.23 (dd, 1H, J = 8.8, 1.6Hz), 7.80 (dt, 1H, J = 9.8, 2.2 Hz), 7.48 (dd, 1H, J = 9.8, 2.2 Hz), 7.48 (d, 1H, J = 6.0, 2.2 Hz).



B) N-(4-Metoxibencil)-4-(2-fluoro-4-nitrofenoxi)pirimidin-2-amina

Una mezcla de 2-cloro-4-(2-fluoro-4-nitrofenoxi)pirimidina (0.66 g, 2.44 mmol), 4-metoxibencilamina (0.34 g, 3.45 mmol), K_2CO_3 (0.37 g, 2.66 mmol), y DMF (15 mL) se calentó a 100°C por 1H. La mezcla se enfrió, se diluyó con agua (100 mL) y se extrajo con EtOAc (100 mL). La fase orgánica se lavó dos veces cada una con solución acuosa saturada de carbonato ácido de sodio y salmuera. Los materiales orgánicos se secaron (sulfato de magnesio) y se concentraron para dar el producto crudo. Cromatografía instantánea sobre SiO_2 utilizando 1-3% de McOH en cloruro de metileno como el eluyente, dio el compuesto del título (275 mg, 29%) como un sólido amarillo pálido. RMN-^{1}H (DMSO-d_6) δ 8.40-8.21 (m, 2H), 8.16 (dd, 1H, J = 8.8, 1.7 Hz), 7.98 (br s, 0.5H), 7.73-7.55 (m, 1.5 H), 7.16 (br s, 1H), 6.85-6.71 (m, 3H), 6.37 (s, 1H), 4.43 (br s, 1H), 3.95 (br s, 1H), 3.69 (s, 3H).



C) N-(4-Metoxibencil)-4-(4-amino-2-fluorofenoxi)pirimidin-2-amina

El compuesto del título se obtuvo mediante la reducción

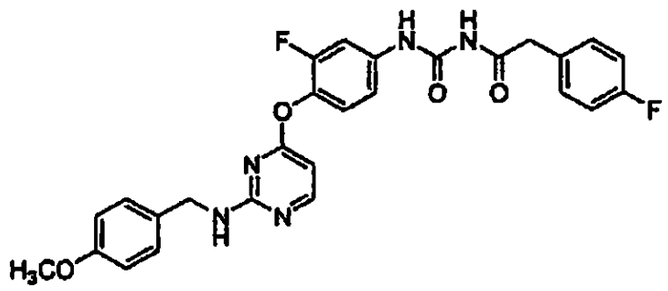
de N-(4-metoxibencil)-4-(2-fluoro-4-nitrofenoxi)pirimidin-2-amina (270 mg, 0.73 mmol) con polvo de zinc (475 mg. 7.3 mmol) y NH_4Cl (387 mg, 7.3 mmol) en THF/MeOH 1:1 (20 mL) utilizando un procedimiento similar al descrito para el Compuesto C del Ejemplo 11. Cromatografía instantánea sobre SiO_2 utilizando 1-3 % de McOH en cloruro de metileno como el eluyente dio el compuesto del título (235 mg, 95%) como una película café. RMN-^{1}H (DMSO-d_6) δ 8.01 (s, 1H), 7.65 (br s. 0.5 H). 7.49 (br s, 0.5H), 7.08 (br s. 1H), 6.83 (br s, 2H), 6.81 (m, 1H). 6.69 (br s. 2H). 6.39 (br s, 0. 5H), 6.31 (br s, 0. 5H), 6.01 (m, 1H), 5.26 (br s, 2H), 4.24 (br s, 1H). 3.95 (br s, 1H), 3.61 (s, 3H); MS(ESI$^+$) m/z 341.16 $(M + H)^+$.

D) N^1-(4-(2-(4-Metoxibencilamino)pirimidin-4-iloxi)-3-fluorofenil)-N^3-(4-fluorofenil)malonamida

El compuesto del título se obtuvo a partir de la N-(4-metoxibencil)-4-(4-amino-2-fluorofenoxi)pirimidin-2-amina (34 mg,0.10 mmol), ácido 3-(4-fluorofenilamino)-3-oxopropanoico (Compuesto B del Ejemplo 1, 22 mg, 0.11 mmol), TBTU (39 mg, 0.12 mmol) y DIPEA (23 mL, 0.17 mmol) utilizando un procedimiento similar descrito para la preparación del Compuesto C del Ejemplo 1. El producto crudo se trituró con éter isopropílico/EtOAc 3:1 para dar el compuesto del título (35 mg, 61%) como un sólido blanquecino. RMN-^{1}H (DMSO-d_6) δ 10.47 (br s, 1H), 10.26 (s, 1H), 8.15 (s, 1H), 7.77 (m, 3H). 7.61 (m, 2H), 7.35-7.25 (m, 2H), 7.15 (dd, 2H. J = 8.8, 8.8

Hz), 6.81-6.73 (m, 2H), 6.24 (s, 1H), 4.32 (br s, 1H), 3.96 (br s, 1H), 3.68 (s, 1H), 3.48 (s, 2H); MS (ESI^+) m/z 520.14$(M + H)^+$.

EJEMPLO 15

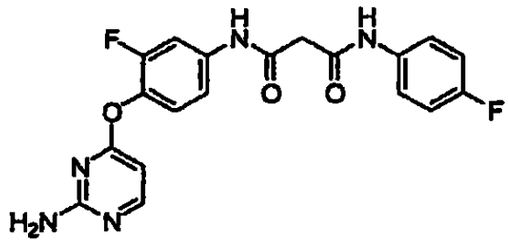


1-(4-(2-(4-Metoxibencilamino)pirimidin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea

Una solución de N-(4-metoxibencil)-4-(4-amino-2-fluorofenoxi)pirimidin-2-amina (Compuesto C del Ejemplo 14, 34 mg, 0.10 mmol) en THF (1 ml) se trató con isocianato de 2-(4-fluorofenil)acetilo 0.36 M en tolueno (Compuesto D del Ejemplo 11, 0.31 mL, 0.11 mmol) y la mezcla se agitó a temperatura ambiente por 1 h. La mezcla se concentró a vacío y el sólido obtenido se trituró primeramente con éter isopropílico/EtOAc 3:1 y luego cloruro de metileno para dar el compuesto del título (32 mg, 62%) como un sólido blanquecino. RMN-^{1}H (DMSO-d_6) δ 10.47 (s, 1H). 10.26 (s, 1H), 8.15 (s, 1H), 7.76 (d, 1H, J 12.6 Hz). 7.61 (dd, 3H, J = 9. 1, 5.0 Hz). 7.29 (s, 2H). 7.31-7.21 (m, 3H). 6.81 (s, 3H), 6.24 (s, 1H), 4.32 (s, 1H), 3.96 (s, 1H), 3.68 (s, 3H). 3.48

(s, 2H); MS (ESI^+) m/z 520.14 $(M + H)^+$.

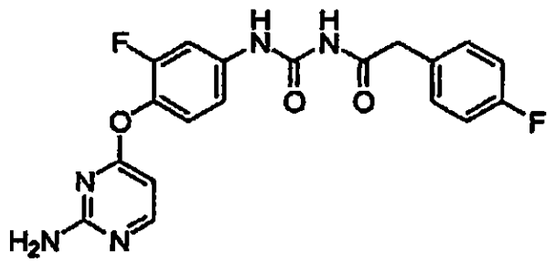
Ejemplo 16



N^1-(4-(2-Aminopirimidin-4-iloxi)-3-fluorofenil)-N^3-(4-fluorofenil)malonamida

Una mezcla de N^1-(4-(2-(4-metoxibencilamino)pirimidin-4-iloxi)-3-fluorofenil)-A-(4-fluorofenil)malonamida (Ejemplo 14, 25 mg, 0.048 mmol), anisol (52 mg, 0.48 mmol) en TFA (1 mL) se calentó a 85 °C por 6 h. El TFA se retiró a vacío y el residuo se dividió entre EtOAc y solución acuosa saturada de carbonato ácido de sodio. La fase de EtOAc se lavó con salmuera, se secó (sulfato de magnesio), y se concentró a vacío. Cromatografía instantánea sobre SiO_2 utilizando EtOAc luego 1-2 % de McOH en cloruro de metileno como eluyentes dio el compuesto del título (12 mg. 63%) como un sólido blanquecino. RMN-^{1}H (DMSO-d_6) δ 11.00(s, 1H), 10.51 (s, 1H), 8.02(s, 1H), 7.66 (dd, 1H. J = 12.6. 2.0 Hz). 7.42-7.31 (m, 2H), 7.32-7.27 (m, 1H), 7.23 (t, 2H, J = 8.6 Hz). 7.16 (t, 2H, J = 9.1 Hz), 6.91 (s, 2H), 3.73 (s, 2H); MS(ESI^+)m/z400.11 $(M + H)^+$.

Ejemplo 17



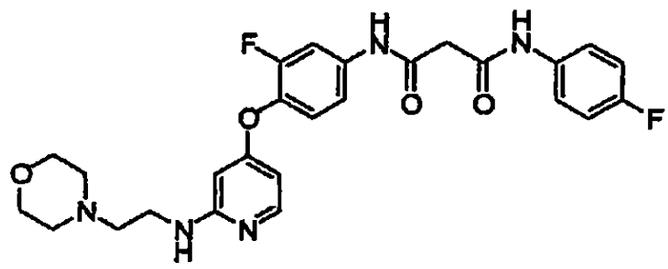
1-(4-(2-Aminopirimidin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea

El compuesto del título se preparó a partir de 1-4-(2-(4-metoxibencilamino)pirimidin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea (Ejemplo 15, 20 mg, 0.039 mmol) utilizando un procedimiento similar descrito para el Ejemplo 16.

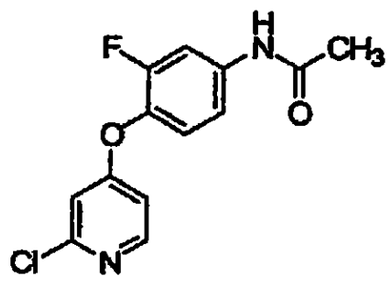
Cromatografía instantánea sobre SiO_2 utilizando EtOAc luego 1-2 % de McOH en cloruro de metileno como eluyentes dio el compuesto del título (10 mg. 62%) como un sólido blanquecino.

RMN-^{1}H (DMSO-d_6) δ 11.01 (s, 1H), 10.52 (s, 1H), 8.20 (d, 1H, J = 6.0 Hz), 7.70 (dd, 1H, J = 12.1, 2.0 Hz), 7.36-7.30 (m, 6H), 7.16 (dd, 2H, J = 8.8, 8.8 Hz), 6.45 (d, 1H, J = 6.1 Hz), 3.73 (s, 2H); MS (ESI$^+$) m/z 400.09 $(M + H)^+$.

Ejemplo 18



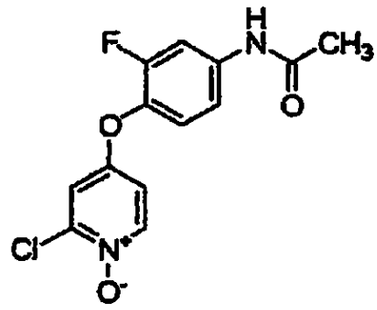
N^1-(3-Fluoro-4-(2-(2-morfolinoetilamino)piridin-4-iloxi)fenil)-N^3-(4-fluorofenil)malonamida, sal de clorhidrato



A) N-(4-(2-Cloropiridin-4-iloxi)-3-fluorofenil) cetamida

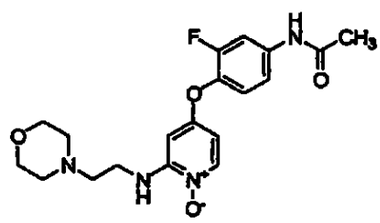
Una mezcla de N-(3-fluoro-4-hidroxifenil)acetamida (Compuesto A del Ejemplo 13, 1.33 g. 7.87 mmol), 2-cloro-4-nitropiridina (Aldrich, 1.24 g, 7.87 mmol), K_2CO_3 (1.6 g, 11.8 mmol), y DMF (25 mL) se calentó a 100°C por 9 h. La mezcla de reacción se concentró a vacío y el residuo se dividió entre EtOAc y solución acuosa saturada de carbonato ácido de sodio. La fase de EtOAc se lavó con salmuera, se secó (sulfato de magnesio), y se concentró. Cromatografía instantánea utilizando 30-80 % de EtOAc en hexanos como el eluyente dio el compuesto del título (1.6 g, 73%) como un sólido amarillo

pálido. RMN-^{1}H (DMSO-d_6) δ 10.24 (s, 1H), 8.65 (s, 1H), 7.89-7.64 (m, 1H), 7.56 (s, 1H), 7.46-7.19 (m, 2H), 2.06 (s, 3H); MS(ESI$^+$) m/z 281.16 $(M + H)^+$.



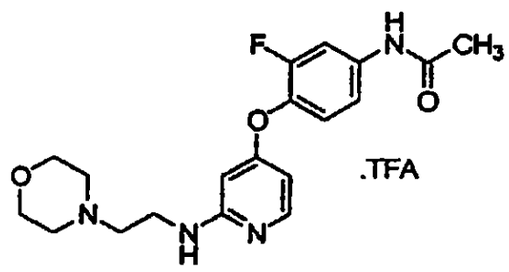
B) N-(4-(2-Cloropiridin-4-iloxi-1-óxido)-3-fluorofenil)acetamida

Una mezcla de N-(4-(2-cloropiridin-4-iloxi)-3-fluorofenil)acetamida (0.98 g, 3.5 mmol), ácido m-cloroperoxibenzoico (> 90 %, 1.3 g, 7.6 mmol). y $CHCl_3$ (50 mL) se agitó a temperatura ambiente por 60 h. La mezcla se 5 concentró y el residuo se trituró con Et_2O (2 x 100 mL) para dar el compuesto del título (0.89 g, 87%) como un sólido amarillo pálido. RMN-^{1}H (DMSO-d_6) δ 10.25 (s, 1H), 8.34 (d, 1H, J = 7.1 Hz), 7.80 (d, 1H, J = 13.2 Hz), 7.49 (d, 1H, J = 3.3 Hz). 7.33 (d, 2H, J = 4.9 Hz), 7.02 (dd, 1H, J = 7.1, 3.3 Hz), 2.06 (s, 3H); MS(ESI$^+$) m/z 295.04 (M - H).



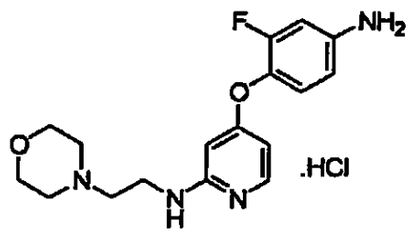
C) N-(3-Fluoro-4-(2-(2-morfolinoetilamino)piridin-4-iloxi-1-óxido)fenil)acetamida

Una mezcla de N-(4-(2-cloropiridin-4-iloxi-1-óxido)-3-fluorofenil)acetamida (205 mg. 0.62 mmol), 4-(2-aminoetil)morfolina (Aldrich, 169 mg, 1.30 mmol), y etanol absoluto se calentó a reflujo 16 h. La mezcla de reacción se concentró a vacío, el residuo se trató con agua (3 mL) y se aplicó a un cartucho Varian C-10 de 10 g. El cartucho se eluyó primeramente con H_2O luego con 30 % de McOH en H_2O. Las fracciones que contenían el producto deseado se combinaron, se concentraron a un volumen de 5 mL, y se extrajo 3 veces con EtOAc. Los extractos combinados se lavaron con salmuera, se secaron (sulfato de magnesio) y se concentraron para dar el compuesto del título (100mg, 40%). RMN-^{1}H (DMSO-d_6) δ 10.22(s, 1H), 7.84 (d, 1H, J = 6.1 Hz), 7.77 (dd, 1H, J = 13.2, 2.2 Hz), 7.31 (dd, 1H, J = 8. 8, 2.2 Hz), 7.24 (t, 1H, J = 8.8 Hz), 6.41 (m, 1H), 6.13 (dd, 1H, J = 5.5. 2.2 Hz), 5.81 (d, 1H.J = 2.2 Hz), 3.60-3.52 (m, 4H), 3.31-3.28 (m, 2H), 2.38 (t, 2H, J = 7.1 Hz), 2.34 (m, 4H), 2.06 (s, 3H); MS (ESI$^+$) m/z 405.22 $(M + H)^+$.



D) N-(3-Fluoro-4-(2-(2-morfolinoetilamino)piridin-4-iloxi)fenil)acetamida, sal del ácido trifluoroácetico

Una mezcla de N-(3-fluoro-4-(2-(2-morfolinoetilamino)piridin-4-iloxi-1-óxido)fenil)acetamida (100 mg, 0.26 mmol), y polímero de trifenilfosfina suportado (1.4 -2.0 mmol/g) sobre poliestireno (500 mg) y DMF (2 mL) se agitó a 135°C por 1 5 h. La mezcla se filtró para retirar la resina y la resina se lavó cpn DMF y EtOAc. El filtrado y los lavados. se combinaron y se concentraron. El producto crudo se purificó mediante HPLC preparativa (Shimadzu S5 VP-ODS 20 x 100 mm) para dar el compuesto del título (45 mg, 46%) como un sólido blanco. RMN-^{1}H (DMSO-d_6) δ 10.33 (s, 1H), 8.02 (d, 1H, J = 6.6 Hz), 7.84 (dd, 1H, J = 13.2. 2.0 Hz), 7.39-7.31 (m, 2H), 6.52 (s, 1H), 6.10 (s, 1H), 3.83 (br s, 4H), 3.64 (m, 2H), 3.28 (m, 6H), 2.08 (s, 3H); MS(ESI$^+$) m/z 375.12 (M + H)$^+$.



E) 4-(4-Amino-2-fluorofenoxi)-N-(2-morfolinoetil)piridin-2-amina, sal de clorhidrato

Una mezcla de trifluoroacetato de N-(3-fluoro-4-(2-(2-

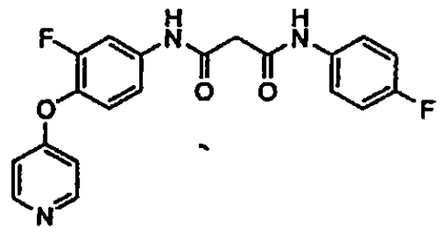
morfolinoetilamino)piridin-4-iloxi)fenil)acetamida (40 mg), MeOH (1 mL), y HCl 6 M (0.2 mL) se calentó a reflujo por 3 h. La mezcla de reacción se concentró en un evaporador rotatorio y el residuo se liofilizó para dar el compuesto del título (30 mg, 76%) como un sólido blanco. RMN-^{1}H (DMSO-d_6) δ 11.12 (brs, 1H), 8.85 (br s, 1H), 7.95 (d, 1H, J = 7.2 Hz), 7.08 (dd, 1H, J = 8.8, 8.8 Hz), 6.65-6.63 (m, 2H), 6.54 (d, 1H, J = 8.3 Hz), 6.31 (br s, 1H), 3.85 (m, 6H), 3.33 (m, 6H); MS(ESI$^+$) m/z 373.14 (M - H).

F) N^1-(3-Fluoro-4-(2-(2-morfolinoetilamino)piridin-4-iloxi)fenil)-N^3-(4-fluorofenil)malonamida

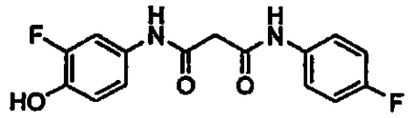
El compuesto del título se preparó a partir de una mezcla de 4-(4-amino-2-fluorofenoxi)-N-(2-morfolinoetil)piridin-2-amina, sal de clorhidrato (15 mg, 0.043 mmol), ácido 3-(4-fluorofenilamino)-3-oxopropanoico (Compuesto B del Ejemplo 1, 10 mg, 0.052 mmol), TBTU (17 mg, 0.052 mmol), DIPEA (30 µL), y DMF (1 mL) utilizando un procedimiento similar descrito para la preparación del Compuesto C del Ejemplo 1. El producto crudo se purificó mediante HPLC preparativa (Shimadzu S5 VP-ODS 20 x 100 mm). El producto obtenido a partir de la purificación por HPLC se trató con 1 M HCl y se liofilizó para dar el compuesto del título (10 mg. 40%) como un sólido blanco. RMN-^{1}H (DMSO-d_6) δ 10.37 (s, 1H), 10.05 (s, 1H), 9.90 (br s, 1H), 7.90 (d, 1H, J = 6.1 Hz), 7.75 (d, 1H, J = 13.2 Hz), 7.58-7.55 (m, 2H),

7.53-7.50 (m, 1H), 7.40 (d, m, J = 8.8 Hz), 7.24 (t, 1H, J = 8.8 Hz), 7.08 - 7.03 (m, 3H), 6.39 (d, 1H, J = 6.1 Hz), 6.11 (s, 1H), 3.80 -3.81 (m, 4H), 3.67- 3.65 (m, 2H), 3.47 (br s, 2H), 3.20 (br s, 4H); MS (ESI^+) m/z 512.12 $(M + H)^+$.

Ejemplo 19



N^1-(3-Fluoro-4-(piridin-4-iloxi)fenil)-N^3-(4-fluorofenil)malonamida



A) N^1-(3-Fluoro-4-hidroxifenil)-N^3-(4-fluorofenil)malonamida

A una solución de 2-fluoro-4-nitrofenol (Avacado. 1.00 g, 6.37 mmol) en 4 mL de tetrahidrofurano y 6 mL de metanol a 0°C se agregó polvo de zinc (2.08 g, 31.8 mmol, <10 micrómetro) seguido por cloruro de amonio (1.70 g, 31.8 mmol). La mezcla se agitó a temperatura ambiente toda la noche. La mezcla heterogénea se filtró a través de un lecho

delgado de Celite® con metanol y el filtrado se concentró a vacío para dar 4-amino-2-fluorofenol como un sólido café que se utilizó sin purificación adicional (656 mg, 81%).

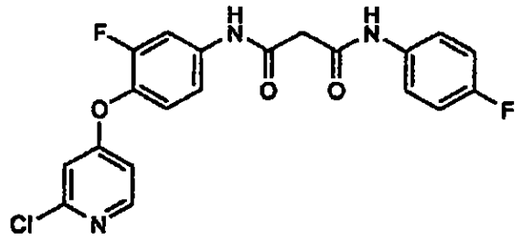
Se disolvió ácido 3-(4-Fluorofenilamino)-3-oxopropanoico (Compuesto B del Ejemplo 1, 197 mg, 1.00 mmol) en dimetilformamida (4 mL). Se agregó trietilamina (140 µL, 1.00 mmol) y la solución se enfrió a 0°C. Se agregó 4-amino-2-fluorofenol (Paso A del Ejemplo 19, 127 mg, 1.00 mmol) seguido por hexafluorofosfato de benzotriazol-1-iloxitris(dimetilamino)fosfonio (reactivo BOP, 442 mg, 1.00 5 mmol). La reacción se dejó calentar a temperatura ambiente y fue luego agitada a temperatura ambiente por 3 h. La mezcla de reacción se concentró para remover el cloruro de metileno y se agregó agua para precipitar el producto. La filtración y trituración con agua dio el compuesto del título (211 mg, 69%) como un sólido blanco. RMN-^{1}H (CD_3OD) δ 7.61-7.57 (m, 2H), 7.51 (dd, 1H. J = 13, 2.5 Hz), 7.08-6.99 (m, 3H), 6.88 (t, 1H, J = 9.4 Hz), 3.51 (s, 2H); MS (ESI^+) m/z 307.44 $(M+H)^+$.

B) N^1-(3-Fluoro-4-(piridin-4-iloxi)fenil)-N^3-(4-fluorofenil)malonamida.

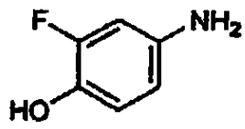
N^1-(3-Fluoro-4-hidroxifenil)-N^3-(4-fluorofenil)malonamida (31 mg, 0.10 mmol), acetato de cobre (II) (27 mg, 0.15 mmol), ácido piridin-4-ilborónico (25 mg, 0.20 mmol), y piridina (16 µL, 0.20 mmol) se colocaron en un tubo a presión, en ese

orden. El tubo se cargó con cloruro de metileno (0.5 mL) y se selló. La reacción se agitó a 120°C por 5 h. La mezcla de reacción se filtró a través de gel de sílice utilizando 5% de metanol/acetato de etilo. Después de la concentración, el producto crudo se purificó mediante HPLC preparativa. La fracción apropiada se concentró para remover el metanol y la solución acuosa resultante se alcalinizó con solución acuosa saturada de carbonato ácido de sodio (5 mL). La solución acuosa se extrajo con EtOAc (3 x 10 mL) y los extractos orgánicos combinados se secaron sobre sulfato de sodio anhidro y se concentró a vacío. El producto se trató con HCl 4N en dioxano y se concentró. La liofilización con agua dio el compuesto del título (8 mg, 21%) como un sólido amarillo. RMN-^{1}H (CD_3OD) δ 8.31 (d, 2H, J = 6.1 Hz), 7.72 (dd, 1H, J = 12.7, 2.4 Hz), 7.49-7.46 (m, 2H), 7.27-7.25 (m, 1H), 7.15 (t, 1H, J = 8.8 Hz), 6.97 (t, 2H, J = 8.7 Hz), 6.85 (dd, 2H, J = 5.1, 1.2 Hz), 3.46 (s, H); MS(ESI$^+$) m/z 3 84.21 $(M + H)^+$.

Ejemplo 20

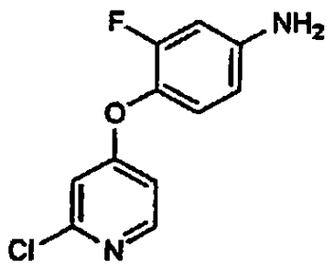


N^1-(4-(2-Cloropiridin-4-iloxi)-3-fluorofenil)-N^3-(4-fluorofenil)malonamida



A) 2-Fluoro-4-aminofenol

Una mezcla de óxido de platino (0.010 g) y 2-fluoro-4-nitrofenol (Aldrich, 1.24 g, 7.78 mmol, 1.0 eq) en MeOH (100 ml) se agitaron bajo una atmósfera de hidrógeno a 50 psi a temperatura ambiente. La mezcla de reacción se filtró a través de celite y el filtrado se concentró a vacío para proporcionar el compuesto del título (1.00 g, 100%), como un sólido que se utilizó sin purificación adicional. RMN-^{1}H (DMSO-d_6) δ 8.57 (s, 1H), 6.46-6.47 (m, 1H), 6.33-6.46 (m, 1H), 6.19-6.21 (m, 1H), 4.79 (s, 2H); MS (ESI$^+$) m/z 128 (M + H)$^+$.



B) 4-(2-Cloropiridin-4-iloxi)-3-fluorobencenamina

Se agregó hidruro de sodio (60%, 0.104 g, 2.60 mmol, 1.1 eq) a una solución de 2-fluoro-4-aminofenol (0.30 g, 2.36 mmol, 1.0 eq) en DMF (6.5 mL) a temperatura ambiente y la mezcla de reacción se agitó por 30 minutos. Se agregó 2-

cloro-4-nitropiridina (Aldrich, 0.374 g, 2.36 mmol, 1.0 eq) y la mezcla de reacción se calentó a 90°C por 12 h. La mezcla de reacción se enfrió a temperatura ambiente, se apagó con solución acuosa saturada de cloruro de sodio y se extrajo con acetato etilo (3 x 70 mL). Los extractos orgánicos combinados se lavaron con solución acuosa de LiCl al 10% (3 x 70 mL), se secó sobre sulfato de sodio. Se filtró y el filtrado se concentró a vacío para proporcionar el compuesto del título (0.430 g, 76%) que se utilizó sin purificación adicional. RMN-^{1}H (DMSO-d_6) δ 8.27 (d, 1H, J = 5.7 Hz), 6.90- 7.04 (m, 3H), 6.42-6.54 (m, 2H), 5.54 (s, 2H); MS(ESI$^+$) m/z 239 (M+H)$^+$; HRMS (ESI$^+$) calculado: 239.0387, encontrado: 239.0391.

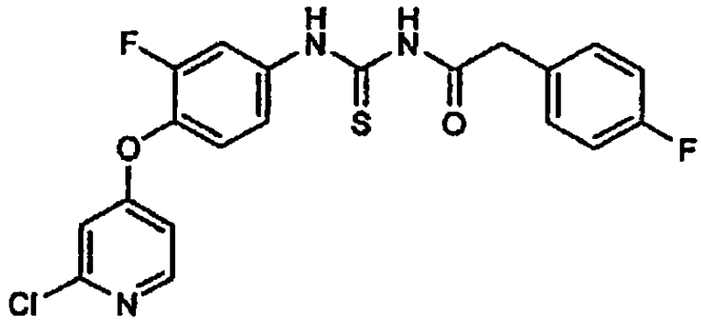
C) N^1-(4-(2-Cloropiridin-4-iloxi)-3-fluorofenil)-N^3-(4-fluorofenilmalonamida

Se agregó diisopropiletilamina (0.091 mL, 0.525 mmol, 2.5 eq) a una solución de 4-(2-cloropiridin-4-iloxi)-3-fluorobencenamina (0.050 g, 0.21 mmol, 1.0 eq), ácido 3-(4-fluorofenilamino)-3-oxopropanoico (Compuesto B del Ejemplo 1, 0.041 g. 0.21 mmol, 1.0 eq), y PyBroP (0.117 g, 0.252 mmol, 1.2 eq) en cloruro de metileno (1.0 mL) a 0°C. La mezcla de reacción se calentó a temperatura ambiente y se agitó por 12 h. La mezcla de reacción se apagó con solución acuosa saturada de cloruro de sodio, y la mezcla se extrajo con cloruro de metileno (3 x 20 mL). Los extractos orgánicos combinados se secaron sobre sulfato de sodio, se filtró y el

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filtrado se concentró a vacío. El residuo se purificó mediante cromatografía instantánea sobre gel de sílice (Merck, 40-63 µM, malla 230-240, fluyendo con acetato de etilo/hexano 3/1) para proporcionar el compuesto del título (0.056 g, 64%) como un sólido. RMN-^{1}H (DMSO-d_6) δ 10.61 (s, 1H), 10.34 (s, 1H), 8.36-8.38 (m, 1H), 7.91-7.93 (m, 1H), 7.67-7.71 (m, 2H), 7.46-7.48 (m, 2H), 7.04-7.26 (m, 4H), 3.56 (s, 2H); MS(ESI$^+$) m/z 418 $(M + H)^+$; HRMS (ESI*) calculado: 418.0770, encontrado: 418.0767.

Ejemplo 21

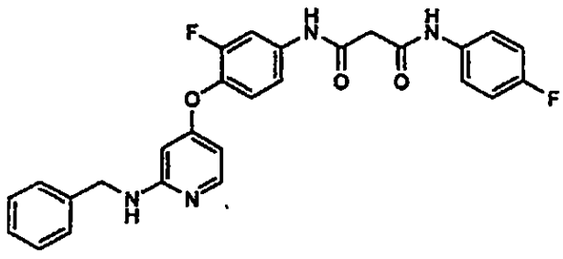


1-(4-(2-Cloropiridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)tiourea

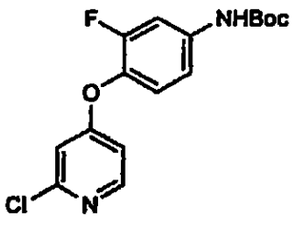
Cloruro de 4-fluorofenilacetilo (Aldrich, 0.072 mL. 0.525 mmol, 2.5 eq) se agregó a una solución de tiocianato de sodio (0.056 g, 0.695 mmol, 3.3 eq) en acetato de etilo (2.0 mL) a temperatura ambiente y la mezcla de reacción se agitó por 1.5 h para proporcionar una solución de isotiocianato de 2-(4-fluorofenil)etanoilo (0.263 M). Una solución de 4-(2-

cloropiridin-4-iloxi)-3-fluorobencenamina (0.050 g, 0.21 mmol. 1.0 eq) en cloruro de metileno (1.0 mL) se agregó gota a gota una solución de isotiocianato de 2-(4-fluorofenil)etanoilo y la mezcla de reacción se agitó a temperatura ambiente por 12 h. La mezcla de reacción se concentró a vacío y el residuo resultante se purificó mediante cromatografía instantánea sobre gel de sílice (Merck, 40-63 µM, malla 230-240, eluyendo con 3/1 hexano/acetato de etilo) para proporcionar el compuesto del título (0.058 g, 64%) como un sólido. RMN-^{1}H (DMSO-d_6) δ 12.46 (s, 1H), 11.84 (s, 1H), 8.35-8.33 (m, 1H), 8.02-8.33 (m, 1H), 6.99-7.52 (m, 8H), 3.84 (s, 2H); MS(ESI$^+$) m/z 434 (M+ H)$^+$; HRMS (ESI$^+$) calculado: 434.0542, encontrado: 434.0547.

Ejemplo 22



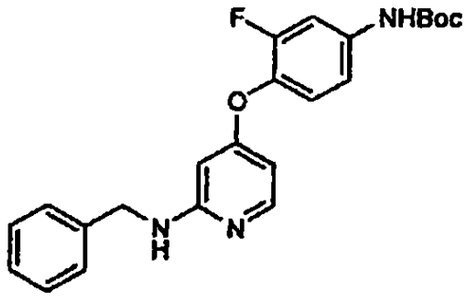
N^1-(4-(2-(Bencilamino)piridin-4-iloxi)-3-fluorofenil)-N^3-(4-fluorofenil)malonamida



A) 4-(2-cloropiridin-4-iloxi)-3-fluorofenilcarbamato de ter-butilo

Se agregó dicarbonato de di-tert-butilo (0.920 g, 4.22 mmol, 4.5 eq) a una solución de 4-(2-cloropiridin-4-iloxi)-3-fluorobencenamina (Compuesto B del Ejemplo 20, 0.224 g, 0.939 mmol, 1.0 eq) y trietilamina (0.391 mL, 3.00 mmol, 3.0 eq) en THF (10 mL) y la mezcla de reacción se calentó a 55 °C por 14 h. La mezcla de reacción se enfrió a temperatura ambiente y se apagó con HCl 1N. La solución se extrajo con cloruro de metileno (3 x 70 mL), los extractos orgánicos combinados se lavaron con NaOH 1N (100 mL), se secó (sulfato de sodio), se filtró y se concentró a vacío. El residuo se purificó mediante cromatografía instantánea sobre gel de sílice (Merck, 40-63 HM, malla 230-240, eluyendo con 4:1 hexano/acetato de etilo) para proporcionar el compuesto del título (0.270 g, 85%).

RMN-^{1}H (DMSO-d_6) δ 8.35-8.36 (m, 1H), 7.55-7.57 (m, 1H), 7.45-7.46 (m, 1H), 7.21-7.24 (m, 1H), 6.96-6.97 (m, 2H), 1.40 (s, 9H); MS (ESI$^+$) m/z 339 (M+ H)$^+$; HRMS (ESI$^+$) calculado: 339.0912, encontrado: 339.0915..



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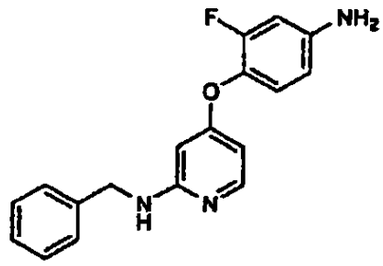
B) 4-(2-(bencilamino)piridin-4-iloxi)-3-fluorofenilcarbamato de ter-butilo

Se agregó 4-(2-cloropiridin-4-iloxi)-3-fluorofenilcarbamato de ter-butilo (0.100 g, 0.295 mmol, 1.0 eq) a una solución desgasificada de dppf.$PdCl_2$ (Matrix Scientific, 0.011 g, 0.0148 mmol, 0.05 eq), dppf (0.012 g, 0.022 mmol, 0.075 eq), y NaOt-Bu (0.040 g, 0.414 mmol, 1.4 eq) en tolueno a temperatura ambiente.

Bencilamina (0.045 mL, 0.414 mmol, 1.4 eq) se agregó a la mezcla de reacción y la solución resultante se agitó a 80°C por 4 h.

La mezcla de reacción se enfrió a temperatura ambiente, se apagó con HCl 1N y la solución se extrajo con $CHCl_3$ (3 x 50 mL). Los extractos orgánicos combinados se lavaron con 1 N NaOH (70 mL), se secó (sulfato de sodio), se filtró y se concentró a vacío.

El residuo se purificó mediante cromatografía instantánea sobre gel de sílice (Merck, 40-63 µM, malla 230-240, eluyendo con 2:1 hexano/acetato de etilo) para proporcionar el compuesto del título (0.020 g, 17%). RMN-^{1}H ($CDCl_3$) δ 7.80-7.90 (m, 1H), 7.35-7.45 (m, 1H), 7.19-7.24 (m, 3H), 6.91-6.93 (m, 2H), 6.59 (br m, 1H), 6.10-6.20 (m, 1H), 5.75 (br m, 1H), 5.30-5.40 (m, 1H), 4.34 (s, 2H), 1.46 (s, 9H); MS (ESI^+) m/z 410 $(M + H)^+$; HRMS (ESI^+) calculado: 410.1880, encontrado: 410.1884.



C) 4-(4-Amino-2-fluorofenoxi)-N-bencilpiridin-2-amina, sal de clorhidrato

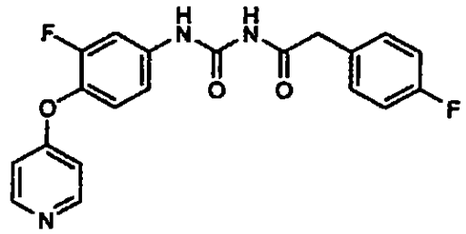
Se agregó HCl anhidro en dioxano (4N, 2.00 mL, 8.00 mmol. 165 eq) a 4-(2-(bencilamino)piridin-4-iloxi)-3-5 fluorofenilcarbamato de ter-butilo (0.020 g, 0.0489 mmol, 1.0 eq) y la mezcla de reacción se agitó a temperatura ambiente por 12 h. La mezcla de reacción se concentró a vacío para proporcionar el compuesto del título (0.017 g. 100%) un sólido que se utilizó sin purificación adicional. MS(ESI$^+$) m/z 310 $(M + H)^+$; HRMS (ESI$^+$) calculado: 310.1356, encontrado: 310.1364.

D) N^1-(4-(2-(Bencilamino)piridin-4-iloxi)-3-fluorofenil)-N^3-(4-fluorofenil) malonamida

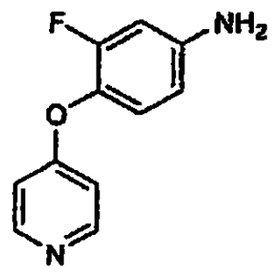
Se agregó diisopropiletilamina (0.014 mL, 0.081 mmol, 3.5 eq) a una solución de sal de clorhidrato de 4-(4-amino-2-fluorofenoxi)-N-bencilpiridin-2-amina (0.008 g. 0.023 mmol, 1.0 eq), ácido 3-(4-fluorofenilamino)-3-oxopropanoico (Compuesto B del Ejemplo 1, 0.005 g, 0.023 mmol, 1.0 eq), y PyBroP (0.013 g, 0.028 mmol. 1.2 eq) en cloruro de metileno (1.0 mL) a 0°C. La mezcla de reacción se calentó a

temperatura ambiente y se agitó por 16 h. La mezcla de reacción se concentró a vacío y el residuo se purificó mediante HPLC de fase inversa (YMC-ODS-A, C-18, S10, 30x500 mm, eluyendo con MeOH acuoso al 20-90% con 0.1% de TFA, 30 minutos en gradiente). Las fracciones apropiadas se concentraron a vacío, se neutralizaron con solución acuosa saturada de carbonato ácido de sodio y la mezcla se extrajo con $CHCl_3$ (3x10 mL). Los extractos orgánicos combinados se secaron (sulfato de sodio), se filtraron y se concentraron a vacío para proporcionar el compuesto del título (0.0025 g, 45%) como un sólido. MS (ESI^+) m/z 489 $(M + H)^+$; HRMS (ESI+) calculado: 489.1738, encontrado: 489.1743.

Ejemplo 23



1-(3-Fluoro-4-(piridin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)urea



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A) 3-Fluoro-4-(piridin-4-iloxi)bencenamina

Se agregó hidruro de potasio (30%, 0.520 g, 3.90 mmol, 3.0 eq) a una solución de 2-fluoro-4-aminofenol (Compuesto A del Ejemplo 20, 0.254 g. 2.00 mmol. 1.5 eq) en DMF (5.0 mL) a temperatura ambiente y la mezcla de reacción se agitó por 15 minutos. se agregó 4-cloro-piridina (Aldrich, 0.200 g, 1.30 mmol, 1.0 eq) y la mezcla de reacción se calentó a 150°C por 2 h. La mezcla de reacción se enfrió a temperatura ambiente, se apagó con NaOH 1N y la solución se extrajo con acetato de etilo (3 x 50 mL). Los extractos orgánicos combinados se lavaron con NaOH 1N acuoso (2 x 30 mL) seguido por LiCl acuoso al 10% (3 x 50 mL). Los extractos orgánicos combinados se secaron (sulfato de sodio), se filtraron y se concentraron a vacío para proporcionar el compuesto del título como un sólido. RMN-^{1}H (DMSO-d_6) δ 8.44-8.46 (m, 2H), 6.89-7.03 (m, 1H), 6.87-6.88 (m, 2H), 6.44-6.56 (m, 2H), 5.51 (s, 2H); MS (ESI^+) m/z 205 $(M + H)^+$; HRMS (ESI^+) calculado: 205.0777, encontrado: 205.0775.

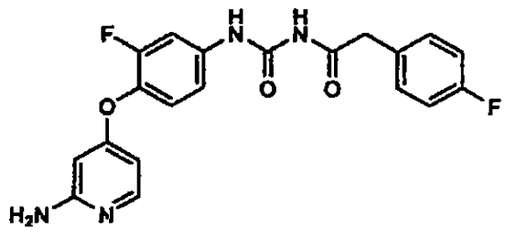
B) 1-(3-Fluoro-4-(piridin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)urea

Se agregó cianato de plata (0.912 g, 6.08 mmol, 1.05 eq) a una solución de cloruro de 4-fluorofenilacetilo (Aldrich, 0.794 mL, 5.79 mmol, 1.0 eq) en tolueno (16 mL) a temperatura ambiente protegido de la luz. La mezcla de reacción se calentó a reflujo por 60 minutos y luego se enfrió a

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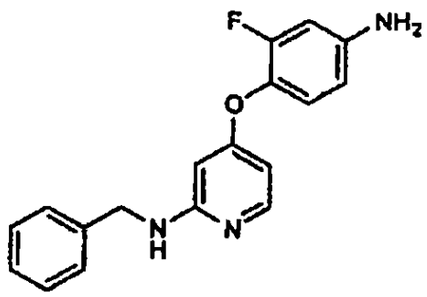
temperatura ambiente. La mezcla de reacción se filtró (Acrodisc, PTFE 0.2uM) y la solución resultante de isocianato de 2-(4-fluorofenil)acetilo (0.36 M, 0.75 mL, 0.27 mmol, 1.1 eq) se agregó a una solución de 3-fluoro-4-(piridin-4-iloxi)bencenamina (0.050 g, 0.245 mmoL 1.0 eq) en cloruro de metileno (2.0 mL) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente por 1 h, se apagó con solución acuosa saturada de cloruro de sodio y la mezcla se extrajo con cloruro de metileno (3 x 30 mL). Los extractos orgánicos combinados se secaron (sulfato de sodio), se filtró y se concentró a vacío. El residuo se purificó mediante cromatografía instantánea sobre gel de sílice (Merck, 40-63 µM, malla 230-240, eluyendo con 0-5% de MeOH en $CHCl_3$) para proporcionar el compuesto del título (0.043 g, 46%) como un sólido. RMN-^{1}H (DMSO-d_6) δ 1 1.06 (s, 1H), 10.60 (s, 1H), 8.47 (s, 2H), 7.77-7.80 (m, 1H), 6.92-7.48 (m, 8H), 3.75 (s, 2H); MS (ESI^+) m/z 384 $(M + H)^+$; HRMS(ESI^+) calculado: 384.1160, encontrado: 384.1147.

Ejemplo 24



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1-(4-(2-Aminopiridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea

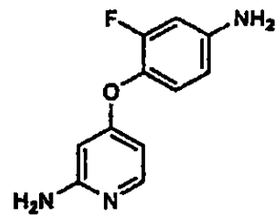


A) 4-(4-Amino-2-fluorofenoxi)-N-bencilpiridin-2-amina

Se agregó bencilamina (9.1 mL, 83.8 mmol, 20 eq) a 4-(2-cloropiridin-4-iloxi)-3-fluorobencenamina (Compuesto B del Ejemplo 20, 1.0 g, 4.19 mmol, 1.0 eq), polvo de cobre (0.266 g, 4 19 mmol, 1.0 eq) y K_2CO_3 (0.578 g, 4.19 mmol, 1.0 eq) en un tubo sellado y la mezcla de reacción se calentó a 160 °C por 12 h. La mezcla de reacción se enfrió a temperatura ambiente y se apagó con solución acuosa saturada de cloruro sodio. La solución se extrajo con acetato de etilo (3 x 100 mL), los extractos orgánicos combinados se secaron (sulfato de sodio), se filtraron y se concentraron a vacío. El residuo se purificó mediante HPLC preparativa de fase inversa (YMC C-18 ODS-A S10 50 x 500 mm, eluyendo con MeOH acuoso al 10-90% con 0.1% de TFA, gradiente 30 minutos) y las fracciones apropiadas se concentraron a vacío. El concentrado se neutralizó con solución acuosa saturada de carbonato ácido de sodio y se extrajo con cloruro de metileno (3 x 100 mL). Los

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extractos orgánicos combinados se secaron (sulfato de sodio), se filtraron y se concentraron a vacío para proporcionar el compuesto del título (0.675 g, 52%) como un sólido. RMN-^{1}H (CD_3OD) δ 7.78-7.80 (m, 1H), 7.28-7.30 (m, 5H), 6.80-6.90 (m, 1H), 6.52-6.55 (m, 2H), 6.18-6.20 (m, 1H), 5.87-5.88 (m, 1H), 4.40 (s, 2H); MS(ESI$^+$) m/z 310 $(M + H)^+$; HRMS(ESI$^+$) calculado: 310.1356, encontrado: 310.1360.



B) 4-(4-Amino-2-fluorofenoxi)piridin-2-amina

Hidróxido de paladio sobre carbón (10%, 0.050 g) se agregó a una solución de 4-(4-amino-2-fluorofenoxi)-N-bencilpiridin-2-amina (0.245 g. 0.790 mmol, 1.0 eq) en 5% HCO_2H-MeOH (10 mL) bajo una atmósfera de hidrógeno (de un globo) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente por 12 h, se filtró a través de Celite$^{\$}$ y el filtrado se concentró a vacío. El residuo se purificó mediante HPLC preparativa de fase inversa (YMC ODS-A S10 30 x 500 mm, McOH acuoso al 10-90% con 0.1% de TFA, gradiente 30 minutos) y Las fracciones apropiadas se concentraron a vacío. El concentrado se neutralizó con solución acuosa saturada de carbonato ácido de sodio y la

404 408

mezcla se extrajo con $CHCl_3$ (3 x 35 mL). Los extractos orgánicos combinados se secaron (sulfato de sodio), se filtraron y se concentraron a vacío para proporcionar el compuesto del título (0.045 g, 26%) como un sólido. RMN-^{1}H (CD_3OD) δ 7.62-7.63 (m, 1H), 6.77-6.82 (m, 1H), 6.38-6.47 (m, 2H), 6.09-6.11 (m, 1H), 5.83-5.84 (m, 1H); MS(ESI$^+$) m/z 220 $(M + H)^+$; HRMS(ESI$^+$) calculado: 220.0886, encontrado: 220.0877.

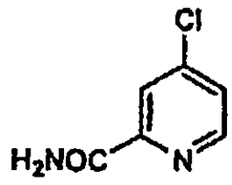
C) 1-(4-(2-Aminopiridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea

Se agregó isocianato de 2-(4-fluorofenil)acetilo (Compuesto D del Ejemplo 11, 0.362 M, 0.351 mL, 0.127 mmol, 1.3 eq) a una solución de 4-(4-amino-2-fluorofenoxi)piridin-2-amina (0.022 g. 0.100 mmol, 1.0 eq) en cloruro de metileno (2.0 mL) a temperatura ambiente. La mezcla de reacción se agitó por 13 h a temperatura ambiente y luego se concentró a vacío. El residuo se purificó mediante cromatografía instantánea sobre gel de sílice (Merck gel 40-63 µM, malla 230-240, acetato de etilo/hexano 1:1) para proporcionar el compuesto del título (0.025 g. 64%) como un sólido. RMN-^{1}H (CD_3OD) δ 7.62-7.67 (m, 2H). 7.23-7.29 (m, 2H), 7.07-7.12 (m, 2H), 6.95-6.99 (m, 2H), 6.12-6.14 (m, 1H), 5.86-5.87 (m, 1H). 3.61 (s, 2H); MS (ESI$^+$) m/z 399 $(M + H)^+$: HRMS (ESI$^+$) calculado: 399.1269. encontrado: 399.1269.

Alternativamente, se preparó el **Ejemplo 24** de la

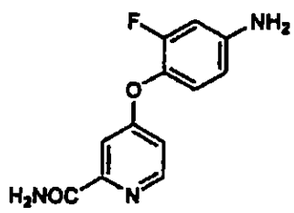
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siguiente manera



A') 4-Cloropicolinamida

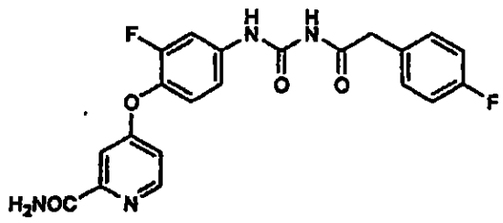
Una mezcla heterogénea de ácido 4-cloropicolínico (TCI America, 5.4 g, 34.2 mmol, 1.0 eq) y cloruro de tionilo (30 mL) se calentó a 80°C por 2h. La mezcla de reacción se enfrió a temperatura ambiente y se concentró a vacío. El residuo se trató con una solución de amoniaco en McOH (7N, 45 mL) en un baño de hielo y la mezcla de reacción se agitó por 15 minutos. El baño de hielo fue luego retirado y la reacción se calentó a temperatura ambiente y luego se agitó por 3 h. La mezcla de reacción se concentró a vacío y el residuo se purificó mediante recristalización a partir de EtOAc para proporcionar el producto (5.14 g, 96%) como un sólido. RMN-^{1}H (DMSO-d_6) δ 8.61-8.63 (m, 1H), 8.21 (m, 1H), 8.03-8.04 (m, 1H), 7.76-7.83 (m, 2H); MS (ESI$^+$) m/z157 $(M + H)^+$.



B') 4-(4-Amino-2-fluorofenoxi)picolinamida

Una solución de 4-amino-2-fluorofenol (Compuesto A del

Ejemplo 20, 0.81 g, 6.4 mmol. 1.0 eq) en DMF (6.5 mL) se trató con ter-butóxido de potasio (0.79 g, 7.1 mmol. 1.1 eq) a temperatura ambiente y la mezcla de reacción se agitó por 1 hora. 4-Cloropicolinamida (1.0 g, 6.4 mmol, 1.0 eq) se agregó y la mezcla de reacción se calentó a 110°C por 8 h. La reacción se enfrió a temperatura ambiente y la mezcla de reacción se apagó con agua. La solución heterogénea resultante se filtró y el sólido material se lavó con agua. El sólido se trituró con una pequeña cantidad de MeOH seguido por Et_2O. El sólido se filtró se secó a vacío para proporcionar el producto (1.3 g, 82%) como un sólido. RMN-^{1}H (DMSO-d_6) δ 8.49-8.50 (m, 1H). 8.12 (br s, 1H), 7.71 (br s, 1H), 7.35-7.36 (m, 1H), 7.14-7.16 (m, 1H), 7.01-7.06 (m, 1H), 6.44-6.47 (m, 2H), 5.53 (s, 2H); MS(ESI$^+$) m/z 248 $(M + H)^+$.



C') 1-(4-(2-Carbamoilpiridin-4-iloxi)-3-fluorofenil)-3-(2-(4- fluorofenil)acetil)urea

Una solución de isocianato de 2-(4-fluorofenil)acetilo (Compuesto D del Ejemplo 11, 0.29 M en tolueno, 54.9 mL, 15.9 mmol, 2.1 eq) se agregó a 4-(4-amino-2-fluorofenoxi)picolinamida (1.86 g. 7.53 mmol, 1.0 eq) en

~~427~~ 427

DCM/DMF 10/3 (65 mL) a temperatura ambiente y la mezcla de reacción se agitó por 17 h. La mezcla de reacción se concentró a vacío y el residuo se volvió a disolver en CHCl3. La capa orgánica se lavó con solución acuosa saturada de cloruro de sodio, la fracción orgánica separada, se secó (sulfato de sodio), se filtró y se concentró a vacío. El residuo se purificó mediante cromatografía sobre gel de sílice (eluyendo con hexano/EtOAc 1/3, luego se eluyó el producto con 5% de McOH en $CHCl_3$), y las fracciones apropiadas se concentraron a vacío para proporcionar el producto (2.2 g, 69%) como un sólido. RMN-^{1}H (DMSO-d_6) δ 11.07 (s, 1H), 10.62 (s, 1H), 8.54 (d, 1H, J = 5.60 Hz), 8.16-8.19 (m, 1H), 7.76-7.84 (m, 2H), 7.35-7.49 (m, 5H). 7.16-7.23 (m, 3H), 3.76 (s, 2H); MS(ESI$^+$) m/z 427 $(M + H)^+$. HRMS (ESI$^+$) calculado: 427.1218, encontrado: 427.1214.

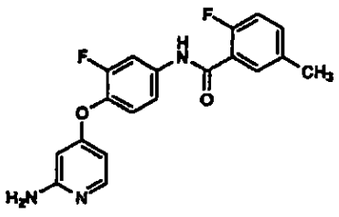
D') 1-(4-(2-Aminopiridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea, sal de clorhidrato

Se agregó bis-(trifluoroacetoxi)-yodobenzeno (Aldrich, 3.09 g, 7.20 mmol, 1.4 eq) a una solución de 1-(4-(2-carbamoilpiridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea (2.19 g, 5.14 mmol, 1.0 eq), agua (0.241 mL, 13.4 mmol, 2.6 eq) y piridina (1.62 mL, 20 mmol, 3.9 eq) en DMF (20 mL) a TA y la mezcla de reacción se agitó por 5 h. La mezcla de reacción se apagó con HCl 1 N y la solución acuosa se extrajo con Et_2O, desechando la capa

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orgánica. La capa acuosa se neutralizó con NaOH 1 N y se extrajo con EtOAc. Las capas orgánicas combinadas se lavaron con Lic. Acuoso al 10%, se secó (Na_2SO_4), se filtró y se concentró a vacío. El residuo se purificó mediante cromatografía sobre gel de sílice (eluyendo con 0-5% de MeOH en $CHCl_3$) y las fracciones apropiadas se concentraron a vacío. El residuo se disolvió en THF (50 mL) se enfrió a 0°C y se trató con HCl anhidro (4N, 10 mL, 40 mmol, 7.8 eq). La mezcla de reacción se dejó calentar a temperatura ambiente y se agitó por 2h dando como resultado una solución heterogénea. La solución se filtró y el sólido se lavó con Et_2O, se secó a vacío para proporcionar el compuesto del título (1.38 g, 63%) como un sólido. RMN-^{1}H (DMSO-d_6) δ 11.09 (s, 1H), 10.65 (s, 1H), 7.97-8.00 (m, 1H), 7.83-7.90 (m, 3H), 7.35-7.48 (m, 4H), 7.15-7.21 (m, 2H), 6.70-6.72 (m, 1H), 6.16-6.17 (m, 1H), 3.77 (s, 2H); MS(ESI$^+$) m/z 399 $(M + H)^+$. HRMS (ESI+) calculado: 399.1269; encontrado: 399.1258. Análisis elemental para $C_{20}H_{16}N_4O_3F_2$ 1.0 HCl 0.22 H_2O Calculado: C; 54.75, H; 4.01, N; 12.77, Cl; 8.08. Encontrado: C; 54.75, H; 4.35, N; 4.35, Cl; 8.06.

Ejemplo 25



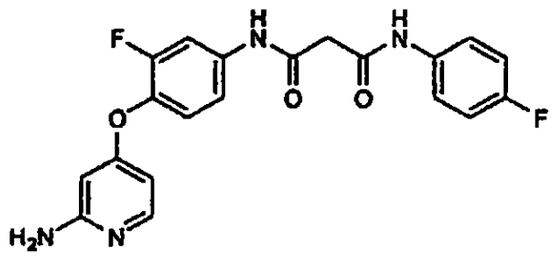
414 473

N-(4-(2-Aminopiridin-4-iloxi)-3-fluorofenil)-2-fluoro-5-metilbenzamida

Se agregó diisopropiletilamina (0.035 mL, 0.200 mmol, 2.0 eq) a una solución de 4-(4-amino-2- fluorofenoxi)piridin-2-amina (Compuesto B del Ejemplo 24. 0.022 g. 0.100 mmol, 1.0 eq), ácido 2-fluoro-5-metilbenzoico (Aldrich, 0.015 g, 0.100 mmol, 1.0 eq), EDCI (0.021 g, 0.11 mmol, 1.1 eq) y HOBT (0.014 g. 0.100 mmol. 1.0 eq) en DMF (0.700 mL) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente por 8 h, se apagó con solución acuosa saturada de carbonato ácido de sodio y se extrajo con $CHCl_3$ (3x10 mL). Los extractos orgánicos combinados se secaron (sulfato de sodio), se filtraron y se concentraron a vacío. El residuo se purificó mediante HPLC preparativa de fase inversa (YMC ODS-A S10 30 x 500 mm, McOH acuoso al 30- 90% con 0.1% de TFA, gradiente 30 minutos) y las fracciones apropiadas se concentraron a vacío. El concentrado se neutralizó con solución acuosa saturada de carbonato ácido de sodio y la mezcla se extrajo con $CHCl_3$ (3 x 30 mL). Los materiales orgánicos combinados se secaron (sulfato de sodio), se filtraron y se concentraron a vacío para proporcionar el compuesto del título (0.014 g, 40%) como un sólido. RMN-^{1}H (CD_3OD) δ 7.67-7.80 (m, 2H), 7.36-7.45 (m, 3H), 7.03-7.14 (m, 2H), 6.14-6.16 (m, 1H), 5.89-5.90 (m, 1H), 2.29 (s, 3H); MS (ESI^+) m/z 356 $(M+ H)^+$; HRMS (ESI^+) calculado: 356.1211,

encontrado: 356.1203.

Ejemplo 26



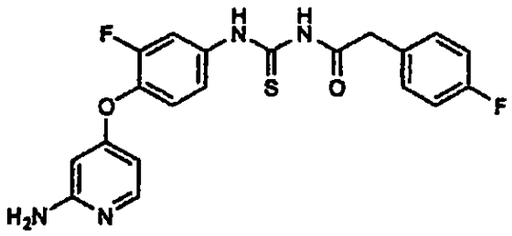
N^1-(4-(2-Aminopiridin-4-iloxi)-3-fluorofenil)-N^3-(4-fluorofenilmalonamida

Se agregó diisopropiletilamina (0.105 mL. 0.604 mmol, 3.3 eq) a una solución de 4-(4-amino-2- fluorofenoxi)piridin-2-amina (Compuesto B del Ejemplo 24. 0.040 g. 0.183 mmol, 1.0 eq), ácido 3-(4-fluorofenilamino)-3-oxopropanoico (Compuesto B del Ejemplo 1, 0.054 g, 0.274 mmol, 1.5 eq), y PyBroP (0.139 g, 0.298 mmol. 1.6 eq) en cloruro de metileno; (2.0 mL) a 0°C. La mezcla de reacción se calentó a temperatura ambiente y se agitó por 18 h. La mezcla de reacción se apagó con solución acuosa saturada de carbonato ácido de sodio y la solución se extrajo con $CHCl_3$ (3x10 mL). Los extractos orgánicos combinados se secaron (sulfato de sodio), se filtraron y se concentraron a vacío. El residuo se purificó mediante cromatografía instantánea sobre gel de sílice (Merck 40-63 µM, malla 230- 240), eluyendo con 0-6% de McOH en $CHCl_3$ para proporcionar el compuesto del título (0.056 g, 77%) como

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un sólido. RMN-^{1}H (CD_3OD) δ 7.67-7.68 (m, 2H), 7.48-7.52 (m, 2H), 7.13-7.25 (m, 1H), 7.10-7.12 (m, 1H), 6.94-6.99 (m, 2H), 6.16-6.17 (m, 1H), 5.88-5.89 (m, 1H), 3.30 (s, 2H) : MS (ESI^+) m/z 399 (M - H^+); HRMS(ESI^+) calculado: 399.1269, encontrado: 399.1261.

Ejemplo 27



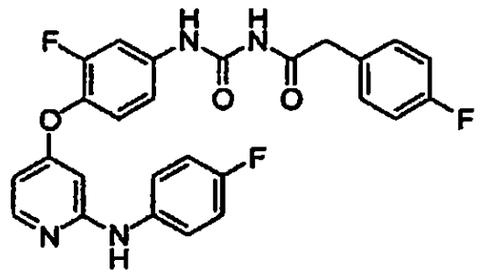
1-(4-(2-Aminopiridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)tiourea

Se agregó cloruro de 4-fluorofenilacetilo (Aldrich, 0.017 mL, 0.126 mmol, 2.5 eq) a una solución de tiocianato de sodio (0.014 g, 0.176 mmol, 3.5 eq) en acetato de etilo (1.0 mL) a temperatura ambiente y la mezcla de reacción se agitó por 1.5 h para proporcionar isotiocianato de 2-(4-fluorofenil)etanoilo en solución (0.126 M). 4-(4-Amino-2-fluorofenoxi)piridin-2-amina (Compuesto B del Ejemplo 24, 0.011 g, 0.050 mmol, 1.0 eq) se disolvió en cloruro de metileno (1.0 mL) y se agregó isotiocianato de 2-(4-fluorofenil)etanoilo (0.126 M, 0.50 mL, 0.063 mmol, 1.3 eq) y la mezcla de reacción se agitó a temperatura ambiente por 20

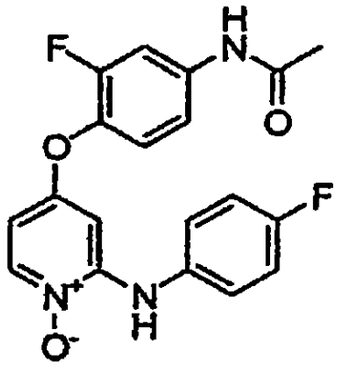
h. La mezcla de reacción se concentró a vacío y el residuo resultante se purificó mediante cromatografía instantánea sobre gel de sílice (Merck, 40-63 µM, malla 230-240. eluyendo con 0-6% de McOH en $CHCl_3$) para proporcionar el compuesto del título (0.008 g, 38%) como un sólido.

RMN-^{1}H (CD_3OD) δ 7.85-7.95 (m, 1H), 7.67-7.69 (m, 1H), 7.13-7.28 (m, 4H), 6.95-7.00 (m, 2H), 6.05-6.15 (m, 1H), 5.90-5.91 (m, 1H). 3.65 (s, 2H); MS (ESI^+) m/z 415 $(M + H)^+$; HRMS (ESI^+) calculado: 415.1040, encontrado: 415.1041.

Ejemplo 28



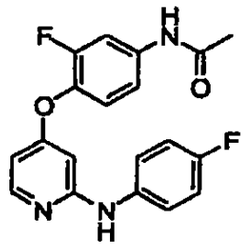
1-(3-Fluoro-4-(2-(4-fluorofenilamino)piridin-4-iloxi)fenil)-3-(2-(4-fluorofenil) acetil) urea



A) N-(3-Fluoro-4-(2-(4-fluorofenilamino)piridin-4-iloxi-1-óxido)fenil)acetamida

Una mezcla de N-(4-(2-cloropiridin-4-iloxi-1-óxido)-3-fluorofenil)acetamida (Compuesto B del Ejemplo 18, 62 mg, 0.21 mmol), 4-fluoroanilina (47 mg, 0.42 mmol), y 2-metoxietil-éter (91 mL) se calentó a 140°C por 15 min. La mezcla se enfrió a TA, se diluyó con EtOAc (20 mL), se lavó con solución acuosa saturada de carbonato ácido de sodio y salmuera (varias veces), se secó ($MgSO_4$), y se concentró a vacío para dar una mezcla 4:1 del compuesto del título y la piridina progenitora como un aceite café claro (45 mg, 58%).

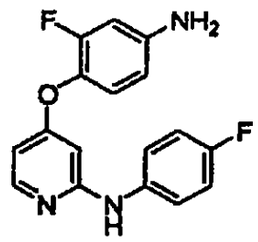
El producto se utilizó en el paso subsecuente sin ninguna purificación adicional. MS(ESI^+) m/z 372.1 $(M + H)^+$.



B) N-(3-Fluoro-4-(2-(4-fluorofenilamino)piridin-4-iloxi)fenil)acetamida

Una mezcla de N-(3-fluoro-4-(2-(4-fluorofenilamino)piridin-4-iloxi-1-óxido) fenil)acetamida (45 mg), polímero de trifenilfosfina soportado (-3 mmol/g) sobre poliestireno (200 mg, Fluka) y DMF (3 mL) se calentó a 135°C por 48 h. La resina se filtró, se lavó con DMF y EtOAc. El

filtrado y los lavados se combinaron y se concentraron a vacío. El producto crudo se purificó mediante cromatografía instantánea utilizando 30-80 de EtOAc en hexanos como el eluyente para dar el compuesto del título (22 mg, 51%) como un sólido rosado. RMN-^{1}H (DMSO-d_6) δ 10.24 (s, 1H), 8.99 (s, 1H), 8.03 (d, 1 H, J = 6.3 Hz), 7.80 (dd, 1H, J = 13.0.2.1 Hz), 7.63-7.60 (m, 2H). 7.36-7.29 (m, 2H). 7.05 (dd, 1H, J = 9.1, 8.6 Hz), 6.44 (dd, 1H, J = 5.5, 2.2 Hz), 6.09 (d, 1H, J = 2 Hz). 2.07 (s, 3H); MS (ESI$^+$) m/z 356.7 $(M + H)^+$.



C) 4-(4-Amino-2-fluorofenoxi)-N-(4-fluorofenil) piridin-2-amina

Una mezcla de N-(3-fluoro-4-(2-(4-fluorofenilamino)piridin-4-iloxi)fenil)acetamida (18 mg, 0.051 mmol), 6 M HCl (0.1 mL, 0.60 mmol) y MeOH (1.5 mL) se calentó a reflujo por 2 h. La mezcla se concentró a vacío y el residuo se alcalinizó con solución acuosa saturada de carbonato ácido de sodio luego se extrajo con EtOAc. El extracto se secó (sulfato de magnesio) y se concentró a 3 vacío para dar el compuesto del título (14 mg, 88%) como una goma roja. RMN-^{1}H (DMSO-d_6) δ 8.97 (s, 1H), 7.98 (d, 1H, J =

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5.8 Hz), 7.64 -7.60 (m, 2H), 7.05 (dd, 2H, J = 9. 1, 8.8 Hz). 6.97 (dd, 1H, J = 9.4, 8.8 Hz), 6.51 (dd, 1H, J = 13.3, 2.6 Hz). 6.40 (ddd, 2H, J = 9.0, 6.2, 2.1 Hz), 6.08 (d, 1H, J = 2.0 Hz), 5.44 (br s, 2H); MS(ESI$^+$) m/z 314.17 $(M + H)^+$.

D) 1-(3-Fluoro-4-(2-(4-fluorofenilamino)piridin-4-iloxi)fenil)-3-(2-(4-fluorofenil) acetil) urea

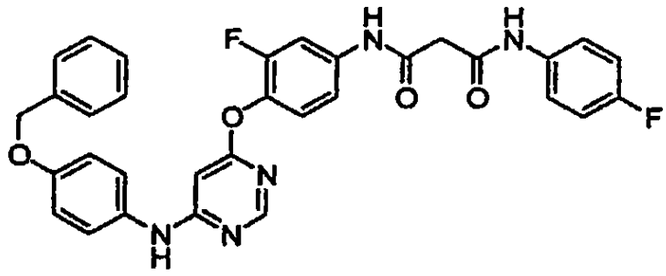
Una solución 4-(4-amino-2-fluorofenoxi)-N-(4-)-fluorofenil)piridin-2-amina (11 mg, 0.035 mmol) en THE (1 mL) se enfrió en un baño de hielo y se trató con una solución de isocianato de 2-(4-fluorofenil)acetilo en tolueno (Compuesto D del Ejemplo 11, 250 µL, 0.070 mmol) y se agitó a temperatura ambiente por 2 h.

La mezcla se concentró a vacío y el residuo se trituró con éter isopropílico para dar el compuesto del título (11 mg, 65%) como un sólido blanco.

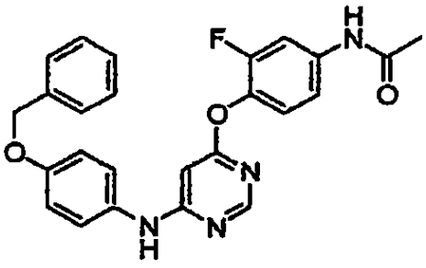
RMN-^{1}H (DMSO-d_6) δ 11.04 (s, 1H), 10.56 (s, 1H), 9.01 (s, 1H), 8.03 (d, 1H, J = 5.6 Hz), 7.77 (dd, 1H, J = 13.3, 2.0 Hz), 7.63-7.60 (m, 2H), 7.41-7.31 (m, 5H), 7.19-7.14 (m, 2H), 7.05 (dd, 1H, J = 9.1, 8.5 Hz). 6.43 (dd, 1H. J = 6.2, 2.1 Hz), 6.10 (d, 1H, J = 2.1 Hz), 3.74 (s, 2H); MS(ESI$^+$) m/z 493.2$(M + H)^+$.

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Ejemplo 29



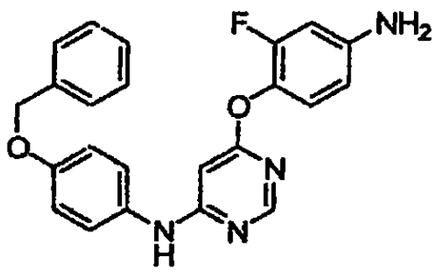
N^1-(4-(6-(4-(Benciloxi)fenilamino)pirimidin-4-iloxi)-3-fluorofenil)-N^3-(4-fluorofenil)malonamida



A) N-(4-(6-(4-(Benciloxi)fenilamino)pirimidin-4-iloxi)-3-fluorofenil)acetamida

Una mezcla de N-(4-(6-cloropirimidin-4-iloxi)-3-fluorofenil)acetamida (Compuesto B del Ejemplo 13, 281 mg, 1.00 mmol), 4-Benciloxianilina (Aldrich, 398 mg, 2.00 mmol), y 2-metoxietil-éter (2 mL) se calentó a 160 °C por 45 min. La mezcla enfriada se trató con agua (50 mL) y se extrajo con EtOAc (100 mL). El extracto de EtOAc se lavó con salmuera (3 x 25 mL), se secó (sulfato de magnesio) y se concentró a vacío para dar el compuesto del título (200 mg, 22%) como un sólido morado. RMN-^{1}H (400 MHz, DMSO-d_6) δ 10.19 (s, 1H), 9.43

(s, 1H), 8.23 (s, 1H), 7.72 (dd, 1H, J.= 12.5. 2.0 Hz), 7.44-7.42 (m, 4H), 7.38 (dd, 2H, J = 8.0, 6.9 Hz), 7.33-7.23 (m, 3H), 6.98 (d, 2H. J = 9.0 Hz), 6.07 (s, 1H), 5.07 (s, 2H), 2.05 (s, 3H); MS(ESI$^+$) m/z 445.13 $(M + H)^+$.



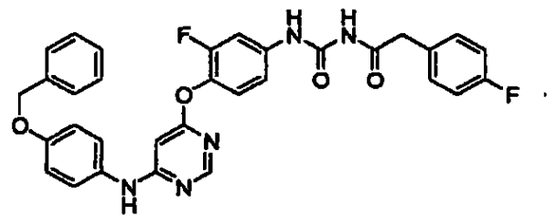
B) 6-(4-Amino-2-fluorofenoxi)-N-(4-(benciloxi)fenil)pirimidin-4-amina

Una mezcla de N-(4-(6-(4-(benciloxi)fenilamino)pirimidin-4-iloxi)-3-fluorofenil)acetamida (150 mg, 0.34 mmol), HCl 6 M (0.5 mL) y MeOH (3 mL) se calentó a reflujo por 2 h. La mezcla se concentró para remover el MeOH y el residuo se trató con solución acuosa saturada de carbonato ácido de sodio y se extrajo con EtOAc. La fase orgánica se secó (sulfato de magnesio) y se concentró a vacío para dar el compuesto del título (123 mg, 90%) como un sólido rosado . RMN-^{1}H (DMSO-d_6) δ 9.37 (s, 1H). 8.24 (s, 1H). 7.46-7.31 (m, 7H), 6.99-6.92 (m, 3H), 6.48 (dd, 1H, J = 12.5. 2.7 Hz), 6.39 (dd, 1H. J = 8.6. 2.7 Hz), 5.97 (s, 1H), 5.39 (br s, 2H), 5.08 (s, 2H); MS(ESI$^+$) m/z 403.09 $(M + H)^+$.

C) N^1-(4-(6-(4-(Benciloxi) fenilamino)pirimidin-4-iloxi)-3-fluorofenil)-N^3-(4-fluorofenil)malonamida

El compuesto del título se preparó a partir de una mezcla 6-(4-amino-2-fluorofenoxi)-N-(4-(benciloxi)fenil)pirimidin-4-amina (45 mg, 0.11 mmol), ácido 3-(4-fluorofenilamino)-3-oxopropanoico (Compuesto B del Ejemplo 1. 24 mg, 0.12 mmol), TBTU (48 mg. 0.15 mmol), DIPEA (0.26 mL, 0.15 mmol), y DMF (1 mL) utilizando un procedimiento similar descrito para la preparación del compuesto C del Ejemplo 1. El producto crudo se trituró con éter isopropílico para dar el compuesto del título (56 mg. 88%) como un sólido rosado . RMN-^{1}H (DMSO-d_6) δ 10.47 (s, 1H), 10.27 (s, 1H), 9.45 (s, 1H), 8.25 (s, 1H), 7.77 (dd, 1H, J = 12.7. 2.0 Hz), 7.65-7.62 (m, 2H), 7.46 (d, 4H, J = 7.3 Hz), 7.40 (dd, 2H. J = 7. 6, 7.3 Hz), 7.37-7.29 (m, 3H), 7.17 (dd, 2H, J = 9.0, 8.3 Hz), 7.00 (d, 2H, J = 9.0 Hz) 6.09 (s, 1H), 5.09 (s, 2H), 3.49 (s, 2H); MS (ESI$^+$) m/z 582.3 (M + H)$^+$.

Ejemplo 30

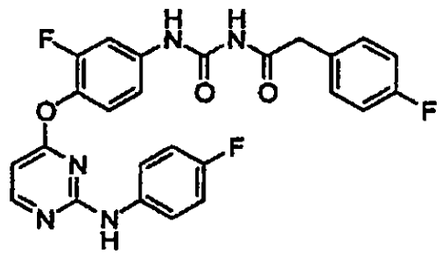


1-(4-(6-(4-(Benciloxi)fenilamino)pirimidin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil) acetil) urea

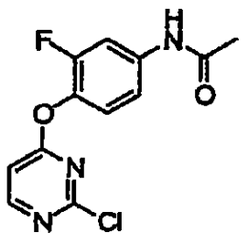
El compuesto del título se preparó a partir de 6-(4-

amino-2-fluorofenoxi)-N-(4-(benciloxi)fenil)pirimidin-4-amina (Compuesto B del Ejemplo 29, 45 mg, 0.11 mmol) y una solución de isocianato de 2-(4-fluorofenil)acetilo en tolueno (Compuesto D del Ejemplo 11. 0.13 mmol) en THF utilizando un procedimiento similar al descrito para la preparación del Compuesto E del Ejemplo 11. El producto crudo se trituró con éter isopropílico para dar el compuesto del título (58 mg. 90%) como un sólido rosado. RMN-^{1}H (DMSO-d_6) δ 11.02(s, 1H), 10.54 (s, 1H), 9.46 (s, 1H), 8.24(s, 1H). 7.70 (dd, 1H, J = 12.7, 2.4 Hz), 7.46-7.26 (m, 9H). 7.18 (dd, 2H, J = 9. 6, 8.3 Hz). 7.00 (d, 2H, J = 9.6 Hz), 6.11 (s, 1H), 5.09 (s, 2H), 3.75 (s, 2H); MS(ESI$^+$) m/z 582.3 (M + Hf).

Ejemplo 31



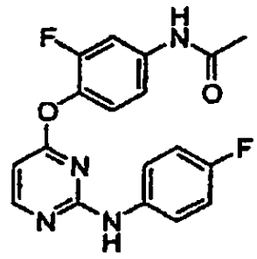
1-(3-Fluoro-4-(2-(4-fluorofenilamino)pirimidin-4-iloxi)fenil)-3-(2-(4-fluorofenıl) acetil) urea



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A) N-(4-(2-Cloropirimidin-4-iloxi)-3-fluorofenil) acetamida

Una mezcla de 2,4-dicloropirimidina (Aldrich, 1.5 g, 10.0 mmol), N-(3-fluoro-4-hidroxifenil)acetamida (0.85 g, 5.0 mmol), K_2CO_3 (0.76 g. 5.5 mmol), y CH_aCN (100 mL) se calentó a reflujo por 2 h. La mezcla se concentró y el residuo se dividió entre EtOAc y solución acuosa saturada de carbonato ácido de sodio. La fase de EtOAc se lavó con solución acuosa saturada de carbonato ácido de sodio, salmuera, se secó ($MgSO_4$) y se concentró a vacío. El producto crudo se purificó mediante cromatografía instantánea utilizando un gradiente de 30% de EtOAc en hexanos hasta 100% de EtOAc para dar el compuesto del título (1.1 g, 78%) como un sólido blanco. RMN-^{1}H (DMSO-d_6) δ 10.22 (s, 1H), 8.63 (d, 1H, J = 5.6 Hz), 7.74 (dd, 1H, J = 12.6, 2.4 Hz), 7.34-7.26 (m, 3H), 2.01 (s, 3H).

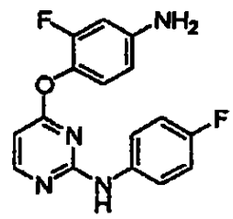


B) N-(3-Fluoro-4-(2-(4-fluorofenilamino)pirimidin-4-iloxi)fenil)acetamida

Una mezcla de N-(4-(2-cloropirimidin-4-iloxi)-3-fluorofenil)acetamida (100 mg, 0.36 mmol), 4-fluoroanilina (Aldrich, 40 mg. 0.36 mmol) y 1,4-dioxano (3 mL) se calentó a reflujo por 2 h. La mezcla se concentró a vacío y el residuo

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se trituró con éter para dar un sólido gris. El producto se disolvió en McOH, se trató sobre gel de sílice (150 mg) y la mezcla se concentró hasta sequedad. El compuesto se concentró sobre gel de sílice y se aplicó a una columna de gel de sílice y se eluyó primeramente con EtOAc luego con McOH/NH_4OH 100:1 en cloruro de metileno para dar el compuesto del título (40 mg, 31%) como un sólido blanco. RMN-^{1}H (DMSO-d_6) δ 10.19 (s, 1H), 9.61 (s, 1H), 8.33 (d, 1H, J = 5.6 Hz), 7.71 (d, 1H. J = 12.7 Hz), 7.40 (s, 2H), 7.30-7.26 (m, 2H), 6.86 (dd, 2H, J = 8.3, 8.3 Hz), 6.50 (d, 1H, J = 5.4 Hz), 2.05 (s, 3H); MS (ESI^+) m/z 357.13 $(M + H)^+$.



C) 4-(4-Amino-2-fluorofenoxi)-N-(4-fluorofenil)pirimidin-2-amina

Una mezcla de N-(3-fluoro-4-(2-(4-fluorofenilamino)pirimidin-4-iloxi)fenil)acetamida (32 mg, 0.09 mmol), HCl 6 Ml (0.2 mL) y McOH (2 mL) se calentó a reflujo por 2 h. La mezcla se enfrió, se diluyó con EtOAc (20 mL), se lavó con solución acuosa saturada de carbonato ácido de sodio y salmuera, se secó (sulfato de magnesio), y se concentró a vacío. La cromatografía instantánea sobre SiO_2

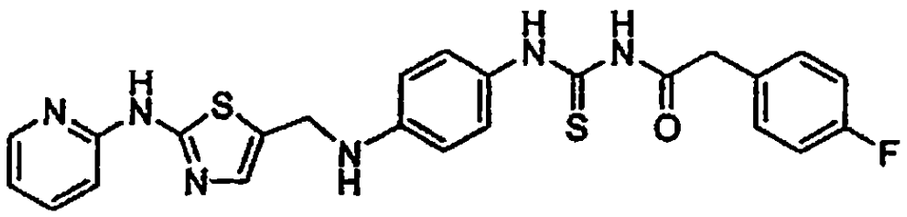
424 426

utilizando 30-40 de EtOAc en hexanos que contenía 1% de Et_3N dio el compuesto del título (15 mg, 46%) como un sólido blanco. RMN-^{1}H (DMSO-d_6) δ 9.55 (s, 1H), 8.25 (d, 1H, J = 5.5 Hz), 7.43 (br s. 2H), 6.92-6.85 (m, 3H), 6.45 (dd, 1H, J = 13.5, 2.1 Hz), 6.38-6.35 (m, 2H), 5.35 (br s, 2H). MS (ESI$^+$) m/z 315.17 $(M + H)^+$.

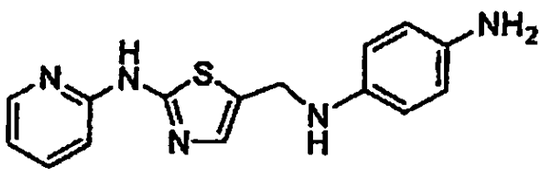
D) 1-(3-Fluoro-4-(2-(4-fluorofenilamino)pirimidin-4-iloxi)fenil)-3-(2-(4-fluorofenil) acetil)urea

Una solución de 4-(4-amino-2-fluorofenoxi)-N-(4-fluorofenil)pirimidin-2-amina (10 mg, 0.032 mmol) en THF (1 mL) se enfrió en un babo de hielo y se trató con una solución de isocianato de 2-(4-fluorofenil)acetilo en tolueno (Compuesto D del Ejemplo 11, 228 µL, 0.064 mmol) y se agitó a temperatura ambiente por 2 h. La mezcla de reacción se concentró a vacío y el residuo se trituró con éter isopropilico para dar el compuesto del título (15 mg, 93%) como un sólido blanco. RMN-^{1}H (DMSO-d_6) δ 11.06 (s, 1H), 10.56 (s, 1H), 9.68 (s, 1H), 8.39 (d, 1H, J = 5.7 Hz), 7.76 (dd, 1H, J = 13.5, 2.1 Hz), 7.43 (br s, 2H), 7.46-7.35 (m, 6H), 7.18 (dd, 2H, J = 8.8, 8.8 Hz), 6.57 (d, 1H, J = 5.4 Hz), 3.76 (s, 2H); MS (ESI$^+$) m/z 492.0 $(M + H)^+$.

Ejemplo 32



1-(2-(4-Fluorofenil)acetil)-3-(4-((2-(piridin-2-ilamino)tiazol-5-il)metilamino)fenil)tiourea



A) N^1-((2-(Piridin-2-ilamino)tiazol-5-il)metil)bencen-1,4-diamina

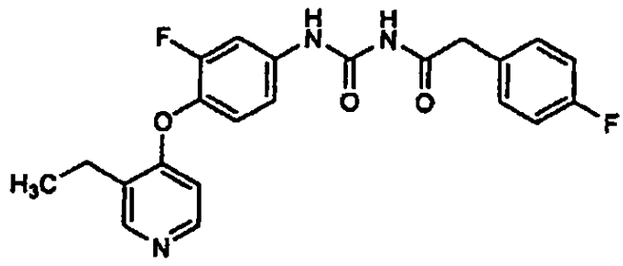
Una solución de 2-(piridina-2-ilamino)-tiazol-5-carbaldehído (0.10 g, 0.49 mmol, WO2004/001059), bencen-1,4-diamina (0.105 g, 0.97 mmol) y trietilsilano (0.19 mL, 1.2 mmol) en CH_2Cl_2-TFA (3:1,4 mL) se agitó a temperatura ambiente por 4 h. La mezcla de reacción se concentró a vacío y el residuo se dividió entre cloruro de metileno y solución acuosa saturada de carbonato ácido de sodio. La fase orgánica se lavó con solución acuosa saturada de carbonato ácido de sodio, salmuera, se secó (sulfato de magnesio) y se concentró a vacío. El producto crudo que contenía el compuesto del

título junto con el aldehído inicial y bencen-1,4-diamina se llevó directamente al siguiente paso.

B) 1-(2-(4-Fluorofenil)acetil)-3-(4-((2-(piridin-2-ilamino)tiazol-5-il)metilamino)fenil)tiourea

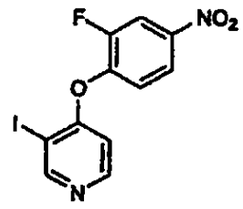
Cloruro de 4-fluorofenilacetilo (7.4 µL, 0.053 mmol) se agregó a una suspensión de NaSCN (4.5 mg, 0.055 mmol) en EtOAc (0.5 mL) y la mezcla resultante se agitó a temperatura ambiente por 30 min. Esta mezcla se agregó luego a una solución de la mezcla anterior obtenida en A (14.5 mg) en cloruro de metileno (0.5 ml) y la mezcla resultante se agitó a temperatura ambiente por 2 h. La mezcla de reacción se concentró a vacío y el residuo se purificó mediante cromatografía instantánea sobre SiO_2 utilizando un gradiente elución de 2-5% de McOH-$CHCl_3$ para dar el compuesto del título (2 mg) como una película anaranjada. MS(ESI^+) m/z 493.2 $(M + H)^+$.

Ejemplo 33



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1-(4-(3-Etilpiridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea, sal de clorhidrato

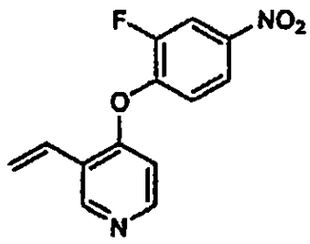


A) 4-(2-Fluoro-4-nitrofenoxi)-3-yodopiridina

Una mezcla de 4-cloro-3-yodopiridina (1.50 g, 6.30 mmol, preparado de acuerdo a Tabanella, S. et al. Org. Biomol. Chem. 2003, 7, 4254-4261.), 2-fluoro-nitrofenol (Lancaster, 2.0 g, 12.7 mmol), DIPEA (5 mL) y NMP (10 mL) se calentó a 150°C. Después de 12 h, se agregó más 2-fluoro- nitrofenol (0.50 g, 3.18 mmol) a la mezcla de reacción y el calentamiento se continuó por 4 h. Los componentes más volátiles fueron eliminados a vacío a 75°C, el residuo se trató con solución acuosa saturada de carbonato ácido de sodio (150 mL) y se extrajo con EtOAc (2 x 100 mL). Los extractos combinados se lavaron con salmuera, se secaron (sulfato de magnesio) y se concentraron a vacío para dar el producto crudo. La purificación mediante cromatografía instantánea sobre gel de sílice, utilizando 0-100 % de cloruro de metileno/hexanos luego 2% de McOH/cloruro de metileno dio el compuesto del título (1.0 g, 43%) como un sólido amarillo. RMN-^{1}H (DMSO-d_6) δ 8.96 (s, 1H), 8.47 (d, 2H,

(47) 430

J = 5.5 Hz), 8.44 (dd, 1H,J = 2.7, 9.2 Hz), 7.49 (dd, 1H, J = 8. 8, 8.2 Hz), 7.07 (d, 1H, J = 5.5 Hz); MS (ESI^+) : m/z 361.05 $(M + H)^+$.



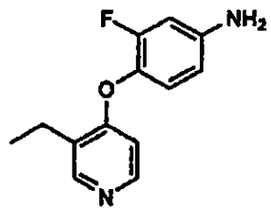
B) 4-(2-Fluoro-4-nitrofenoxi)-3-vinilpiridina

Una solución de 4-(2-fluoro-4-nitrofenoxi)-3-yodopiridina (200 mg. 0.56 mmol), tributilvinilestaño (212 mg. 0.67 mmol) en DMF (1 mL) se trató con CsF (169 mg. 1.12 mmol) seguido por $(Ph_3P)_4Pd$ (36 mg, 0.031 mmol) y CuI (10 mg, 0.056 mmol) y la mezcla se calentó a 45 °C por 1 h. La mezcla se enfrió, se diluyó con cloruro de metileno (15 mL) y agua (10 mL), se agitó vigorosamente y luego se filtró a través de Celite®. La torta de filtro prensa se lavó con cloruro de metileno/EtOAc 1:1 y los lavados se combinaron con el filtrado. La solución se lavó con salmuera, se secó (sulfato de magnesio) y se concentró a vacío para dar un aceite café. El producto crudo se purificó mediante cromatografía instantánea sobre SiO_2 utilizando 0-2 de NeOH/cloruro de metileno para dar un producto semipuro. El producto se trató con 2 M HCl/Et_2O (10 mL) y el derivado clorhidrato

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precipitado se recolectó mediante filtración y se lavó con Et_2O y EtOAc hasta obtener un sólido amarillo (145 mg, 87%). RMN-^{1}H (DMSO-d_6) δ 9.1 1 (s, 1H), 8.64 (s, 1H). 8.51-8.48 (m, 1H). 8.24 (d, 1H.J = 7.7 Hz), 7.83-7.79 (m, 1H), 7.28 (d, 1H, J = 6.0 Hz). 7.02-6.95 (m, 1H). 6.24 (d, 1H, J = 17.6 Hz), 5.68 (d, 1H, 11.5 Hz); MS(ESI$^+$): m/z 261.18$(M + H)^+$.

La sal anterior de clorhidrato se convirtió a la base libre como sigue: El clorhidrato de piridina (230 mg) se agitó con $NaHCO_3$ (25 mL) y EtOAc (20 mL) hasta la homogeneidad y la fase de EtOAc se separó, se lavó con salmuera, se secó (sulfato de magnesio) y se concentró. El compuesto del título (190 mg) se obtuvo como un aceite amarillo.



C) 4-(3-Etilpiridin-4-iloxi)-3-fluorobencenamina

Una solución de 4-(2-fluoro-4-nitrofenoxi)-3-vinilpiridina (80 mg, 0.30 mmol) en EtOAc/MeOH 1:1 (2 mL) se hidrogenó sobre 10 de paladio-carbono (30 mg) por 1 h utilizando H_2 de un globo de látex. Se agregó Pt_2O (10 mg) a la mezcla y la reacción continuó por 1 h. La mezcla se filtró a través de Celite® y se concentró a vacío para dar el compuesto del título (50 mg, 63%) como un aceite amarillo.

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RMN-^{1}H (DMSO-d_6) δ 8.33 (s, 1H), 8.22 (d, 1H, J = 5.6 Hz), 6.96 (dd, 1H. J = 8.7. 9.1 Hz), 6.50 (dd, 1H, J = 2.0, 13.7 Hz), 6.56 (d, 1H.J = 5.6 Hz), 6.41 (dd, 1H, J = 2.5, 6.1 Hz), 2.69 (q, 2H, J=7.6 Hz), 1.21 (t, 3H, J = 7.6 Hz).

D) 1-(4-(3-Etilpiridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea, sal de clorhidrato

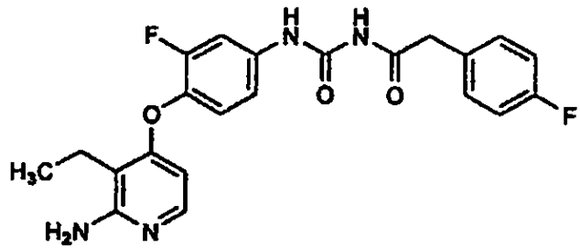
Una solución de 4-(3-etilpiridin-4-iloxi)-3-fluorobencenamina (23 mg, 0.10 mmol) en cloruro de metileno (1 mL) se trató con una solución 0.3 M de isocianato de 2-(4-fluorofenil)acetilo en tolueno (Compuesto D del Ejemplo 11, 0.33 mL. 0.11 mmol) y la mezcla se agitó a temperatura ambiente por 2.5 h.

La mezcla se concentró a vacío y el residuo se trituró con éter isopropílico/EtOAc 1:1 para dar un sólido amarillo. El producto se trató con metanol absoluto (1 mL) y HCl 2M/Et_2O (1 mL), se agitó a temperatura ambiente por 5 min y se concentró a vacío para dar el compuesto del título (15 mg. 36%) como un sólido amarillo pálido.

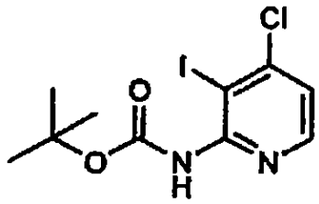
H NMR (DMSO-40 8 11.04(s, 1H), 10.57 (s, 1H), 8.41 1H), 8.26 (d, 1H, J = 5.6 Hz). 7.76 (dd, 1H. J = 2.0. 12.7 Hz), 7.40 - 7.28 (m, 4H), 7.19-7.14 (m, 3H), 6.54 (d, 1H, J = 5.6 Hz), 3.73 (s, 2H), 2.72 (q, 2H, J = 7.6 Hz), 1.23 3H, J = 7.6 Hz); MS (ESI^+) : m/z 412.20 $(M + H)^+$.

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Ejemplo 34



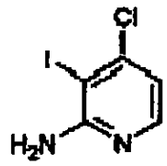
1-(4-(2-Amino-3-etilpiridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea, sal del ácido trifluoroacético



A) Ester ter-butilico del ácido (4-cloro-3-yodopiridin-2-il)-carbámico

Una solución de éster ter-butílico del ácido (4-cloro-piridin-2-il)-carbámico (CB Research & Development Inc., 5.0 g, 22.0 mmol), TMEDA (8 mL) en THF anhidro (100 mL) se colocó bajo una atmósfera de nitrógeno y se enfrió a -70°C, y se trató gota a gota con n-BuLi 2.5 M en hexanos (22.0 mL, 54.8 mmol) en un periodo de 30 min. La mezcla se agitó a -70°C por 1 h luego se trató gota a gota con una solución de I_2 (14 g, 110 mmol) en THF anhidro (16 mL) a -70°C. Después de que se completó la adición, la reacción se agitó a -70°C por 30 min luego se dejó calentar a temperatura ambiente. La mezcla se trató con una solución de sulfito ácido de sodio (16 g) en

H_2O (100 mL) y se agitó por 30 min, luego se extrajo con EtOAc. El extracto se lavó con salmuera, se secó (sulfato de magnesio) y se concentró a vacío. El producto se purificó mediante cromatografía instantánea sobre SiO_2 eluyendo con 0-5 de McOH /cloruro de metileno para dar el compuesto del título (5.8 g, 78%) como un sólido blanco. RMN-^{1}H (DMSO-d_6) δ 9.46 (s, 1H), 8.29 (d, 1H, J = 5.6 Hz), 7.46 (d, 1H, J = 5.0 Hz), 1.44 (s, 9H); MS (ESI^-) : m/z 352.99 (M-H)$^-$.

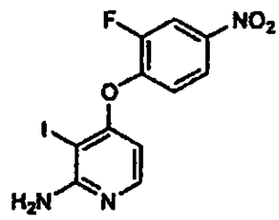


B) 4-Cloro-3-yodopiridin-2-amina

Una suspensión de éster ter-butílico del ácido (4-cloro-3-yodo-piridin-2-il)-carbámico (5.6 g. 15.8 mmol) en 48 ácido bromhídrico se calentó a 100°C por 10 min para dar una solución clara. La mezcla se enfrió, se trató con hielo triturado y se alcalinizó con NaOH 6M. El producto precipitado se recolectó mediante filtración a vacío, se lavó con H_2O y se succionó parcialmente sobre el embudo para dar un sólido blanco. El producto se disolvió en THF y la solución se secó sobre sulfato de magnesio y se concentró a vacío para dar el compuesto del título (3.7 g, 93%) como un sólido blanco. RMN-^{1}H (DMSO-d_6) δ 7.84 (d, 1H.J = 5.1 Hz), 6.73 (d, 1H, J = 5.6 Hz), 6.51 (br s, 2H); MS (ESI^+) : m/z

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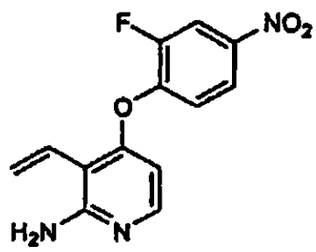
254.97 $(M + H)^+$.



C) 4-(2-Fluoro-4-nitrofenoxi)-3-yodopiridin-2-amina

Una mezcla de 4-cloro-3-yodopiridin-2-amina (3.6 g, 14.2 mmol) y 2-fluoro-4-nitrofenol (Lancaster, 4.5 g, 28.4 mmol), DIPEA (3.6 mL, 20.7 mmol) y NMP (8 mL) se colocó en un recipiente de vidrio a presión y se calentó rápidamente a 170°C y el calentamiento continuó por 18 h. Los componentes volátiles se destilaron bajo presión reducida y el residuo viscoso se vació en hielo-agua (150 mL). La mezcla se sonicó por 15 min con el fin de romper el sólido gomoso y el pH de la mezcla se ajustó a 7.5 con solución acuosa saturada de carbonato ácido de sodio. El sólido se recolectó mediante filtración a vacío, se lavó con agua, se secó parcialmente por succión sobre el embudo. El sólido parcialmente seco se suspendió en tolueno (150 mL) y la mezcla se concentró a vacío y el proceso se repitió 3 veces para dar un sólido café. El producto se disolvió en MeOH (150 mL), se trató con HCl 4M/1,4-dioxano (8 mL) y se agitó a temperatura ambiente por 5 min y luego la mezcla se concentró a vacío. El clorhidrato obtenido así se lavó y trituró con EtOAc y se

dividió entre EtOAc y solución acuosa saturada de carbonato ácido de sodio. La fase de EtOAc se separó, se lavó con salmuera, y luego se secó (sulfato de magnesio). La solución de EtOAc se trató con carbón mineral activado, se agitó a temperatura ambiente por 10 min y el carbón mineral se filtró. La solución se concentró a vacío para dar el compuesto del título (3.9 g, 74%) como un sólido amarillo. RMN-^{1}H (DMSO-d_6) δ 8.39 (dd, 1H, 7 = 2.5, 10.7 Hz). 8.12 (dd, 1H, J = 1.5, 9.2 Hz), 7.86 (d, 1H, J = 5.6 Hz), 7.32 (dd, 1H, J = 8.6, 8.6 Hz), 6.40 (br s, 2H), 6.18 (d, 1H, J = 5.6 Hz).

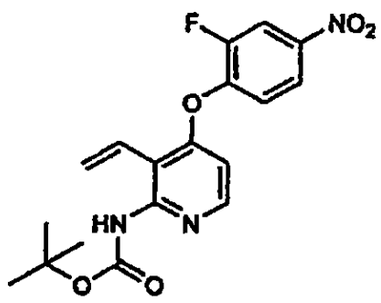


D) 4-(2-Fluoro-4-nitrofenoxi)-3-vinilpiridin-2-amina

El compuesto del título se preparó a partir de 4-(2-fluoro-4-nitrofenoxi)-3-yodopiridin-2-amina y tributilvinilestaño vía una reacción de acoplamiento de Stille de la misma manera que se describe en el Paso B del Ejemplo 33. RMN-^{1}H (DMSO-d_6) δ 8.35 (dd, 1H, J = 10.7.3.1 Hz), 8.09 (d, 1H, J = 9.2 Hz), 7.85 (d, 1H, J = 5.6 Hz), 7.31-7.15 (m, 1H), 6.54 (dd, 1H, J = 17.8, 11.7 Hz), 6.24 (br s, 2H),

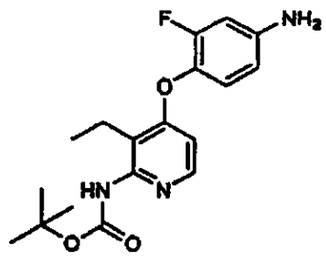
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6.20 (d, 1H, J = 5.6 Hz), 5.71 (d, 1H, J = 17.8 Hz), 5.46 (d, 1H, J = 11.7 Hz); MS (ESI^+) : m/z 276.17 $(M + H)^+$.



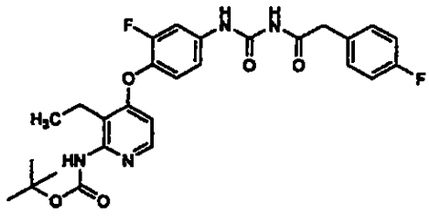
E) 4-(2-fluoro-4-nitrofenoxi)-3-vinilpiridin-2-ilcarbamato de ter-butilo

Una solución de 4-(2-fluoro-4-nitrofenoxi)-3-vinilpiridin-2-amina (60 mg, 0.22 mmol) en 1,4-dioxano (0.5 mL) y alcohol ter-butílico (1.5 mL) se trató con Boc_2O (140 mg, 0.64 mmol) y se calentó a 65 °C por 5 h. La mezcla se enfrió, se dividió entre EtOAc y solución acuosa saturada de carbonato ácido de sodio. La fase de EtOAc se separó, se lavó con salmuera, se secó (sulfato de magnesio) y se concentró a vacío. El producto crudo se purificó mediante cromatografía instantánea sobre SiO_2 para dar el compuesto del título (50 mg, 60%) como un sólido amarillo. RMN-^{1}H (DMSO-d_6) δ 9.37 (s, 1H), 8.41 (dd, 1H, J = 10.7. 2.5 Hz), 8.22 (d, 1H, J = 5.6 Hz), 8.15 (d, 1H, J = 8.6 Hz), 7.42 (t, 1H, J = 8.6 Hz), 6.86 (d, 1H. J = 5.6 Hz), 6.58 (dd, 1H, J = 17.8, 11.7 Hz), 5.82 (d, 1H, J = 16.3 Hz), 5.52 (d, 1H, J = 11.7 Hz), 1.42 (s, 9H); MS (ESI^+) : m/z 376.18 $(M + H)^+$.



F) 4-(4-amino-2-fluorofenoxi)-3-etilpiridin-2-ilcarbamato de ter-butilo

Una solución de 4-(2-fluoro-4-nitrofenoxi)-3- vinilpiridin-2-ilcarbamato de ter-butilo (48 mg, 0.13 mmol) se hidrogenó sobre 10 de paladio-carbono (10 mg) y Pt_2O (5 mg) por 1.5 h utilizando H2 de un globo de caucho. La mezcla se filtró a través de Celite® y el filtrado se concentró a vacío para dar el compuesto del título (40 mg, 89%) como un sólido amarillo pálido. RMN-^{1}H (DMSO-d_6) δ 9.04 (s, 1H), 8.03 (d, 1H, J = 5.6 Hz), 6.95 (dd, 1H, J = 8.6, 8.6 Hz), 6.50 (dd, 1H.J = 2.5, 13.2 Hz), 6.41 (dd, 1H, J = 2.5, 9.4 Hz), 6.36 (d, 1H, J = 5.6 Hz), 5.44 (s, 2H), 2.67-2.62 (m, 2H). 1.43 (s,9H), 1.11 (t, 3H, J = 7.1 Hz); MS(ESI$^+$): m/z 348.22 $(M + H)^+$.



G) 3-etil-4-(2-fluoro-4-(3-(2-(4-fluorofenil)acetil)ureido)fenoxi)piridin-2-ilcarbamato de ter-butilo

El compuesto del título se preparó a partir de 4-(4-

amino-2-fluorofenoxi)-3-etilpiridin-2-ilcarbamato de ter-butilo (20 mg, 0.058 mmol) y solución 0.3 M de isocianato de 2-(4-fluorofenil)acetilo en tolueno (232 µL, 0.070 mmol) en THF de la misma manera que el Paso D del Ejemplo 33. MS (ESI$^+$) : m/z 527.31 $(M + H)^+$.

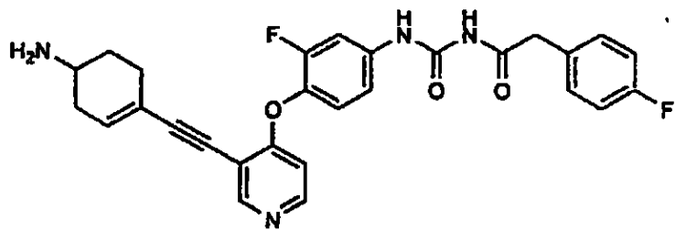
H) 1-(4-(2-Amino-3-etilpiridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea, sal del ácido trifluoroacético

Una solución de 3-etil-4-(2-fluoro-4-(3-(2-(4-fluorofenil)acetil)ureido) fenoxi)piridin-2-ilcarbamato de ter-butilo (16 mg, 0.03 mmol) se disolvió en THF anhidro (0.5 mL) y se trató con HCl 4 M/1,4-dioxano (1.5 mL) y se agitó a temperatura ambiente por 3 h.

La mezcla se concentró a vacío y el producto se purificó mediante HPLC preparativa método A para dar el compuesto del título (5 mg. 36%) como un sólido blanco.

RMN-^{1}H (DMSO-d_6) δ 11.06 (s, 1H), 10.6 (s, 1H). 7.80-7.79 (m, 4H). 7.43 - 7.33 (m, 4H), 7.16 (dd, 2H. J = 8.9. 8.9 Hz), 6.19 (d. 1H, J = 7.1 Hz). 3.73 (s, 2H). 2.71 -2.66 (m, 2H), 1.10 (t, 3H, J = 7.1 Hz); MS (ESI$^+$) : m/z 427.18 $(M + H)^+$.

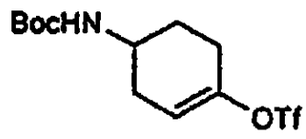
Ejemplo 35



1-(4-(3-(2-(4-Aminociclohex-1-enil)etinil)piridin-4-iloxi)-3-

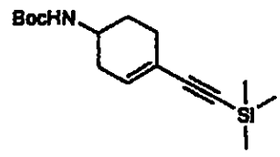
CHT 440

fluorofenil)-3-(2-(4-fluorofenil) acetil) urea



A) trifluorometansulfonato de 4-(ter-butoxicarbonil)ciclohex-1-enilo

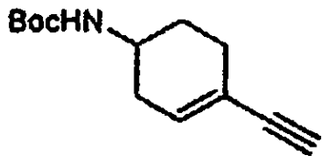
Una solución de N-Boc-4-aminociclohexanona (Astatech Inc., 213 mg, 1.0 mmol) en THF (7 mL) se enfrió a -70 °C y se trató con una solución 0.5 M de KHMDS en tolueno (2.4 ml, 1.2 mmol). La mezcla se agitó a -70 °C por 20 min, se trató gota a gota con una solución de feniltrifluorometansulfonimida (392 mg, 1.1 mmol) en THF (4 mL) y se agitó a -70 °C por 25 min. La mezcla se apagó con solución acuosa saturada de cloruro de amonio, se diluyó con EtOAc, se lavó con carbonato ácido de sodio al 10 y salmuera, se secó (sulfato de magnesio) y se concentró a vacío. El producto crudo se purificó mediante cromatografía instantánea sobre SiO_2 eluyendo con 10-25 de EtOAc/hexanos para dar el compuesto del título (180 mg, 52%) como un sólido blanco. RMN-^{1}H (DMSO-d_6) δ 5.68 (s, 1H), 4.50 (s, 1H). 3.82 (s, 1H), 2.68-2.25 (m, 3H), 2.22-1.89 (m, 2H), 1.87-1.63 (m, 1H), 1.43 (s, 9H).



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B) 4-(2-(trimetilsilil)etinil)ciclohex-3-enilcarbamato de ter-butilo

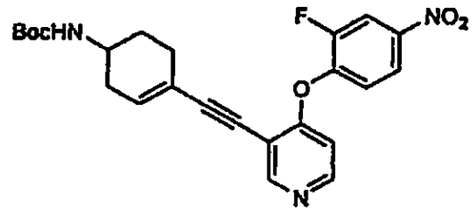
Una mezcla de 4-(ter-butoxicarbonil)ciclohex-1-enil trifluorometansulfonato (170 mg. 0.49 mmol), trimetilsililacetileno (138 µL. 0.98 mmol), Et_3N (0.68 mL) y THF (8 mL) en un matraz de reacción se purgó con argón y se trató a su vez con CuI (14 mg, 0.072 mmol) y $(Ph_3P)_4Pd$ (27 mg, 0.024 mmol). La mezcla de reacción se agitó a temperatura ambiente por 25 min, y luego se diluyó con EtOAc (50 mL), se lavó con solución acuosa saturada de carbonato ácido de sodio y salmuera, se secó (sulfato de magnesio) y se concentró a vacío. El producto crudo se purificó mediante cromatografía instantánea sobre SiO_2 eluyendo con 0-25 de EtOAc/hexanos para dar el compuesto del título (116 mg. 81%) como un sólido amarillo. RMN-^{1}H (DMSO-d_6) δ 6.06 (s, 1H), 4.50 (s, 1H). 3.76(s, 1H), 2.46 (d, 1H. J = 18.8 Hz), 2.36-2.14 (m, 2H), 2.00-1.78 (m, 2H), 1.66-1.50 (m, 1H), 1.43 (s, 9H), 0.27-0.05 (m, 9H).



C) 4-etinilciclohex-3-enilcarbamato de ter-butilo

Una solución de 4-(2-(trimetilsilil)etinil)ciclohex-3-enilcarbamato de ter-butilo (112 mg, 0.38 mmol) en THF se enfrió a -15°C, se trató con fluoruro de tetrabutilamonio 1.0

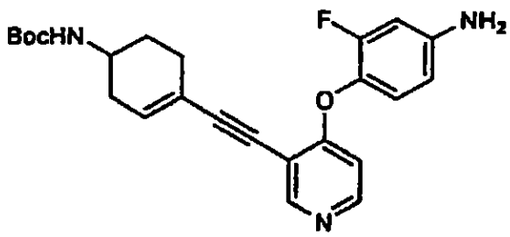
M en THF (Aldrich, 440 µL, 0.44 mmol) y la mezcla se agitó a -15°C por 40 min. La mezcla se trató con Na_2CO_3 al 5 (25 mL) y se extrajo con éter. El extracto de éter se lavó con Na_2CO_3 al 5% y salmuera, se secó (sulfato de magnesio) y se concentró a vacío para dar el compuesto del título (83 mg, 99%) como un aceite café. RMN-^{1}H (DMSO-d_6) δ 6.09 (s, 1H),4.51 (s, 1H), 3.77 (s, 1H), 2.82 (s, 1H), 2.47(d, 1H, J = 18.3 Hz), 2.35-2.16 (m,2H), 2.04-1.79 (m,2H), 1.72-1.51 (m, 1H), 1.43(s,9H).



D) 4-(2-(4-(2-fluoro-4-nitrofenoxi)piridin-3-il)etinil)ciclohex-3-enilcarbamato de ter-butilo

Una solución de 4-(2-fluoro-4-nitrofenoxi)-3-yodopiridina (Compuesto A del Ejemplo 33, 130 mg, 0.36 mmol) y N-Boc-4-etinilciclohex-3-enamina (80 mg. 0.36 mmol) en THF anhidro (2 mL) se trató con Et_3N (2 mL) y se desgasificó por vacío/purga de argón. La solución se trató con tetrakistrifenilfosfina-paladio (20 mg, 0.0018 mmol) y CuI (10 mg, 0.054 mmol) y luego se calentó a reflujo por 2 h. La mezcla se enfrió y se dividió entre solución acuosa saturada de carbonato ácido de sodio y EtOAc. La fase de EtOAc se separó, se lavó con salmuera, se secó (sulfato de magnesio) y

se concentró a vacío. El producto crudo se purificó mediante cromatografía instantánea sobre gel de sílice eluyendo con 0-40 % de EtOAc/hexanos para dar el compuesto del título (124 mg, 76%) como un sólido amarillo. RMN-^{1}H (DMSO-d_6) δ 8.68 (s, 1H), 8.51 (d, 1H, J = 5.6 Hz), 8.43 (dd, 1H, .7 = 2.5, 10. 7 Hz), 8.15 (d, 1H, J = 9.2 Hz), 7.49 (dd, 1H, J = 8.6, 8.6 Hz), 7.14 (d, 1H, J = 5.6 Hz), 6.85 (d, 1H, J = 7.1 Hz), 6.04- 6.00 (m, 1H), 3.48-3.35 (m, 1H), 2.36 - 2.25 (m, 1H), 2.17 - 2.04 (m,2H), 2.03 -1.89 (m, 1H), 1.78 - 1.69 (m, 1H), 1.46-1.35 (m, 1H), 1.36 (s, 9H); MS (ESI$^+$) : m/z 454.27 $(M + H)^+$.

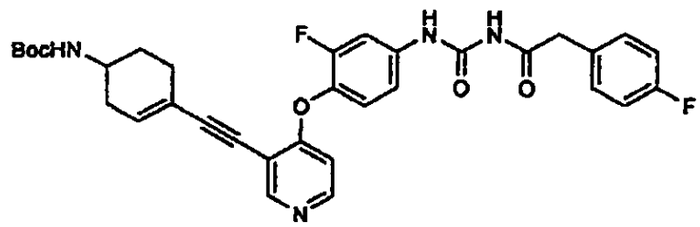


E) 4-(2-(4-(4-amino-2-fluorofenoxi)piridin-3-il)etinil)ciclohex-3-enilcarbamato de ter-butilo

Una mezcla de 4-(2-(4-(2-fluoro-4-nitrofenoxi)piridin-3-il)etinil) ciclohex-3-enilcarbamato de ter-butilo (110 mg, 0.24 mmol), polvo de hierro, malla aprox. 325 (150 mg, 2.7 mmol), cloruro de amonio (280 mg, 5.3 mmol), DMF (1 mL), H_2O (1 mL) y EtOH (1 mL) se calentó a 100°C por 30 minutos. La mezcla se filtró a través de un lecho de Celite® utilizando DMF para lavar la torta de filtro prensa y el filtrado se alcalinizó a pH 8 con

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solución acuosa saturada de carbonato ácido de sodio. La mezcla se extrajo dos veces con EtOAc, se secó (sulfato de magnesio) y se concentró a vacío para dar el compuesto del título (105 mg) el cual se utilizó sin ninguna purificación adicional. MS (ESI^+) : m/z 424.27 $(M + H)^+$.



F) 4-(2-(4-(2-fluoro-4-(3-(2-(4-fluorofenil)acetil)ureido)fenoxi)piridin-3-il)etinil)ciclohex-3-enilcarbamato de ter-butilo

Una solución de 4-(2-(4-(4-amino-2-fluorofenoxi)piridin-3-il)etinil)ciclohex-3-enilcarbamato de ter-butilo (50 mg, 0.12 mmol) en cloruro de metileno anhidro(2 mL) se trató con una solución 0.3 M de isocianato de 2-(4-fluorofenil)acetilo en tolueno (Compuesto D del Ejemplo 11, 0.8 mL, 0.24 mmol) y la mezcla se agitó a TA por 1 h. Los solventes se evaporaron a vacío y el residuo se purificó mediante cromatografía instantánea sobre gel de sílice eluyendo con 10-60 % de EtOAc/hexanos para dar el compuesto del título (50 mg, 69%) como un sólido blanco. RMN-^{1}H (DMSO-d_6) δ 11.03 (s, 1H), 10.57 (s, 1H), 8.57 (s, 1H), 8.36 (d, 1H, J = 5.7 Hz), 7.78 (dd,

1H, J = 1.8, 13.1 Hz), 7.41 - 7.29 (m, 3H), 7.16 (dd, 3H, J = 8.6, 8.6 Hz), 6.85 (d, 1H, J = 8.3 Hz), 6.70 (d, 1H. J = 5.7 Hz). 6.13 - 6.08 (m, 1H), 3.73 (s, 2H), 3.51 - 3.41 (m, 1H). 2.38 - 2.27 (m, 1H), 2.27-2.20 (m,2H), 1.82-1.72 (m, 1H), 1.54-1.28 (m, 2H). 1.37(s, 9H); ESI MS) : m/z 603.24 $(M + H)^+$.

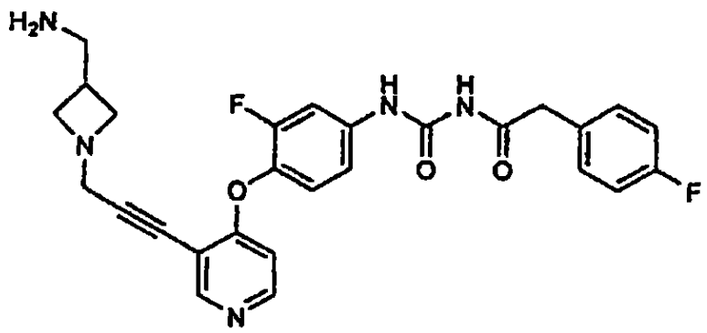
G) 1-(4-(3-(2-(4-Aminociclohex-1-enil)etinil)piridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil) acetil) urea, sal de diclorhidrato

Una solución de 4-(2-(4-(2-fluoro-4-(3-(2-(4-fluorofenil)acetil)ureido)fenoxi)piridin-3-il)etinil)ciclohex-3-enilcarbamato de ter-butilo (40 mg, 0.066 mol) en anhidro 1,4-dioxano (2 mL) se enfrió a -10°C y se trató con HCl 4 M/1,4-dioxano (4 mL). La mezcla se agitó a -5°C por 2.5 h luego a TA por 1 h.

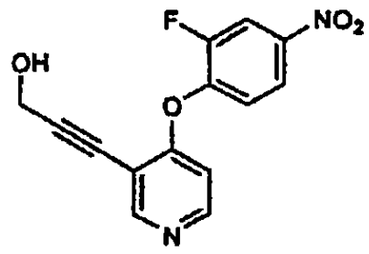
La mezcla se concentró a vacío sin calentamiento para dar el compuesto del título (32 mg, 84%) como un sólido amarillo.

RMN-^{1}H (DMSO-d_6) δ 11.05 (s, 1H). 10.61 (s, 1H), 8.69 (s, 1H), 8.44 (d, 1H, J = 6.1 Hz), 8.06 (d, 1H, J = 2. 0Hz), 7.80 (dd, 1H, J = 12.7. 2.0 Hz), 7.46-7.38 (m, 1H), 7.35 (dd, 1H, J = 8. 6, 5.6 Hz), 7.19- 7.13 (m, 1H), 6.82 (d, 1H, J = 5.6 Hz), 6.17 (s, 1H), 3.74 (s, 2H), 3.73-3.62 (m, 2H). 3.62-3.54 (m, 1H), 3.34-3.22 (m, 1H), 2.31 (s, 1H), 1.99-1.96 (m, 1H), 1.71-1.66 (m, 1H); MS (ESI^+) : m/z 503.12 $(M + H)^+$.

Ejemplo 36



1-(4-(3-(3-(3-(Aminometil)azetidin-1-il)prop-1-inil)piridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil) acetil) urea, sal de triclorhidrato

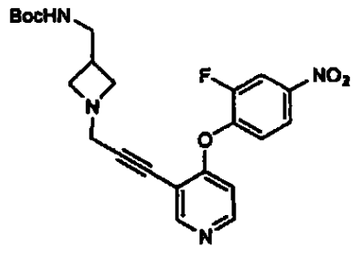


A) 3-(4-(2-Fluoro-4-nitrofenoxi)piridin-3-il)prop-2-in-1-ol

Una solución de 4-(2-fluoro-4-nitrofenoxi)-3-yodopiridina (Compuesto A del Ejemplo 33. 300 mg, 0.83 mmol), propargilalcohol (Aldrich, 145 µL, 2.50 mmol), Et_3N (2 mL) y THF anhidro (2 mL) se desgasificó mediante vacío/purga de argón y se trató con $Pd(Ph_3P)_4$ (31 mg, 0.027 mmol) y CuI (10 mg, 0.054 mmol). La mezcla se calentó a reflujo bajo atmósfera de argón por 10 min, se enfrió a TA y se diluyó con EtOAc (25 mL) y H_2O (20 mL). La fase de EtOAc se lavó con agua y salmuera, se secó (sulfato de magnesio) y se concentró

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a vacío. El residuo crudo se purificó mediante cromatografía instantánea sobre gel de sílice utilizando 0-3 % de McOH/cloruro de metileno para dar el producto deseado (185 mg, 77%) como un sólido amarillo pálido. RMN-^{1}H (DMSO-d_6) δ 8.69 (s, 1H), 8.49 (d, 1H, J = 5.6 Hz), 8.43 (dd, 1H, J = 10.7, 2.5 Hz), 8.17 (d, 1H, J = 9.2 Hz), 7.57 (t, 1H. J =8.6 Hz), 7.04 (d, 1H, J = 5.6 Hz), 5.40 (t, 1H, J = 6.1), 4.28 (d, 2H. J = 6.1 Hz): MS(ESI$^+$): m/z 289.13 $(M + H)^+$.

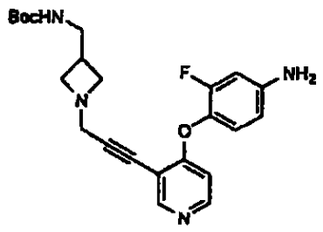


B) (1-(3-(4-(2-fluoro-4-nitrofenoxi)piridin-3-il)prop-2-inil)azetidin-3-il)metilcarbamato de ter-butilo

Una solución de 3-(4-(2-fluoro-4- nitrofenoxi)piridin-3-il)prop-2-in-1-ol (43 mg, 0.15 mmol) y DIPEA (45 µL, 0.26 mmol) en THF anhidro (1.5 mL) se enfrió a 0°C y se trató con cloruro de metansulfonilo (15 mg, 0.11 mmol) en porciones. Después de agitar a 0°C por 1 h, la mezcla se concentró bajo presión reducida. El residuo se trató con DMF (1.0 mL), DIPEA (45 µL, 0.26 mmol) y éster ter-bu-tilico del ácido azetidin-3-ilmetil-carbámico (Beta Pharma Inc. 145 mg, 0.78 mmol) y se agitó a TA por 2 h. La mezcla de reacción se dividió entre

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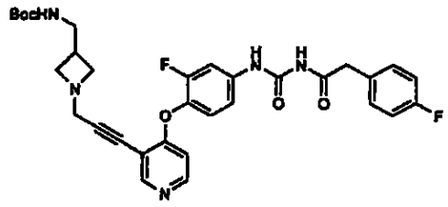
EtOAc y solución acuosa saturada de carbonato ácido de sodio y la fase de EtOAc se separó, se lavó con salmuera, se secó ($MgSO_4$) y se concentró a vacío. El residuo se purificó mediante cromatografía instantánea sobre SiO_2 eluyendo con 1-5 de McOH/cloruro de metileno para proporcionar el compuesto del título (33 mg, 48%) como un aceite incoloro. RMN-^{1}H (DMSO-d_6) δ 8.74 (s, 1H). 8.51 (d, 1H, J = 5. 6Hz), 8.41 (dd, 1H.J = 10. 7, 2.5 Hz), 8.15 (d, 1] J = 9.2 Hz), 7.53 (t, 1H, J = 8.6 Hz), 7.09 (d, 1H. J = 6 Hz), 6.86 (t, IH, J = 5.6 Hz), 3.39 (s, 2H), 3.24-3.14 (r 2H), 3.07-2.98 (m, 2H). 2.94-2.87 (m, 2H), 2.37-2.26 (m, 1H 1.33 (s, 9H); MS (ESI^+) : m/z 401.20 (100), [($M-C_4H_9$)]+; m, 457.20 (25). $(M + H)^+$.



C) (1-(3-(4-(4-amino-2-fluorofenoxi) piridin-3-il) prop-2-inil) azetidin-3-il)metilcarbamato de ter-butilo

El compuesto del título se preparó mediante la reducción de (1-(3-(4-(2-fluoro-4-nitrofenoxi)piridin-3- il)prop-2-inil)azetidin-3-il)metilcarbamato de ter-butilo (30 mg. 0.66 mmol) de la misma manera que en el Paso E del Ejemplo 35 utilizando Polvo de hierro (50 mg. 0.091 mmol) y NH_4Cl (96 mg, 1.82 mmol). El producto se utilizó en reacciones

subsecuentes sin ninguna purificación. MS(ESI+): m/z 371.24 (100), $[(M-C_4H_9)]^+$; m/z 427.27 (25), $(M + H)^+$.



D) (1-(3-(4-(2-fluoro-4-(3-(2-(4-fluorofenil)acetil)ureido)fenoxi)piridin-3-il)prop-2-inil)azetidin-3-il)metilcarbamato de ter-butilo

El compuesto del título se preparó a partir de (1-(3-(4-(4-amino-2-fluorofenoxi)piridin-3-il)prop-2- inil)azetidin-3-il)metilcarbamato de ter-butilo (25 mg, 0.059 mmol) y una solución 0.3 M de isocianato de 2-(4-fluorofenil)acetilo en tolueno (Compuesto D del Ejemplo 11, 0.37 mL, 0.11 mmol) de la misma manera que el Paso D del Ejemplo 33 para dar el compuesto del título como un sólido blanco (20 mg. 57%).

RMN-^{1}H (DMSO-d_6) δ 11.04 (s, 1H). 10.58 (s, 1H), 8.63 (s, 1H), 8.37 (d, 1H, J = 5.5 Hz), 7.78 (d, 1H, J = 12.6 Hz), 7.40 - 7.33 (m, 4H), 7.16 (dd, 2H. J = 8.8. 8.9 Hz), 6.89 - 6.87 (m, 1H), 6.68 (d, 1H, J = 5.5 Hz), 3.73 (s, 2H), 3.45 (s, 2H), 3.26-3.24 (m, 2H), 3.07-3.04 (m, 2H), 2.98 - 2.96 (m, 2H), 2.38 - 2.35 (m, 2H), 1.32 (s, 9H); MS (ESI^+) : m/z 606.26 $(M + H)^+$.

E) 1-(4-(3-(3-(3-(Aminometil)azetidin-1-il)prop-1-inil)piridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea, sal de triclorhidrato

El (1-(3-(4-(2-fluoro-4-(3-(2-(4-fluorofenil)acetil)ureido)fenoxi)piridin-3-il)prop-2-inil)azetidin-3-il)metilcarbamato de ter-butilo (20 mg. 0.033 mmol) se disolvió en cloruro de metileno (2 mL) y se trató con TFA (0.5 mL) y la mezcla se agitó a temperatura ambiente por 1.5 h.

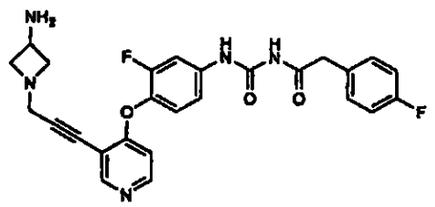
La mezcla se concentró a vacío y se purificó mediante HPLC preparativa (Columna A) para dar la sal de TFA.

La sal de TFA se disolvió en metanol absoluto y se trató con 1.0 M HCl/éter se agitó por 5 min y se concentró a vacío para dar el compuesto del título (9 mg, 45%) como un sólido blanco.

RMN-^{1}H (DMSO-d_6) δ 11.07 (s, 1H), 10.06 (s, 1H), 8.96 (m, 1H). 8.61 - 8.52 (m, 1H), 8.36 - 8.25 (s, 2H), 7.82 (d, 1H, J = 12.2 Hz). 7.45 - 7.42 (m, 2H), 7.37 - 7.33 (m, 2H), 7.18-7.14 (m, 2H). 6.92 (d, 1H, J = 6.1 Hz), 4.48 (s, 2H), 4.27 - 3.98 (m, 2H), 3.76 (s, 2H), 3.30 - 3.20 (m, 1H), 3.16 -3.00 (m, 2H): MS(ESI$^+$): m/z 506.18 $(M + H)^+$.

Los Ejemplos 37-40 se prepararon de una manera similar a aquella que se describe en el Ejemplo 36.

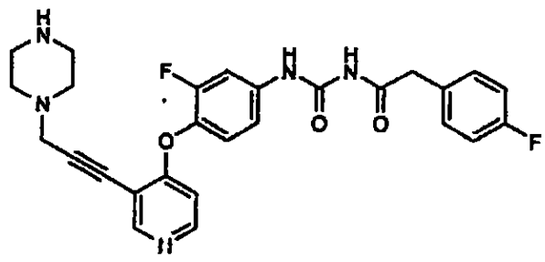
Ejemplo 37



1-(4-(3-(3-(3-Aminoazetidin-1-il)prop-1-inil)piridin-4-iloxi)-3-fluorofenıl)-3-(2-(4-fluorofenil) acetil) urea, sal de triclorhidrato

MS (ESI^+) : m/z 492.17 $(M + H)^+$

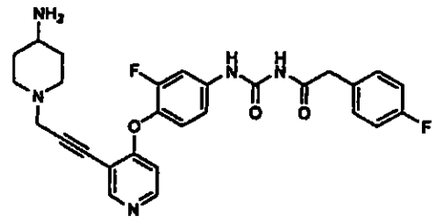
Ejemplo 38



1-(3-Fluoro-4-(3-(3-(piperazin-1-il)prop-1-inil)piridin-4-iloxi)fenil)-3-(2-(4-fluorofenil) acetil)urea, sal de triclorhidrato

RMN-^1H (DMSO-d_6) δ 11.07 (s, 1H), 10.63 (s, 1H), 9.44 (s, 1H), 8.91 (s, 1H), 8.50 (d, IR, J = 6.2 Hz), 7.84- 7.78 (m, 1H), 7.45-7.39 (m, 2H), 7.38-7.32 (m, 2H), 7.16 (t, 2H, J = 8.8 Hz), 6.85 (d, 1H, J = 6.2 Hz), 4.26 (s, 2H), 3.75 (s, 2H), 3.34 (br s, 4H), 2.49 (br s, 4H); MS(ESI^+): m/z 506.23 $(M + H)^+$.

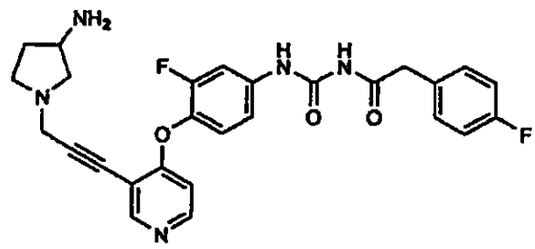
Ejemplo 39



1-(4-(3-(3-(4-Aminopiperidin-1-il)prop-1-inil)piridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil) acetil) urea, sal de triclorhidrato

RMN-^{1}H (DMSO-d_6) δ 11.07(s, 1H), 10.62 (s, 1H), 8.81 (s, 1H), 8.48 (d, 1H, .7 =6.1 Hz), 8.31 (s, 2H), 7.80 (dd, 1H, J = 2.2, 12.7 Hz), 7.44 - 7.33 (m, 4H), 7.19-7.13 (m, 2H), 6.78 (d, 1H, J = 5.7 Hz), 4.40 (s, 2H), 3.74 (s, 2H), 3.64 - 3.60 (m, 2H), 3.34 - 3.22 (m, 1H), 3.19 - 3.13 (m, 2H), 2.16 - 2.13 (m, 2H), 1.99 -1.88 (m, 2H); MS(ESI+): m/z 506.23 $(M + H)^+$.

Ejemplo 40



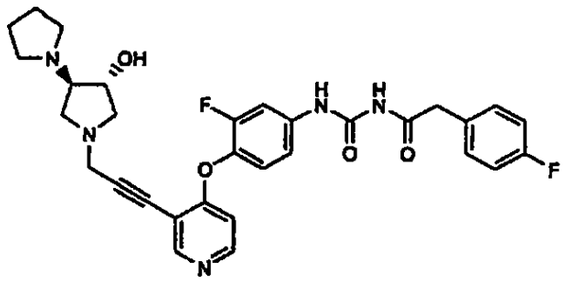
(±)-1-(4-(3-(3-(3-Aminopirrolidin-1-il)prop-1-inil)piridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil) acetil) urea, sal

CAS 453

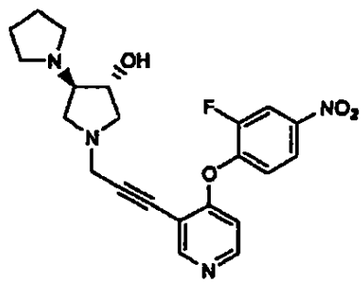
de triclorhidrato

RMN-^{1}H (DMSO-d_6) δ 11.08 (s, 1H), 10.65 (s, 1H), 8.96 (s, 1H). 8.54 (d, 1H, J = 6.1 Hz), 7.83 (d, 1H, J = 12.7 Hz), 7.43 (s, 2H), 7.37 - 7.33 (m, 2H), 7.16 -7.14 (m, 2H), 6.90 (d, 1H, J = 5.6 Hz), 4.62 (s, 2H), 4.06 - 3.87 (m, 1H), 3.75 (s, 2H), 3.70 - 3.55 (m, 3H), 3.49 - 3.44 (m, 2H), 2.25 - 2.08 (m, 1H); MS (ESI$^+$) : m/z 506.22 (M + H)4".

Ejemplo 41



1-(3-Fluoro-4-(3-(3-((3R,4R)-3-hidroxi-4-(pirrolidin-1-il)pirrolidin-1-il)prop-1-inil)piridin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)urea, sal de triclorhidrato



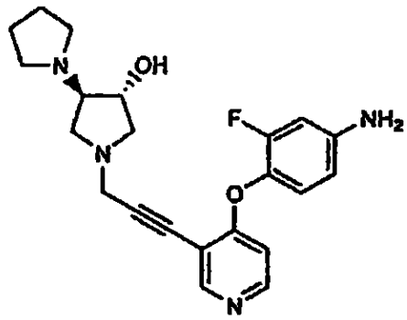
A) (3R,4R)-1-(3-(4-(2-Fluoro-4-nitrofenoxi)piridin-3-il)prop-2-inil)-4-(pirrolidin-1-il)pirrolidin-3-ol

Una solución de 3-(4-(2-fluoro-4-nitrofenoxi)piridin-3-

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il)prop-2-in-1-ol (Compuesto A del Ejemplo 36, 43 mg, 0.15 mmol) y DIPEA (45 µL, 0.26 mmol) en THF anhidro (1.5 mL) se enfrió a 0°C y se trató con cloruro de metansulfonilo (15 mg, 0.11 mmol) en porciones. Después de agitar a 0°C por 1 h, la mezcla se concentró bajo presión reducida. El residuo se trató con DMF (1.0 mL), DIPEA (45 µL, 0.26 mmol) y (3R,4R)-4-(pirrolidin-1-il)pirrolidin-3-ol (Lexicón Pharmaceutical Corp., 94 mg, 0.6 mmol) y se agitó a temperatura ambiente por 2 h. La mezcla de reacción se dividió entre EtOAc y solución acuosa saturada de carbonato ácido de sodio y la fase de EtOAc se separó, se lavó con salmuera, se secó (sulfato de sodio) y se concentró a vacío. El producto crudo se purificó mediante cromatografía instantánea sobre SiO_2 eluyendo con 0-1.5 % de MeOH/cloruro de metileno para dar el compuesto del título (38 mg, 59%) como un aceite café. RMN-^{1}H (DMSO-d_6) δ 8.72 (s, 1H), 8.54 (d, 1H, J = 5.6 Hz), 8.40 (dd, 1H, J = 10.7. 2.5 Hz), 8.14 (d, 1H, J = 9.2 Hz), 7.43 (t, 1H. J = 8.6 Hz), 7.15 (d, 1H, J = 5.6 Hz), 4.99-4.81 (m, 1H), 4.11-4.10 (m, 0.5H), 3.92-3.84 (m, 1H), 3.54 (s, 2H), 3.59-3.50 (m, 0.5H), 3.16-3.15 (m, 1H), 2.79-2.75 (m, 1H), 2.60-2.32 (m, 4H), 1.70-1.59 (m, 4H); MS (ESI^+) : m/z 427.24 $(M + H)^+$.

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B) (3R,4R)-1-(3-(4-(4-Amino-2-fluorofenoxi) piridin-3-il)prop-2-inil)-4-(pirrolidin-1-il)pirrolidin-3-ol

Una mezcla de (3R, 4R)-1-(3-(4-(2-fluoro-4-nitrofenoxi)piridin-3-il)prop-2-inil)-4-(pirrolidin-1-il)pirrolidin-3-ol (35 mg, 0.082 mmol), DMF (1 mL), EtOH (1 mL) y agua (1 mL) se trató con polvo de hierro (67 mg, 1.2 mmol, 2.4 mmol) y se calentó a 100°C por 45 min. La mezcla se filtró a través de Celite®, se alcalinizó con carbonato ácido de sodio y se concentró a vacío. El residuo se dividió entre EtOAc y solución acuosa saturada de carbonato ácido de sodio. La fase de EtOAc se secó ($MgSO_4$) y se concentró a vacío para dar la anilina cruda (16 mg, 50%) la cual se utilizó directamente en el siguiente paso sin purificación adicional. MS (ESI^+) : m/z 397.28 $(M + H)^+$.

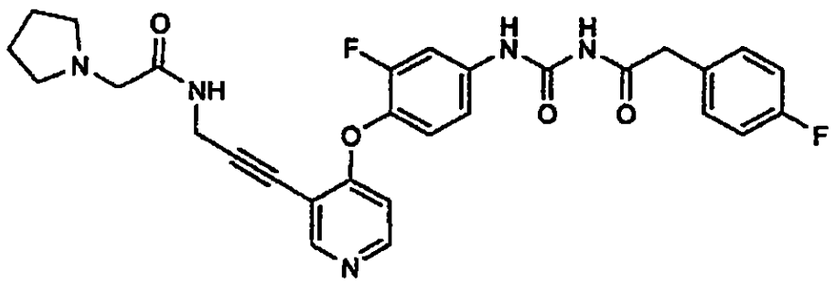
C) 1-(3-Fluoro-4-(3-(3-((3R,4R)-3-hidroxi-4-(pirrolidin-1-il)pirrolidin-1-il)prop-1-inil)piridin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)urea, sal de triclorhidrato

El compuesto del título se preparó a partir de (3R,4R)-1-(3-(4-(4-amino-2-fluorofenoxi)piridin-3 -il)prop-2-inil)-4-

(pirrolidin-1 -il)pirrolidin-3-ol (16 mg, 0.04 mmol) y una solución 0.3 M de isocianato de 2-(4-fluorofenil)acetilo en tolueno (Compuesto D del Ejemplo 11, 0.13 mL, 0.04 mmol) de una manera similar a aquella del Paso D del Ejemplo 33. El producto se purificó mediante HPLC preparativa (Columna A) se convirtió a la sal de clorhidrato de la misma manera que en el Paso E del Ejemplo 36, para dar el compuesto del título (9 mg, 33%) como un sólido blanco.

RMN-^{1}H (DMSO-d_6) δ 11.06(s, 1H), 10.62 (s, 1H), 8.86 (s, 1H), 8.45 (d, 1H. J = 6.1 Hz), 7.81 (d, 1H, J = 12.2 Hz), 7.45 - 7.40 (m, 4H), 7.33 - 7.28 (m, 4H), 7.16 (dd, 2H. J = 9.2, 8.6 Hz), 6.80 (d, 1H. J = 6.1 Hz), 4.64 (s, 1H), 4.34 (s, 2H). 3.84 - 3.70 (m, 4H), 2.70 - 3.55 (m, 2H). 3.55 - 2.98 (m, 3H), 2.08 - 1.92 (m, 2H), 1.92 - 1.75 (m, 2H); MS (ESI$^+$) : m/z 576.25(M + H)$^+$.

Ejemplo 42



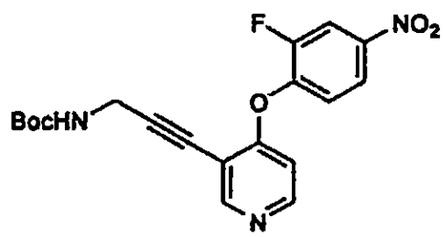
1-(3-Fluoro-4-(3-(3-(2-(pirrolidin-1-il)acetamido)prop-1-inil)piridin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)urea, sal de diclorhidrato

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A) N-Boc-propargilamina



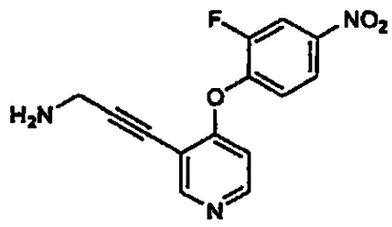
Dicarbonato de di-ter-butilo (21.8 mg, 100.0 mmol) se disolvió en THF (25 mL) y la solución se enfrió a 0°C y se trató gota a gota con una solución de propargilamina (Aldrich. 5.0 g, 90.0 mmol) manteniendo la temperatura debajo de 15 °C. La mezcla se agitó a temperatura ambiente por 1.5 h, luego se concentró a vacío. El residuo se disolvió en hexanos y se filtró a través de una Columna de gel de sílice utilizando 0-100% cloruro de metileno/hexanos para eluir el producto. El eluyente que contenía el producto se concentró a vacío para dar un aceite incoloro el cual se disolvió en hexanos (150 mL) y se enfrió a 0°C para dar cristales blancos. Los cristales se recolectaron mediante filtración y se secaron a vacío para dar el compuesto del título (10.5 g, 75%). RMN-^{1}H ($CDCl_3$) δ 4.75 (s, 1H), 3.95 (s, 2H), 2.25-2.24 (m, 1H), 1.48 (s, 9H).



B) 3-(4-(2-fluoro-4-nitrofenoxi) piridin-3-il) prop-2-

inilcarbamato de ter-butilo

El compuesto del título se preparó a partir de A-Boc-propargilamina (98 mg, 0.63 mmol) y 4-(2-fluoro-4-nitrofenoxi)-3-yodopiridina (Compuesto A del Ejemplo 33, 150 mg, 0.42 mmol) vía una reacción de acoplamiento cruzado de Sonagashira utilizando $Pd(Ph_3P)_4$ (9 mg, 0.008 mmol) y CuI (1.5 mg, 0.008 mmol) en Et_3N / THF 1:1 (3 mL) de acuerdo al Paso C del Ejemplo 35. El compuesto del título (124 mg. 76%) se obtuvo como un aceite rojo. RMN-^{1}H (DMSO-d_6) δ 8.66 (s, 1H), 8.50 (d, 1H, J = 5.6 Hz), 8.40 (dd, 1H,7 = 2.5, 10.7 Hz), 8.15 (d, 1H, J = 9.2 Hz), 7.52 (dd, 1H, J = 8.1, 8.6 Hz). 7.33-7.30 (m, 1H), 7.07 (d, 1H, J = 5.6 Hz), 3.95 (d, 2H, J = 5.6 Hz), 1.35 (s, 9H); MS(ESI$^+$): m/z 388.21 $(M + H)^+$.

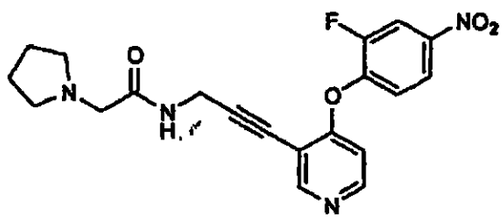


C) 3-(4-(2-Fluoro-4-nitrofenoxi)piridin-3-il)prop-2-in-1-amina

Una solución de 3-(4-(2-fluoro-4- nitrofenoxi)piridin-3-il)prop-2-inilcarbamato de ter-butilo (300 mg, 0.78 mmol) en cloruro de metileno (10 mL) se trató con TFA (2 mL) y se agitó a temperatura ambiente.por 45 min. La mezcla se concentró a vacío y el solución acuosa saturada de carbonato

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ácido de sodio. La fase de EtOAc se separó y se lavó con salmuera, se secó (sulfato de magnesio) y se concentró a vacío para dar el compuesto del título (180 mg, 80%) como un aceite rojo. RMN-^{1}H (DMSO-d_6) δ 8.65 (s, 1H), 8.47 (d, 1H, J = 5.6 Hz), 8.43 (dd, 1H, J = 10.7, 2.5 Hz), 8.17 (d, 1H, J = 8.6 Hz), 7.54 (t, 1H, J = 8.6 Hz), 7.04 (d, 1H, J = 5.6 Hz), 3.49 (s, 2H); MS (ESI$^+$) : m/z 288.17$(M + H)^+$.

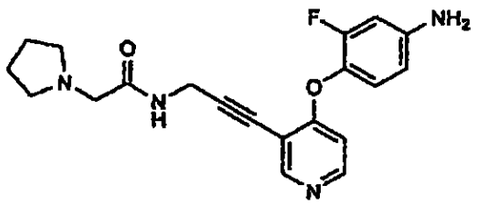


D) N-(3-(4-(2-Fluoro-4-nitrofenoxi)piridin-3-il)prop-2-inil)- 2-(pirrolidin-1-il)acetamida

Una solución de 3-(4-(2-fluoro-4- nitrofenoxi)piridin-3-il)prop-2-in-1-amina (80 mg, 0.26 mmol) en cloruro de metileno anhidro (2.5 mL) se enfrió a 0°C y se trató con cloruro de cloroacetilo (40 mg, 0.37 mmol) la mezcla se agitó a temperatura ambiente por 1 h. La mezcla se concentró a vacío para remover el solvente y el reactivo en exceso y el residuo se volvió a disolver en CH_3CN (1.5 mL), se trató con pirrolidona (55 mg, 0.78 mmol) y se agitó a temperatura ambiente por 4 h. La mezcla se dividió entre EtOAc y solución acuosa saturada de carbonato ácido de sodio y la fase orgánica se separó, se lavó con salmuera, se secó (sulfato de

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magnesio) y se concentró para dar el producto crudo. El residuo se purificó mediante cromatografía instantánea sobre gel de sílice eluyendo con 0-10% de McOH/ cloruro de metileno para proporcionar el compuesto del título (40 mg, 39%) como un aceite café. RMN-^{1}H (DMSO-d_6) δ 8.66 (s, 18), 8.50 (d, 1H J = 6.1 Hz), 8.41 (dd, 1H, J = 2. 8, 10.4 Hz), 8.18 - 8.15 (m, 2H), 7.51 (dd, 1H. J = 8.3, 8.8 Hz), 7.06 (d, 1H, J = 5.5 Hz) 4.10 (d, 2H, J = 5.5 Hz), 3.01 (s, 2H), 2.47 - 2.43 (m, 4H), 1.67 - 1.63 (m, 4H); MS (ESI$^+$) : m/z 399.27 $(M + H)^+$.



E) N-(3-(4-(4-Amino-2-fluorofenoxi)piridin-3-il)prop-2-inil)-2-(pirrolidin-1-il) acetamida

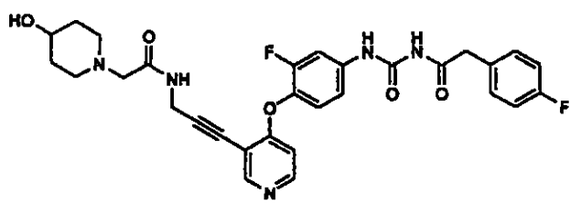
El compuesto del título se preparó mediante la reducción de N-(3-(4-(2-fluoro-4-nitrofenoxi)piridin-3-il)prop-2-inil)-2-(pirrolidin-1-il)acetamida (35 mg, 0.088 mmol) de una manera similar a aquella del Paso E del Ejemplo 35 utilizando polvo de hierro (67 mg, 1.21 mmol) y NH_4Cl (128 mg, 2.42 mmol). El producto se utilizó in reacciones subsecuentes sin ninguna purificación. Aceite amarillo (30 mg, 93%). MS (ESI$^+$): m/z 319.24$(M + H)^+$.

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F) 1-(3-Fluoro-4-(3-(3-(2-(pirrolidin-1-il) acetamido)prop-1-inil)piridin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)urea, sal de diclorhidrato

El compuesto del título se preparó a partir de N-(3-(4-(4-amino-2-fluorofenoxi)piridin-3-il)prop-2-inil)-2-(pirrolidin-1-il)acetamida (32 mg, 0.088 mmol) y solución 0.3 M de isocianato de 2-(4-fluorofenil)acetilo en tolueno (Compuesto D del Ejemplo 11, 0.40 ml, 0.12 mmol) utilizando THF (0.5 ml), de una manera similar a aquella del Paso D del Ejemplo 33. El producto se purificó mediante HPLC preparativa (Columna B). La fracción que contenía el producto se trató con ácido clorhídrico 1M en exceso, se concentró a vacío y se liofilizó para dar el compuesto del título (30 mg, 63%) como un sólido amarillo pálido. RMN-^{1}H (DMSO-d_6) δ 11.07 (s, 1H), 10.62 (s, 1H), 10.09 (s, 1H), 9.17-9.14 (m, 1H), 8.65 (s, 1H), 8.43 (d, 1H, J = 5.6 Hz), 7.81 (dd, 1H, J = 2.5, 12.7 Hz), 7.44 - 7.33 (m, 4H), 7.19 - 7.12 (m, 2H), 4.31 (d, 2H, J = 5.6 Hz), 4.05 (d, 2H. J = 5.6 Hz), 3.74 (s, 2H), 3.56 - 3.51 (m, 2H), 3.05 - 2.99 (m, 2H), 1.96 - 1.90 (m, 2H), 1.88 - 1.79 (m, 2H); MS (ESI$^+$) : m/z 548.26 $(M + H)^+$.

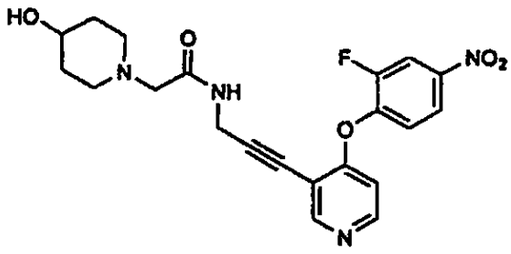
Ejemplo 43



1-(3-Fluoro-4-(3-(3-(2-(4-hidroxipiperidin-1-

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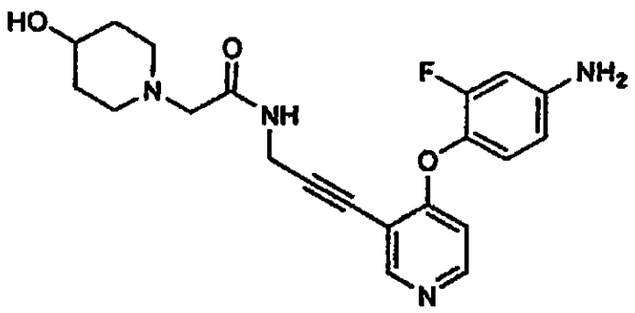
il)acetamido)prop-1-inil)piridin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)urea, sal de diclorhidrato



A) N-(3-(4-(2-Fluoro-4-nitrofenoxi)piridin-3-il)prop-2-inil)-2-(4-hidroxipiperidin-1-il)acetamida

El compuesto del título se preparó a partir de 3-(4-(2-fluoro-4-nitrofenoxi)piridin-3-il)prop-2-in-1-amina (Compuesto A del Ejemplo 36, 80 mg, 0.26 mmol), 4-hidroxipiperidina (79 mmol, 0.78 mmol) y cloruro de cloroacetilo (40 mg, 0.36 mmol) de la misma manera que para el Paso D del Ejemplo 42. El residuo se purificó mediante cromatografía instantánea sobre gel de sílice eluyendo con 1-3 de McOH/cloruro de metileno para dar una espuma blanca (40 mg, 36%). RMN-^{1}H (DMSO-d_6) δ 8.65 (s, 1H), 8.49 (d, 1H, J = 5.5 Hz), 8.41 (dd, 1H, J = 10.4, 2.7 Hz), 8.18 - 8.12 (m, 2H), 7.55-7.50 (m, 1H), 7.05 (d, 1H. J = 6.0 Hz), 4.54 (d, 1H, J = 3.8 Hz), 4.11 (d, 2H, J = 6.0 Hz), 3.43-3.36 (m, 1H), 2.86 (s, 2H), 2.64-2.58 (m, 2H), 2.12-2.05 (m, 2H), 1.67-1.61 (m, 2H), 1.44-1.36 (m, 2H); MS (ESI$^+$) : m/z 429.18 $(M + H)^+$.

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B) N-(3-(4-(4-Amino-2-fluorofenoxi)piridin-3-il)prop-2-inil)-2-(4-hidroxipiperidin-1-il)acetamida

El compuesto del título se preparó mediante la reducción N-(3-(4-(2-fluoro-4-nitrofenoxi)piridin-3-il)prop-2-inil)-2-(4-hidroxipiperidin-1-il)acetamida (33 mg, 0.077 mmol) de una manera similar a aquella del Paso E del Ejemplo 35 utilizando polvo de hierro (67 mg, 1.21 mmol), NH_4Cl (128 mg, 2.42 mmol). El producto (30 mg, 100%) se obtuvo como un aceite amarillo el cual se utilizó directamente en el paso subsiguiente. MS(ESI^+): m/z 399.27 $(M + H)^+$.

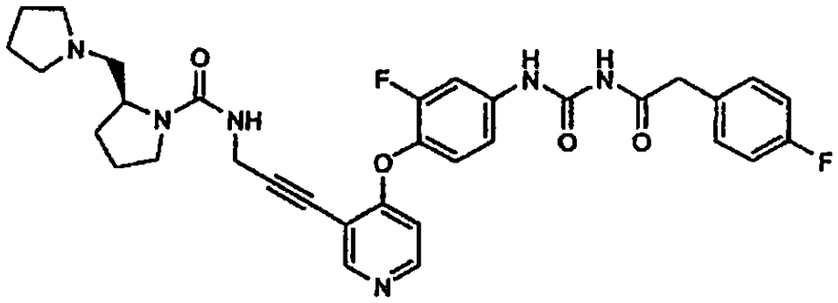
C) 1-(3-Fluoro-4-(3-(3-(2-(4-hidroxipiperidin-1-il)acetamido)prop-1-inil)piridin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)urea, sal de diclorhidrato

El compuesto del título se preparó a partir de N-(3-(4-(4-amino-2-fluorofenoxi)piridin-3-il)prop-2-inil)-2-(4-hidroxipiperidin-1-il)acetamida (25 mg, 0.063 mmol) y solución 0.3 M de isocianato de 2-(4-fluorofenil)acetilo en tolueno (Compuesto D del Ejemplo 11, 0.40 mL, 0.12 mmol) utilizando THF (0.5 ml), de una manera similar a aquella del

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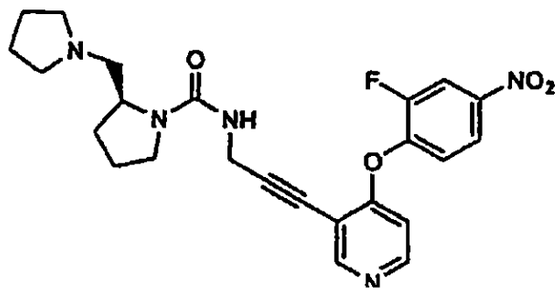
Paso D del Ejemplo 33. El producto se purificó mediante HPLC preparativa (Columna B). La fracción que contenía el producto se trató con ácido clorhídrico 1 N en exceso, se concentró y se liofilizó para dar el Compuesto del título (10 mg, 30%) como un sólido amarillo pálido. RMN-^{1}H (DMSO-d_6) δ 11.08 (s, 1H), 10.64 (s, 1H), 9.83-9.72 (m, 1H), 9.25 -9.20 (m, 1H), 8.66 (s, 1H), 8.45 (d, 1H, J = 6.1 Hz), 7.83 (dd, 1H, J = 2.0, 13.2 Hz), 7.46 - 7.35 (m, 3H), 7.21 - 7.11 (m, 2H), 6.77 (d, 1H, J = 6.1 Hz), 4.33 -4.31 (m, 2H), 3.99 - 3.94 (m, 2H), 3.92 - 3.89 (m, 1H), 3.76 (s, 2H), 3.46 - 3.40 (m,2H), 3.29-3.21 (m, 2H), 3.10-3.00 (m, 1H), 1.98 - 1.87 (m, 2H), 1.72-1.62 (m, 2H); MS (ESI$^+$) : m/z 528.25 $(M + H)^+$.

Ejemplo 44



(S)-1-(3-Fluoro-4-(3-(3-(2-(pirrolidin-1-ilmetil)pirrolidin-1-carboxamido)prop-1-inil)piridin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)urea, sal de diclorhidrato

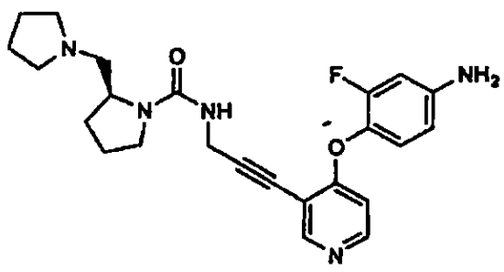
467 465



A) (S)-N-(3-(4-(2-Fluoro-4-nitrofenoxi)piridin-3-il)prop-2-inil)-2-(pirrolidin-1-ilmetil)pirrolidin-1-carboxamida

3-(4-(2-Fluoro-4-nitrofenoxi)piridin-3-il)prop-2-in-1-amina (Compuesto A del Ejemplo 36, 55 mg, 0.19 mmol) se disolvió en cloruro de metileno (5 mL), se trató con cloroformiato de 4-nitrofenilo (0.38 mg, 0.19 mmol) y piridina (15 µL, 0.19 mmol). La mezcla de reacción se agitó a TA. Después de 1 h, la mezcla se trató con Et_3N (30 mL, 0.20 mmol) y (S)-(+)-1-(2-pirrolidinilmetil)pirrolidona (Aldrich, 32 mg, 0.21 mmol) y se agitó a temperatura ambiente por 15 h. La mezcla se diluyó luego con cloruro de metileno (50 mL), se lavó con NaOH 1 M y salmuera, se secó ($MgSO_4$) y se concentró a vacío para dar el producto crudo. El residuo se purificó mediante cromatografía instantánea sobre gel de sílice eluyendo con 0-10 de McOH /cloruro de metileno para dar el compuesto del título (53 mg. 60%) como un aceite amarillo. RMN-^{1}H (DMSO-d_6) δ 8.65 (s, 1H). 8.49 (d, 1H, J = 6.1 Hz). 8.41 (dd, 1H, J = 2.8Hz, 10.5 Hz), 8.16 (d, 1H, J = 7.7 Hz), 7.52 (dd, 1H, J = 8.3, 8.8 Hz), 7.05 (d, 1H, J = 6.1 Hz),

4.11 -4.06 (m, 2H), 3.99 - 3.95 (m, 2H), 3.76 (s, 2H), 3.16 - 3.11 (m, 2H), 2.57 - 2.48 (m, 2H), 2.43 - 2.41 (m, 2H), 3.36 - 2.34 (m, 2H), 1.90 - 1.86 (m, 2H), 1.76 - 1.62 (m, 3H) : MS (ESI^+): m/z 468.27 $(M + H)^+$.



B) (S)-N-(3-(4-(4-Amino-2-fluorofenoxi)piridin-3-il)prop-2-inil)-2-(pirrolidin-1-ilmetil)pirrolidin-1-carboxamida

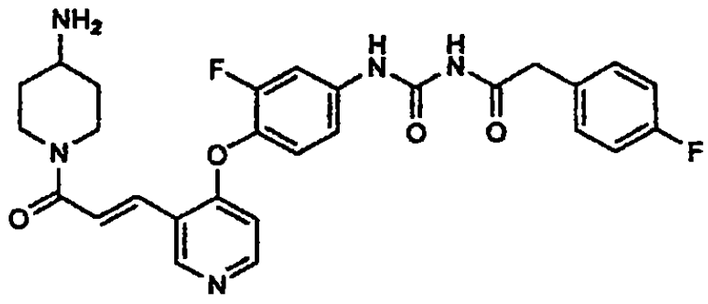
El compuesto del título se preparó mediante la reducción de (S)-N-(3-(4-(2-fluoro-4-nitrofenoxi)piridin-3- il)prop-2-inil)-2-(pirrolidin-1-ilmetil)pirrolidin-1-carboxamida (50 mg, 0.11 mmol) de una manera similar a aquella del Paso E del Ejemplo 35 utilizando Fe (polvo, 67 mg, 1.21 mmol), NH_4Cl (128 mg. 2.42 mmol). El producto (36 mg, 75%) se obtuvo como un aceite amarillo el cual se utilizó directamente en el paso subsiguiente. MS(ESI^+): m/z 438.30 $(M + H)^+$.

C) (S)-1-(3-Fluoro-4-(3-(3-(2-(pirrolidin-1-ilmetil)pirrolidin-1-carboxamido)prop-1-inil)piridin-4-iloxi)fenil)-3-(2-(4-fluorofenil) acetil)urea, sal de diclorhidrato

El compuesto del título se preparó a partir de (S)-N-(3-

(4-(4-amino-2-fluorofenoxi)piridin-3-il)prop-2-inil)-2-(pirrolidin-1-ilmetil)pirrolidin-1-carboxamida (36 mg, 0.057 mmol) y solución 0.3 M de isocianato de 2-(4-fluorofenil)acetilo en tolueno (Compuesto D del Ejemplo 11, 0.37 mL, 0.11 mmol) de la misma manera que en el Paso D del Ejemplo 33. El producto se purificó mediante HPLC preparativa (Columna B) y se convirtió a su clorhidrato de acuerdo al Paso C del Ejemplo 43 para dar el compuesto del título (10 mg, 25%) como un aceite de color ámbar. RMN-^{1}H (DMSO-d_6) δ 11.06 (s, 1H), 10.60 (s, 1H), 9.56 (s, 1H), 8.58 (s, 1H), 8.38 (d, IH, J = 5.6 Hz), 7.80 (dd, 1H, J = 2.6. 12.7 Hz), 7.42 (dm, 1H, J = 10.6 Hz), 7.38-7.31 (m, 2H), 7.30-7.25 (m, 1H), 7.20-7.10 (m,2H), 6.69 (d, 1H, J = 6.1 Hz), 4.26-4.12 (m, 2H), 3.79-3.69 (m, 3H), 3.56 (s, 2H), 3.31-3.18 (m, 2H), 3.17-2.93 (m, 2H), 2.14-2.02 (m, 4H), 2.03-1.76 (m,5H), 1.71-1.61 (m, 1H); MS(ESI$^+$): m/z 617.20 $(M + H)^+$.

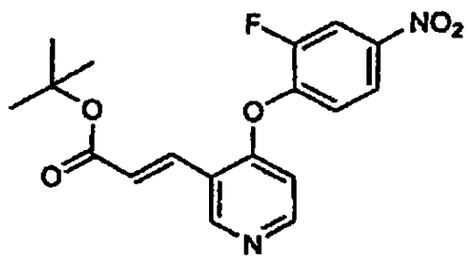
Ejemplo 45



(E)-1-(4-(3-(3-(4-Aminopiperidin-1-il)-3-oxoprop-1-enil)piridin-4-iloxi)-3-fluorofenil)-3-(2-(4-

47 468.

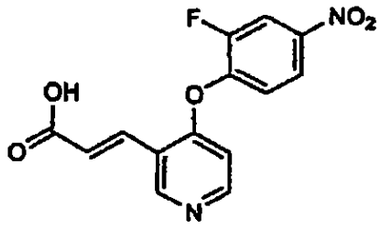
fluorofenil)acetil)urea, sal del ácido ditrifluoroacético



A) 3-(4-(2-fluoro-4-nitrofenoxi)piridin-3-il)acrilato de (E)-ter-butilo

Una mezcla de 4-(2-fluoro-4-nitrofenoxi)-3- yodopiridina (Compuesto A del Ejemplo 33, 150 mg, 0.42 mmol), ter-butilacrilato (Aldrich, 107 mg, 0.84 mmol), tri-n-butilamina (0.21 mL. 0.92 mmol) y DMF (2 mL) se desgasificó mediante vacío/purga de argón y luego se trató con $Pd(OAc)_2$ (17 mg, 0.078 mmol). La mezcla se calentó a 100-130 °C bajo argón por 45 min, luego la mezcla se enfrió a temperatura ambiente, se dividió entre EtOAc y solución acuosa saturada de carbonato ácido de sodio. Las fases se separaron y los extractos de EtOAc se lavaron con solución acuosa saturada de carbonato ácido de sodio y salmuera, se secó (sulfato de magnesio) y se concentró a vacío. El producto crudo se purificó mediante cromatografía instantánea sobre SiO_2 eluyendo con 0-20 de EtOAc /cloruro de metileno para dar el compuesto del título (118 mg, 78%) como un aceite amarillo pálido el cual solidificó a temperatura ambiente. RMN-^{1}H (DMSO-d_6) δ 9.02 (s, 1H), 8.49 (d, 1H, J = 5.5 Hz), 8.46 (dd, 1H, J = 2.5, 11.7

Hz), 8.21 (dm, 1H, J = 9.2 Hz), 7.74 (d, 1H, J = 16.3 Hz). 7.65 (dd, 1H, J = 8. 1, 8.6 Hz), 6.95 (d, 1H, J = 6.1 Hz), 6.77 (d, 1H, J = 16.3 Hz), 1.47 (s, 9H); MS (ESI^+) : m/z 361.15 $(M + H)^+$.

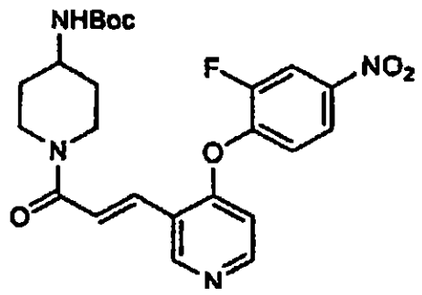


B) ácido (E)-3-(4-(2-Fluoro-4-nitrofenoxi)piridin-3-il)acrílico

3-(4-(2-fluoro-4-nitrofenoxi)piridin-3-il)acrilato de (E)-ter-butilo (115 mg, 0.32 mmol) se trató con TFA/cloruro de metileno 1:1 (6 mL) y se agitó a temperatura ambiente por 1.5 h. La mezcla se concentró a vacío y el residuo se trató con McOH (5 mL) y HCl 2 M/Et_2O (15 mL) y se concentró a vacío.

Un segundo tratamiento con McOH (5 mL) y 2 M HCl/Et_2O (15 mL) y reconcentración dio el compuesto del título (120 mg).

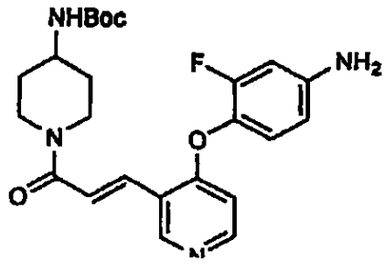
RMN-^{1}H (DMSO-d_6) o 9.17 (s, 1H). 8.62 (d, 1 H, J = 6.6 Hz), 8.50 (dd, 1H.J = 2. 6, 10.1 Hz), 8.25 (d, 1H, J = 9.1 Hz), 7.78 (d, 1H, J = 16.3 Hz), 7.74 (dd, 1H, J = 8.1, 8.6 Hz), 7.17 (d, 1H, J = 6.1 Hz). 6.87 (d, 1H, J = 16. 3Hz); MS (ESI^+) : m/z 305.11 $(M + H)^+$.



C) 1-(3-(4-(2-fluoro-4-nitrofenoxi) piridin-3-il)acriloil)piperidin-4-ilcarbamato de (E)-ter-butilo

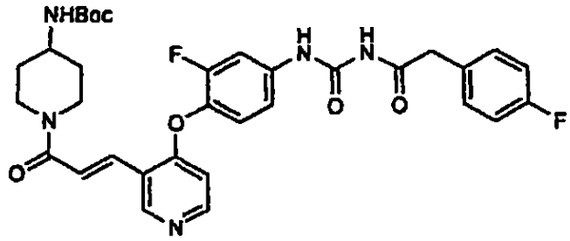
Una solución de ácido (E)-3-(4-(2-fluoro-4-nitrofenoxi)piridin-3-il')acrílico (143 mg. 0.42 mmol), 4-N-Boc-aminopiperidina (Aldrich, 84 mg, 0.42 mmol) en DMF (1.5 mL) se trató con DIPEA (160 µL, 0.92 mmol), y TBTU (160 mg, 0.50 mmol) y la mezcla se agitó a temperatura ambiente por 2 h. La mezcla se diluyó con EtOAc, se lavó con solución acuosa saturada de carbonato ácido de sodio y salmuera, se secó (sulfato de magnesio) y se concentró a vacío. El producto crudo se purificó mediante cromatografía instantánea sobre gel de sílice eluyendo primeramente con 30-100 % de EtOAc/hexanos luego 5 % de MeOH /cloruro de metileno para dar el compuesto del título (110 mg, 54%) como un sólido café claro. RMN-^{1}H (DMSO-d_6) δ 9.15 (s, 1H), 8.48 (d, 1H, J = 5.6 Hz), 8.44 (dd, 1H, J = 2.5, 10.5 Hz), 8.18 (d, 1H, J = 9.2 Hz), 7.69 (d, 1H, J = 15.3 Hz), 7.58 (dd, 1H, J = 8. 6, 8.6 Hz), 7.50 (d, 1H, J = 15.7 Hz), 6.97 (d, 1H, J = 5.6 Hz), 6.89 (d, 1H. J = 7.6 Hz), 4.31 -4.16 (m, 2H), 3.55 -3.46 (m, 1H), 3.20-3.14 (m, 1H), 2.83-2.81 (m, 1H), 1.82-1.71 (m, 2H),

1.34-1.18 (m, 2H). 1.37 (s, 9H); MS(ESI$^+$): m/z 431.04 (100) [(M-C_4H_9)$^+$H]$^+$; m/z 487.10 (90) (M + H)$^+$.



D) 1-(3-(4-(4-amino-2-fluorofenoxi) piridin-3-0 il)acriloil)piperidin-4-ilcarbamato de (E)-ter-butilo

El compuesto del título se preparó mediante la reducción de 1-(3-(4-(2-fluoro-4-nitrofenoxi)piridin-3-il)acriloil)piperidin-4-ilcarbamato de (E)-ter-butilo (100 mg, 0.21 mmol) de una manera similar a aquella del Paso E del Ejemplo 35 utilizando polvo de hierro (55 mg, 2.7 mmol), cloruro de amonio (280 mg, 5.3 mmol). El producto (90 mg, 95%) se obtuvo como un sólido café claro el cual se utilizó directamente en el paso subsiguiente. MS (ESI$^+$) : m/z 457.18(M + H)$^+$.



E) 1-(3-(4-(2-fluoro-4-(3-(2-(4-fluorofenil)acetil)ureido)fenoxi)piridin-3-

477 472

il)acriloil)piperidin-4-ilcarbamato de (E)-ter-butilo

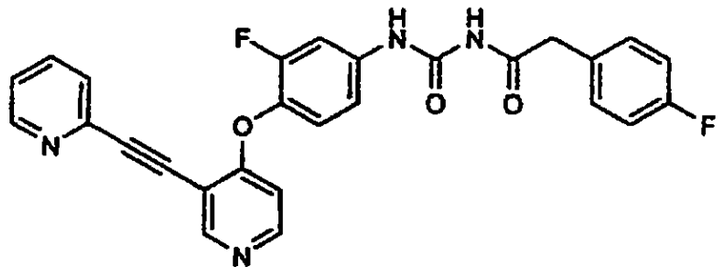
El compuesto del título se preparó a partir de 1-(3-(4-(4-amino-2-fluorofenoxi)piridin-3- il)acriloil)piperidin-4-ilcarbamato de (E)-ter-butilo (42 mg, 0.092 mmol) y solución 0.3 M de isocianato de 2-(4-fluorofenil)acetilo en tolueno (Compuesto D del Ejemplo 11, 0.50 mL, 0.15 mmol) de una manera similar a aquella del Paso D del Ejemplo 33. El producto crudo se adsorbió sobre gel de sílice y se purificó mediante cromatografía instantánea eluyendo con 0-5 de MeOH/EtOAc para dar el producto (20 mg. 33%) como un sólido blanco. RMN-^{1}H (DMSO-d_6) δ 11.05 (s, 1H). 10.59 (s, 1H), 9.03 (s, 1H), 8.37 (d, 1H, J = 5.6 Hz), 7.82-7.74 (m, 2H), 7.47 (d, 1H, J = 15.8 Hz), 7.42-7.33 (m, 4H). 7.20-7.13 (m, 2H), 6.89 (d, 1H, J = 8.1 Hz), 6.63 (d, 1H, J = 5.6 Hz), 4.31 (d m, J = 13.7 Hz), 4.19 (d 1H, J = 12.7 Hz), 3.74 (s, 2H), 3.56-3.47 (m, 1H), 3.22-3.13 (m, 1H), 2.84-2.76 (m, 1H), 1.76 (s, 2H), 1.37 (s, 9H), 1.32-1.20 (m, 2H); MS (ESI^+) : m/z 636.23 $(M + H)^+$.

F) (E)-1-(4-(3-(3-(4-Aminopiperidin-1-il)-3-oxoprop-1-enil)piridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea, sal del ácido ditrifluoroacético

1-(3-(4-(2-fluoro-4-(3-(2-(4-fluorofenil)acetil)ureido)fenoxi)piridin-3-il)acriloil)piperidin-4-ilcarbamato de (E)-ter-butilo (15 mg, 0.024 mmol) se disolvió en MeOH anhidro (0.5 mL), se trató

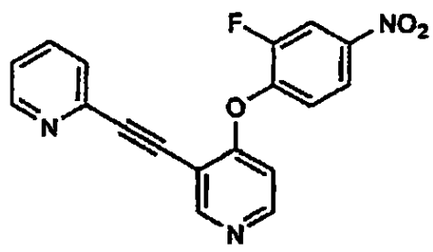
con HCl 4M/1,4-dioxano (1.5 mL) y se agitó a temperatura ambiente por 1 h. La mezcla se concentró a vacío para dar el producto crudo el cual se purificó mediante HPLC preparativa (Columna A). La fracción que contenía el producto se trató con ácido clorhídrico 1M en exceso, se concentró y se liofilizó para dar el compuesto del título (8 mg, 44%) como un sólido amarillo pálido. RMN-^{1}H (DMSO-d_6) S 11.07 (s, 1H), 10.61 (s, 1H), 9.10 (s, 1H), 8.44 (s, 1H), 7.91 (m, 3H), 7.86-7.69 (m, 2H), 7.55-7.28 (m, 5H), 7.23-7.08 (m, 2H), 6.80-6.72 (m, 1H), 5.61-5.33 (m, 1H), 4.45-4.20 (m, 2H), 3.74 (s, 2H), 3.39-3.07 (m, 2H), 2.82-2.68 (m, 1H), 1.91-1.51 (m, 5 2H), 1.50-1.15 (m, 1H); MS (ESI$^+$) : m/z 536.16 $(M + H)^+$.

Ejemplo 46



1-(3-Fluoro-4-(3-(2-(piridin-2-il)etinil)piridin-4-iloxi)fenil)-3-(2-(4-fluorofenil) acetil) urea, sal de diclorhidrato

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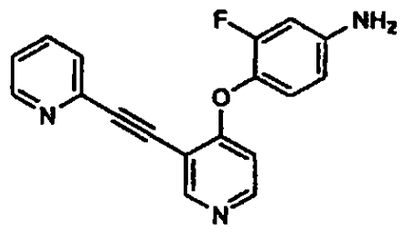


A) 2-(2-(4-(2-Fluoro-4-nitrofenoxi)piridin-3-il)etinil)piridina

Una mezcla de 4-(2-fluoro-4-nitrofenoxi)-3-yodopiridina (Compuesto A del Ejemplo 33, 50 mg, 0.14 mmol) y 2-etinilpiridina (Aldrich, 57 mg, 0.54 mmol), THF (1 mL) y Et_3N (1 mL) se desgasificó mediante vacío/purga con argón y se trató a su vez con CuI (3 mg. 0.016 mmol) y $(Ph_3P)_4Pd$ (10. mg, 0.009 mmol). La mezcla se calentó a 60 °C 45 minutos, se enfrió, se dividió entre EtOAc y solución acuosa saturada de carbonato ácido de sodio y la fase de EtOAc se secó (sulfato de magnesio) y se concentró a vacío para dar el producto crudo. La purificación del residuo mediante cromatografía instantánea en Columna sobre SiO_2 eluyendo con 0-1.5 de McOH/cloruro de metileno dio el compuesto del título (42 mg, 89%) como un sólido café.

RMN-^{1}H (DMSO-d_6) δ 8.91 (s, 1H), 8.60 (d, IR J = 4.5 Hz), 8.45 (dd, 1H, J = 2.6. 10.7 Hz), 8.19 (d, 1H, J = 9.1 Hz), 7.86-7.83 (m, 1H), 7.66 (dd, 1H, J = 8.7. 8.7 Hz), 7.57 (d, 1H, J = 7.6 Hz), 7.45 -7.42 (m, 2H), 7.14 (d, 1H, J = 4.5 Hz); MS(ESI$^+$): m/z 336.20 $(M + H)^+$.

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B) 3-Fluoro-4-(3-(2-(piridin-2-il)etinil)piridin-4-iloxi)bencenamina

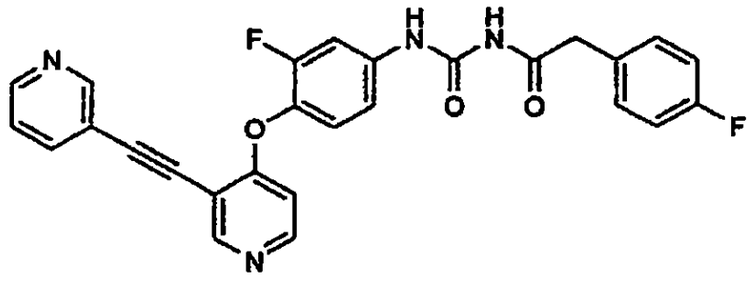
El compuesto del título se preparó a partir de 2-(2-(4-(2-fluoro-4-nitrofenoxi)piridin-3-il)etinil)piridina (30 mg, 0.090 mmol) de una manera similar a aquella del Paso E del Ejemplo 35 para dar el compuesto del título (20 mg) como un sólido café. MS(ESI$^+$): m/z 306.20 $(M + H)^+$.

C) 1-(3-Fluoro-4-(3-(2-(piridin-2-il)etinil)piridin-4-iloxi)fenil)-3-(2-(4-fluorofenil) acetil) urea, sal de diclorhidrato

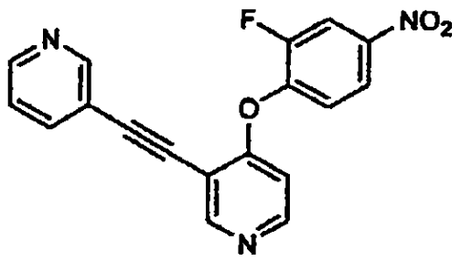
El compuesto del título se preparó a partir de 3-fluoro-4-(3-(2-(piridin-2-il)etinil)piridin-4-iloxi)bencenamina (19 mg, 0.062 mmol) y solución 0.3 M de isocianato de 2-(4-fluorofenil)acetilo en tolueno (Compuesto D del Ejemplo 11, 0.50 mL. 0.15 mmol) de una manera similar a aquella del Paso D del Ejemplo 33. La purificación de la mezcla de reacción mediante cromatografía instantánea sobre SiO_2 eluyendo con 0-100 % de EtOAc /cloruro de metileno dio un sólido blanco el cual se convirtió al clorhidrato de una

manera similar al Paso D del Ejemplo 33, para dar el compuesto del título (19 mg. 60%) como un sólido blanco. RMN-^{1}H (DMSO-d_6) δ 11.07 (s, 1H), 10.61 (s, 1H), 8.79 (s, 1H), 8.63 (d, 1H, J = 5.6 Hz), 8.47 (d, 1H, J = 5.6 Hz), 7.89 - 7.86 (m, 1H), 7.83 (dd, 1H, J = 1.5, 12.7 Hz), 7.67 (d, 1H. J = 7.6 Hz), 7.47 - 7.43 (m, 2H), 7.39 - 7.35 (m, 1H), 7.30 - 7.27 (m, 1H), 7.20 - 7.16 (m, 2H), 7.14-7.10 (m, 1H), 6.77 (d, 1H, J = 5.6 Hz), 3.75 (s, 2H); MS (ESI$^+$) : m/z 485.17 (M + H)$^+$.

Ejemplo 47



1-(3-Fluoro-4-(3-(2-(piridin-3-il)etinil)piridin-4-iloxi)fenil)-3-(2-(4-fluorofenil) acetil) urea, sal de diclorhidrato

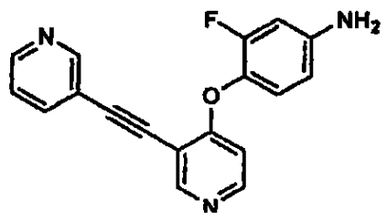


A) 3(2-(4-(2-Fluoro-4-nitrofenoxi)piridin-3-

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il)etinil)piridina

Una mezcla de 4-(2-fluoro-4-nitrofenoxi)-3-yodopiridina (Compuesto A del Ejemplo 33, 50 mg, 0.14 mmol) y 3-etinilpiridina (57 mg, 0.54 mmol), THE (1 mL) y Et_3N (1 mL) se desgasificó mediante vacío/purga con argón y se trató a su vez con CuI (3 mg, 0.016 mmol), y $(Ph_3P)_4Pd$ (10 mg, 0.009 mmol). La mezcla se calentó a 60°C 45 minutos, se enfrió, se dividió entre EtOAc y solución acuosa saturada de carbonato ácido de sodio y la fase de EtOAc se secó (sulfato de magnesio) y se concentró a vacío. La purificación del residuo mediante cromatografía instantánea sobre SiO_2 eluyendo con 0-1.5 de McOH/cloruro de metileno dio el compuesto del título (33 mg, 77%) como un sólido café. RMN-^{1}H (DMSO-d_6) δ 8.86 (s, 1H), 8.65 (s, 1H), 8.61 - 8.57 (m, 2H), 8.45 (dd, IR J = 2.6, 10.7 Hz), 8.18 (d, 1H, J = 9.2 Hz), 7.90 (d, 1H, J = 9.2 Hz), 7.62 (dd, 1H, J = 8.7, 8.7 Hz). 7.46 (dd, 1H, J = 4.6, 8.1 Hz), 7.17 (d, 1H. J = 5.6 Hz); MS (ESI+) : m/z 336.19 $(M + H)^+$.



B) 3-Fluoro-4-(3-(2-(piridin-3-il)etinil)piridin-4-iloxi)bencenamina

El compuesto del título se preparó a partir de 3 -(2-(4-

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(2-fluoro-4-nitrofenoxi)piridin-3-il)etinil)piridina (30 mg, 0.090 mmol) de una manera similar al Paso E del Ejemplo 35 para dar el compuesto del título como un sólido café (25 mg, 93%). MS (ESI^+) : m/z 306.20 $(M + H)^+$.

c) 1-(3-Fluoro-4-(3-(2-(piridin-3-il)etinil)piridin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil) urea, sal de diclorhidrato

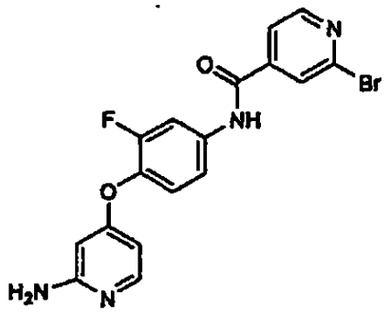
El compuesto del título se preparó a partir de 3-fluoro-4-(3-(2-(piridin-3-il)etinil) piridin-4-iloxi)bencenamina (22 mg, 0.072 mmol) y solución 0.3 M de isocianato de 2-(4-fluorofenil)acetilo en tolueno (Compuesto D del Ejemplo 11. 0.50 mL. 0.15 mmol) de una manera similar al Paso D del Ejemplo 33.

La purificación de la mezcla de reacción mediante cromatografía instantánea en Columna sobre SiO_2 eluyendo con 0-100 de EtOAc/cloruro de metileno dio un sólido blanco el cual se convirtió al clorhidrato de una manera similar al Paso D del Ejemplo 33, para dar el compuesto del título (15 mg, 38%) como un sólido blanco.

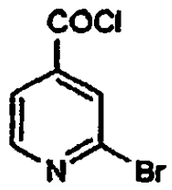
RMN-^{1}H (DMSO-d_6) δ 11.04 (s, 1H), 10.59 (s, 1H), 8.76 (s, 1H), 8.74 (d, 1H. J = 1.1 Hz). 8.60 (dd, 1H, J = 5. 6, 1.1 Hz), 8.45 (d, 1H, J = 6.1 Hz), 7.98 (d, 1 H, J = 7.7 Hz), 7.80 (d, 1H, J = 12.1 Hz), 7.47 - 7.45 (m, 1H), 7.41 (s, 2H), 7.36-7.34 (m, 2H), 7.16 (dd, 2H, J = 8.8, 8.9 Hz), 6.78 (d, 1H, J = 5.5 Hz), 3.74 (s, 2H); MS (ESI^+) : 485.13 m/z.

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Ejemplo 48



N-(4-(2-Aminopiridin-4-iloxi)-3-fluorofenil)-2-bromoisonicotinamida sal del ácido trifluoroacético



A) Cloruro 2-bromo-isonicotinicacilo

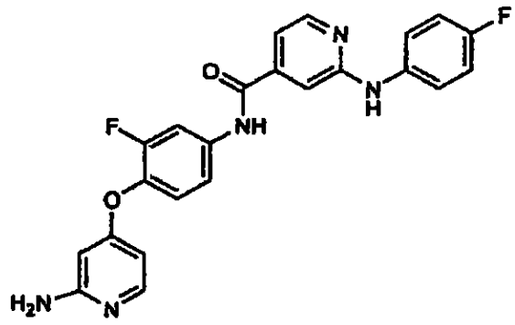
Una solución de ácido 2-bromo-isonicotínico (Lancaster, 70 mg, 0.34 mmol) en cloruro de tionilo (1.2 mL) se calentó a reflujo temperatura por 1.5 h. La mezcla se concentró y el producto crudo de cloruro de 2-bromoisonicotinoilo se utilizó directamente en el siguiente paso sin purificación adicional.

B) N-(4-(2-Aminopiridin-4-iloxi)-3-fluorofenil)-2-bromoisonicotinamida

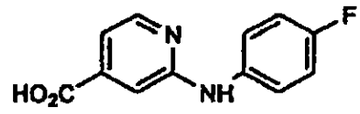
Al residuo anterior se agregó una solución de 4-(4-amino-2-fluorofenoxi)piridin-2-amina (Compuesto B del Ejemplo 24, 70 mg, 0.32 mmol) en cloruro de metileno (3 mL) a TA, y la reacción se agitó por 1 h. La mezcla de reacción se

concentró y el residuo se purificó mediante HPLC preparativa para obtener el compuesto del título (75 mg, 45 %) como un sólido amarillo (sal de TFA). RMN-^{1}H (DMSO-d_6) δ 11.03 (s, 1H). 8.62 (d, 1H, J = 5.0 Hz), 8.17 (s, 1 H), 7.89-8.04 (m, 4H), 7.71 (d, 1H. J = 8.8 Hz), 7.51 (t, 1H, J = 9.3 Hz), 6.72 (dd, 1H, J = 7.1. 2.2 Hz), 6.18 (d, 1H, J = 2.2 Hz); MS (ESI+) m/z 403, 405 $(M + H)^+$.

Ejemplo 49



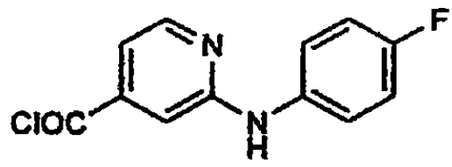
N-(4-(2-Aminopiridin-4-iloxi)-3-fluorofenil)-2-(4-fluorofenilamino)isonicotinamida, sal del ácido bis-trifluoroacético



A) Ácido 2-(4-fluorofenilamino)isonicotínico

A una mezcla de ácido 2-fluoro-isonicotínico (Aldrich. 423 mg, 3.0 mmol) y 4-fluoroanilina (555 mg, 5.0 mmol) en DMF (18 mL) a temperatura ambiente se agregó NaH (500 mg de 60%

en aceite), y la mezcla se calentó a 85°C por 75 min. Se agregó ácido acético (0.7 mL) a la mezcla de reacción y se concentró a vacío. Al residuo se agregaron EtOAc (100 mL) y agua (20 mL), se agitó por 20 min y el sólido se filtró, se lavó con EtOAc y se secó para obtener el producto deseado (600 mg. 50 %) como un sólido tostado. RMN-^{1}H (DMSO-d_6) δ 8.98 (s, 1H), 8.43 (s, 1H). 8.04 (d, 1H. J 4.9 Hz). 7.69 (dd, 2H, J = 8.8, 4.9 Hz), 7.24 (s, 1H), 7.05 (dd, 2H. J = 8.2. 6.0 Hz); MS(ESI$^+$) m/z 233.3 $(M + H)^+$.



B) cloruro de 2-(4-fluorofenilamino)isonicotinicacilo

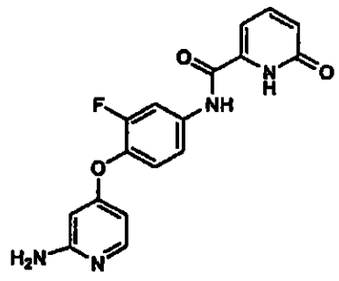
Una mezcla de ácido 2-(4-fluorofenilamino)isonicotínico (464 mg, 2.0 mmol) y cloruro de tionilo (10 mL) se calentó a temperatura de reflujo por 2 h. La reacción se concentró a vacío, y el producto crudo se utilizó directamente en el siguiente paso.

C) N-(4-(2-Aminopiridin-4-iloxi)-3-fluorofenil)-2-(4-fluorofenilamino) isonicotinamida

Una solución de 4-(4-amino-2-fluorofenoxi)piridin- 2-amina (Compuesto B del Ejemplo 24, 450 mg. 2.1 mmol) en 1,2-dicloroetano (10 mL) se agregó lentamente a una solución de

cloruro acilo obtenido anteriormente en 1,2-dicloroetano (10 mL) en un baño de hielo con agitación. La mezcla de reacción se dejó reposar a temperatura ambiente toda la noche. A la mezcla de reacción se agregaron EtOAc (150 mL) y solución acuosa saturada de carbonato ácido de sodio (50 mL). La capa de EtOAc se separó, se secó sobre sulfato de magnesio y se concentró a vacío. El residuo se purificó mediante HPLC preparativa para obtener el compuesto del título (69 mg, 6.3 %) como un sólido amarillo (Sal de bis-TFA). RMN-^{1}H (DMSO-d_6) δ 10.90 (s, 1H), 9.32 (s, 1H), 8.27 (d, 1H, J = 5.5 Hz), 7.92-7.07 (m, 11H), 6.68 (dd, 1H, J = 7.1, 2.2 Hz), 6.10 (d, 1H. J = 2.2 Hz); MS (ESI$^+$) m/z 217.9 $(M + H)^+$.

Ejemplo 50

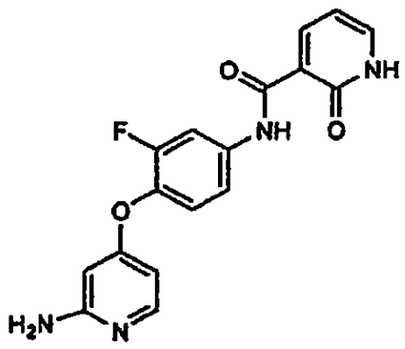


N-(4-(2-Aminopiridin-4-iloxi)-3-fluorofenil)-6-oxo-1,6-dihidropiridin-2-carboxamida, sal del ácido trifluoroacético

A una solución de ácido 6-hidroxipicolínico (Aldrich. 28 mg, 0.20 mmol) y HOBt (28 mg. 0.21 mmol) en DMF (2 mL) a temperatura ambiente se agregó EDCI.HCl (50 mg, 0.26 mmol) seguido por 4-(4-amino-2-fluorofenoxi)piridin-2-amina

(Compuesto B del Ejemplo 24. 42 mg. 0.19 mmol), y la mezcla de reacción se agitó toda la noche a TA. La purificación de la mezcla de reacción mediante HPLC preparativa proporcionó el producto deseado (24 mg, 25 %) como un sólido café claro (Sal de TFA). RMN-^{1}H (DMSO-d_6) δ 8.03 (dd, 1H, J = 12.6. 2.2 Hz), 7.79-7.36 (m, 5H), 6.85 (d, 1H, J = 8.8 Hz), 6.67 (dd, 1H, J = 7.2, 4.4 Hz), 6.22 (d, 1H. J = 2.2 Hz); MS(ESI$^+$) m/z 341.3 $(M + H)^+$.

Ejemplo 51

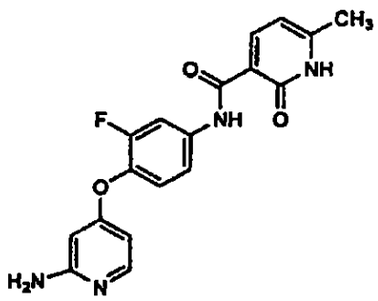


N-(4-(2-aminopiridin-4-iloxi)-3-fluorofenil)-2-oxo-1,2-dihidropiridin-3-carboxamida, sal del ácido trifluoroacético

A una solución de ácido 2-hidroxinicotínico (Aldrich, 42 mg, 0.30 mmol) y HOBt (18 mg) en DMF (2 mL) a temperatura ambiente se agregó EDCI.HCl (80 mg, 0.42 mmol) seguido por 4-(4-amino-2-fluorofenoxi)piridin-2-amina (Compuesto B del Ejemplo 24, 65 mg, 0.30 mmol), y la mezcla de reacción se agitó por 20 h a temperatura ambiente. Purificación de la mezcla de reacción mediante HPLC preparativa proporcionó el

producto deseado (70 mg, 49 %) como un sólido beige (Sal de TFA). RMN-^{1}H (CD_3OD) δ 8.59 (dd, 1H, J = 7. 1, 2.2 Hz), 8.03 (dd, 1H. J = 12.6, 2.2 Hz), 7.83 (d, 1H, J = 7.7 Hz), 7.75 (dd, 1H. J = 6. 6, 2.2 Hz), 7.44 (d, 1H, J = 8.8 Hz), 7.32 (t, 1H, J = 8.8 Hz), 6.67 (m, 2H), 6.21 (d, 1H, J = 2.2 Hz); MS (ESI^+) m/z 341.2 $(M + H)^+$.

Ejemplo 52

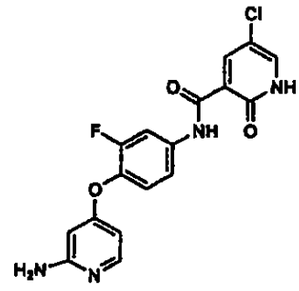


N-(4-(2-Aminopiridin-4-iloxi)-3-fluorofenil)-6-metil-2-oxo-1,2-dihidropiridin-3-carboxamida, sal del ácido trifluroacético

A una solución de ácido 2-hidroxi-6-metilnicotínico (Lancaster, 72 mg, 0.47 mmol) y HOBt (50 mg) en DMF (5 mL) a temperatura ambiente se agregó EDCI.HCl (130 mg, 0.68 mmol) seguido por 4-(4-amino-2-fluorofenoxi)piridin-2-amina (Compuesto B del Ejemplo 24, 110 mg, 0.50 mmol), y la mezcla de reacción se agitó a temperatura ambiente por 72 h. La purificación de la mezcla de reacción mediante HPLC preparativa proporcionó el producto deseado (125 mg. 55 %) como un sólido beige (Sal de TFA). RMN-^{1}H (CD_3OD) δ 8.46 (d,

1H, J = 7.9 Hz), 8.03 (dd, 1H, J = 12.7, 2.8 Hz), 7.83 (d, 1H, J = 7. 1Hz), 7.44 (dd, 1H, J = 8. 8, 2.2 Hz), 7.33 (t, 1H, T = 8.8 Hz), 6.67 (dd, 1H, J = 7.7, 2.7 Hz), 6.45 (d, 1H, J = 7.7 Hz), 6.21 (d, 1H, J = 2.8 Hz), 2.40 (s, 3H); MS (ESI$^+$) m/z 355.2 $(M + H)^+$.

Ejemplo 53

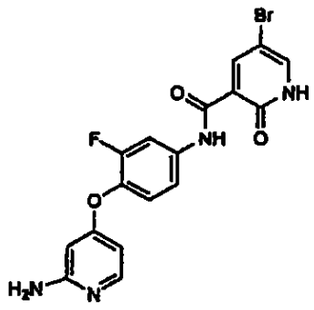


N-(4-(2-Aminopiridin-4-iloxi)-3-fluorofenil)-5-cloro-2-oxo-1,2-dihidropiridin-3-carboxamida, sal del ácido trifluroacético

A una solución del ácido 2-hidroxi-5-cloronicotínico (Avocado, 87 mg, 0.50 mmol) y HOBt (40 mg) en DMF (4 mL) a temperatura ambiente se agregó EDCI.HCl (130 mg, 0.68 mmol) seguido por 4-(4-amino-2-fluorofenoxi)piridin-2-amina (Compuesto B del Ejemplo 24. 110 mg. 0.50 mmol), y la mezcla de reacción se agitó por 72 h. La purificación de la mezcla de reacción mediante HPLC preparativa proporcionó el producto deseado (115 mg, 45 %) como un sólido beige (Sal de TFA). RMN-^{1}H (CD_3OD) δ 8.50 (d, 1H, J = 3.3 Hz), 8.03 (dd, 1H, J = 12.6, 2.1 Hz). 7.84 (m, 2H). 7.46 (d, IR J = 8.8 Hz). 7.34

(t, 1H, J = 8.8 Hz), 6.67 (dd, 1H. J = 7.2. 2.2 Hz), 6.21 (d, IR J = 2.2 Hz); MS (ESI^+) m/z 375.1, 377.1 $(M + H)^+$.

Ejemplo 54

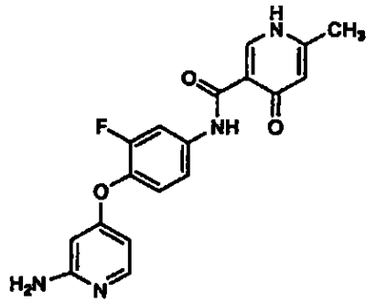


N-(4-(2-Aminopiridin-4-iloxi)-3-fluorofenil)-5-bromo-2-oxo-1,2-dihidropiridin-3-carboxamida, sal del ácido trifluoroacético

A una solución del ácido 2-hidroxi-5-bromo-nicotínico (147 mg, 0.67 mmol, Sin. Comm. 1989,19. 553-559) y HOBt (30 mg) en DMF (4 mL) a temperatura ambiente se agregó EDCI.HCl (160 mg. 0.83 mmol) seguido por 4-(4-amino-2-fluorofenoxi)piridin-2-amina (Compuesto B del Ejemplo 24, 147 mg, 0.67 mmol), y la mezcla de reacción se agitó a temperatura ambiente toda la noche. La purificación de la mezcla de reacción mediante HPLC preparativa proporcionó el compuesto del título (120 mg, 33 %) como un sólido beige (Sal de TFA). RMN-^{1}H (DMSO-d_6) δ 13.22 (s, 1H), 12.23 (s, 1H), 8.40 (d, 1H, J = 2.8 Hz), 8.14 (d, 1H, J = 2.8 Hz), 8.12-7.46 (m, 5H), 6.68 (dd, 1H, J = 7.2, 2.2 Hz), 6.14 (d, 1H, J = 2.2 Hz); MS (ESI^+) m/z 419 / 421 $(M + H)^+$.

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Ejemplo 55

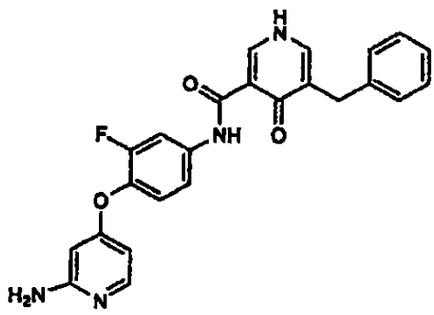


N-(4-(2-Aminopiridin-4-iloxi)-3-fluorofenil)-6-metil-4-oxo-1,4-dihidropiridin-3-carboxamida, sal del ácido trifluoroacético

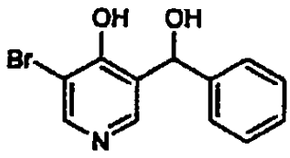
A una solución del ácido 4-hidroxi-6-metil-nicotínico (Wako, 77 mg, 0.50 mmol) y HOBt (50 mg) en DMF (5 mL) a temperatura ambiente se agregó EDCI.HCl (130 mg, 0.68 mmol) seguido por 4-(4-amino-2-fluorofenoxi)piridin-2-amina (Compuesto B del Ejemplo 24, 110 mg, 0.50 mmol), y la mezcla de reacción se agitó a temperatura ambiente toda la noche, y luego se calentó a 75 °C por 1.5 h. Después de enfriar la mezcla de reacción a temperatura ambiente la purificación mediante HPLC preparativa proporcionó el compuesto del título (70 mg, 29 %) como un sólido blanco (Sal de TFA). RMN-^{1}H (DMSO-d_6) δ 13.22 (br s, 1H), 12.53 (s, 1H), 8.47 (d, 1H, J = 5.5 Hz), 8.04 (d, 1H, J = 2.2 Hz), 7.95 (d, 1H, J = 8.2 Hz), 7.82 (s, 2H), 7.46-7.42 (m, 2H), 6.70 (dd, 1H, J = 7.7, 2.7 Hz), 6.39 (s, 1H), 6.14 (d, 1H, J = 2.2 Hz); MS (ESI^+) m/z 355.3 $(M + H)^+$.

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Ejemplo 56



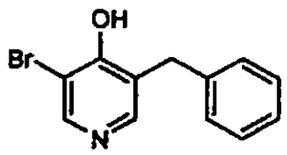
N-(4-(2-Aminopiridin-4-iloxi)-3-fluorofenil)-5-bencil-4-oxo-1,4-dihidropiridin-3-carboxamida, sal del ácido trifluoroacético



A) 3-Bromo-5-(hidroxi(fenil)metil)piridin-4-ol

A una mezcla heterogénea de 3,5-dibromo-4-hidroxipiridina (2.53 g, 10 mmol, preparada siguiendo el procedimiento en Synthesis, 2001, 14, 2175-2179) en THF anhidro (20 mL) a -78°C bajo atmósfera de argón se agregó bromuro de fenilmagnesio en solución (11 mL de solución 1 M en THF, 11 mmol). Después de agitación por 15 min, se agregó solución de n-BuLi (5.5 mL de solución 2 M en ciclohexano), y la mezcla de reacción se agitó por 15 min a -78°C bajo atmósfera de argón. A esta mezcla se agregó benzaldehído (2.15 mL) y la mezcla de reacción se agitó por 2 h a -78°C

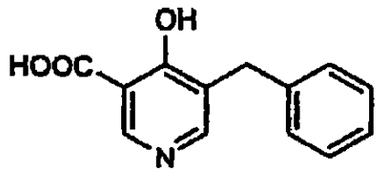
bajo atmósfera de argón. La mezcla de reacción se apagó por adición de HOAc (3 mL) y TFA (3 mL), se concentró a vacío y el residuo se purificó mediante cromatografía instantánea en Columna sobre gel de sílice eluyendo con hexano/EtOAc/MeOH // 750:250:50 seguido por hexano/EtOAc/MeOH/Et3N // 460:460:50:10 para proporcionar el producto deseado (2.85 g, 91%) como un sólido blanco. RMN-^{1}H (CD_3OD) δ 8.13 (s, 1H), 8.04 (s, 1H), 7.41-7.20 (m, 5H), 5.94 (s, 1H); MS(ESI$^+$) m/z 280, 282 $(M + H)^+$.



B) 3-Bencil-5-bromopiridin-4-ol

Una mezcla de 3-bromo-5-(hidroxi(fenil)metil)piridin-4-ol (2.55g, 91 mmol), TFA (16 mL) y Et_3SiH en cloruro de metileno (30 mL) se agitó a temperatura ambiente por 10 h. La mezcla de reacción se concentró a vacío y el residuo se purificó mediante cromatografía instantánea en Columna sobre gel de sílice eluyendo con hexano/EtOAc/MeOH // 600:300:50 seguido por hexano/EtOAc/MeOH // 400:400:50:10 para proporcionar un producto impuro el cual se trituró con una pequeña cantidad de McOH y Et_2O para obtener el producto deseado (255 mg, 10 %) como un sólido blanco. RMN-^{1}H (DMSO-d_6) δ 11.75 (br s, 1H). 8.13 (s, 1H), 7.54 (s, 1H), 7.26-7.14 (m,

5H), 2.49 (s, 2H).



C) ácido 5-bencil-4-hidroxinicotínico

A una solución de 3-bencil-5-bromopiridin-4-ol (220 mg. 0.83 mmol) en THE anhidro (8 mL) a -78°C bajo atmósfera de argón se agregó solución de MeLi (0.61 mL de 1.5 M solución en THF, 0.92 mmol). Después de agitar por 5 minutos se agregó n-BuLi en solución (0.5 mL de 2 M solución en ciclohexano, 1.0 mmol) y la mezcla se agitó por 15 min a -78°C bajo atmósfera de argón. Se burbujeó dióxido de carbono a través de la mezcla de reacción por 20 min a -78°C. La mezcla de reacción se apagó luego por adición de HOAc (2 mL), se concentró a vacío y el residuo se purificó mediante HPLC preparativa para proporcionar el producto deseado (100 mg, 35%) como un sólido blanco (sal de TFA). RMN-^{1}H (DMF-d_7) δ 12.99 (br s, 1H), 8.69 (s, 1H), 8.28 (s, 1H), 7.35-7.19 (m, 5H), 3.90 (s, 2H); MS(ESP) m/z 230.1 $(M + H)^+$.

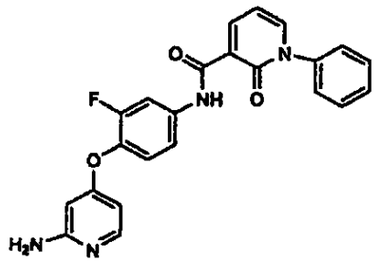
D) N-(4-(2-Aminopiridin-4-iloxi)-3-fluorofenil)-5-bencil-4-oxo-1,4-dihidropiridin-3-carboxamida, sal del ácido trifluoroacético

A una solución del ácido 4-hidroxi-5-bencilnicotínico (35 mg, 0.15 mmol) y HOBt (30 mg) en DMF (2.5 mL) a

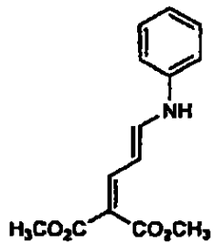
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temperatura ambiente se agregó EDCI.HCl (80 mg, 0.42 mmol) seguido por 4-(4-amino-2-fluorofenoxi)piridin-2-amina (Compuesto B del Ejemplo 24, 35 mg, 0.16 mmol), y la mezcla de reacción se agitó por 40 h a temperatura ambiente. La purificación de la mezcla de reacción mediante HPLC preparativa proporcionó el producto deseado (35 mg, 43%) como sal sólida blanca de TFA. RMN-^{1}H (DMSO-d_6) δ 13.25 (br s, 1H). 12.44 (s, 1H), 8.59 (d, 1H, J = 4.9 Hz), 8.08 (dd, 1H, J = 13.2. 2.2 Hz), 7.97 (d, 1H, J = 7.1 Hz). 7.81 (d, 1H, J = 9.4Hz), 7.52-7.19 (m.7H). 6.72 (dd, 1H, J = 7.2, 2.2 Hz), 6.15 (d, 1H, J = 2.5 Hz), 3.81 (s,2H), 3.51 (br s, 2H); MS(ESI+) m/z 431.2 $(M + H)^+$.

Ejemplo 57



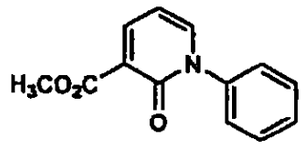
N-(4-(2-Aminopiridin-4-iloxi)-3-fluorofenil)-2-oxo-1-fenil-1,2-dihidropiridin-3-carboxamida, sal del ácido trifluoroacético



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A) 2-(3-(fenilamino) aliliden)malonato de (E)-dimetilo

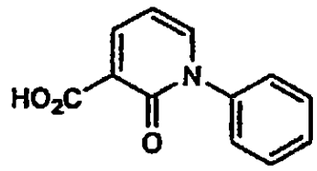
A una solución del éster dime-tilico del ácido 2-(3-metoxialiliden)malónico (Acros Organics, 200 mg, 1.0 mmol) en THF (2 mL) a temperatura ambiente se agregó anilina (300 mg, 3.2 mmol) y la mezcla de reacción se calentó a 60°C por 8.5 h. La purificación de la mezcla de reacción mediante HPLC preparativa proporcionó el producto deseado (150 mg, 57%) como un sólido amarillo. RMN-^{1}H (DMSO-d_6) δ 10.16 (d, 1H, J = 12.7 Hz), 8.06 (t, 1H, J = 12.7 Hz), 7.74 (d, 1H, J = 12.7 Hz), 7.30 (t, 2H, J = 8.7 Hz), 7.16 (d, 2H, J = 1.1 Hz), 6.98 (t, 1H, J = 1.1 Hz), 6.35 (t, 1H, J = 12.1 Hz), 3.69 (s, 3H). 3.65 (s, 3H).



B) 2-oxo-1-fenil-1,2-dihidropiridin-3-carboxilato de metilo

A una solución del aducto de anilina obtenido anteriormente (130 mg. 0.50 mmol) en metanol (8 mL) a temperatura ambiente se agregó NaH (50 mg de NaH al 60% en aceite, 1.2 mmol) y la mezcla se agitó a temperatura ambiente por 3 h. Se agregó ácido acético (0.3 mL) a la mezcla, se concentró hasta un volumen de -4 mL, y La purificación de la mezcla de reacción mediante HPLC preparativa proporcionó el producto deseado (105 mg, 92 %) como un sólido amarillo. RMN-^{1}H (CD_3OD) δ 8.30 (dd, 1H, J = 7.2. 2.2 Hz). 7.87 (dd, 1H, J =

6. 6, 1.7 Hz), 7.57-7.38 (m, 5H), 6.53 (t, 1H, J = 7.0 Hz), 3.84 (s, 3H); MS (ESI^+) m/z 230.3 $(M + H)^+$.



C) ácido 2-oxo-1-fenil-1,2-dihidropiridin-3-carboxílico

Una mezcla de 2-oxo-1-fenil-1,2-dihidropiridin-3-carboxilato de metilo (70 mg. 0.31 mmol) y LiOH (40 mg) en metanol (6 mL) y agua (1 mL) se agitó a temperatura ambiente toda la noche. A la mezcla de reacción se agregaron EtOAc (50 mL) y HCl 1 N acuoso (15 mL). La capa de EtOAc se separó, se secó sobre sulfato de magnesio, y se concentró a vacío para proporcionar el producto (55 mg, 83 %) como un sólido amarillo claro. RMN-^{1}H (DMF-d_7) δ 11.77 (br s, 1H), 8.57 (dd, 1H, J = 7.4, 2.0 Hz), 8.26 (dd, 1H, J = 6.6, 1.6 Hz), 7.64-7.55 (m, 5H), 6.88 (t, 1H, J = 7.0 Hz); MS (ESI^+) m/z 216.2 $(M + H)^+$.

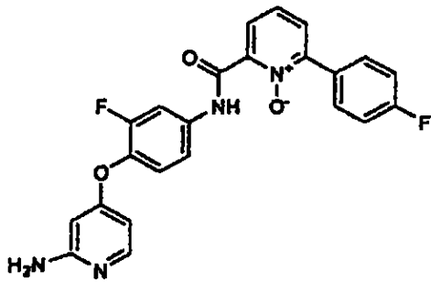
D) N-(4-(2-Aminopiridin-4-iloxi)-3-fluorofenil)-2-oxo-1-fenil-1,2-dihidropiridin-3-carboxamida

A una solución del ácido 2-oxo-1-fenil-1,2-dihidropiridin-3-carboxílico (36 mg, 0.17 mmol) y HOBt (18 mg) en DMF (3 mL) a temperatura ambiente se agregó EDCI.HCl (45 mg, 0.23 mmol) seguido por 4-(4-amino-2-fluorofenoxi)piridin-2-amina (Compuesto B del Ejemplo 24, 36

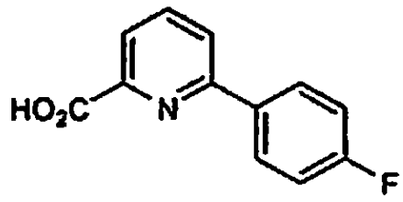
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mg, 0.17 mmol), y la mezcla de reacción se agitó a temperatura ambiente toda la noche. La purificación de la mezcla de reacción mediante HPLC preparativa proporcionó el compuesto del título (32 mg, 36 %) como un sólido beige (Sal de TFA). RMN-^{1}H (DMSO-d_6) δ 13.35 (br s, 1H), 12.11 (s, 1H), 8.52 (dd, 1H, J = 7.3, 2.1 Hz), 8.08 (dd, 1H, J = 6.6, 2.1 Hz), 8.03 (d, 1H, J = 2.3 Hz), 7.89 (d, 1H. J = 7.2 Hz), 7.81 (s, 1H), 7.54-7.36 (m, 6H), 6.69-6.63 (m, 2H), 6.08 (d, 1H, J = 2.4 Hz), 3.55 (br s, 1H); MS(ESI$^+$)m/z 417.2 $(M + H)^+$.

Ejemplo 58



N-(4-(2-Aminopiridin-4-iloxi)-3-fluorofenil)-6-(4-fluorofenil)piridil-N-óxido-amida, sal del ácido trifluoroacético

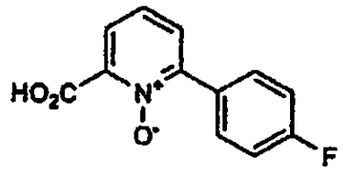


A) ácido 6-(4-fluorofenil)picolínico

Una solución de ácido 2-bromo-picolínico (Aldrich, 2.02

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g, 10 mmol) en DME que contenía 4 mL de Na_2CO_3 acuoso al 10% se purgó con gas Ar. A esta mezcla se agregó Pd(PPh3)4 seguido por 2-(4-fluorofenil)-5,5-dimetil-1,3,2-dioxaborinano (Aldrich, 2.40 g, 11.5 mmol) y EtOH (20 mL), y la mezcla se purgó con gas Ar. La mezcla de reacción se calentó a 100 °C por 2.5 h en un tubo sellado. Se agregó adicional 2-bromo-picolínico (900 mg) y $Pd(PPh_3)_4$, y después de purgar con gas Ar se calentó a 100 °C por 4.5 h. Se agregó ácido trifluoroacético (20 mL) a la reacción y la mezcla se concentró a vacío. Se agregó MeOH (150 mL) al residuo y el material insoluble se filtró, y el filtrado en solución se concentró a vacío. La purificación del residuo resultante mediante cromatografía instantánea en columna sobre gel de sílice eluyendo con EtOAc/MeOH // 900:100 seguido por EtOAc/MeOH/HOAc // 700:1500:50 proporcionó el producto deseado (1.0 g, 40 basado en el material inicial de borinano) como un sólido blanco. RMN-^{1}H (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) ácido-N-óxido 6-(4-fluorofenil)picolínico

Una mezcla del derivado de ácido picolínico (1.0 g. 4.6

mmol), Na_2HPO_4 (1.2 g) y m-CPBA (1.1 g, aprox. al 70% de Aldrich) en CH_2ClCH_2Cl (30 mL) se agitó a temperatura ambiente por 2 h. Se agregó Na_2HPO_4 adicional (0.8 g) y m-CPBA (1.0 g) a la mezcla de reacción y se agitó por 3 h a temperatura ambiente. Se agregó más Na_2HPO_4 (0.5 g) y m-CPBA (0.5 g) a la mezcla de reacción y se agitó a temperatura ambiente toda la noche. Se agregaron $CHCl_3$ (160 mL) y solución aq. 2 N de HCl (50 mL) a la mezcla de reacción y la capa orgánica se separó, se secó sobre sulfato de magnesio y se concentró a vacío. El residuo se purificó mediante cromatografía instantánea en columna sobre gel de sílice eluyendo con EtOAc/MeOH /HOAc // 700:240:60 para obtener el producto deseado el cual estaba contaminado con m-CPBA. Este material impuro se purificó mediante HPLC preparativa para obtener el producto deseado (175 mg, 16 %) como un sólido blanco. RMN-^{1}H (DMF-dfl 8.45 (dd, 1H. J = 8. 3, 2.2 Hz), 8.15 (d, 1 H, J = 2.2 Hz), 8.13-8.00 (m, 4H), 7.45 (t, 2H, J = 8.7 Hz).

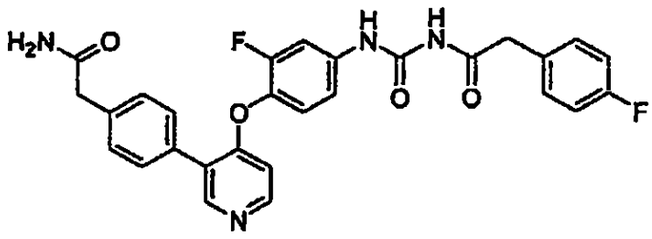
C) N-(4-(2-Aminopiridin-4-iloxi)-3-fluorofenil)-6-(4-fluorofenil)piridil-N-óxido-amida, sal del ácido trifluoroacético

A una solución de ácido-N-óxido 6-(4-fluorofenil)picolínico (23 mg, 0.1 mmol) y HOBt (10 mg) en DMF (2 mL) a temperatura ambiente se agregó EDCI.HCl (30 mg, 0.16 mmol) seguido por 4-(4-amino-2-fluorofenoxi)piridin-2-amina (Compuesto B del Ejemplo 24, 22 mg. 0.1 mmol), y la

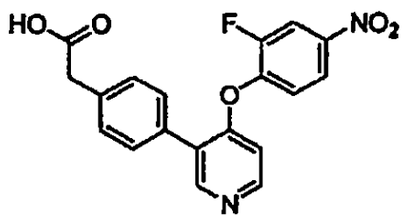
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mezcla de reacción se agitó a temperatura ambiente toda la noche. La purificación de la mezcla de reacción mediante HPLC preparativa proporcionó el compuesto del título (25 mg, 46 %) como un sólido blanco (Sal de TFA). RMN-^{1}H (DMF-dfl 6 14.00 (s, 1H), 8.43 (dd, 1H, J = 8.0, 2.2 Hz). 8.15 (dd, 1H, J = 12.8, 2.4 Hz). 8.08 (d, 1H, J = 7.1 Hz), 7.99-7.37 (m, 9H), 6.72 (dd, 1H, J = 7.0, 2.4 Hz), 6.32 (d, 1H, J = 2.3 Hz), 3.7 (br s, 2H); MS (ESI$^+$) m/z 417.2(M + H)$^+$.

Ejemplo 59



1-(4-(3-(4-(2-Amino-2-oxoetil)fenil)piridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil) acetil) urea, sal de clorhidrato

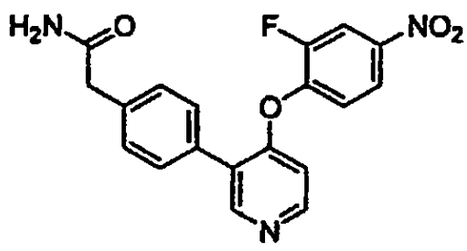


A) ácido 2-(4-(4-(2-fluoro-4-nitrofenoxi)piridin-3-il)fenil)acético

Un matraz de fondo redondo de 25 ml se cargó con 4-(2-

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fluoro-4-nitrofenoxi)-3-yodopiridina (Compuesto A del Ejemplo 33, 120 mg, 0.33 mmol), ácido 2-(4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)acético (Frontier Scientific, 131 mg, 0.50 mmol), tetrakis(trifenilfosfina)paladio(0) (Strem Chemicals, 38 mg, 0.033 mmol), y carbonato de sodio (245 mg, 2.3 mmol). El matraz se inundó con nitrógeno y luego se cargó con dioxano y agua (1 mL cada uno). Después de agitar a 80 °C por 10 h, la mezcla se enfrió a temperatura ambiente y luego se concentró a vacío. El producto crudo se purificó mediante cromatografía instantánea en columna sobre gel de sílice (30% de McOH/EtOAc) para dar el compuesto del título (120 mg, 99%) como un sólido blanco. RMN-^{1}H (CD_3OD) δ 8.61 (s, 1H), 8.48 (d, 1H, J = 5.6 Hz), 8.22 (dd, 1H, J = 10.4, 2.8 Hz), 8.14-8.11 (m, 1H), 7.54 (d, 2H, J = 8.1 Hz), 7.41 (d, 2H, J = 8.0 Hz), 7.40 (m, 1H), 7.05 (d, 1H, J = 5.7 Hz), 3.56 (s, 2H) MS (ESI^+) m/z 369.16 $(M + H)^+$.



B) 2-(4-(4-(2-Fluoro-4-nitrofenoxi)piridin-3-il)fenil)acetamida

Un matraz de fondo redondo de 25 ml se cargó con ácido

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2-(4-(4-(2-fluoro-4-nitrofenoxi)piridin-3-il)fenil)acético (50 mg, 0.136 mmol), HOBT (46 mg, 0.34 mmol), y EDCI (65 mg, 0.34 mmol). El matraz se inundó con nitrógeno y luego se agregó DMF (1 mL). Después de agitar a temperatura ambiente por 1 hora la solución se enfrió a 0°C y luego se cargó con hidróxido de amonio (0.5 mL). La reacción se agitó a 0°C por 1 h y luego se diluyó con salmuera (5 mL) y se extrajo con acetato de etilo (3 x 5 mL). Los extractos orgánicos combinados se secaron sobre sulfato de sodio anhidro y se concentró a vacío. El producto crudo se purificó mediante cromatografía instantánea en columna sobre gel de sílice (20% de McOH / EtOAc) para dar el compuesto del título (33 mg. 66%) como un aceite incoloro. RMN-^{1}H (CD_3OD) δ 8.49 (s, 1H), 8.38 (d, 1H, J = 5.6 Hz), 8.10 (dd, 1H, J = 10.4, 2.4 Hz), 7.99 (m, 1H), 7.45 (d, 2H, J = 8.2 Hz), 7.30 (d, 2H. J = 8.2 Hz), 7.28 (m, 1H), 6.93 (d, 1H, J = 5.6 Hz), 3.44 (s, 2H); MS (ESI^+) m/z 368.18 $(M + H)^+$.

C) 1-(4-(3-(4-(2-Amino-2-oxoetil) fenil)piridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea

Una solución de 2-(4-(4-(2-flouro-4-nitrofenoxi)piridin-3-il)fenil)acetamida (33 mg. 0.09 mmol) en THF (0.8 mL) y metanol (1.2 mL) se trató con polvo de Zn (59 mg, 0.9 mmol) seguido por cloruro de amonio (48 mg, 0.9 mmol). La mezcla se agitó a temperatura ambiente por 4 h y luego se filtró a través de lecho delgado de Celite® con metanol. El filtrado

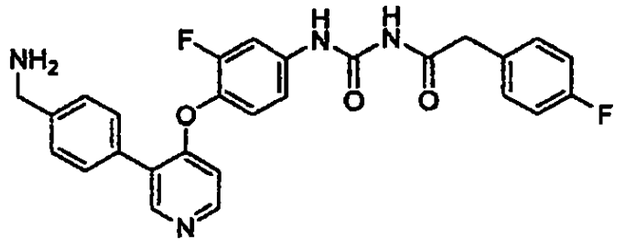
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se concentró y el residuo se dividió entre EtOAc y solución acuosa saturada de carbonato ácido de sodio. La fase de EtOAc se secó sobre sulfato de sodio anhidro y se concentró a vacío para dar el producto crudo (25 mg, 82%) como un aceite amarillo que fue suficientemente puro para utilizarse en el siguiente paso sin purificación adicional. RMN-^{1}H (CD_3OD) δ 8.33 (s, 1H), 8.19 (d, 1H, J = 5.6 Hz), 7.49 (d, 2H, J = 8.1 Hz), 7.32 (d, 2H, J = 8.2 Hz), 6.82 (t, 1H, J = 8.8 Hz). 6.61 (d, 1H, J = 5.6 Hz), 6.44 (qd, 1H. J = 12.8, 2.8 Hz), 3.48 (s, 2H); MS (ESI^+) m/z 338.25 $(M + H)^+$.

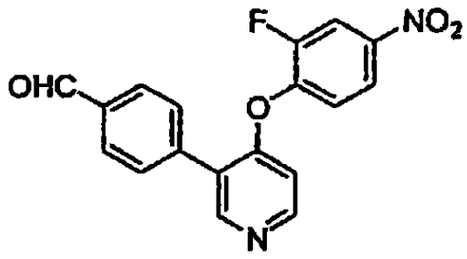
La amina anterior se disolvió en THF (1 mL) y luego se cargó con isocianato de 2-(4-fluorofenil)acetilo (Compuesto D del Ejemplo 11. 250 µL. 0.074 mmol, 0.3 M en tolueno). Después de agitar a temperatura ambiente por 1 h. la reacción se purificó directamente mediante cromatografía instantánea sobre gel de sílice (10% de McOH / EtOAc) para dar el compuesto del título como un sólido blanco. El sólido se disolvió en dioxano (2 mL) y se enfrió a 0°C. Se agregó HCl anhidro (2 mL, 1 N en éter). Después de agitar a 0°C por 5 minutos la solución se concentró a vacío. La sal de HCl resultante se liofilizó a partir acetonitrilo/agua para dar el compuesto del título (23 mg, 57%) como un sólido blanco. RMN-^{1}H (DMSO-d_6) δ 11.02 (s, 1H), 10.59 (s, 1H), 8.83 (s, 1H), 8.58 (d, 1H. J = 6.4 Hz), 7.79 (dd, 1H. J = 12.8, 2.4 Hz), 7.60 (d, 2H, J = 8.4 Hz), 7.46-7.34 (m, 4H), 7.31-7.28 (m,

2H), 7.11 (t, 2H. J = 8.7 Hz), 6.88 (d, 1H, J = 5.6 Hz), 3.70 (s, 2H), 3.40 (s, 2H) : MS(ESP) m/z 517.19 $(M + H)^+$.

Ejemplo 60



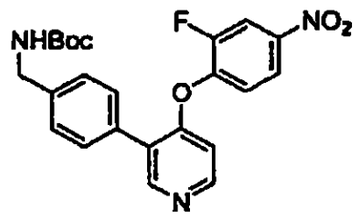
1-(4-(3-(4-(Aminometil) fenil)piridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil) acetil) urea, sal del ácido trifluoroacético



A) 4-(4-(2-Fluoro4-nitrofenoxi)piridin-3-il)benzaldehído

Preparado de una manera similar al Paso A del Ejemplo 59, para dar el compuesto del título (86%) como un aceite incoloro. RMN-^{1}H (CD_3OD) 6 9.92 (s, 1H), 8.56 (s, 1H), 8.41 (d, 1H, J = 6 Hz), 8.12 (dd, 1H, J = 10.3, 2.6 Hz), 8.05-8.01 (m, 1H), 7.90 (d, 2H, J = 8.3 Hz), 7.73 (d, 2H, J = 8.2 Hz), 7.35 (t, 1H, J = 8.4 Hz), 6.95 (d, 1H. J = 6 Hz); MS(ESI^+)

m/z 339.19 $(M + H)^+$.



B) 4-(4-(2-fluoro-4-nitrofenoxi)piridin-3-il)bencilcarbamato de ter-butilo

Al 4-(4-(2-fluoro-4-nitrofenoxi)piridin-3-il)benzaldehído (81 mg. 0.24 mmol) en metanol (2 mL) se agregó acetato de amonio (185 mg, 2.4 mmol) seguido por cianoborohidruro de sodio (16 mg, 0.24 mmol). La reacción se agitó a temperatura ambiente por 4 h y luego se concentró a vacío. El residuo se disolvió en agua (5 mL) y se extrajo con EtOAc (2x5 mL). Los extractos orgánicos combinados se lavaron con solución acuosa saturada de carbonato ácido de sodio, se secó sobre sulfato de sodio anhidro, y se concentró a vacío. El producto crudo se disolvió en diclorometano (2 mL) y luego se agregaron secuencialmente trietilamina (50 µL, 0.36 mmol), DMAP (punta de la espátula), y dicarbonato de di-ter-butilo (Aldrich, 57 mg, 0.26 mmol). La reacción se agitó a temperatura ambiente por 2 h y luego se purificó directamente mediante cromatografía instantánea en columna sobre gel de sílice (EtOAc) para dar el compuesto del título (13 mg, 12%) como un aceite incoloro. MN-^{1}H (CD_3OD) δ 8.50 (s, 1H), 8.37

(d, 1H, J = 5.6 Hz), 8.09 (dd, 1H, J = 6.1, 2.6 Hz), 8.01-7.99 (m, 1H), 7.45 (d, 2H, J = 8 Hz), 7.26 (d, 2H, J = 8.2 Hz), 7.25 (m, 1H), 6.95 (d, 1H, J = 5.6 Hz), 4.16 (s, 2H), 1.35 (s, 9H); MS(ESI$^+$) m/z 440.19 $(M + H)^+$.

C) 1-(4-(3-(4-(Aminometil)fenil)piridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil) acetil)urea

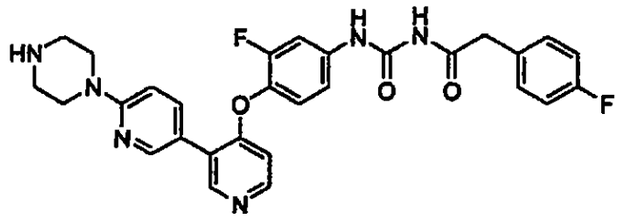
Preparado de una manera similar al Paso C del Ejemplo 59. Después de la formación de la acilurea, se agregó HCl 4 N en dioxano (5 mL). Después de agitar a temperatura ambiente por 5 min, la reacción se concentró a vacío. El residuo se suspendió en EtOAc, se lavó con solución acuosa saturada de carbonato ácido de sodio, se secó sobre sulfato de sodio anhidro, y se concentró a vacío.

El material crudo se purificó mediante HPLC preparativa. Las fracciones apropiadas se concentraron a vacío para remover el metanol. Se agregó tolueno y luego se concentró (2x5 mL).

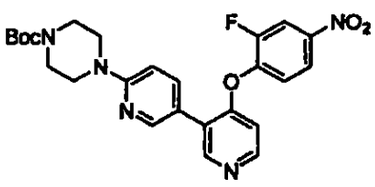
El sólido resultante se liofilizó a partir de acetonitrilo/agua para dar la sal de TFA del compuesto del título (6 mg. 25%) como un sólido blanco. RMN-^{1}H (DMSO-d_6) δ 11.00 (s, 1H), 10.53 (s, 1H), 8.55 (s, 1H), 8.40 (d, 1H, J = 4 Hz), 7.73 (dd, 1H, J = 12, 4 Hz), 7.67 (d, 2H, J = 8 Hz). 7.51 (d, 2H, J = 8 Hz), 7.34-7.27 (m, 4H), 7.13-7.09 (m, 2H), 6.73 (d, 1H, J = 4 Hz), 4.03 (s, 2H), 3.68 (s, 2H); MS (ESI$^+$) m/z 489.18 $(M + H)^+$.

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Ejemplo 61

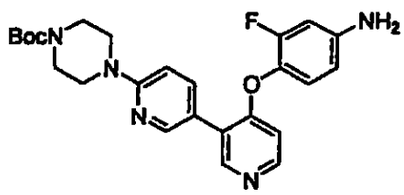


1-(3-Fluoro-4-(3-(6-(piperazin-1-il)piridin-3-il)piridin-4-iloxi) fenil)-3-(2-(4-fluorofenil) acetil) urea, sal de clorhidrato



A) 4-(5-(4-(2-fluoro-4-nitrofenoxi)piridin-3-il)piridin-2-il)piperazin-1-carboxilato de ter-butilo

Preparado de una manera similar al Paso A del Ejemplo 59 para dar el compuesto del título (87%) como un aceite incoloro. RMN-^{1}H (CD_3OD) δ 8.62 (s, 1H), 8.46 (d, 1H, J = 6 Hz), 8.36 (d, 1 H, J = 2.4 Hz), 8.24 (dd, 1H, J = 10.4, 2.8 Hz), 8.15-8.11 (m, 1H), 7.84 (dd, 1H, J = 8.8, 2.4 Hz), 7.41 (t, 1H, J = 8.4 Hz), 7.04 (d, 1H, J = 5.6 Hz), 6.92 (d, 1H, J = 8.8 Hz), 3.61-3.59 (m, 4H), 3.56-3.54 (m, 4H), 1.50 (s, 9H); MS (ESI^+) m/z 496.23 $(M + H)^+$.



B) 4-(5-(4-(4-amino-2-fluorofenoxi)piridin-3-il)piridin-2-il)piperazin-1-carboxilato de ter-butilo

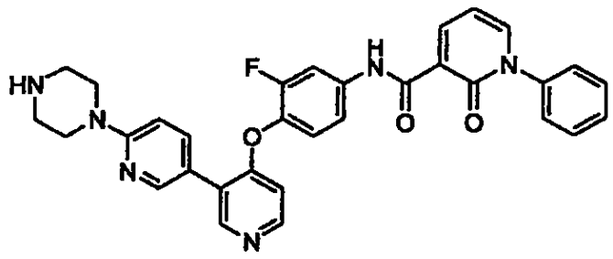
Preparado de una manera similar al Paso C del Ejemplo 59 para dar el compuesto del título (96%) como un aceite incoloro. RMN-^{1}H (CD_3OD) δ 8.34 (s, 1H), 8.29 (d, 1H, J = 2 Hz), 8.18 (d, 1H. J = 6 Hz), 7.78 (dd, 1H, J = 9.2, 2.8 Hz), 6.87-6.83 (m, 2H), 6.61 (d, 1H, J = 5.6 Hz), 6.48 (dd, 1H, J = 12.8, 2.8 Hz), 6.44-6.41 (m, 1H), 3.50-3.46 (m, 8H), 1.38 (s, 9H); MS (ESI^+) m/z 466.25 $(M+ H)^+$.

C) 1-(3-Fluoro-4-(3-(6-(piperazin-1-il)piridin-3-il)piridin-4-iloxi) fenil)-3-(2-(4-fluorofenil) acetil) urea

Preparado de una manera similar al Paso C del Ejemplo 59 para dar el compuesto del título (28%) como la sal de HCl. RMN-^{1}H (DMSO-d_6) δ 11.33 (s, 1H), 10.76 (s, 1H), 9.09 (s, 1H), 8.74 (d, 1H, J = 6.8 Hz), 8.57 (d, 1H, J = 2.4 Hz), 8.16 (dd, 1H, J = 8. 8, 2 Hz), 7.91 (dd, 1H.J = 12.8, 2 Hz), 7.61 (t, 1H.J = 8.8 Hz), 7.55-7.50 (m, 1H), 7.42-7.38 (m, 2H), 7.28 (d, 1H, J = 6.5 Hz), 7.27-7.18 (m, 3H), 3.98 (m, 4H),

3.82 (s, 2H), 3.23 (m, 4H); MS(ES1$^+$) m/z 545.19 (M + H)$^+$.

Ejemplo 62



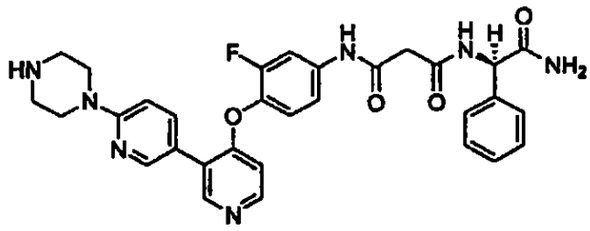
N-(3-Fluoro-4-(3-(6-(piperazin-1-il)piridin-3-il)piridin-4-iloxi)fenil)-2-oxo-1-fenil-1,2-dihidropiridin-3-carboxamida, sal de clorhidrato

Al 4-(5-(4-(4-amino-2-fluorofenoxi)piridin-3-il)piridin-2-il)piperazin-1-carboxilato de ter-butilo (Compuesto B del Ejemplo 61, 32 mg, 0.069 mmol) en THF/DMF (1 mL cada uno) se agregó ácido 2-oxo-1-fenil-1,2- dihidropiridin-3-carboxílico (Compuesto C del Ejemplo 57, 15 mg, 0.069 mmol), DIPEA (60 µL. 0.35 mmol), luego TBTU (Fluka, 33 mg. 0.10 mmol). Después de agitar a temperatura ambiente por 18 h. la reacción se diluyó con EtOAc (5 mL), se lavó con 10% solución acuosa de cloruro de litio de (2 x 5 mL) seguido por solución acuosa saturada de carbonato ácido de sodio (1x5 mL), se secó sobre sulfato de sodio anhidro, y se concentró a vacío. El residuo se suspendió en éter, se enfrió a 0°C y se trató con HCl 4 N en dioxano (5 mL). La solución se dejó calentar a temperatura ambiente y luego se agitó a temperatura ambiente por 2 h. La

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solución se concentró a vacío y el producto crudo resultante se purificó mediante HPLC preparativa. Las fracciones apropiadas se concentraron para remover el metanol y luego se alcalinizó con solución acuosa saturada de carbonato ácido de sodio. La solución acuosa se extrajo con EtOAc (2x10 mL) y los extractos orgánicos combinados se secaron sobre sulfato de sodio anhidro y luego se concentró a vacío. El residuo se disolvió en THF (2 mL), se enfrió a 0°C, y se trató con HCl 1N en éter (0.5 mL). Después de agitar a 0°C por 5 min, la mezcla se concentró. El sólido blanco resultante se liofilizó a partir de acetonitrilo/agua para dar la sal de HCl del compuesto del título (26 mg, 56%) como un sólido amarillo pálido. RMN-^{1}H (DMSO-d_6) δ 12.16 (s, 1H), 8.92 (s, 1H), 8.59 (d, 1H, J = 6.4 Hz). 8.53 (dd, 1H, J = 7.2, 2 Hz), 8.47 (d, 1H, J = 2.4 Hz), 8.10 (dd, 1H, J = 6.4, 2 Hz), 8.04 (d, 1H, J = 12 Hz), 7.99 (dd, 1H, J = 8. 8, 2.4 Hz), 7.54-7.46 (m, 7H), 7.20 (d, 1H, J = 6.4 Hz), 7.97 (d, 1H, J = 9.2 Hz), 6.68 (t, 1H, J = 6.8 Hz), 3.82-3.80 (m, 4H), 3.12 (m, 4H); MS(ESI+) m/z 545.19 $(M + H)^+$.

Ejemplo 63



N^1-((R)-2-Amino-2-oxo-1-feniletil)-N^3-(3-fluoro-4-(3-(6-

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(piperazin-1-il)piridin-3-il)piridin-4-iloxi)fenil)malonamida, sal de clorhidrato

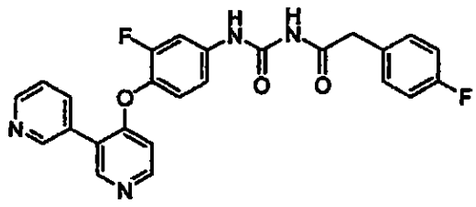
Al 4-(5-(4-(4-amino-2-fluorofenoxi)piridin-3-il)piridin-2-il)piperazin-1-carboxilato de terbutilo(Compuesto B del Ejemplo 61. 32 mg, 0.069 mmol) en THF (1 mL) se agregó DIPEA (60 µL, 0.35 mmol) luego 3-cloro-3-oxopropanoato de etilo (Aldrich, 10 µL, 0.076 mmol). Después de agitar a temperatura ambiente por 2 h. la reacción se diluyó con EtOAc (5 mL), se lavó con solución acuosa saturada de carbonato ácido de sodio (1x5 mL), se secó sobre sulfato de sodio anhidro, y se concentró a vacío. El aceite amarillo resultante (65 mg) se disolvió en THF (2 mL) y luego se cargó con solución acuosa de hidróxido de sodio 1 N (2 mL). La solución se agitó a temperatura ambiente por 6 h. La solución se concentró para eliminar el THF y luego acidificó a pH 4-5 con solución acuosa de HCl 1N. El sólido se recolectó mediante filtración a vacío y se lavó con agua para dar el ácido correspondiente como un sólido blanco (30 mg, 78% 2 pasos). MS(ESI) m/z 552.21 $(M + H)^+$.

El ácido anterior se acopló con D(-)-fenilglicinamida (Bachem) utilizando TBTU como se describió anteriormente para dar la sal de HCl del compuesto del título (32%) como un sólido blanco. RMN-^{1}H (DMSO-d_6) δ 10.64 (s, 1H), 8.89 (s, 1H), 8.74 (d, 1H, J = 8 Hz), 8.56 (d, 1H. J = 5.6 Hz), 8.46 (d, 1H, J = 2.4 Hz), 7.96 (d, 1H, J = 8.8 Hz), 7.84 (d, 1H, J =

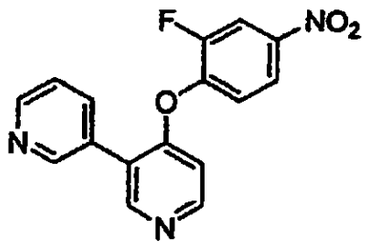
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12 Hz), 7.74 (s, 1H), 7.46-7.37 (m, 4H), 7.31-7.22 (m, 5H), 7.06 (d, 1H, J = 9.2 Hz), 5.34 (d, 1H, J = 8 Hz), 3.81-3.78 (m, 4H), 3.40 (s, 2H), 3.12 (m, 4H); MS (ESI^+) m/z 584.25 $(M + H)^+$.

Ejemplo 64



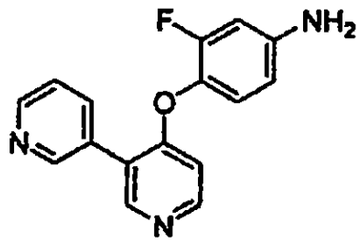
1-(3-Fluoro-4-(3-(piridin-3-il)piridin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)urea, sal de clorhidrato



A) 3-(4-(2-Fluoro-4-nitrofenoxi)piridin-3-il)piridina

Preparado de una manera similar al Paso A del Ejemplo 59 da el compuesto del título como un aceite incoloro. RMN-^1H (CD_3OD) δ 8.83 (d, 1H, J = 1.6 Hz), 8.69 (s, 1H), 8.61 (d, 1H, J = 5 Hz). 8.56 (d, 1H, J = 5.8 Hz). 8.27 (dd, 1H, J = 10.4, 2.8 Hz), 8.20-814 (m, 2H), 7.72-7.55 (m, 1H), 7.53 (t, 1H, J = 8.6 Hz), 7.08 (d, 1H, J = 6 Hz); MS (ESI^+) m/z 312.15 $(M + H)^+$.

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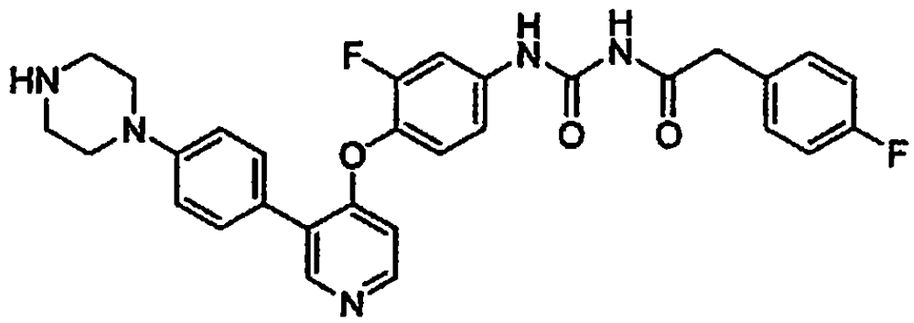
B) 3-Fluoro-4-(3-(piridin-3-il)piridin-4-iloxi)bencenamina

Preparado de una manera similar al Paso C del Ejemplo 59 da el compuesto del título como un aceite incoloro. MS (ESI^+) m/z 282.12 $(M+H)^+$.

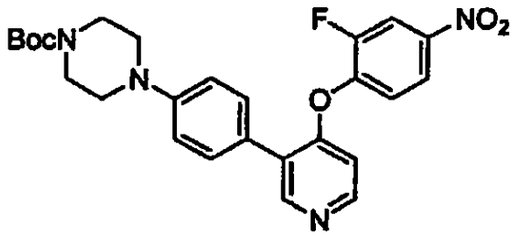
C) 1-(3-Fluoro-4-(3-(piridin-3-il)piridin-4-iloxi)fenil)-3-(2-(4-fluorofenil) acetil) urea

Preparado de una manera similar al Paso C del Ejemplo 59 da la sal de HCl del compuesto del título (47% rendimiento combinado para los pasos B y C) como un sólido amarillo. RMN-^1H (DMSO-d_6) δ 11.14(s, 1H), 10.73 (s, 1H), 9.16 (d, 1H, J = 1.6 Hz), 9.08 (s, 1H), 8.90 (dd, 1H, J = 5.2. 1.2 Hz), 8.78 (d, 1H, J = 6.4 Hz), 8.56 (d, 1H, J = 8Hz), 7.95-7.90 (m, 2H), 7.60 (t, 1H, J = 8.8 Hz), 7.55-7.52 (m, 1H), 7.44-7.41 (m, 2H), 7.26-7.21 (m, 3H), 3.82 (s, 2H); MS (ESI^+) m/z 461.16 $(M + H)^+$.

Ejemplo 65

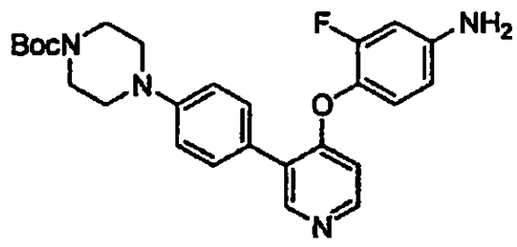


1-(3-Fluoro-4-(3-(4-(piperazin-1-il)fenil)piridin-4-iloxi)fenil)-3-(2-(4-fluorofenil) acetil) urea, sal de triclorhidrato



A) 4-(4-(4-(2-fluoro-4-nitrofenoxi)piridin-3-il)fenil)piperazin-1-carboxilato de ter-butilo

Preparado de una manera similar al Paso A del Ejemplo 59 da el compuesto del título como un aceite incoloro. NMR-^{1}H (CD_3OD) δ 8.48 (s, 1H), 8.32 (d, 1H, J = 5.6 Hz), 8.08 (dd, 1H, 7 = 12, 4 Hz), 7.97 (d, 1H, J = 8 Hz), 7.38 (d, 2H, J = 8.8 Hz), 7.21-7.18 (m, 1H), 6.95-6.92 (m, 3H), 3.46 (m, 4H), 3.09-3.06 (m, 4H). 1.10 (s, 9H); MS(ESI+) m/z 495.23 $(M + H)^+$.



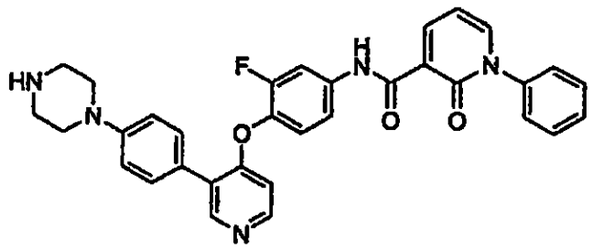
B) 4-(4-(4-(4-amino-2-fluorofenoxi)piridin-3-il)fenil)piperazin-1-carboxilato de ter-butilo

Preparado de una manera similar al Paso C del Ejemplo 59 para dar el compuesto del título (94% de rendimiento combinado para los pasos A y B) como un aceite incoloro. RMN-^{1}H (CD_3OD) δ 8.30 (s, 1H), 8.14 (d, 1H, J = 5.6 Hz), 7.45 (d, 2H, J = 8.8 Hz), 6.98 (d, 2H, J = 8.8 Hz), 6.83 (t, 1H, J = 8.8 Hz), 6.58 (d, 1H, J = 5.6 Hz), 6.48 (dd, 1H, J = 12.8, 2.4 Hz), 6.43-6.41 (m, 1H), 3.49 (m, 4H), 3.11-3.09 (m, 4H), 1.16 (s, 9H); MS(ESI$^+$) m/z 465.24 $(M + H)^+$.

C) 1-(3-Fluoro-4-(3-(4-(piperazin-1-il)fenil)piridin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil) urea

Preparado de una manera similar al Paso C del Ejemplo 59 para dar la sal de HCl del compuesto del título (37%) como un sólido amarillo pálido. RMN-^{1}H (DMSO-d_6) δ 11.01 (s, 1H), 10.60 (s, 1H), 8.77 (s, 1H), 8.51 (d, 1H, J = 6.4 Hz), 7.78 (d, 1H, J = 12Hz), 7.59 (d, 2H. J = 8.4 Hz), 7.44-7.40 (m, 2H), 7.31-7.28 (m, 2H), 7.13-7.08 (m, 4H), 7.03 (d, 1H, J = 6.4 Hz), 3.70 (s, 2H), 3.42 (m, 4H), 3.15 (m, 4H); MS(ESI$^+$) m/z 544.26 (M + H)T.

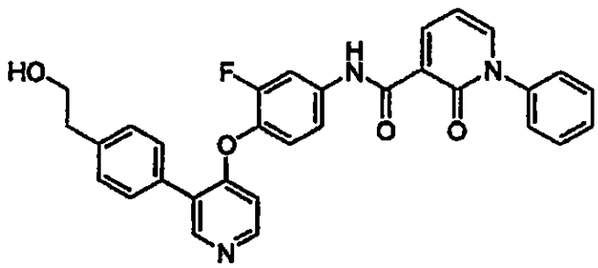
Ejemplo 66



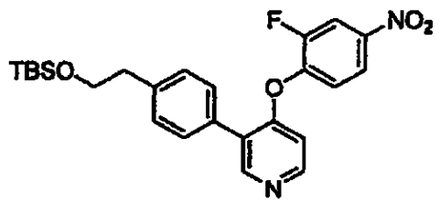
N-(3-Fluoro-4-(3-(4-(piperazin-1-il)fenil)piridin-4-iloxi)fenil)-2-oxo-1-fenil-1,2-dihidropiridin-3-carboxamida, sal de triclorhidrato

Preparado de una manera similar a aquella del Ejemplo 62 para dar la sal de HCl del compuesto del título (43%) como un sólido amarillo pálido. RMN-^{1}H (DMSO-d_6) δ 12.15 (s, 1H), 8.83 (s, 1H), 8.56-8.52 (m, 2H), 8.10 (dd, 1H, J = 6.8, 2.4 Hz), 8.04 (dd, 1H, J = 11.6, 2 Hz), 7.61 (d, 2H, J = 8.8 Hz), 7.55-7.45 (m, 7H), 7.15 (d, 1H, J = 6.8 Hz), 7.09 (d, 2H.J = 8.8 Hz), 6.61 (t, 1H, J = 6.8 Hz), 3.44 (m, 4H), 3.15 (m, 4H); MS(ESI$^+$) m/z 562.36 $(M + H)^+$.

Ejemplo 67

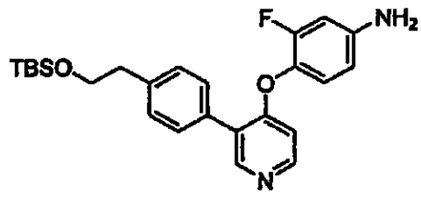


N-(3-Fluoro-4-(3-(4-(2-hidroxietil)fenil)piridın-4-iloxi)fenil)-2-oxo-1-fenil-1,2-dihidropiridin-3-carboxamıda



A) 3-(4-(2-(ter-butildimetilsililoxi)etil)fenil)-4-(2-5-fluoro-4-nitrofenoxi)piridina

Preparado de una manera similar al Paso A del Ejemplo 59 para dar el compuesto del título (77%) como un aceite incoloro. RMN-^{1}H (CD_3OD) δ 8.67 (s, 1H), 8.56 (d, 1H, J = 8 Hz), 8.27 (dd, 1H, J = 12, 4 Hz), 8.16 (d, 1H, J = 8 0 Hz), 7.58 (d, 2H, J = 8 Hz), 7.39 (d, 2H, J = 8 Hz), 7.36 (m, 1H), 7.15 (d, 1H, J = 4 Hz), 3.91 (t, 2H, J = 8 Hz), 2.90 (t, 2H, J = 8 Hz), 0.90 (s, 9H), 0.00 (s, 6H); MS(ESI$^+$) m/z 469.25 (M + H)$^+$.



B) 3-(4-(2-(ter-butildimetilsililoxi)etil)fenil)-4-(2-fluoro-4-nitrofenoxi)piridina

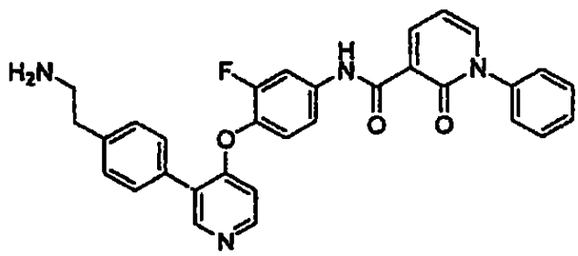
Preparado de una manera similar al Paso C del Ejemplo 59 para dar el compuesto del título (76%) como un aceite amarillo. RMN-^{1}H (CD_3OD) δ 8.44 (s, 1H), 8.32 (d, 1H, J = 4 Hz), 7.57 (d, 2H, J = 8 Hz), 7.36 (d, 2H, J = 8.4 Hz), 6.95 (t, 1H, J = 8 Hz), 6.75 (d, 1H, J = 4 Hz), 6.61 (d, 1H, J = 8

Hz), 6.55 (d, 1H, J = 4 Hz), 3.90 (t, 2H, J = 6.8 Hz), 2.89 (t, 2H, J = 6.4 Hz), 0.87 (s, 9H), 0.00 (s, 6H); MS(ESI$^+$) m/z 439.26 $(M + H)^+$.

C) N-(3-Fluoro-4-(3-(4-(2-hidroxietil)fenil)piridin-4-iloxi)fenil)-2-oxo-1-fenil-1,2-dihidropiridin-3-carboxamida

Preparado de una manera similar al Paso C del Ejemplo 62. Después de formación de amida, el aceite amarillo resultante se disolvió en THF (2 mL) y luego se trató con TBAF (Aldrich, 180 µL, 1 M en THF) a temperatura ambiente por 1 h. La reacción se diluyó con EtOAc (10 mL), se lavó sucesivamente con agua y salmuera (5 mL cada uno), se secó sobre sulfato de sodio anhidro, y se concentró a vacío. El producto crudo se purificó mediante cromatografía instantánea sobre gel de sílice (10% metanol/EtOAc) para dar el compuesto del título (72%) como un sólido amarillo pálido. RMN-^{1}H (CD_3OD) δ 8.59 (dd, 1H, J = 7. 6, 2.0 Hz), 8.41 (s, 1H), 8.26 (d, 1H, J = 5.6 Hz), 7.91-7.85 (m, 2H), 7.55-7.46 (m, 5H), 7.41 (d, 2H, J = 6.7 Hz), 7.29 (d, 2H, J = 8.1 Hz), 7.26 (m, 1H), 7.13 (t, 1H, J = 8.7 Hz), 6.69 (d, 1H, J = 6 Hz), 6.64 (t, 1H, J = 7.2 Hz), 3.73 (t, 2H, J = 7.2 Hz), 2.82 (t, 2H, J = 6.8 Hz); MS (ESI$^+$) m/z 522.27 $(M + H)^+$.

Ejemplo 68



N-(4-(3-(4-(2-Aminoetil)fenil)piridin-4-iloxi)-3-fluorofenil)-2-oxo-1-fenil-1,2-dihidropiridin-3-carboxamida, sal de diclorhidrato

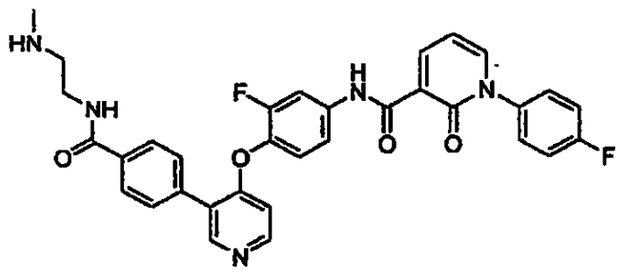
A la N-fluoro-4-(3-(4-(2- hidroxietil)fenil)piridin-4-iloxi)fenil)-2-oxo-1-fenil-1,2- dihidropiridin-3-carboxamida (Compuesto C del Ejemplo 67, 40 mg, 0.077 mmol) en THF (1 mL) se agregó DIPEA (27 µL, 0.154 mmol) seguido por cloruro de metansulfonilo (Aldrich, 7 µL, 0.092 mmol). Después de agitar a temperatura ambiente por 30 min., la reacción se concentró a vacío. El residuo se disolvió en 3 mL de etanol y se transfirió a un tubo a presión. Se agregó hidróxido de amonio (7 mL) y el tubo se selló y se calentó a 50°C por 8 h. Después de enfriar a temperatura ambiente la reacción se diluyó con EtOAc (10 mL), se lavó con agua (2x10 mL) luego salmuera (1x10 mL), se secó sobre sulfato de sodio anhidro y se concentró a vacío. El producto crudo se purificó mediante HPLC preparativa. Las fracciones apropiadas se concentraron para remover el metanol y se alcalinizó con solución acuosa saturada de carbonato ácido de sodio. La capa acuosa se

extrajo con EtOAc (2 x 20 mL) y los extractos orgánicos combinados se lavaron con salmuera (1x10 mL), se secó sobre sulfato de sodio anhidro, y se concentró. El residuo se disolvió en dioxano (2 mL) y se cargó con HCl 1N en éter (1 mL).

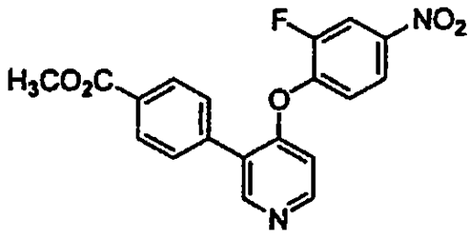
La solución se concentró y el sólido resultante se liofilizó a partir de acetonitrilo/agua para dar la sal de HCl del compuesto del título (24 mg, 53%) como un sólido blanco.

RMN-^{1}H (DMSO-d_6) δ 12.13 (s, 1H). 8.74 (s, 1H), 8.55-8.51 (m, 2H), 8.09 (dd, 1H, J = 6.4. 2 Hz), 8.03 (m, 1H), 7.64 (d, 2H, J = 6 Hz), 7.63 (m, 1H), 7.54-7.41 (m, 6H), 7.38 (d, 2H, J = 8.4 Hz), 7.04 (d, 1H, J = 6 Hz), 6.68 (t, 1H, J = 6.8 Hz), 3.02 (m, 2H). 2.89 (m, 2H); MS(ESI$^+$) m/z 521.27 $(M + H)^+$.

Ejemplo 69

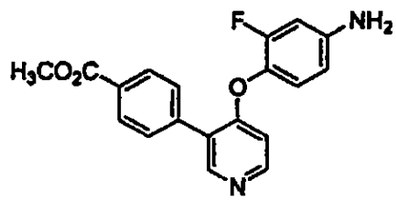


N-(4-(3-(4-((2-(Metilamino)etil)carbamoil)fenil)piridin-4-iloxi)-3-fluorofenil)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridin-3-carboxamida, sal de diclorhidrato



A) 4-(4-(2-fluoro-4-nitrofenoxi)piridin-3-il)benzoato de metilo

Preparado de una manera similar al Paso A del Ejemplo 59 para dar el compuesto del título (77%) como un aceite incoloro. RMN-^{1}H (CD_3OD) δ 8.66 (s, 1H), 8.52 (d, 1H. J = 6 Hz), 8.22 (dd, 1H, J = 10.4, 2.8 Hz), 8.16-8.13 (m, 1H). 8.10 (d, 2H, J = 8.4 Hz), 7.97 (d, 2H, J = 8 Hz), 7.44 (t, 1H, J = 8.5 Hz), 7.06 (d, 1H, J = 6 Hz), 3.93 (s, 3H); MS (ESI^+) m/z 369.22 $(M + H)^+$.

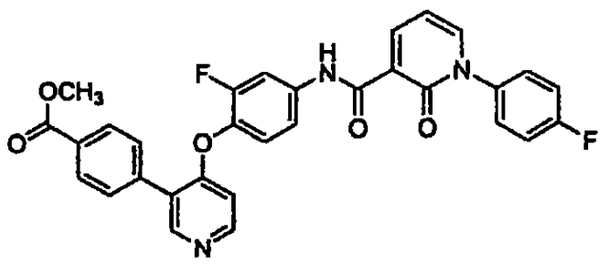


B) 4-(4-(4-amino-2-fluorofenoxı)piridin-3-il)benzoato de metilo

Preparado de una manera similar al Paso C del Ejemplo 59 para dar el Compuesto del título (99%) como un aceite amarillo. RMN-^{1}H (CD_3OD) δ 8.38 (s, 1H), 8.24 (d, 1H. J = 6 Hz), 8.01 (d, 2H, J = 8.4 Hz), 7.66 (d, 2H, J = 8.4 Hz), 6.85 (t, 1H, J = 9.2 Hz), 6.65 (d, 1H, J = 6 Hz), 6.48 (dd, 1H. J

519

= 12.8, 2.4 Hz), 6.43 (d, 1H. J = 2.8 Hz), 3.82 (s, 3H); MS(ESI$^+$) m/z 339.28 $(M + H)^+$.



C) 4-(4-(2-fluoro-4-(1-(4-fluorofenil)-2-oxo-1,2-dihidropiridin-3-carboxamido)fenoxi)piridin-3-il)benzoato de metilo

Preparado de una manera similar al Paso C del Ejemplo 62 para dar el compuesto del título (81%) como un aceite amarillo. RMN-^{1}H (CD_3OD) δ 8.66 (dd, 1H. J = 7.2, 2 Hz), 8.56 (s, 1H), 8.40 (d, 1H, J = 6 Hz), 8.13 (d, 2H, J = 8.4 Hz), 7.97-7.95 (m, 2H), 7.78 (d, 2H, J = 8.4 Hz), 7.55-7.52 (m, 2H), 7.38-7.31 (m, 3H), 7.26 (t, 1H, J = 7.2 Hz), 6.82 (d, m, J = 5.6 Hz), 6.72 (t, 1H, J = 6.7 Hz), 3.94 (s, 3H); MS (ESI$^+$) m/z 554.21 $(M + H)^+$.

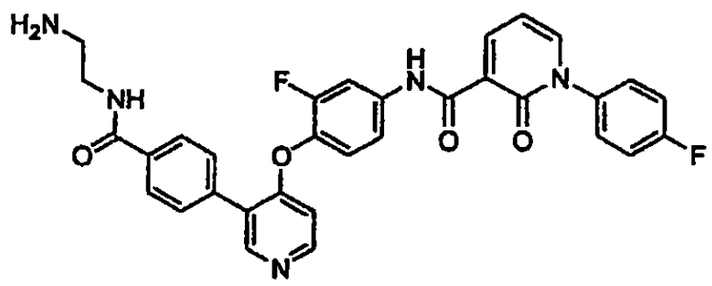
D) N-(4-(3-(4-((2-(Metilamino)etil)carbamoil)fenil)piridin-4-iloxi)-3-fluorofenil)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridin-3-carboxamida

Al éster anterior (159 mg, 0.29 mmol) en THF (5 mL) se agregó solución acuosa de hidróxido de sodio 1 N (5 mL). Después de agitar a temperatura ambiente por 20 h, la reacción se concentró para eliminar el THF. La solución

acuosa se acidificó a pH 4 con HCl acuoso 1N. El ácido se recolectó mediante filtración y se lavó con agua para dar el producto deseado (144 mg, 92%) como un sólido tostado. MS (ESI^+) m/z 540.21 $(M + H)^+$.

La amida se preparó como se describió anteriormente utilizando TBTU para dar la sal de HCl del compuesto del título (62%) como un sólido blanco. RMN-^{1}H (DMSO-d_6) δ 12.21 (s, 1H), 8.93-8.90 (m, 2H), 8.68-8.64 (m, 2H), 8.21 (dd, 1H, J = 6.4, 2 Hz), 8.16 (m, 1H), 8.11 (d, 2H, J = 8 Hz), 7.90 (d, 2H, J = 8.4 Hz), 7.69-7.65 (m, 2H), 7.60-7.47 (m, 4H), 7.16 (d, 1H, J = 5.6 Hz), 6.80 (t, 1H, J = 1 Hz), 3.64 (t, 2H, J = 5.2 Hz), 3.17 (t, 2H, J = 5.2 Hz), 2.65 (s, 3H): MS(ESI^+) m/z 596.37 $(M + H)^+$.

Ejemplo 70

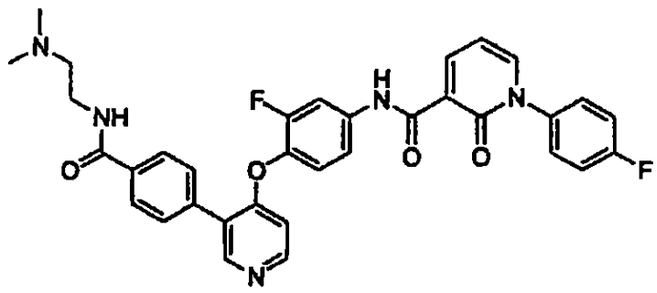


N-(4-(3-(4-((2-Aminoetil)carbamoil)fenil)piridin-4-iloxi)-3-fluorofenil)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridin-3-carboxamida, sal de diclorhidrato

Preparado de una manera similar al Ejemplo 69 para dar la sal de HCl del compuesto del título como un sólido blanquecino. RMN-^{1}H (DMSO-d_6) δ 12.17 (s, 1H), 8.87-8.85 (m,

2H), 8.64 (d, 1H, J = 6.4 Hz), 8.59 (dd, 1H, J = 7.6, 2.4 Hz), 8.16 (dd, 1H, J = 6.8, 2.4 Hz), 8.10 (m, 1H), 8.06 (d, 2H, J = 8.4 Hz), 8.00 (br s, 2H), 7.85 (d, 2H, J = 8.4 Hz), 7.64-7.60 (m, 2H), 7.55-7.42 (m, 4H), 7.13 (d, 1H, J = 6 Hz), 6.75 (t, 1H, J = 7.2 Hz), 3.56-3.53 (m, 2H), 3.04-2.99 (m, 2H); MS (ESI^+) m/z 582.32 $(M + H)^+$.

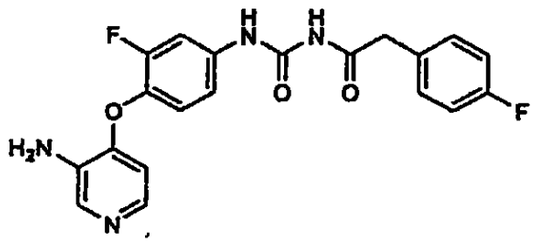
Ejemplo 71



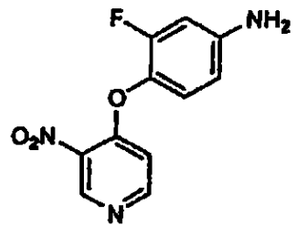
N-(4-(3-(4-((2-(Dimetilamino)etil)carbamoil)fenil)piridin-4-iloxi)-3-fluorofenil)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridin-3-carboxamida, sal de diclorhidrato

Preparado de una manera similar al Ejemplo 69 para dar la sal de HCl del compuesto del título (56%) como un sólido blanquecino. RMN-^1H (DMSO-d_6) δ 12.08 (s, 1H), 8.87 (brs. 1H), 8.75 (s, 1H), 8.54-8.51 (m, 2H), 8.08 (dd, 1H, J = 6.8, 2.4 Hz), 8.02 (m, 1H). 7.99 (d, 2H, J = 8.4 Hz), 7.77 (d, 2H, J = 8.4 Hz), 7.56-7.53 (m, 2H), 7.47-7.34 (m, 4H). 6.99 (d, 1H. J = 5.6 Hz), 6.67 (t, 1H, J = 6.8 Hz), 3.61-3.57 (m, 2H), 3.23-3.21 (m, 2H), 2.77 (s, 3H), 2.76 (s, 3H); MS (ESI^+) m/z 610.30 $(M + H)^+$.

Ejemplo 72



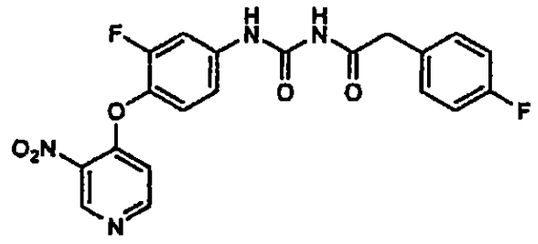
1-(4-(3-Aminopiridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea



A) 3-Fluoro-4-(3-nitropiridin-4-iloxi)bencenamina

Al 4-amino-2-fluorofenol (ver Paso A del Ejemplo 19, 127 mg, 1.0 mmol) en DMF (5 mL) a temperatura ambiente bajo nitrógeno se agregó hidruro de sodio (80 mg, 2 mmol, 60%). Después de agitar a temperatura ambiente por 10 min, se agregó clorhidrato de 4-cloro-3-nitropiridina (Lancaster. 195 mg, 1.0 mmol). La mezcla se agitó a temperatura ambiente por 1 h y luego se diluyó con EtOAc (50 mL) y se lavó con agua, solución acuosa al 10% de cloruro de litio, y luego salmuera (1 x 30 mL cada uno). La capa orgánica se secó sobre Na_2SO_4 anhidro y se concentró a vacío. El producto crudo se purificó mediante cromatografía instantánea en columna sobre gel de sílice eluyendo con EtOAc para dar el compuesto del título

(150 mg, 60%) como un sólido amarillo-naranja. RMN-^{1}H (DMSO-d_6) δ 9.13 (s, 1H), 8.63 (d, 1H. J = 6 Hz), 7.09 (t, 1H, J = 9.2 Hz), 6.92 (d, 1H, J = 6 Hz), 6.55 (dd, 1H, J = 13.2, 2.4 Hz), 6.45 (dd, 1H, J = 9.2, 2.4 Hz), 5.61 (s, 2H); MS (ESI$^+$) m/z 250.18 $(M + H)^+$.



B) 1-(3-Fluoro-4-(3-nitropiridin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)urea

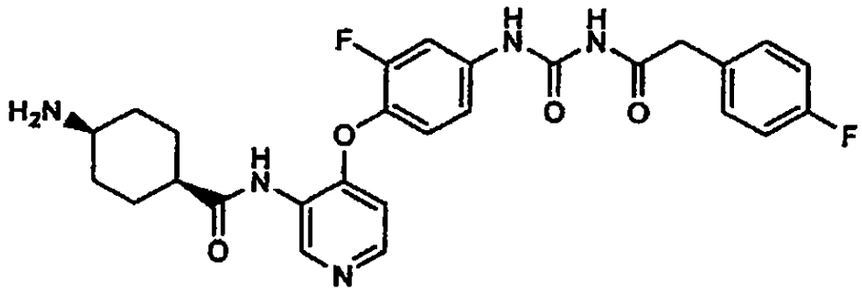
Una solución de 3-fluoro-4-(3-nitropiridin-4-iloxi)bencenamina (158 mg, 0.63 mmol) en THF (3 mL) se trató con una solución de isocianato de 2-(4-fluorofenil)acetilo en tolueno (Compuesto D del Ejemplo 11, 1.3 mmol) y se agitó a temperatura ambiente por 2 h luego a 50 °C por 5 min. La mezcla se concentró y el residuo se trató con DMF (15 mL) y SiO_2 (150 mg) y la mezcla se concentró hasta sequedad a vacío y se aplicó a una columna de SiO_2. La columna se eluyó con 20-60% de EtOAc/hexanos para dar el producto, el cual se purificó mediante trituración con éter isopropílico para dar un sólido amarillo pálido (120 mg, 25%). RMN-^{1}H (DMSO-d_6) δ 11.07 (s, 1H), 10.63 (s, 1H), 9.19 (s, 1H), 8.67 (d, 1H, J =

5.6 Hz), 7.85 (d, 1H, J = 11.7 Hz), 7.46 - 7.45 (m, 2H), 7.39 - 7.35 (m, 2H), 7.18 (dd, 2H, J = 8. 6, 8.6 Hz), 7.01 (d, 1H, J = 6.1 Hz), 3.76 (s, 2H).

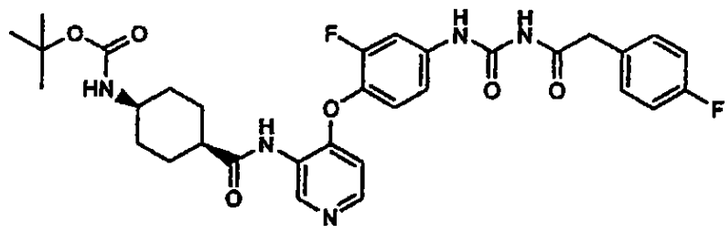
C) 1-(4-(3-Aminopiridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea

Una suspensión de 1-(3-fluoro-4-(3-nitropiridin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)urea (125 mg, 0.29 mmol) en McOH/THF 3:1 (20 mL) se hidrogenó sobre Pt_2O (50 mg) utilizando H_2 de un globo de látex por 6 h. El catalizador se filtró con la ayuda de Celite® y el filtrado se concentró para dar el compuesto del título (85 mg, 74%) como un sólido blanco. RMN-^{1}H (DMSO-d_6) δ 11.03 (s, 1H), 10.55 (s, 1H), 8.03 (s, 1H), 7.75 (dd, 1H, J = 2. 5, 13.2 Hz), 7.65 (d, 1H, J = 5.1 Hz), 7.38 - 7.35 (m, 3H), 7.23 - 7.16 (m, 3H), 6.42 (d, 1H, J = 5.1 Hz), 5.26 (s, 2H), 3.75 (s, 2H); MS (ESI^+) : m/z 399.35 $(M + H)^+$.

Ejemplo 73



1-(4-(3-((1S,4S)-4-Aminociclohexancarboxamido)piridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil) acetil) urea, sal del ácido trifluoroacético



A) (1S,4S)-4-((4-(2-fluoro-4-(3-(2-(4-fluorofenil)acetil)ureido)fenoxi)piridin-3-il)carbamoil)ciclohexilcarbamato de ter-butilo

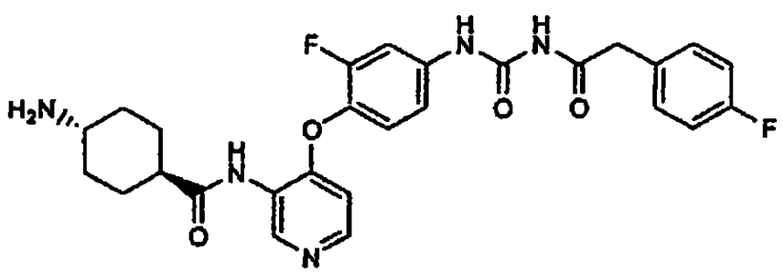
Una solución de ácido N-Boc-cis-1,4-diaminociclohexancarboxílico (Chem-Imprex International, 24 mg, 0.10 mmol) en THF (1 mL) se enfrió a 0°C, y se trató con Et_3N y luego cloroformiato de isobutilo. Después de 5 min, la mezcla se trató con una solución de 1-(4-(3-aminopiridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil) urea (Compuesto C del Ejemplo 72, 27 mg, 0.068 mmol) en THF (0.5 mL) y la agitación continuó a 0 °C por 10 min y luego a temperatura ambiente por 2 h.

La mezcla se dividió entre EtOAc y solución acuosa saturada de carbonato ácido de sodio y la fase de EtOAc se separó, se secó (sulfato de magnesio) y se concentró a vacío para dar el producto crudo. La purificación del residuo mediante cromatografía instantánea en columna sobre SiO_2 eluyendo con 50-100% de EtOAc/hexanos dio el compuesto del título (13 mg, 21%) como un sólido blanco. MS(ESP): m/z 624.25 $(M + H)^+$.

B) 1-(4-(3-((1S,4S)-4-Aminociclohexancarboxamido)piridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil) acetil) urea, sal del ácido trifluoroacético

Una solución de (1S, 4S)-4-((4-(2-fluoro-4-(3-(2-(4-fluorofenil)acetil)ureido)fenoxi)piridin-3-il)carbamoil)ciclohexilcarbamato de ter-butilo (10 mg, 0.016 mmol) en MeOH anhidro (0.5 mL) se enfrió a 0°C y se trató con HCl 4 M/1,4-dioxano (2 mL). La mezcla se agitó a 0°C por 1.5 h y luego a temperatura ambiente por 20 min y finalmente se concentró a vacío para dar el producto crudo. La purificación del residuo mediante HPLC preparativa (Columna A) dio el compuesto del título (4 mg. 33%) como un sólido amarillo. RMN-^{1}H (DMSO-d_6) δ 11.07 (s, 1H), 10.64 (s, 1H). 9.28 (s, 1H), 8.40-8.37 (m, 1H), 7.94 (s, 1H), 7.83 (dd, 1H, J = 2.1, 12.7 Hz), 7.47 - 7.33 (m, 5H), 7.19-7.14 (m, 3H), 7.07 - 7.02 (m, 1H), 3.75 (s, 2H), 3.25-3.15 (m, 1H), 2.85 - 2.76 (m, 1H), 1.97-1.84 (m, 2H), 1.85 -1.61 (m, 5H); MS (ESI$^+$) : m/z 524.26 $(M + H)^+$.

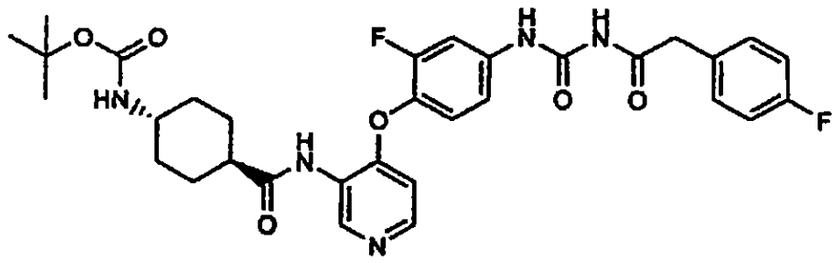
Ejemplo 74



1-(4-(3-((1R,4R)-4-Aminociclohexancarboxamido)piridin-4-

520 527

iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil) acetil) urea, sal del ácido bis-trifluoroacético



A) (1R,4R)-4-((4-(2-fluoro-4-(3-(2-(4-fluorofenil) acetil)ureido)fenoxi)piridin-3-il)carbamoil)ciclohexilcarbamato de ter-butilo

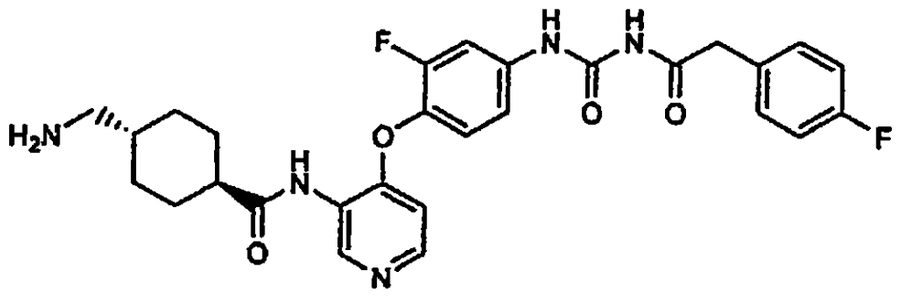
El compuesto del título se preparó a partir de 1-(4-(3-aminopiridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea (Compuesto C del Ejemplo 72, 57 mg, 0.14 mmol) y ácido N-Boc-trans-4-aminociclohexano-1-carboxílico (Anaspec Inc., 51 mg, 0.21 mmol) de una manera similar a la que se describe para el Paso A del Ejemplo 73 para dar el compuesto del título (32 mg, 66%) como un sólido blanco. MS (ESI^+) : m/z 624.41 $(M + H)^+$.

B) 1-(4-(3-((1R,4R)-4-Aminociclohexancarboxamido)piridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil) acetil) urea, sal del ácido bis-trifluoroacético

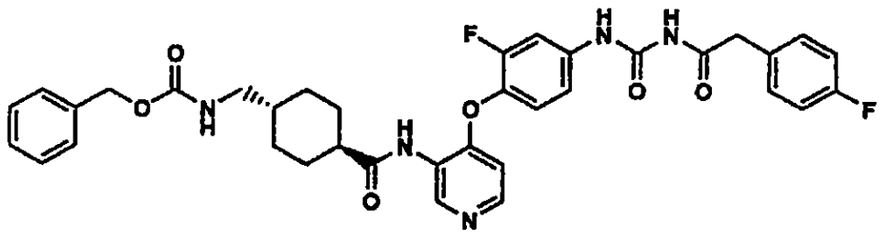
El compuesto del título se preparó a partir del (1S, 4S)-4-((4-(2-fluoro-4-(3-(2-(4-fluorofenil)acetil)ureido)fenoxi)piridin-3-

il)carbamoil)ciclohexilcarbamato de ter-butilo (25 mg) de una manera similar a la que se describe para el Ejemplo 73. La purificación de la mezcla de reacción mediante HPLC preparativa (Columna A) dio el compuesto del título (7 mg, 23%) como un sólido blanco. RMN-^{1}H (DMSO-d_6) δ 11.06 (s, 1H), 10.61 (s, 1H), 9.94 (s, 1H), 9.19 (s, 1H), 8.28 (d, 1H, J = 5.6 Hz), 7.82 (dd, 1H, J = 2.0. 13.2 Hz), 7.79 - 7.76 (m, 3H), 7.43 (dd, 1H, J = 2.0, 8.6 Hz), 7.38 - 7.33 (m, 2H), 7.17 (dd, 2H, J = 9.2, 6.6 Hz), 6.86 (d, 1H. J = 5.6 Hz), 3.74 (s, 2H), 3.08 -2.95 (m, 1H), 2.67-2.43 (m, 1H), 2.01 - 1.88(m, 4H), 1.53 - 1.43 (m, 2H), 1.37-1.27 (m, 2H); MS (ESI$^+$) : m/z 524.35 $(M + H)^+$.

Ejemplo 75



1-(4-(3-((1R,4R)-4-(Aminometil)ciclohexancarboxamido)piridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil) acetil) urea



A) (1R,4R)-4-((4-(2-fluoro-4-(3-(2-(4-fluorofenil)acetil)ureido)fenoxi)piridin-3-il)carbamoil)ciclohexil)metilcarbamato de bencilo

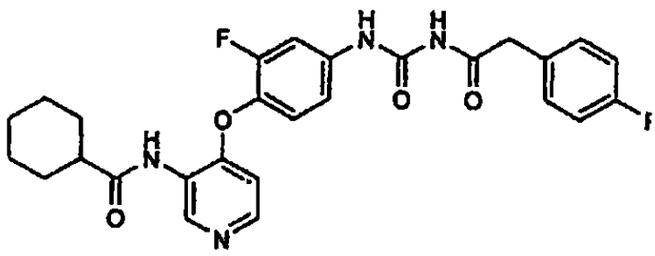
El compuesto del título se preparó a partir de 1-(4-(3-aminopiridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea (Compuesto C del Ejemplo 72, 50 mg, 0.13 mmol) y ácido trans-4-((benciloxicarbonil)metil)ciclohexancarboxílico (40 mg. 0.14 mmol, preparado de acuerdo a la ruta sintética (descrita en Schaus, J. M. et al. J. Med. Chem. 1998, 41, 1943-1955) de acuerdo al Paso A del Ejemplo 73 para dar el compuesto del título (30 mg, 34%) como un sólido blanco. MS(ESI$^+$): m/z 672.34 $(M + H)^+$.

B) 1-(4-(3-((1R,4R)-4-(Aminometil)ciclohexancarboxamido)piridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil) acetil) urea

Una solución de ((1R,4R)-4-((4-(2-fluoro-4-(3-(2-(4-fluorofenil)acetil)ureido)fenoxi)piridin-3-il)carbamoil)ciclohexil)metilcarbamato de bencilo (25 mg 0.037 mmol) en McOH (1.5 mL) se hidrogenó sobre 10 de

paladio-carbono (15 mg) por 4 h utilizando H_2 desde un globo de caucho. El catalizador se filtró y el filtrado se concentró a vacío para dar el compuesto del título (18 mg, 90%) como un sólido amarillo. RMN-^{1}H (DMSO-d_6) δ 10.62 (s, 1H), 9.64 (s, 1H), 9.01 (s, 1H), 8.17 (d, 1H, J = 5.6 Hz), 7.79 (dd, 1H, J = 2.5, 12.7 Hz), 7.42 - 7.35 (m, 4H), 7.30 (dd, 1H, J = 8.6, 9.2 Hz), 7.18 (m, 2H), 6.66 (d, 1H, J = 5.6 Hz), 3.75 (s, 2H), 2.39 (d, 2H, J = 6.6 Hz), 1.87-1.81 (m, 4H), 1.46-1.35 (m, 1H), 1.33 - 1.10 (m, 1H), 0.95-0.77 (m, 4H) : MS (ESI$^+$) : m/z 538.28(M + H)$^+$.

Ejemplo 76



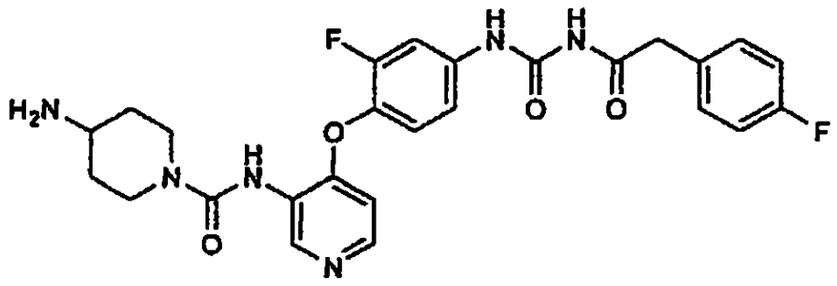
1-(4-(3-(Ciclohexancarboxamido)piridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil) acetil) urea

Una solución de 1-(4-(3-aminopiridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea (Compuesto C del Ejemplo 72, 25 mg, 0.062 mmol) en cloruro de metileno (2 mL) se trató con Et_3N (10 µL, 0.074 mmol) y cloruro de ciclohexancarbonilo (Aldrich, 11 mg, 0.074 mmol) y se agitó a temperatura ambiente por 2 h. Se agregó una porción adicional

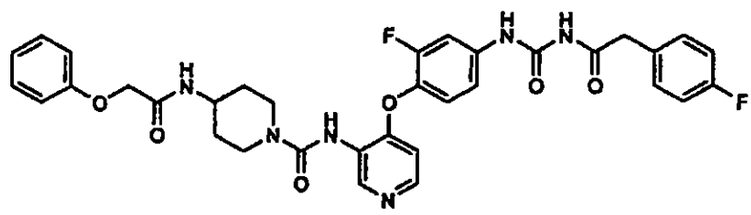
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de cloruro de ciclohexancarbonilo (11 mg, 0.074 mmol) a la mezcla, y la reacción continuó por 18 h. La mezcla se diluyó con cloruro de metileno, se lavó con solución acuosa saturada de carbonato ácido de sodio, se secó (sulfato de magnesio) y se concentró a vacío. El residuo se purificó mediante cromatografía instantánea en columna sobre SiO_2 eluyendo con 50-100 de EtOAc/hexanos para dar el compuesto del título (19 mg, 61%) como un sólido blanco. RMN-^{1}H (DMSO-d_6) δ 11.03 (s, 1H), 10.57 (m, 1H), 9.60 (m, 1H), 8.99 (s, 1H), 8.15 (d, 1H, J = 5.6 Hz), 7.76 (dd, 1H, J = 2.0, 13.2 Hz), 7.39 - 7.33 (m, 3H), 7.28 (dd, 1H, J = 8.6, 9.2 Hz), 7.18 -7.14 (m,2H), 6.65 (d, 1H, J = 5.1 Hz), 3.73 (s, 2H), 1.81 -1.71 (m, 5H), 1.64-1.61 (m, 1H), 1.43 - 1.34 (m, 2H), 1.29- 1.14 (m, 3H); MS(ESI+): m/z 509.27 $(M + H)^+$.

Ejemplo 77



1-(4-(3-(4-Aminopiperidin-1-carboxamido)piridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil) acetil) urea, sal del ácido bis-trifluoroacético



A) 1-(3-Fluoro-4-(3-(4-(2-fenoxiacetamido)piperidin-1-carboxamido)piridin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)urea

Una solución de trifosgeno (50 mg, 0.17 mmol), en cloruro de metileno (0.4 mL) se enfrió a -10°C y se trató con una solución de 1-(4-(3-aminopiridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea (Compuesto C del Ejemplo 72, 67 mg, 0.17 mmol) y DIPEA (65 µL, 0.37 mmol) en cloruro de metileno (0.4 mL). La mezcla se agitó a -10°C por 10 minutos y luego se trató con una solución de 4-((carbobenciloxi)amido)piperidina (40 mg, 0.17 mmol, preparada utilizando el procedimiento descrito en Schaus, J. M. et al. J. Med. Chem. 1998, 41, 1943-1955) y DIPEA (65 µl, 0.37 mmol) en cloruro de metileno (0.4 mL). Después de agitar por 2 minutos, la mezcla se calentó a temperatura ambiente luego se calentó a 40°C por 10 min. La mezcla se diluyó con EtOAc, se lavó con solución acuosa saturada de carbonato ácido de sodio y salmuera, se secó (sulfato de magnesio) y se concentró a vacío. El producto se purificó mediante

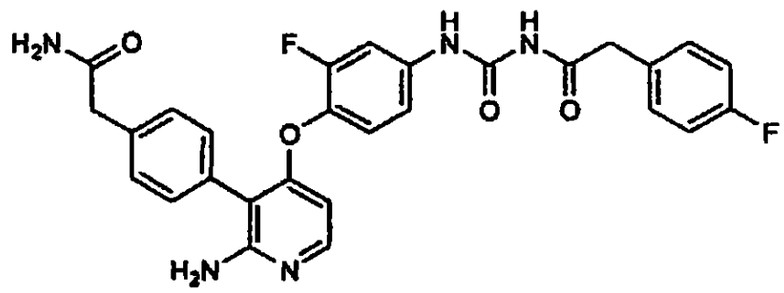
cromatografía instantánea en columna sobre Si02 eluyendo con 0-5% de NeOH/cloruro de metileno para dar el compuesto del título (50 mg, 45%) como un sólido amarillo. MS(ESI+) m/z 659.29 $(M + H)^+$.

B) 1-(4-(3-(4-Aminopiperidin-1-carboxamido)piridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea, sal del ácido bis-trifluoroacético

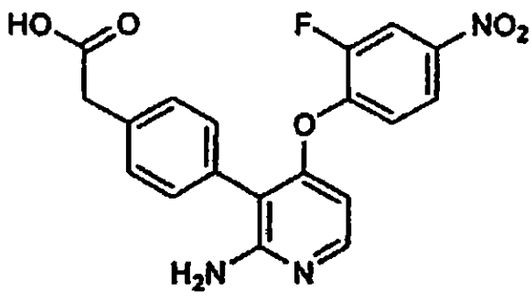
Una solución de 1-(3-fluoro-4-(3-(4-(2-fenoxiacetamido)piperidin-1-carboxamido)piridin-4-iloxi)fenil)-3-(2-(4-fluorofenil) acetil) urea (45 mg, 0.068 mmol) en metanol absoluto (2.5 mL) se hidrogenó sobre 10 % de paladio-carbono (15 mg) utilizando H2 de un globo de caucho por 2.5 h. El catalizador se filtró y el filtrado se concentró a vacío y el residuo se purificó mediante HPLC preparativa (Columna A) para proporcionar el compuesto del título. RMN-^{1}H (DMSO-d_6) δ 10.57 (s, 1H), 8.55 (s, 1H), 8.27 (m, 1H), 8.14 (d, 1H, J = 5.6 Hz), 7.75 (dd, 1H, J = 2.0, 12.7 Hz), 7.37-7.33 (m, 3H), 7.23 - 7.14 (m, 3H), 6.65 (d, 1H, J = 5.1 Hz), 4.05 - 3.98 (m, 2H), 3.73 (s,2H), 3.05-2.91 (m, 1H), 2.88-2.83 (m, 2H), 1.83 - 1.74 (m, 2H), 1.34-1.20 (m, 2H); MS(ESI+) m/z 525.35 $(M + H)^+$.

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Ejemplo 78



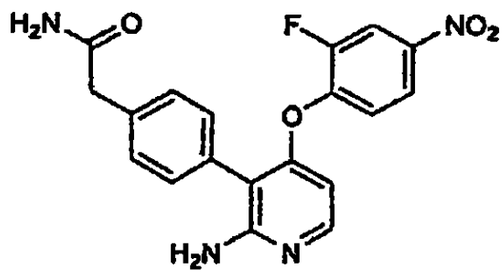
1-(4-(2-Amino-3-(4-(2-amino-2-oxoetil)fenil)piridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea, sal del ácido trifluoroacético



A) 2-(4-(2-Amino-4-(2-fluoro-4-nitrofenoxi)piridin-3-il)fenil)ácido acético

Una mezcla de 4-(2-fluoro-4-nitrofenoxi)-3- yodopiridin-2-amina (Compuesto C del Ejemplo 34, 88 mg, 0.23 mmol), éster de pinacol del ácido 4-(dihidroxiboran)fenilacético (Frontier Scientific Inc., 92 mg, 0.35 mmol), Na_3CO_3 (170 mg, 1.61 mmol), 1,4-dioxano (2 mL) y agua (2 mL), se desgasificó mediante vacío/purga con argón y se trató con tetrakis(trifenilfosfina)paladio (27 mg, 0.023 mmol). Después

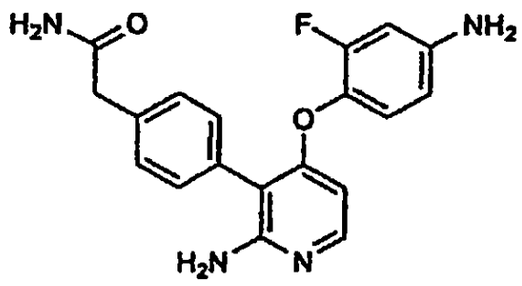
de calentar a 100 °C por 3 h, el pH de la mezcla se ajustó a pH 6 utilizando HCl 1N. La mezcla se concentró a vacío y el residuo se dividió entre EtOAc y amortiguador de fosfato de pH 7. La fase acuosa se extrajo con EtOAc y Los extractos combinados se secaron (sulfato de magnesio) y se concentró a vacío para dar el producto crudo. El producto se trituró con 2:1 EtOAc/MeOH para dar el producto deseado (70 mg, 80%) como un sólido naranja-café. RMN-^{1}H (DMSO-d_6) δ 12.34 (s, 1H), 8.23 (dd, 1H, J = 3. 1, 10.5 Hz), 8.05 (d, 1H, J = 10.2 Hz), 7.94 (d, 1H, J = 6.1 Hz). 7.32 - 7.25 (m, 5H), 6.26 (d, 1H, J = 6.1 Hz), 5.62 (s, 2H), 3.57 (s, 2H); MS (ESI$^+$) : m/z 384.16 $(M + H)^+$.



B) 2-(4-(2-Amino-4-(2-fluoro-4-nitrofenoxi)piridin-3-il)fenil)acetamida

Una solución de ácido 2-(4-(2-amino-4-(2-fluoro-4-nitrofenoxi)piridin-3-il)fenil)acético (65 mg, 0.17 mmol) en DMF anhidra (1.2 mE) se trató con PyBOP (125 mg, 0.24 mmol) y HOBt (32 mg, 0.24 mmol), seguido por DIPEA (60 Hl, 0.35 mmol) y NH_4Cl (19 mg, 0.35 mmol). Después de agitar a temperatura ambiente por 20 min, la mezcla se concentró a vacío y el

residuo se dividió entre EtOAc y solución acuosa saturada de carbonato ácido de sodio. La fase de EtOAc se lavó con salmuera, se secó (sulfato de magnesio) y se concentró a vacío. El producto se purificó mediante cromatografía instantánea en columna sobre SiO_2 eluyendo con 0-8 % de McOH/cloruro de metileno para dar el compuesto del título (40 mg, 62%) como un aceite de color ámbar. RMN-^{1}H (DMSO-d_6) δ 8.23 (dd, 1H, J = 10.7, 2.5 Hz), 8.05 (d, 1H, J = 9.2 Hz), 7.93 (d, 1H, J = 6.1 Hz), 7.42-7.32 (m, 2H), 7.33-7.25 (m, 4H), 6.92 (s, 1H), 6.25 (d, 1H, J = 5.6 Hz), 5.64 (s, 2H), 3.36 (s, 2H); MS(ESI$^+$): m/z 383.17 $(M + H)^+$.



C) 2-(4-(2-Amino-4-(4-amino-2-fluorofenoxi)piridin-3-il)fenil)acetamida

Una mezcla de 2-(4-(2-amino-4-(2-fluoro-4-nitrofenoxi)piridin-3-il)fenil)acetamida (32 mg, 0.086 mmol), DMF (1 mL), EtOH (1 mL) y H_2O (1 mL) se trató con polvo de hierro (67 mg, 1.2 mmol), y cloruro de amonio (128 mg, 2.4 mmol) y la mezcla se calentó a 100 °C por 20 min. La mezcla se filtró a través de Celite®, el pH del filtrado se ajustó a

pH 7 utilizando amortiguador de fosfato, y luego la mezcla se extrajo con EtOAc. El extracto orgánico se secó (sulfato de magnesio) y se concentró para dar el producto deseado (20 mg, 67%) como un sólido amarillo-café. MS (ESI^+) : m/z 353.32 $(M + H)^+$.

D) 1-(4-(2-Amino-3-(4-(2-amino-2-oxoetil)fenil)piridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil) acetil)urea, sal del ácido trifluoroacético

El compuesto del título se preparó a partir de la 2-(4-(2-amino-4-(4-amino-2-fluorofenoxi)piridin-3-il)fenil)acetamida (19 mg, 0.054 mmol) y solución 0.3 M de isocianato de 2-(4-fluorofenil)acetilo en tolueno (Compuesto D del Ejemplo 11, 0.27 mL, 0.081 mmol) de una manera similar a aquella descrita para el Paso D del Ejemplo 33. La purificación de la mezcla de reacción mediante HPLC preparativa (Columna A) dio el compuesto del título (9 mg, 26%) como un sólido blanco. RMN-^{1}H (DMSO-d_6) δ 11.03 (s, 1H), 10.57 (s, 1H), 7.93 (d, 1H, J = 7.1 Hz), 7.76 (dd, 1H, J = 2.0, 13.2 Hz), 7.44 -7.42 (m, 3H), 7.37 - 7.29 (m, 6H), 7.16 (dd, 2H, J = 8.6, 8.8 Hz), 6.94 (s, 1H), 6.31 (d, 1H, J = 7.1 Hz), 3.72 (s, 2H), 3.43 (s, 2H); MS (ESI^+) : m/z 532.24 $(M + H)^+$.

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Maria Vásquez

De: Maria Vásquez
Enviado el: Viernes, 20 de Octubre de 2006 12.33 p m
Para: 'ross kathleen@arentfox com'
Asunto: MARS, INCORPORATED - Design Applications for Twix Fino Candy Bar Designs (with and without wording) - Y/R 022141 00052.PA 36 & 37 O/R. 101

October 20, 2006

E-mail: ross kathleen@arentfox com

Ms Katie Ross
Foreign Filing Specialist
Arent Fox PLLC
1050 Connecticut Avenue, NW
Washington, DC 20036

Re. MARS, INCORPORATED
Design Applications for Twix Fino Candy Bar Designs (with and without wording) Nos 06066473 & 06066477)
Your Ref. 022141.00052 PA.36 & 37
Our Ref Nos 101 643 and 101 644

Dear Ms. Ross

We acknowledge receipt of your today's e-mail attaching the lower view of the design, as well as the assignment document duly legalized by Apostille, in connection with the above-identified design application, for which we thank you.

Considering that the term for filing the assignment document is next Monday October 23, we will proceed to file the assignment copy we have received along with your e-mail under-reply, however, given the fact that this document was issued to be used in trademark procedures in El Salvador, it is very likely that the Patent Office will reject it If it is possible, we would appreciate it if you could make a correction on the Affidavit in order to avoid a possible rejection from the Patent Office

Very truly yours,

BRIGARD & CASTRO

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Tel (571) 744 2200
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BOGOTA, COLOMBIA
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MEV/aac

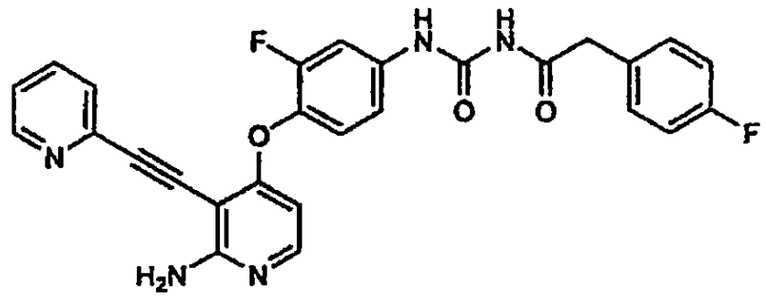
pH 7 utilizando amortiguador de fosfato, y luego la mezcla se extrajo con EtOAc. El extracto orgánico se secó (sulfato de magnesio) y se concentró para dar el producto deseado (20 mg, 67%) como un sólido amarillo-café. MS (ESI^+) : m/z 353.32 $(M + H)^+$.

D) 1-(4-(2-Amino-3-(4-(2-amino-2-oxoetil)fenil)piridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil) acetil)urea, sal del ácido trifluoroacético

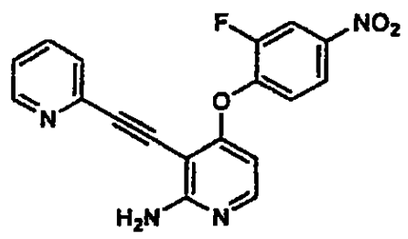
El compuesto del título se preparó a partir de la 2-(4-(2-amino-4-(4-amino-2-fluorofenoxi)piridin-3-il)fenil)acetamida (19 mg, 0.054 mmol) y solución 0.3 M de isocianato de 2-(4-fluorofenil)acetilo en tolueno (Compuesto D del Ejemplo 11, 0.27 mL, 0.081 mmol) de una manera similar a aquella descrita para el Paso D del Ejemplo 33. La purificación de la mezcla de reacción mediante HPLC preparativa (Columna A) dio el compuesto del título (9 mg, 26%) como un sólido blanco. RMN-^{1}H (DMSO-d_6) δ 11.03 (s, 1H), 10.57 (s, 1H), 7.93 (d, 1H, J = 7.1 Hz), 7.76 (dd, 1H, J = 2.0, 13.2 Hz), 7.44 -7.42 (m, 3H), 7.37 - 7.29 (m, 6H), 7.16 (dd, 2H, J = 8.6, 8.8 Hz), 6.94 (s, 1H), 6.31 (d, 1H, J = 7.1 Hz), 3.72 (s, 2H), 3.43 (s, 2H); MS (ESI^+) : m/z 532.24 $(M + H)^+$.

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Ejemplo 79



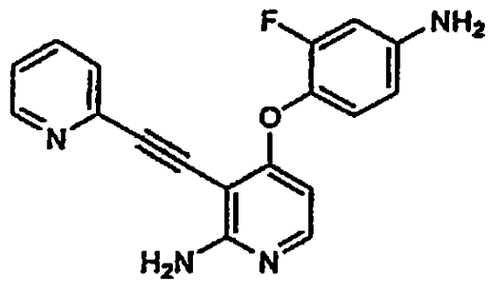
1-(4-(2-Amino-3-(2-(piridin-2-il)etinil)piridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil) acetil) urea, sal de diclorhidrato



A) 4-(2-Fluoro-4-nitrofenoxi)-3-(2-(piridin-2-il)etinil)piridin-2-amina

Una mezcla de 4-(2-fluoro-4-nitrofenoxi)-3- yodopiridin-2-amina (Compuesto C del Ejemplo 34, 100 mg, 0.27 mmol) y 2-etinilpiridina (Aldrich, 57 mg. 0.54 mmol), THF (2 mL) y Et_3N (2 mL) se desgasificó mediante vacío/purga con argón y se trató a su vez con CuI (6 mg, 0.032 mmol) y $(Ph_3P)_4Pd$ (20 mg, 0.017 mmol). La mezcla se calentó a 60°C por 45 minutos, se enfrió, se dividió entre EtOAc y solución acuosa saturada de carbonato ácido de sodio. La fase orgánica se secó (sulfato

de magnesio) y se concentró a vacío para dar el producto crudo. La purificación del residuo mediante cromatografía instantánea en columna sobre SiC_2 eluyendo con 0-1.5 de McOH/cloruro de metileno dio el compuesto del título (55 mg, 58%) como un sólido café. RMN-^{1}H (DMSO-d_6) δ 8.53 (d, 1H, J = 5.1 Hz), 8.39 (dd, 1H, ,7=2.5, 10.7 Hz), 8.15 (dm, 1H, J = 8.1 Hz), 7.97 (d, 1H, J = 5.6 Hz), 7.81 (d, 1H. J = 8.1 Hz), 7.71 (d, 1H, J = 7.6 Hz), 7.52 (dd, 1H, J = 8.6, 8.6 Hz), 7.38 - 7.34 (m, 1H), 6.71 (s, 2H), 6.21 (d, 1H, J = 5.6 Hz); MS(ESI$^+$): m/z 351.25 $(M + H)^+$.



B) 4-(4-Amino-2-fluorofenoxi)-3-(2-(piridin-2-il)etinil)piridin-2-amina

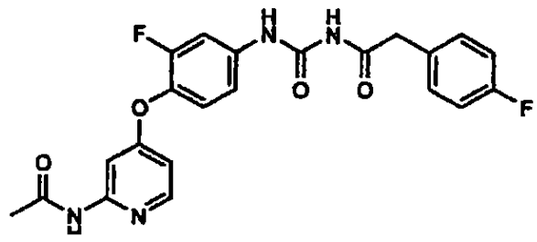
Una mezcla de 4-(2-fluoro-4-nitrofenoxi)-3-(2-(piridin-2-il)etinil)piridin-2-amina (35 mg, 0.1 mmol), THF (1.5 mL) y McOH (1.5 ml) se trató con polvo de zinc (65 mg, 1.0 mmol) y cloruro de amonio (53 mg, 1.0 mmol) y se calentó a 60°C por 45 min. La mezcla de reacción se enfrió, se filtró y se concentró a vacío. El residuo se dividió entre EtOAc y solución acuosa saturada de carbonato ácido de sodio. La fase

orgánica se separó, se lavó con salmuera, se secó (sulfato de magnesio) y se concentró para dar el compuesto del título (25 mg, 78%) como un sólido café. MS (ESI^+) : m/z 321.2 $(M + H)^+$.

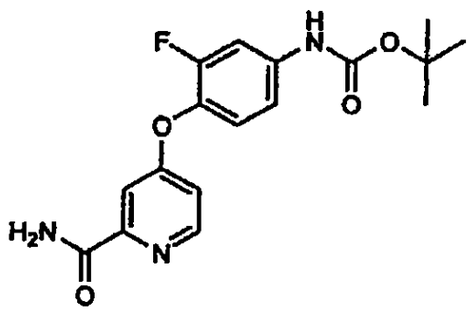
C) 1-(4-(2-Amino-3-(2-(piridin-2-il)etinil)piridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea, sal de diclorhidrato

Una solución de 4-(4-amino-2-fluorofenoxi)-3-(2-(piridin-2-il)etinil)piridin-2-amina (25 mg, 0.078 mmol) en THF (2 mL) se enfrió a 0°C y se trató con solución 0.3 M de isocianato de 2-(4-fluorofenil)acetilo en tolueno (Compuesto D del Ejemplo 11, 0.26 mL. 0.078 mmol). Después de 1 h, la mezcla se calentó a temperatura ambiente y se agitó por 15 min. La mezcla se concentró a vacío y el residuo se purificó mediante HPLC preparativa (Columna A) para dar el compuesto del título como una sal de TFA. La sal de TFA se disolvió en MeOH anhidro y se trató con HCl 1M/Et_2O a 0°C y se agitó por 5 min. La mezcla luego se concentró a vacío para dar el compuesto del título (18 mg, 41%) como un sólido café. RMN-^{1}H (DMSO-d_6) δ 11.06(s, 1H), 10.63 (s, 1H), 8.62 (d, 1H, J = 4.5 Hz), 8.22 (s, 2H), 7.99 (d, 1H. J = 7.1 Hz), 7.94 - 7.81 (m, 3H), 7.48 - 7.44 (m, 3H), 7.37 - 7.33 (m, 2H), 7.16 (dd, 2H, J = 6.2, 9.2 Hz), 6.30 (d, 1H, J = 7.1 Hz), 3.74 (s, 2H); MS (ESI^+) : m/z 500.21 $(M + H)^+$.

Ejemplo 80



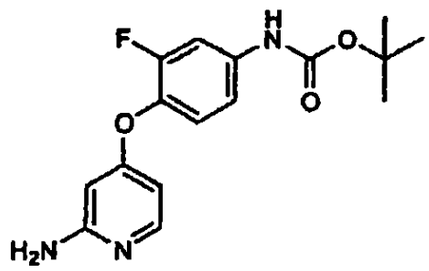
1-(4-(2-Acetamidopiridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea, sal de clorhidrato



A) 4-(2-carbamoilpiridin-4-iloxi)-3-fluorofenilcarbamato de ter-butilo

Una mezcla de 4-(4-amino-2-fluorofenoxi)picolinamida (Compuesto B' del Ejemplo 24, 190 mg, 0.76 mmol), alcohol ter-butílico (2 ml), 1,4-dioxano (1 ml), DMF (1 ml) y Boc_2O (167 mg, 0.76 mmol) se calentó a 65°C por 16 h. Se agregaron porciones adicionales de Boc_2O (85 mg y 60 mg) después de 16 h y 32 h, respectivamente y la mezcla se calentó por un total de 40 h. La mezcla se concentró a vacío y el residuo se dividió entre EtOAc y solución acuosa saturada de carbonato

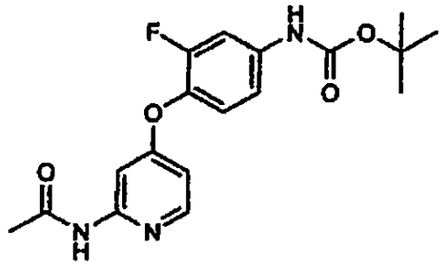
ácido de sodio. La fase de EtOAc se secó (sulfato de magnesio) y se concentró a vacío para dar el producto crudo. La purificación del residuo mediante cromatografía instantánea en columna sobre SiO_2 eluyendo con 30-60 de EtOAc/hexanos dio el compuesto del título (180 mg, 68%) como un sólido café. RMN-^{1}H (DMSO-d_6) δ 9.74 (s, 1H), 8.52 (d, 1H, J = 5.6 Hz), 8.13 (s, 1H), 7.72 (s, 1H), 7.62 (d, 1H, J = 13.7 Hz), 7.35-7.31 (m, 3H), 7.18 (dd, 1H, J = 5. 6, 2.5 Hz), 1.39 (s, 9H); MS (ESI$^+$) : m/z 348.22 $(M + H)^+$.



B) 4-(2-aminopiridin-4-iloxi)-3-fluorofenilcarbamato de ter-butilo

Una solución de KOH (280 mg, 5.0 mmol) en H_2O (2 mL) se enfrió a 0-5°C y se trató gota a gota con bromo (162 mg, 1.0 mmol) y la mezcla se agitó por 5 min. Se agregó 4-(2-carbamoilpiridin-4-iloxi)-3-fluorofenilcarbamato de ter-butilo (347 mg, 1.0 mmol) a la mezcla en una porción como un sólido y luego se agregó 1,4-dioxano (3 mL) para disolver los sólidos. La mezcla de reacción se agitó a temperatura ambiente por 30 min luego a 55 °C por 45 min. La mezcla luego

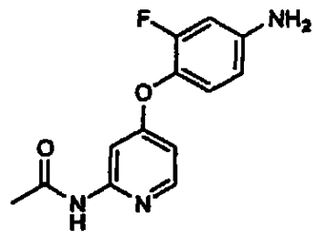
se enfrió a temperatura ambiente, se trató con HOAc (0.5 mL) y se agitó hasta que desapareció la espuma. La mezcla se recalentó a 55°C por 20 min, se enfrió a temperatura ambiente, se trató con KOH (350 mg) y se extrajo con cloruro de metileno. El extracto orgánico se secó (sulfato de magnesio) y se concentró a vacío. El residuo se purificó mediante cromatografía instantánea en columna sobre SiCh eluyendo con 30-70 de EtOAc/hexanos para dar el compuesto del título (265 mg, 83%). RMN-^{1}H (DMSO-d_6) δ 9.67 (s, 1H), 7.77 (d, 1H, J = 6.1 Hz), 7.56 (d, 1H, J = 11.7Hz), 7.26 -7.18 (m, 2H), 6.12 (dd, 1H, J = 2.0, 6.1 Hz), 5.93 (s, 2H), 5.74 (d, 1H, J = 2.5 Hz), 1.47 (s, 9H); MS(ESI$^+$): m/z 320.23 $(M + H)^+$.



C) 4-(2-acetamidopiridin-4-iloxi)-3-fluorofenilcarbamato de ter-butilo

El 4-(2-aminopiridin-4-iloxi)-3-fluorofenilcarbamato de ter-butilo (150 mg, 0.47 mmol) en piridina anhidra (0.5 mL) se enfrió a 10°C y se trató con cloruro de acetilo (33 µL, 0.47 mmol) y la mezcla se agitó por 45 min. Una porción adicional de cloruro de acetilo (16 µL, 0.24 mmol) se agregó a la reacción y la agitación se continuó por 25 min. La

mezcla se diluyó con EtOAc (20 mL), se lavó con salmuera, se secó (sulfato de magnesio) y se concentró a vacío para dar el compuesto del título (115 mg, 68%). RMN-^{1}H (DMSO-d_6) δ 10.55 (s, 1H), 9.71 (s, 1H), 8.16 (d, 1H. J = 5.5 Hz), 7.63-7.55 (m, 2H), 7.29-7.23 (m, 2H), 6.68-6.63 (m, 1H), 2.02 (s, 3H), 1.48 (s, 9H); MS(ESI$^+$): m/z 362.22 $(M + H)^+$.



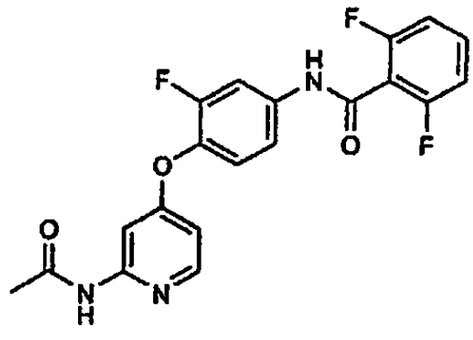
D) N-(4-(4-Amino-2-fluorofenoxi)piridin-2-il)acetamida

Una solución de 4-(2-acetamidopiridin-4-iloxi)-3-fluorofenilcarbamato de ter-butilo (110 mg, 0.30 mmol) en HCl 4 M/1,4-dioxano (1.5 mL) se agitó a 0°C por 20 min luego a temperatura ambiente por 25 min. La mezcla se diluyó con EtOAc (25 mL) y solución acuosa saturada de carbonato ácido de sodio (20 mL), y se agitó vigorosamente por 5 min. La fase de EtOAc se lavó con salmuera, se secó (sulfato de magnesio) y se concentró a vacío para dar el compuesto del título (69 mg, 87%) como un sólido amarillo. RMN-^{1}H (DMSO-d_6) δ 10.49 (s, 1H), 8.13 (d, 1H, J = 5.6 Hz), 7.60 (m, 1H), 6.95 (dd, 1H, J = 8.6. 9.2 Hz), 6.60 (dd, 1H, J = 2.5, 5.6 Hz), 6.48 (dd, 1H, J = 2.5, 13.2 Hz), 6.40 (dd, 1H, J = 2.0, 8.6 Hz), 5.44 (s, 2H), 2.02 (s, 3H).

E) 1-(4-(2-Acetamidopiridin-4-iloxi)-3-fluorofenil)-3-(2-(4- fluorofenil)acetil)urea, sal de clorhidrato

Una solución de N-(4-(4-amino-2- fluorofenoxi)piridin-2-il)acetamida (20 mg, 0.077 mmol) en THF (1 mL) se trató con solución 0.3 M de isocianato de 2-(4-fluorofenil)acetilo en tolueno (Compuesto D del Ejemplo 11, 0.26 mL, 0.77 mmol) y la mezcla se agitó a temperatura ambiente por 1 h. La mezcla se concentró a vacío y el residuo se purificó mediante HPLC preparativa (Columna A) para dar el compuesto del título como una sal de TFA. La sal de TFA se disolvió en McOH anhidro y se trató con HCl 1M/Et_2O a 0°C y se agitó por 5 min. La mezcla luego se concentró a vacío para dar el compuesto del título (12 mg, 33%) como un sólido blanco. RMN-^{1}H (DMSO-d_6) δ 11.04 (s, 1H), 10.65 (s, 1H), 10.58 (s, 1H), 8.18 (d, 1H, J = 6.1 Hz), 7.77 (dd, 1H, J = 2.0, 12.7 Hz), 7.56 (m, 1H), 7.40-7.30 (m, 5H). 7.18 - 7.14 (m, 2H), 6.71 (dd, 1H. J = 2.5. 6.1 Hz), 3.74 (s, 2H). 2.03 (s, 3H); MS (ESI^+) : m/z 441.18 $(M + H)^+$.

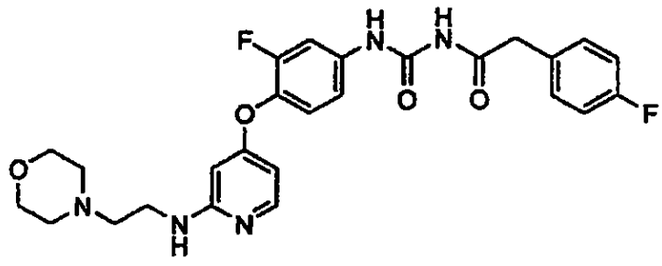
Ejemplo 81



N-(4-(2-Acetamidopiridin-4-iloxi)-3-fluorofenil)-2,6-difluorobenzamida, sal de clorhidrato

Una solución de N-(4-(4-amino-2- fluorofenoxi)piridin-2-il)acetamida (Compuesto B' del Ejemplo 24, 15 mg, 0.057 mmol) en THF (0.5 mL) se trató con DIPEA (15 µl, 0.086 mmol) y cloruro de 2,6-diflurobenzoilo (10 mg. 0.057 mmol) y la mezcla se agitó a temperatura ambiente por 1.5 h. La mezcla se concentró a vacío y el residuo se purificó mediante HPLC preparativa (Columna A) para dar el compuesto del título como una sal de TFA. La sal de TFA se disolvió en MeOH anhidro y se trató con HCl 1 M/Et_2O a 0°C y se agitó por 5 min. La mezcla se concentró luego a vacío para dar el compuesto del título (15 mg, 60%) como un sólido blanquecino. RMN-^{1}H (DMSO-d_6) δ 11.17(s, 1H). 10.79 (s, 1H), 8.21 (d, 1H, J = 6.1 Hz), 7.89 (dd, 1H, J = 2.0. 12.7 Hz). 7.66 - 7.59 (m, 1H), 7.53 - 7.50 (m, 2H), 7.42 (dd, 1H, J = 8.6. 9.2 Hz), 7.28 (dd, 2H, J = 8. 1, 8.1 Hz), 6.80 (dd, 1H, J = 2.0, 6.1 Hz), 2.06 (s, 3H); MS(ESI+): m/z 402.13 $(M + H)^+$.

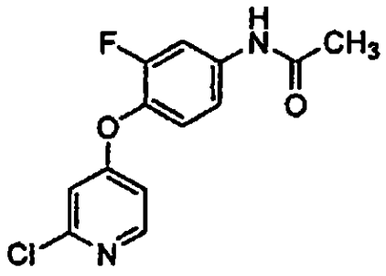
Ejemplo 82



1-(3-Fluoro-4-(2-(2-morfolinoetilamino)piridin-4-

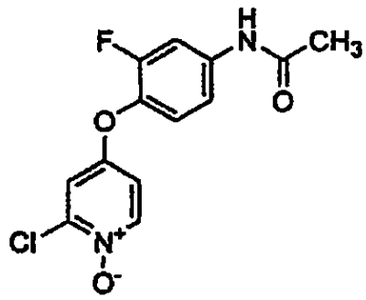
549

iloxi)fenil)-3-(2-(4-fluorofenil) acetil) urea, sal de diclorhidrato



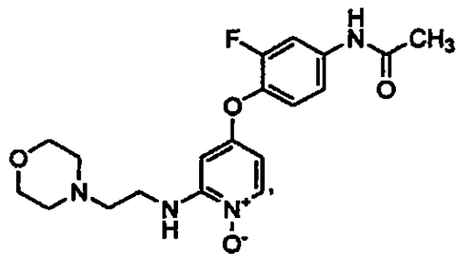
A) N-(4-(2-Cloropiridin-4-iloxi)-3-fluorofenil)acetamida

Una mezcla de N-(3-fluoro-4-hidroxifenil)acetamida (Compuesto A del Ejemplo 13, 1.33 g, 7.87 mmol), 2-cloro-4-nitropiridina (Aldrich, 1.24 g, 7.87 mmol), K_2CO_3 (1.6 g, 11.8 mmol), y DMF (25 mL) se calentó a 100 °C por 9 h. La mezcla se concentró a vacío y el residuo se dividió entre EtOAc y solución acuosa saturada de carbonato ácido de sodio. La fase de EtOAc se lavó con salmuera, se secó (sulfato de magnesio), y se concentró a vacío. El residuo se purificó mediante cromatografía instantánea en columna sobre SiO_2 eluyendo con 30-80 de EtOAc en hexanos para dar el compuesto del título (1.6 g, 73%) como un sólido amarillo pálido. RMN-^{1}H (DMSO-d_6) δ 10.25 (s, 1H), 8.35 (d, 1H, J = 7Hz), 7.80 (d, 1H, J = 14 Hz), 7.50 (d, 1H, J = 3 Hz), 7.33 (m, 2H), 7.02 (m, 1H), 2.06 (s, 3H); MS (ESI^+) : m/z 281.16 $(M + H)^+$.



B) N-(4-(2-Cloropiridin-4-iloxi-1-óxido)-3-fluorofenil)acetamida

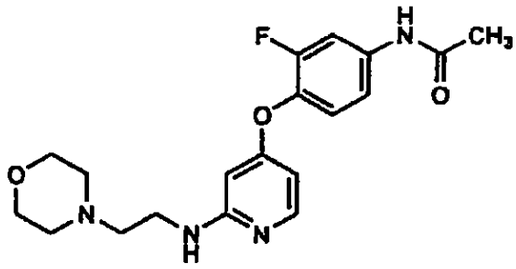
Una mezcla de N-(4-(2-cloropiridin-4-iloxi)-3-fluorofenil)acetamida (0.98 g. 3.5 mmol), >90 ácido m-cloroperoxibenzoico (1.3 g, 7.6 mmol), y $CHCl_3$ (50 mL) se agitó a temperatura ambiente por 60 h. La mezcla se concentró a vacío y el residuo se trituró con Et_2O (2 x 100 mL) para dar el compuesto del título (0.89 g. 86%) como un sólido amarillo pálido. RMN-^{1}H (DMSO-d_6) δ 10.25 (s, 1H), 8.35 (d, 1H, J = 7.3 Hz), 7.80 (d, 1H, J = 13 Hz), 7.33-7.32 (m, 3H), 7.02 (dd, 1H, J = 3.5, 7.5 Hz), 2.06 (s, 3H); MS (ESI^+) : m/z 295.04 $(M + H)^+$.



C) N-(3-Fluoro-4-(2-(2-morfolinoetilamino)piridin-4-iloxi-

1-óxido)fenil)acetamida

Una mezcla de clorhidrato de N-(4-(2-cloropiridin-4-iloxi-1-óxido)-3-fluorofenil)acetamida (205 mg, 0.62 mmol), 4-(2-aminoetil)morfolina (Aldrich, 169 mg, 1.30 mmol), y etanol absoluto se calentó a reflujo 16 h. La mezcla de reacción se concentró a vacío, y el residuo se trató con agua (3 mL) y se aplicó a un cartucho Varían C-18 de 10 g. El cartucho se eluyó primeramente con agua y luego con 30 de NeOH en agua. El eluyente que contenía el producto deseado se combinó, se concentró a un volumen de 5 mL, y se extrajo 3 veces con EtOAc. Los extractos combinados se lavaron con salmuera, se secaron (sulfato de magnesio) y se concentraron a vacío para dar el compuesto del título (100 mg, 40%). RMN-^{1}H (DMSO-d_6) δ 10.22 (s, 1H), 7.84 (d, 1H, J = 6 Hz), 7.77 (dd, 1H, J = 2, 12 Hz). 7.31 (dd, 1H, J = 2, 9 Hz), 7.24 (dd, 1H, J = 9, 9 Hz), 6.41 (m, 1H), 6.13 .(dd, 1H, J = 2, 6 Hz), 5.81 (d, 1H, J = 2.5 Hz), 3.56-3.48 (m, 2H), 3.31-3.19 (m, 4H), 2.38 (t, 2H, J = 1 Hz), 2.40-2.28 (m, 4H), 2.06 (s, 3H) MS ((ESI$^+$): m/z 405.22 $(M + H)^+$.

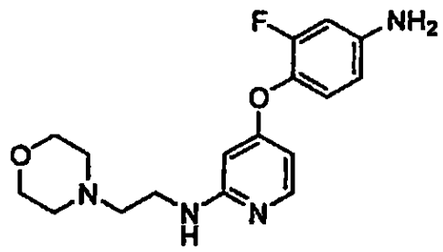


D) N-(3-Fluoro-4-(2-(2-morfolinoetilamino)piridin-4-

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iloxi)fenil)acetamida, sal del ácido trifluoroacético

Una mezcla de N-(3-fluoro-4-(2-(2-morfolinoetilamino)piridin-4-iloxi-1-óxido)fenil)acetamida (100 mg, 0.26 mmol), y polímero de trifenilfosfina soportado (1.4-2.0 mmol/g) sobre poliestireno (500 mg) y DMF (2 mL) se agitó a 135 °C por 15 h. La mezcla se filtró para eliminar la resina y la resina se lavó con DMF y EtOAc. El filtrado y los lavados se combinaron y se concentraron. El producto crudo se purificó mediante HPLC preparativa (Columna A) para dar el compuesto del título (45 mg, 24%) como un sólido blanco. RMN-^{1}H (DMSO-d_6) δ 10.33 (s, 1H), 8.02 (d, 1H, J = 7Hz), 7.84 (dd, 1H, J = 2, 13 Hz), 7.39-7.31 (m, 2H), 6.52 (s, 1H), 6.10 (s, 1H), 3.83 (s, 4H), 3.60-3.48 (m, 2H), 3.32- 3.18 (m, 6H), 2.08 (s, 3H); MS (ESI$^+$) : m/z 375.12(M + H)$^+$.



E) 4-(4-Amino-2-fluorofenoxi)-N-(2-morfolinoetil)piridin-2-amina, sal de clorhidrato

Una mezcla del trifluoroacetato de N-(3-fluoro-4-(2-(2-morfolinoetilamino)piridin-4-iloxi)fenil)acetamida (40 mg), McOH (1 mL), y 6 M HCl (0.2 mL) se calentó a reflujo por 3 h. La mezcla se concentró en un evaporador rotatorio y el

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residuo se liofilizó para dar el compuesto del título (30 mg) como un sólido blanco. RMN-^{1}H (DMSO-d_6) δ 11.12(s, 1H). 8.85 (s, 1H), 7.95 (d, 1H, J = 7 Hz), 7.08 (dd, 1H. J = 9, 9 Hz), 6.65-6.63 (m, 2H), 6.54 (d, 1H, J = 8 Hz), 6.31 (s, 1H), 3.90-3.75 (m 6H), 3.37-3.21 (m, 6H); MS(ESI$^+$): m/z 373.14 (M + H)$^+$.

F) 1-(3-Fluoro-4-(2-(2-morfolinoetilamino)piridin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)urea, sal de diclorhidrato

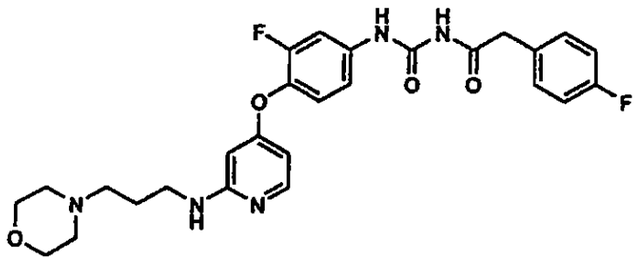
Una solución del clorhidrato de 4-(4-amino-2-fluorofenoxi)-N-(2-morfolinoetil)piridin-2-amina (15 mg, 0.045 mmol) en McOH (5 mL) se trató con Et_3N (2 mL) y la mezcla se agitó a temperatura ambiente por 5 min. La mezcla se concentró a vacío para remover el McOH, el residuo se suspendió en THF (1 mL) y se trató con una solución 0.3 M de isocianato de 2-(4-fluorofenil)acetilo en tolueno (Compuesto D del Ejemplo 11, 180 mL, 0.054 mmol). Después de agitación, la mezcla se concentró a vacío y el residuo se dividió entre EtOAc y carbonato ácido de sodio saturado. La fase de EtOAc se separó, se lavó con salmuera, se secó ($MgSO_4$) y se concentró. La mezcla se concentró a vacío y el residuo se purificó mediante HPLC preparativa (Columna A) para dar el compuesto del título como una sal de TFA. La sal de TFA se disolvió en McOH anhidro y se trató con 1 N HCl/Et_2O a 0°C y se agitó por 5 min. La mezcla luego se concentró a vacío para

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dar el compuesto del título (10 mg, 43%) como un sólido blanco. RMN-^{1}H (DMSO-d_6) δ 11.05 (s, 1H). 10.61 (s, 1H), 7.98 (d, 1H, J = 7.1 Hz), 7.86-7.73 (m, 1H), 7.48-7.38 (m, 1H), 7.37-7.30 (m, 3H), 7.24-7.04 (m, 2H), 6.60 (s, 1H), 6.26 (s, 1H), 3.98-3.60 (m, 8H), 3.74 (s, 2H), 3.39-3.19 (m, 4H); MS (ESI$^+$) : m/z 512.2 $(M + H)^+$.

Los ejemplos 83-85 se prepararon de una manera similar a la que se describe para el Ejemplo 82.

Ejemplo 83

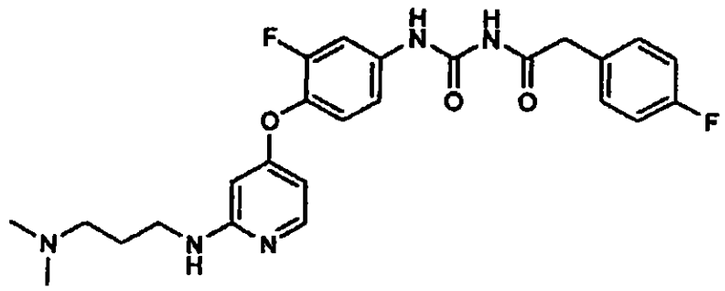


1-(3-Fluoro-4-(2-(3-morfolinopropilamino)piridin-4-iloxi) fenil)-3-(2-(4-fluorofenil) acetil) urea, sal de 1 clorhidrato

RMN-^{1}H (DMSO-d_6) δ 11.06(s, 1H), 10.62 (s, 1H), 7.93 (d, 1H, J = 7.1 Hz), 7.83 (d, m, J = 12.7 Hz), 7.45 - 7.33 (m, 4H), 7.16 (dd, 2H, J = 8.6, 9.2 Hz), 6.64 (s, 1H), 6.23 (s, 1H), 3.95 - 3.76 (m, 4H), 3.74 (s, 2H). 3.70 -3.48 (m, 4H), 3.48 3.35 (m, 2H), 3.20 - 3.-04 (m, 2H), 2.02 - 1.93 (m, 2H).

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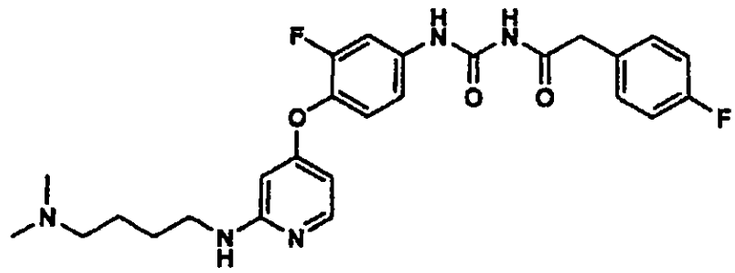
Ejemplo 84



1-(4-(2-(3-(Dimetilamino)propilamino)piridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea, sal de clorhidrato

RMN-^{1}H (DMSO-d_6) δ 11.06 (s, 1H), 10.62 (s, 1H), 10.37 (s, 1H), 7.93 (d, 1H, J = 7.1 Hz), 7.82 (dd, 1H, J = 2.0, 12.7 Hz), 7.45 (dd, 1H, J = 2.6, 8.6 Hz), 7.40 (d, 1H, J = 8.6 Hz), 7.37 - 7.33 (m, 2H), 7.16 (dd, 2H, J = 8.7, 9.1 Hz), 6.65 (s, 1H), 6.24 (s, 1H), 3.75 (s, 2H), 3.45 - 3.36 (m, 2H), 3.13 - 3.03 (m, 2H), 2.73 (s, 3H), 2.72 (s, 3H), 1.94-1.90 (m,2H).

Ejemplo 85



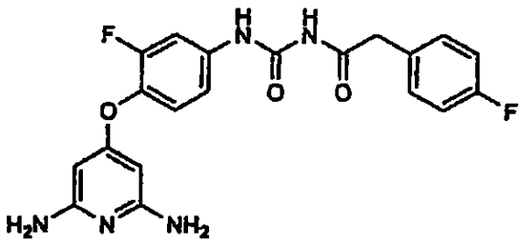
1-(4-(2-(4-(Dimetilamino)butilamino)piridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil) acetil) urea, sal de

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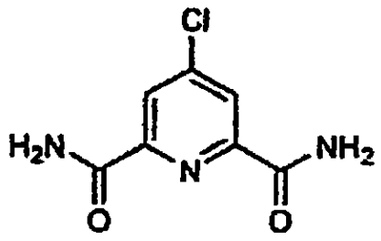
clorhidrato

MS (ESI^+) : m/z 498.2 $(M + H)^+$.

Ejemplo 86



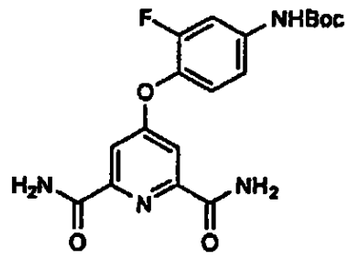
1-(4-(2,6-Diaminopiridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea, sal de clorhidrato



A) 4-Cloropiridin-2,6-dicarboxamida

Una mezcla de ácido chelidámico (3.19 g, 17.0 mmol), PCl_5 (2.1 g) y CCl_4 (30 mL) se calentó a reflujo por 6 h y luego se enfrió a 65°C y se trató con MeOH (5 mL) bajo reflujo suave. La mezcla se calentó a reflujo por 5 h y luego se concentró a vacío. El residuo se trató con hielo-agua (50 mL) y el precipitado sólido se recolectó mediante filtración y se secó por succión sobre el embudo para dar agujas blancas de 2,6-biscarbometoxi-4-cloropiridina (2.4 g). El producto se trató con NH_3 -7 M/MeOH y se agitó a temperatura ambiente por

1 h. La mezcla se filtró para recolectar el compuesto del título como un sólido blanco (1.8 g, 53%). RMN-^{1}H (DMSO-d_6) δ 8.91 (s, 2H), 8.15 (s,2H), 7.87 (s,2H).

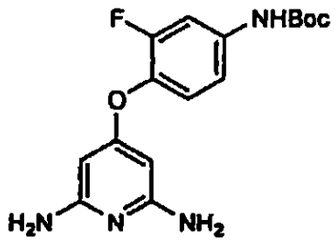


B) 4-(2,6-dicarbamoilpiridin-4-iloxi)-3-fluorofenilcarbamato de ter-butilo

Una solución de N-Boc-4-amino-2-fluorofenol (228 mg, 1.0 mmol) en DMF (2 mL) se trató con t-BuOK (124 mg, 1.1 mmol) y la mezcla se agitó a temperatura ambiente por 2 h. La mezcla se trató con 4-cloropiridin-2,6-dicarboxamida (200 mg, 1.0 mmol) y K_2CO_3 (35 mg, 0.5 mmol) y se calentó a 80°C por 1.5 h. La mezcla se concentró a vacío, se trató con EtOAc (10 mL) y H_2O (10 mL) y se filtró para remover el material insoluble. La fase de EtOAc se lavó con salmuera.

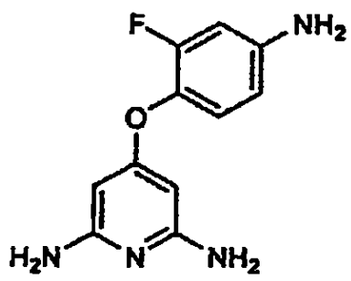
Se secó (sulfato de magnesio) y se concentró a vacío. La purificación del residuo mediante cromatografía instantánea en columna sobre SiO_2 eluyendo con 30-100 % de EtOAc/hexanos dio el compuesto del título (170 mg, 44%) como un sólido blanco que contenía 10 % de la cloropiridina inicial. RMN-^{1}H (DMSO-d_6) δ 9.77 (s, 1H), 8.86 (s, 2H), 7.87 (s, 1H), 7.63

(d, 1H, J = 12.1 Hz), 7.55 (s, 2H), 7.38 - 7.31 (m, 2H), 1.48(s, 9H).



C) 4-(2,6-diaminopiridin-4-iloxi)-3-fluorofenilcarbamato de ter-butilo

El compuesto del título se preparó a partir de 4-(2, 6-dicarbamoilpiridin-4-iloxi)-3-fluorofenilcarbamato de ter-butilo (110 mg, 0.28 mmol) utilizando un procedimiento similar al que se describe para el Paso B del Ejemplo 80. Cromatografía instantánea sobre SiO_2 eluyendo con 0-2 de McOH/EtOAc dio el compuesto del título (60 mg, 63%) como un sólido blanco. RMN-^{1}H (DMSO-d_6) δ 9.60 (s, 1H), 7.50 (dd, 1H, J = 1.8, 13.6 Hz), 7.21 (dd, 1H, J = 2.2, 8.7 Hz), 7.13 (dd, 1H, J = 8.7, 9.2 Hz), 5.40 (s, 4H), 5.13 (s, 2H), 1.47 (s, 9H); MS(ESI$^+$): m/z 335.23 $(M + H)^+$.



D) 4-(4-Amino-2-fluorofenoxi)piridin-2,6-diamina

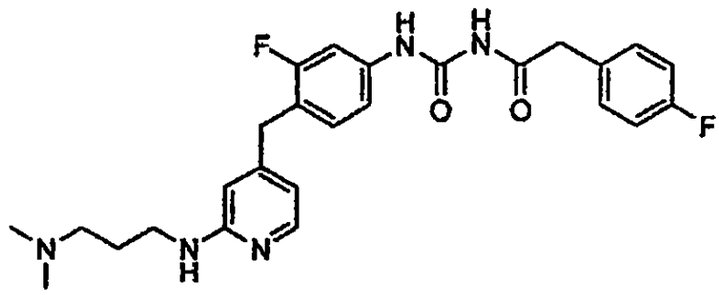
El compuesto del título se preparó a partir del 4-(2,6-diaminopiridin-4-iloxi)-3-fluorofenilcarbamato de ter-butilo (30 mg, 0.089 mmol) de una manera similar a aquella que se describe en el Paso D del Ejemplo 80 para dar un aceite claro (20 mg, 100%). MS (ESI^+) : m/z 235.22 $(M + H)^+$.

E) 1-(4-(2,6-Diaminopiridin-4-iloxi)-3-fluorofenil)-3-(2-(4- fluorofenil)acetil)urea, sal de clorhidrato

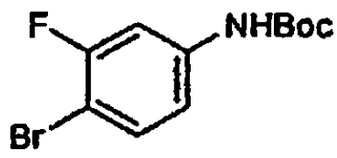
El compuesto del título se preparó a partir de 4-(4-amino-2-fluorofenoxi)piridin-2,6-diamina (19 mg, 0.081 mmol) y una solución de isocianato de 2-(4- fluorofenil)acetilo en tolueno (0.3 M, Compuesto D del Ejemplo 11, 0.27 mL. 0.081 mmol) de una manera similar al Paso D del Ejemplo 33. La mezcla de reacción se purificó mediante HPLC preparativa (Columna A) para dar el compuesto del título como una sal de TFA. La sal de TFA se disolvió en McOH anhidro y se trató con HCl 1 M/Et_2O a 0°C y se agitó por 5 min. La mezcla se concentró luego a vacío para dar el compuesto del título (8 mg, 24%) como un sólido amarillo pálido. RMN-^1H (DMSO-d_6) δ 11.01 (s, 1H), 10.51 (s, 1H), 7.68 (dd, 1H, J = 2.6, 12.7 Hz), 7.36-7.30 (m, 3H), 7.22 - 7.14 (m, 3H), 5.52 (s, 4H), 5.15 (s, 2H), 3.73 (s, 2H); MS (ESI^+) : m/z 414.09 $(M + H)^+$.

562
560

Ejemplo 87



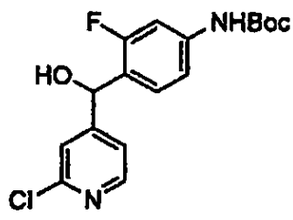
1-(4-((2-(3-(Dimetilamino)propilamino)piridin-4-il)metil)-3-fluorofenil)-3-(2-(4-fluorofenil) acetil) urea, sal de diclorhidrato



A) 4-bromo-3-fluorofenilcarbamato de ter-butilo

A una solución de 4-bromo-3-fluorobencenamina (Lancaster, 7.05 g, 37.1 mmol) en tetrahidrofurano anhidro (40 mL) a temperatura ambiente se agregó $(Boc)_2O$ (8.10 g. 37.1 mmol) y trietilamina (5.17 mL, 37.1 mmol). La mezcla de reacción se calentó a reflujo toda la noche. Después de enfriar la mezcla de reacción se concentró bajo presión reducida. El residuo se purificó mediante cromatografía instantánea en columna sobre SiO_2 eluyendo con 20% de diclorometano en hexano, luego 20% acetato de etilo en hexano para dar 4-bromo-3-fluorofenilcarbamato de ter-butilo (5.30

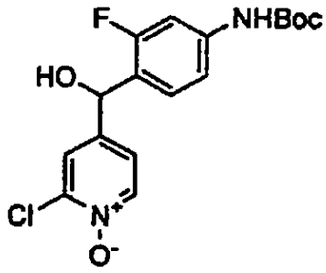
g, 49% de rendimiento). MS (ESI^+) : m/z 290.2 $(M + H)^+$.



B) 4-((2-cloropiridin-4-il)(hidroxi)metil)-3-fluorofenilcarbamato de ter-butilo

A una solución de 4-bromo-3-fluorofenilcarbamato de ter-butilo (2.60 g, 9.0 mmol) en THF anhidro (30 mL) a -78 °C se agregó McMgBr (3.0 M en Et_2O, 3.1 mL, 9.3 mmol) vía una jeringa. La solución se agitó por 10 min a esa temperatura, y luego se calentó a 0°C por 0.5 h. Después de que la solución se enfrió hasta -78 °C, se agregó una solución de t-BuLi (1.7 M en hexano, 10.6 mL, 18.1 mmol) en 4 min. La solución resultante se dejó en agitación por 5 min antes de que agregara una solución de 2-cloroisonicotinaldehído (1.41 g, 10 mmol) (para preparación, ver Frey, L. F. et al. Tetrahedron Lett. 2001, 42. 6815) en THF anhidro (25 mL) en 3 min. La mezcla de reacción se agitó a -78 °C por 20 min y se agregó 2.0 mL de MeOH. La solución se concentró luego bajo presión reducida y el residuo se disolvió en 200 mL de EtOAc. Esta se lavó subsecuentemente con agua (2 x 50 mL), salmuera (2 x 50 mL) y se secó sobre sulfato de magnesio. Después de la filtración y concentración, el residuo se purificó

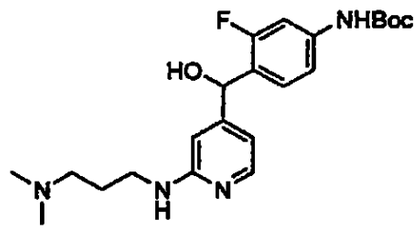
mediante cromatografía instantánea sobre SiO_2 eluyendo con 0-50% de EtOAc en hexano para dar el 4-((2-cloropiridin-4-il)(hidroxi)metil)-3-fluorofenilcarbamato de ter-butilo (1.30 g, 41% de rendimiento). MS(ESI$^+$): m/z 353.28 / 355.24 (M + H)$^+$.



C) 4-((2-cloropiridin-N-óxido-4-il)(hidroxi)metil)-3-fluorofenilcarbamato de ter-butilo

A una solución de 4-((2-cloropiridin-4-il)(hidroxi)metil)-3-fluorofenilcarbamato de ter-butilo (1.20 g, 3.40 mmol) en una mezcla de diclorometano (100 mL) y acetato de etilo (10 mL) se agregó m-CPBA (70%, 2.34 g, 9.48 mmol). La mezcla de reacción se agitó a temperatura ambiente por 2 h, y luego se calentó a reflujo por 5 h. El solvente se retiró bajo presión reducida y el residuo se purificó mediante cromatografía instantánea sobre SiO_2 eluyendo con 50% de EtOAc en hexano, 100% de EtOAc y luego 10 % de MeOH en EtOAc, para dar el 4-((2-cloropiridin-N-óxido-4-il)(hidroxi)metil)-3-fluorofenilcarbamato de ter-butilo (840 mg, 67% de rendimiento). MS (ESI$^+$) : m/z 369.13 / 371.13 (M + H)$^+$.

563

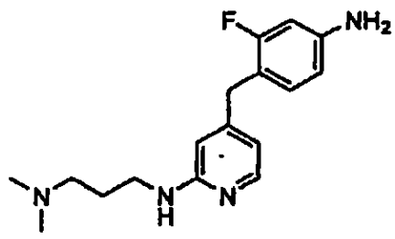


D) 4-((2-(3-(dimetilamino)propilamino)piridin-4-il)(hidroxi)metil)-3-fluorofenilcarbamato de ter-butilo

A una solución de 4-((2-cloropiridin-N-óxido-4-il)(hidroxi)metil)-3-fluorofenilcarbamato de ter-butilo (80 mg, 0.22 mmol) en EtOH (2.0 mL) se agregó N^1,N^1-dimetilpropan-1,3-diamina (225 mg, 2.2 mmol). La mezcla de reacción se calentó a 80°C por 12 h y el solvente se retiró para proporcionar el 4-((2-(3-(dimetilamino)propilamino)piridin-N-óxido-4-il)(hidroxi)metil)-3-fluorofenilcarbamato de ter-butilo crudo, el cual se utilizo directamente en el siguiente paso. MS (ESI^+) : m/z 435.37 $(M + H)^+$.

A una solución de 4-((2-(3-(dimetilamino)propilamino)piridin-N-óxido-4-il)(hidroxi)metil)-3-fluorofenilcarbamato de ter-butilo (~0.22 mmol) en MeOH (2.0 mL) se agregó zinc (114 mg, 1.75 mmol) y NH_4CO_2H (139 mg, 2.20 mmol). La suspensión se calentó a reflujo toda la noche. Se agregó más zinc (114 mg) y NH_4CO_2H (139 mg) y la suspensión se calentó a reflujo por 2 h. Después de enfriar, la solución se filtró y el filtrado se concentró bajo presión reducida. El residuo se purificó luego

mediante cromatografía instantánea sobre SiO_2 eluyendo con 10-30% de MaCH en DCM para dar el 4-((2-(3-(dimetilamino)propilamino)piridin-4-il)(hidroxi)metil)-3-fluorofenilcarbamato de ter-butilo (80 mg, 87% de rendimiento). MS (ESI^+) : m/z 419.34 $(M + H)^+$.



E) 4-(4-Amino-2-fluorobencil)-N-(3-(dimetilamino)propil)piridin-2-amina

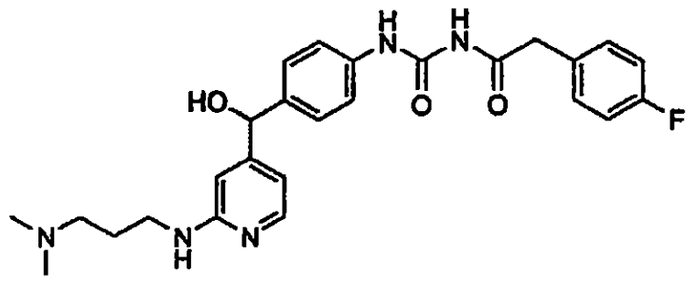
A una solución de 4-((2-(3-(dimetilamino)propilamino)piridin-4-il)(hidroxi)metil)-3-fluorofenilcarbamato de ter-butilo (80 mg. 0.19 mmol) en McOH (5.0 mL) se agregó 2 mL de HCl conc. y paladio sobre carbono (10%. 200 mg). La suspensión se calentó a 75 °C bajo atmósfera de hidrógeno por 24 h. La mezcla se enfrió, se filtró y se concentró a vacío. El residuo se disolvió en 1 mL de NH_4OH conc. y se extrajo con DCM (5x5 mL). La capa orgánica combinada se secó sobre sulfato de sodio. Después de la filtración, se concentró a vacío para dar 4-(4-amino-2-fluorobencil)-N-(3-(dimetilamino)propil)piridin-2-amina (31 mg, 40 % de rendimiento). MS(ESI^+): m/z 303.31 $(M + H)^+$.

F) 1-(4-((2-(3-(Dimetilamino)propilamino)piridin-4-

il)metil)-3-fluorofenil)-3-(2-(4-fluorofenil) acetil) urea, sal de diclorhidrato

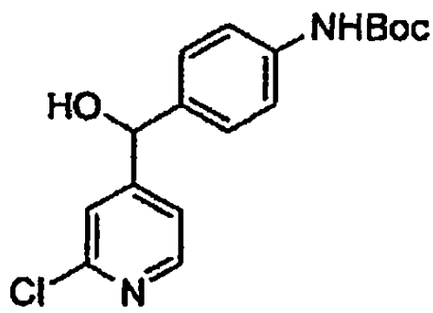
A una solución de 4-(4-amino-2-fluorobencil)-N-(3-(dimetilamino)propil)piridin-2-amina (30 mg, 0.1 mmol) en DCM (2 mL) se agregó una solución de isocianato de 2-(4-fluorofenil)acetilo (Compuesto D del Ejemplo 11, 0.347 M en tolueno, 0.25 mL). La mezcla se agitó a temperatura ambiente por 0.5 h antes de que se apagara con McOH. La solución se concentró a vacío y el residuo se purificó mediante HPLC prep. Las fracciones deseadas se recolectaron y se concentraron a vacío. El residuo se disolvió en McOH y se agregó dietilentriamina enlazada a polímero (50 mg) para remover el ácido trifluoroacético. Después de la filtración y concentración, el residuo se convirtió a la sal de clorhidrato por la adición de HCl 1 N (0.5 mL) y se liofilizó para dar el clorhidrato de 1-(4-((2-(3-(dimetilamino)propilamino)piridin-4-il)metil)-3-fluorofenil)-3-(2-(4-fluorofenil) acetil) urea (8.0 mg, 14% de rendimiento). MS (ESI^+) : m/z 482.24 $(M + H)^+$.

Ejemplo 88



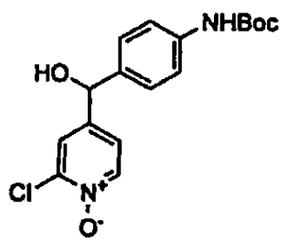
566

1-(4-((2-(3-(Dimetilamino)propilamino)piridin-4-il)(hidroxi)metil)fenil)-3-(2-(4-fluorofenil) acetil) urea



A) 4-((2-cloropiridin-4-il)(hidroxi)metil)fenilcarbamato de ter-butilo

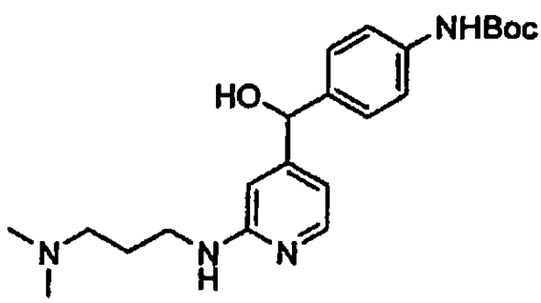
Preparada de una manera similar a aquella que se describe en el Paso B del Ejemplo 87. El 2-cloroisonicotinaldehído (141 mg, 1.0 mmol) se convirtió a 4-((2-cloropiridin-4-il)(hidroxi)metil)fenilcarbamato de ter-butilo (190 mg, 57% de rendimiento). MS(ESI$^+$): m/z 335.27 / 337.27 $(M + H)^+$.



B) 4-((2-cloropiridin-N-óxido-4-il)(hidroxi)metil)fenilcarbamato de ter-butilo

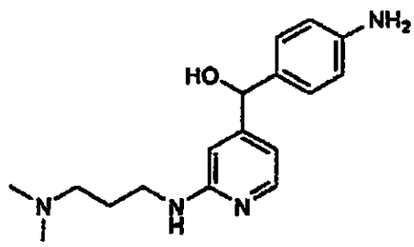
Preparado de una manera similar a aquella que se describe en el Paso C del Ejemplo 87. El 4-((2-cloropiridin-

4-il)(hidroxi)metil)fenilcarbamato de ter-butilo (78 mg, 0.23 mmol) se convirtió a 4-((2-cloropiridin-N-óxido-4-il)(hidroxi)metil)fenilcarbamato de ter-butilo (36 mg, 44% de rendimiento). MS(ESI$^+$): m/z 351.28 / 353.27 $(M + H)^+$.



C) 4-((2-(3-(dimetilamino)propilamino)piridin-4-il)(hidroxi)metil)fenilcarbamato de ter-butilo

Preparado de una manera similar a aquella que se describe en el Paso D del Ejemplo 87. El 4-((2-cloropiridin-N-óxido-4-il)(hidroxi)metil)fenilcarbamato de ter-butilo (36 mg, 0.1 mmol) se convirtió a 4-((2-(3-(dimetilamino)propilamino)piridin-4-il)(hidroxi)metil)fenilcarbamato de ter-butilo (16 mg, 40% de rendimiento). MS (ESI$^+$) : m/z 401.38 $(M + H)^+$.



D) (4-Aminofenil) (2-(3-(dimetilamino) propilamino)

piridin-4-il)metanol

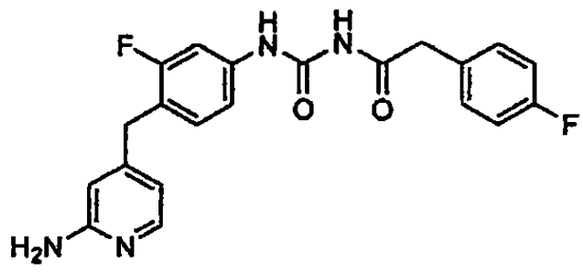
A una solución de 4-((2-(3-(dimetilamino)propilamino)piridin-4-il)(hidroxi)metil)fenilcarbamato de ter-butilo (16 mg, 0.04 mmol) en 1 mL de DCM se agregaron Et_3SiH (0.1 mL) /TFA en DCM (10%, 0.2 mL). La mezcla se agitó por media hora y no se detectó reacción por LC-MS. Se agregó otro 0.1 mL de Et_3SiH y 0.8 mL de TFA en DCM (10%) y la mezcla se agitó por 2 h. El solvente se retiró y se purificó por extracción sólida (cartucho de extracción Waters Oasis® MCX) para dar el (4-aminofenil)(2-(3-(dimetilamino)propilamino)piridin-4-il)metanol (6.0 mg, 50% de rendimiento). MS(ESI$^+$): m/z 301.40 $(M + H)^+$.

E) 1-(4-((2-(3-(Dimetilamino)propilamino)piridin-4-il)(hidroxi) metil) fenil)-3-(2-(4-fluorofenil) acetil) urea

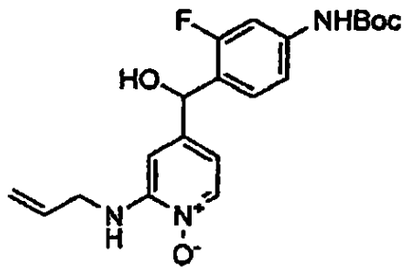
Preparado de una manera similar a aquella que se describe en el Paso F del Ejemplo 87. El 4-aminofenil-(2-(3-(dimetilamino)propilamino)piridin-4-il)metanol (6.0 mg, 0.02 mmol) se convirtió a 1-(4-((2-(3-(dimetilamino)propilamino)piridin-4-il)(hidroxi)metil)fenil)-3-(2-(4-fluorofenil)acetil)urea, ácido bis-trifluoroacético (6.1 mg, 43% de rendimiento). RMN-^{1}H (CD_3OD) δ 7.82 (d, 1H, J = 6.4 Hz), 7.50 (m, 2H), 7.36 (m, 4H), 7.07 (m, 3H), 6.75 (m, 1H), 5.68 (s, 1H). 3.71 (s, 2H), 3.21-3.49 (m, 4H), 2.90 (s, 6H), 2.08 (m, 2H); MS (ESI$^+$) : m/z 480.31 $(M + H)^+$.

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Ejemplo 89



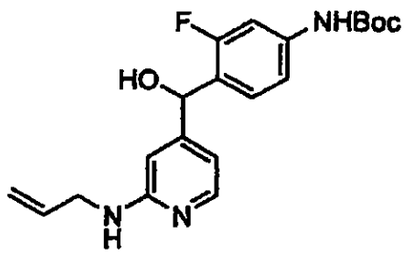
1-(4-((2-Aminopiridin-4-il)metil)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea, sal del ácido trifluoroacético



A) 4-((2-(alilamino)piridin-N-óxido-4-il)(hidroxi)metil)-3-fluorofenilcarbamato de ter-butilo

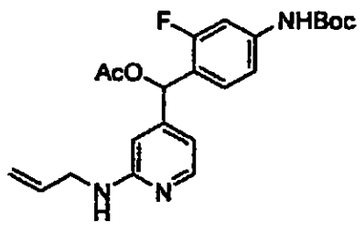
A una solución de 4-((2-cloropiridin-N-óxido-4-il)(hidroxi)metil)-3-fluorofenilcarbamato de ter-butilo (Paso C del Ejemplo 87, 500 mg, 1.36 mmol) en EtOH (14 mL) se agregó alilamina (1.0 mL, 13.6 mmol). La mezcla se calentó a 80 °C toda la noche. Después del enfriamiento, el solvente se retiró y el residuo se purificó mediante cromatografía instantánea sobre SiO_2 eluyendo con 0%-15% de MeOH en DCM para dar el 4-((2-(alilamino)piridin-N-óxido-4-

il)(hidroxi)metil)-3-fluorofenilcarbamato de ter-butilo (440 mg, 83% de rendimiento). MS(ESI$^+$): m/z 390.19 $(M + H)^+$.



B) 4-((2-(alilamino)piridin-4-il)(hidroxi)metil)-3-fluorofenilcarbamato de ter-butilo

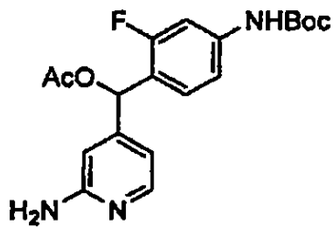
Preparado de una manera similar a aquella que se describe en el Paso D del Ejemplo 87. El 4-((2-(alilamino)piridin-N-óxido-4-il)(hidroxi)metil)-3-fluorofenilcarbamato de ter-butilo (440 mg, 1.13 mmol) se convirtió a 4-((2-(alilamino)piridin-4-il)(hidroxi)metil)-3-fluorofenilcarbamato de ter-butilo (400 mg, 95% de rendimiento). MS(ESI$^+$): m/z 374.33 $(M + H)^+$.



C) acetato de (2-(alilamino)piridin-4-il)(4-(ter-butoxicarbonil)-2-fluorofenil) metilo

A una solución de 4-((2-(alilamino)piridin-4-il)(hidroxi)metil)-3-fluorofenilcarbamato de ter-butilo (400

mg. 1.1 mmol) en THF (10 mL) se agregaron diisopropiletilamina (DIEA) (0.2 mL, 1.1 mmol), 4-dimetilaminopiridina (DMAP) (360 mg. 3.0 mmol) y Ac_2O (0.29 mL, 3.0 mmol). La mezcla se agitó toda la noche y luego se calentó a reflujo por 1 h. Después de enfriar, el solvente se retiró bajo presión reducida y el residuo se purificó mediante cromatografía instantánea sobre SiO_2 eluyendo con 0%-100% de EtOAc en hexano para dar el acetato de (2-(alilamino)piridin-4-il)(4-(ter-butoxicarbonil)-2-fluorofenil)metilo (390 mg. 85% de rendimiento). MS(ESI^+): m/z 416.33 $(M + H)^+$.

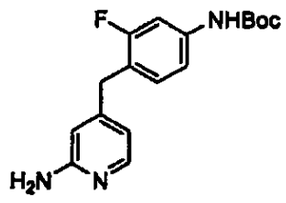


D) acetato de (2-aminopiridin-4-il)(4-(ter-butoxicarbonil)-2-fluorofenil)metilo

Una solución de acetato de (2-(alilamino)piridin-4-il)(4-(ter-butoxicarbonil)-2-fluorofenil)metilo (380 mg, 0.91 mmol) en una mezcla de $EtOH/H_2O$ (10:1, 40 mL) se desgasificó por medio de burbujeo de N2 en la solución por 1 h. A la mezcla se agregó $Rh(PPh_3)_3Cl$ (80 mg, 0.09 mmol). La solución se calentó a reflujo para remover el solvente y el residuo se purificó mediante cromatografía instantánea sobre SiO2r

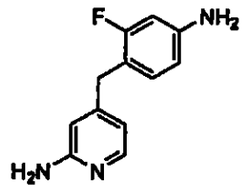
572

seguido por purificación por HPLC preparativa, para dar el acetato de (2-aminopiridin-4-il)(4-(ter-butoxicarbonil)-2-fluorofenil)metilo, sal del ácido trifluoroacético (185 mg, 42% de rendimiento). MS(ESI$^+$): m/z 376.26 $(M + H)^+$.



E) 4-((2-aminopiridin-4-il)metil)-3-fluorofenilcarbamato de ter-butilo

A una solución de acetato de (2-aminopiridin-4-il)(4-(ter-butoxicarbonil)-2-fluorofenil)metilo como una sal de TFA (180 mg, 0.37 mmol) en McOH (10 mL) se agregó 10% Pd/C (90 mg). La suspensión se agitó bajo atmósfera de H_2 por 1 h. El catalizador se retiró y el filtrado se concentró a vacío. El residuo se purificó luego mediante cromatografía instantánea sobre SiO_2 eluyendo con 3% de McOH en DCM, para dar el 4-((2-aminopiridin-4-il)metil)-3-fluorofenilcarbamato de ter-butilo como una sal de TFA (73 mg, 46% de rendimiento). MS(ESI$^+$): m/z 318.24 $(M + H)^+$.



F) 4-(4-Amino-2-fluorobencil)piridin-2-amina

A una solución de 4-((2-aminopiridin-4-il)metil)-3-fluorofenilcarbamato de ter-butilo como una sal de TFA (73 mg, 0.17 mmol) en DCM (4.0 mL) se agregó TFA (1.0 mL). La solución se agitó a temperatura ambiente por 2 h y el solvente se retiró a vacío para dar 4-(4-amino-2-fluorobencil)piridin-2-amina, ácido bis-trifluoroacético (70 mg, 93% de rendimiento). MS(ESI$^+$): m/z 218.12 $(M + H)^+$.

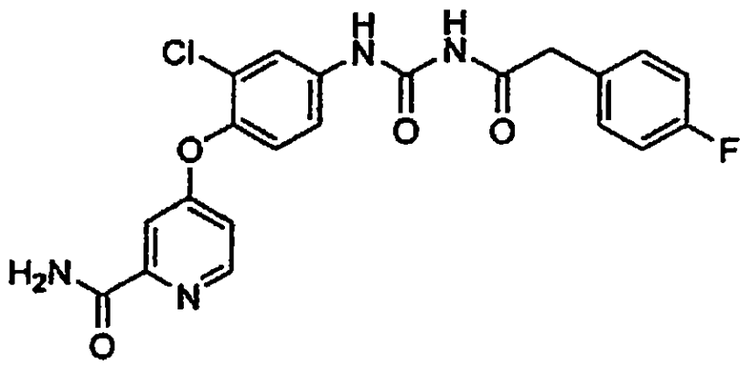
G) 1-(4-((2-Aminopiridin-4-il)metil)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea, sal del ácido trifluoroacético

Preparado de una manera similar a aquella que se describe en el Paso F del Ejemplo 87.

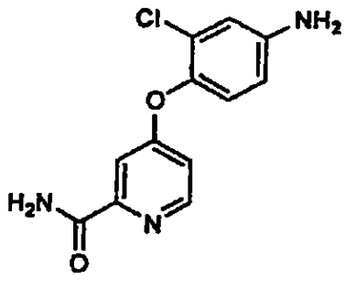
La 4-(4-Amino-2- fluorobencil)piridin-2-amina como la sal de bis-TFA (19 mg, 0.042 mmol) se convirtió a 1-(4-((2-aminopiridin-4-il)metil)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea, sal del ácido trifluoroacético (19 mg. 88% de rendimiento).

RMN-^{1}H (DMSO-d_6) δ 10.94 (s, 1H), 10.47 (s, 1H), 7.76 (m, 3H), 7.50 (d, 1H, J = 11.5 Hz), 7.10-7.26 (m, 4H), 7.10 (m, 2H), 6.65 (d, 1H, J = 6.5 Hz), 6.55 (s, 1H), 3.89 (s, 2H), 3.65 (s, 2H); MS (ESI$^+$) : m/z 397.26 $(M + H)^+$.

Ejemplo 90



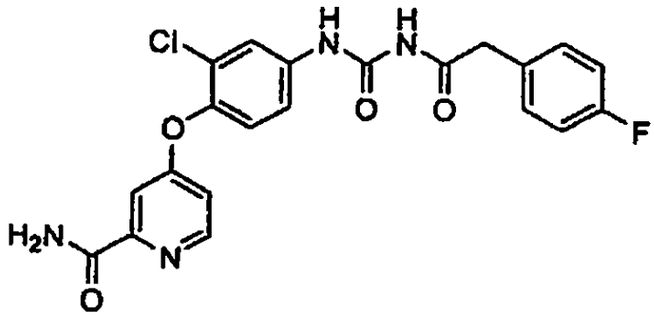
1-(4-(2-Carbamoilpiridin-4-iloxi)-3-clorofenil)-3-(2-(4-fluorofenil)acetil)urea



A) 4-(4-Amino-2-clorofenoxi)picolinamida

A una solución de 4-amino-2-clorofenol (Aldrich, 430 mg, 3.0 mmol) en DMF (2.0 mL) a temperatura ambiente se agregó KOt-Bu (352 mg, 3.2 mmol). La mezcla se dejó agitar a temperatura ambiente por 1 h. A la solución se agregó luego 4-cloropicolinamida (468 mg, 3.0 mmol) y K_2CO_3 (221 mg, 1.6 mmol). La suspensión resultante se calentó a 90 °C toda la noche. Después de enfriar, la suspensión se diluyó con 100 mL de EtOAc y 50 mL de agua. La capa orgánica se separó y se

lavó con salmuera (2 x 25 mL) y se secó sobre $MgSO_4$. Después de la filtración y concentración, el sólido se trituró con 50 mL de DCM. El sólido fue luego recolectado y se lavó con DCM (2 x 20 mL), EtOAc (5.0 mL) se secó para dar 4-(4-amino-2-clorofenoxi)picolinamida (320 mg, 40% de rendimiento). MS (ESI^+) : m/z 264.12 / 266.07 $(M + H)^+$.

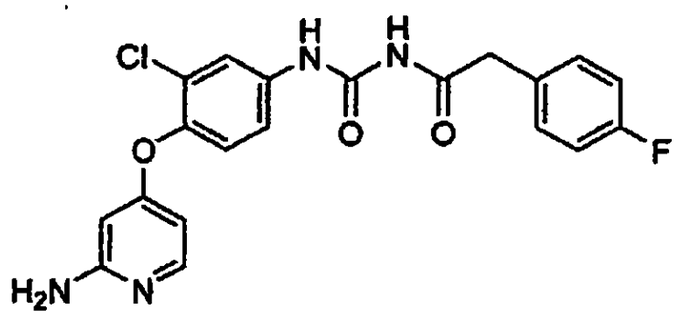


B) 1-(4-(2-Carbamoilpiridin-4-iloxi)-3-clorofenil)-3-(2-(4-fluorofenil)acetil)urea

Preparado de una manera similar a aquella que se describe en el Paso F del Ejemplo 87. La 4-(4-Amino-2-clorofenoxi)picolinamida (79 mg, 0.30 mmol) en DMF (1.0 mL) se convirtió a 1-(4-(2-carbamoilpiridin-4-iloxi)-3-clorofenil)-3-(2-(4-fluorofenil)acetil)urea (65 mg, 49% de rendimiento). RMN-^{1}H (DMSO-d_5) 5 11.05 (s, 1H), 10.58 (s, 1H), 8.52 (d, 1H, J = 4.5 Hz), 8.15 (s, 1H), 7.98 (s, 1H), 7.70 (s, 1H), 7.55 (m, 1H), 7.39 (m, 3H), 7.27 (m, 1H), 7.16 (m, 3H), 3.73 (s, 2H); m/z 443.17$(M + H)^+$.

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Ejemplo 91



1-(4-(2-Aminopiridin-4-iloxi)-3-clorofenil)-3-(2-(4-fluorofenil)acetil)urea, sal de clorhidrato

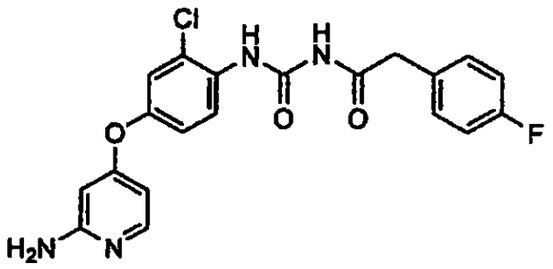
A una solución de 1-(4-(2-carbamoilpiridin-4-iloxi)-3-clorofenil)-3-(2-(4-fluorofenil)acetil)urea (Ejemplo 90, 27 mg, 0.06 mmol) en DMF (1.0 mL) se agregaron H_2O (2.2 mg, 0.12 mmol), piridina (0.04 mL) y bis(trifluoroacetoxi)yodobenzeno (Aldrich, 39 mg, 0.09 mmol) a temperatura ambiente.

La solución se dejó agitar toda la noche y luego se purificó sobre HPLC preparativa para dar el producto deseado, que se convirtió posteriormente a clorhidrato de 1-(4-(2-aminopiridin-4-iloxi)-3-clorofenil)-3-(2-(4-fluorofenil)acetil)urea (19 mg, 70% de rendimiento) por la adición solución de HCl 1N (0.5 mL).

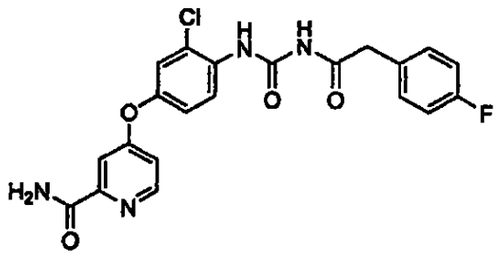
RMN-^{1}H (DMSO-d_6) δ 13.50 (s, 1H), 11.02 (s, 1H), 10.57 (s, 1H), 7.80-7.95 (m, 4H). 7.55 (m, 1H), 7.37 (m, 1H), 7.30 (m, 2H), 7.11 (m, 2H), 6.60 (m, 1H), 6.00 (s, 1H), 3.70 (s, 2H); MS (ESI^+) : m/z 415.16 $(M + H)^+$.

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Ejemplo 92



1-(4-(2-Aminopiridin-4-iloxi)-2-clorofenil)-3-(2-(4-fluorofenil)acetil)urea



A) 1-(4-(2-Carbamoilpiridin-4-iloxi)-2-clorofenil)-3-(2-(4-fluorofenil)acetil)urea

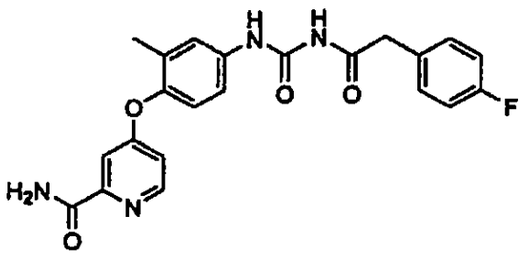
Preparado de una manera similar a aquella que se describe en el Paso A del Ejemplo 90.

La 4-(4-Amino-3-clorofenoxi)picolinamida (39 mg, 0.19 mmol) en DMF (1.0 mL) se convirtió a 1-(4-(2-carbamoilpiridin-4-iloxi)-2- clorofenil)-3-(2-(4-fluorofenil)acetil)urea (18 mg, 41% de rendimiento) después de purificación por HPLC preparativa MS(ESI$^+$): m/z 443.13 / 445.14 $(M + H)^+$.

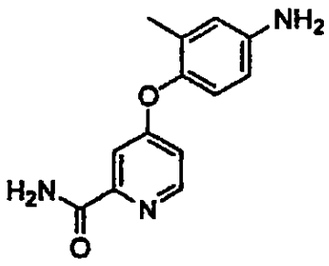
B) 1-(4-(2-Aminopiridin-4-iloxi)-2-clorofenil)-3-(2-(4-fluorofenil)acetil)urea

Preparado de una manera similar a aquella que E describe para el Ejemplo 91. La 1-(4-(2-carbamoilpiridin-4-iloxi)-2-clorofenil)-3-(2-(4-fluorofenil)acetil)urea (18 mg 0.04 mmol) en DMF (1.0 mL) se convirtió a 1-(4-(2 aminopiridin-4-iloxi)-2-clorofenil)-3-(2-(4-fluorofenil)acetil)urea (10 mg. 55% de rendmiento). RMN-1 (DMSO-d_6) δ 13.47 (s, 1H), 11.26(s, 1H), 11.08(s, 1H), 8.3 (d, 1H, J = 8.5 Hz). 7.95 (d, 1H, J = 7.5 Hz), 7.88 (s, 2H) 7.62 (s, 1H), 7.35 (m, 3H), 7.17 (m, 2H), 6.64 (d, 1H, J 7.5 Hz), 6.13 (s, 1H), 3.76 (s, 2H); MS (ESI^+): m/z 415.18 417.17 $(M+H)^+$.

Ejemplo 93



1-(4-(2-Carbamoilpiridin-4-iloxi)-3-metilfenil)-3-(2-(4-fluorofenil)acetil)urea



578 579

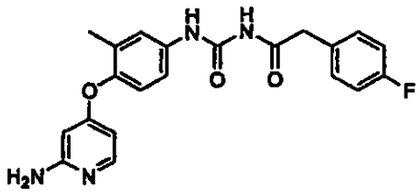
A) 4-(4-Amino-2-metilfenoxi)picolinamida

Preparado de una manera similar a aquella que se describe en el Paso A del Ejemplo 90. El 4-amino-2-metilfenol (246 mg, 2.0 mmol) se convirtió a 4-(4-amino-2-metilfenoxi)picolinamida (230 mg, 47% de rendimiento). MS (ESI^+) : m/z 244.15 $(M + H)^+$.

B) 1-(4-(2-Carbamoilpiridin-4-iloxi)-3-metilfenil)-3-(2-(4-fluorofenil) acetil) urea

Preparado de una manera similar a aquella que se describe en el Paso F del Ejemplo 87. La 4-(4-amino-2-metilfenoxi)picolinamida (48 mg, 0.2 mmol) en DMF (1.0 mL) se convirtió a 1-(4-(2-carbamoilpiridin-4-iloxi)-3-metilfenil)-3-(2-(4-fluorofenil)acetil)urea (35 mg, 41% de rendimiento. RMN-^1H (DMSO-d_6) δ 10.92 (s, 1H), 10.44 (s, 1H), 8.44 (d, 1H, J = 5.5 Hz), 8.06 (s, 1H), 7.63 (s, 1H), 7.50 (s, 1H), 7.42 (m, 1H), 7.31 (m, 2H), 7.24 (d, 1H, J = 2.0 Hz), 7.06-7.12 (m, 4H), 3.69 (s, 2H), 2.02 (s, 3H);). MS (ESI^+) : m/z 423.17 $(M + H)^+$.

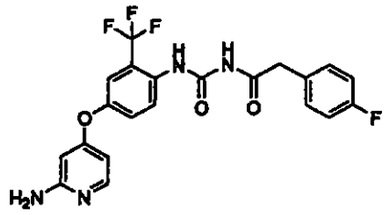
Ejemplo 94



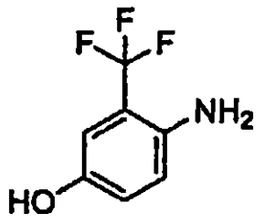
1-(4-(2-Aminopiridin-4-iloxi)-3-metilfenil)-3-(2-(4-fluorofenil)acetil)urea, sal de clorhidrato

Preparado de una manera similar a aquella que se describe en el Paso A del Ejemplo 91. La 1-(4-(2-carbamoilpiridin-4-iloxi)-3-metilfenil)-3-(2-(4-fluorofenil) acetil)urea (27 mg, 0.06 mmol) en DMF (1.0 mL) se convirtió a 1-(4-(2-aminopiridin-4-iloxi)-3-metilfenil)-3-(2-(4-fluorofenil)acetil)urea, sal de clorhidrato (24 mg, 88% de rendimiento) después de purificación por HPLC. RMN-^{1}H (DMSO-D_6) δ 13.18 (s, 1H), 10.93 (s, 1H), 10.45 (s, 1H), 7.88 (d, 1H, J = 7.0 Hz), 7.73 (s, 2H), 7.50 (m, 2H), 7.29 (m, 2H), 7.10 (m, 3H), 6.56 (d, 1H, J = 7.0 Hz), 5.91 (d, 1H, J 2.5 Hz), 3.68 (s, 2H), 2.02 (s, 3H); MS(ESI$^+$): m/z 395.20 (M + H)$^+$.

Ejemplo 95



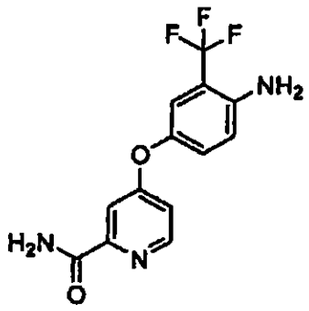
1-(4-(2-Aminopiridin-4-iloxi)-2-(trifluorometil)fenil)-3-(2-(4-fluorofenil)acetil)urea, sal de clorhidrato



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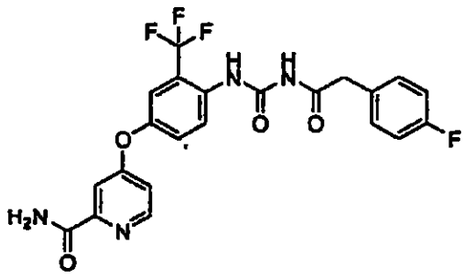
A) 4-Amino-3-(trifluorometil) fenol

A una solución de 4-nitro-3-(trifluorometil)fenol (Aldrich, 414 mg, 2.0 mmol) en 10 mL de McOH se agregó 10% de Pd/C (100mg). La suspensión se agitó bajo atmósfera de H_2 por 12 h y luego se filtró y se concentró a vacío para dar 4-amino-3-(trifluorometil)fenol (350 mg, 95% de rendimiento), que fue suficientemente puro para usarse en el siguiente paso. MS (ESI^+) : m/z 178.02 $(M + H)^+$.



B) 4-(4-Amino-3-(trifluorometil) fenoxi)picolinamida

Preparado de una manera similar a aquella que se describe en el Paso A del Ejemplo 90. El 4-amino-3-(trifluorometil)fenol (177 mg, 1.0 mmol) en DMF (2.0 mL) se convirtió a 4-(4-amino-3-(trifluorometil)fenoxi)picolinamida (180 mg, 61% de rendimiento). MS(ESI^+): m/z 298.20 $(M + H)^+$.



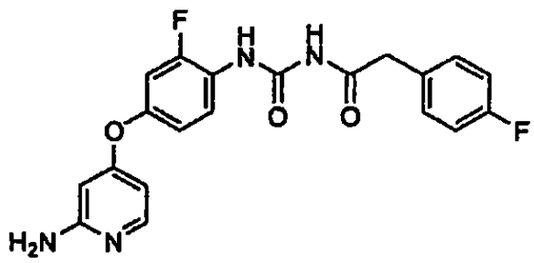
C) 1-(4-(2-Carbamoilpiridin-4-iloxi)-2-(trifluorometil) fenil)-3-(2-(4-fluorofenil) acetil) urea

Preparado de una manera similar a aquella que se describe en el Paso F del Ejemplo 87. La 4-(4-Amino-3-(trifluorometil)fenoxi)picolinamida (30 mg, 0.1 mmol) en DMF (1.0 mL) se convirtió a 1-(4-(2-carbamoilpiridin-4-iloxi)-2-(trifluorometil)fenil)-3-(2-(4-fluorofenil)acetil)urea (30 mg, 63% de rendimiento). MS (ESI^+) : m/z 477.12 $(M + H)^+$.

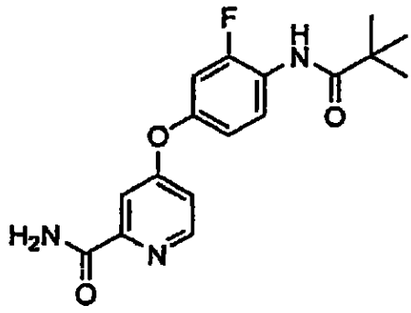
D) 1-(4-(2-Aminopiridin-4-iloxi)-2-(trifluorometil)fenil)-3-(2-(4-fluorofenil)acetil)urea

Preparado de una manera similar a aquella que se describe en el Paso A del Ejemplo 91. La 1-(4-(2-carbamoilpiridin-4-iloxi)-2-(trifluorometil)fenil)-3-(2-(4-fluorofenil)acetil)urea (26 mg, 0.055 mmol) en DMF (1.0 mL) se convirtió a clorhidrato de 1-(4-(2-aminopiridin-4-iloxi)-2-(trifluorometil)fenil)-3-(2-(4-fluorofenil)acetil)urea (15 mg, 56% de rendimiento) después de purificación por HPLC prep. RMN-^1H (DMSO-d_6) δ 13.40 (s, 1H), 11.28 (s, 1H), 10.95 (s, 1H), 8.25 (d, 1H, J = 8.5 Hz), 7.97 (d, 1H, J = 7.0 Hz), 7.88 (s, 2H), 7.72 (d, 1H, J = 2.5 Hz), 7.65 (m, 1H), 7.35 (m, 2H), 7.19 (m, 2H), 6.66 (d, 1H, J = 2.5 Hz), 3.75 (s, 2H); MS (ESI^+) : m/z 449.14 $(M + H)^+$.

Ejemplo 96



1-(4-(2-Aminopiridin-4-iloxi)-2-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea, sal del ácido trifluoroacético

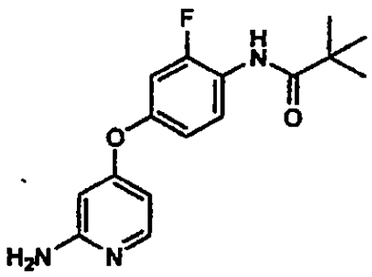


A) 4-(3-Fluoro-4-pivalamidofenoxi)picolinamida

A una solución de 4-amino-3-fluorofenol (Oakwood Products Inc., 252 mg, 2.0 mmol) en NMP (4.0 mL) se agregaron 4-cloropicolinamida (312 mg, 2.0 mmol) y DIEA (0.3 mL). La solución se calentó a 250°C en un horno de microondas. Después de enfriar, la solución se diluyó con agua y la solución se extrajo con EtOAc (3 x 40 mL). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre sulfato de magnesio. Después de la filtración y concentración, el residuo se purificó mediante cromatografía instantánea sobre SiO_2 eluyendo con 0-30% de MeOH en DCM para

dar una fracción que contenía 4-(4-amino-3-fluorofenoxi)picolinamida (50% puro, detección con HPLC-UV). MS (ESI^+) : m/z 248.12 $(M + H)^+$.

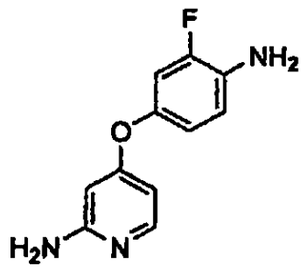
A una solución de 4-(4-amino-3-fluorofenoxi)picolinamida, obtenida del paso previo en THF (3.0 mL) y DCM (10.0 mL) se agregaron NaOH 1 N (5.0 mL) y trimetilcloruro de acetilo (0.25 mL. 2 mmol) a temperatura ambiente. La solución se agitó por 2 h y luego se extrajo con EtOAc. La capa orgánica se lavó con salmuera y se secó sobre sulfato de magnesio. Después de la filtración y concentración, el residuo se purificó mediante cromatografía instantánea sobre SiO_2 eluyendo con 0%-100% de EtOAc en hexano para dar 4-(3-fluoro-4-pivalamidofenoxi)picolinamida (110 mg, 17% de rendimiento para dos pasos). MS(ESI^+): m/z 332.18 $(M + H)^+$.



B) N-(4-(2-Aminopiridin-4-iloxi)-2-fluorofenil)pivalamida

Preparado de una manera similar a aquella que se describe en el Paso A del Ejemplo 91. 4-(3-Fluoro-4-

pivalamidofenoxi)picolinamida (110 mg, 0.33 mmol) en acetonitrilo (4 mL) se convirtió a N-(4-(2-aminopiridin-4-iloxi)-2-fluorofenil)pivalamida (70 mg, 70% de rendimiento). MS (ESI^+) : m/z 304.21 $(M + H)^+$.



C) 4-(4-Amino-3-fluorofenoxi)piridin-2-amina

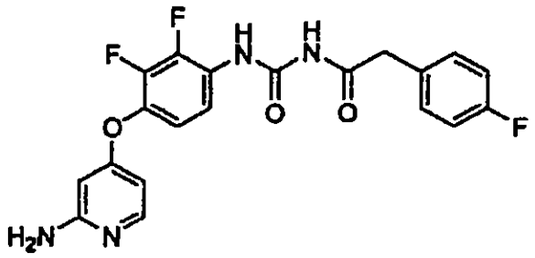
Una solución de N-(4-(2-aminopiridin-4-iloxi)-2-fluorofenil)pivalamida (70 mg, 0.23 mmol) en 3 mL de MeOH se agregó 2 mL de HCl 6 N. La mezcla se calentó luego a reflujo por 48 h. Después de enfriar, el solvente se retiró bajo presión reducida y el residuo se purificó por extracción sólida (cartucho de extracción Waters Oasis® MCX) para dar 4-(4-amino-3-fluorofenoxi)piridin-2-amina (27 mg, 54% de rendimiento). MS (ESI^+) : m/z 220.21 $(M + H)^+$.

D) 1-(4-(2-Aminopiridin-4-iloxi)-2-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea, sal del ácido trifluoroacético

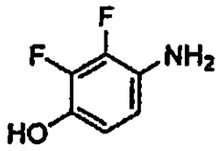
Preparado de una manera similar a aquella que se describe en el Paso F del Ejemplo 87. La 4-(4-amino-3-fluorofenoxi)piridin-2-amina (28 mg. 0.095 mmol) en THF (2.0 mL) se convirtió a ácido 1-(4-(2-aminopiridin-4-iloxi)-2-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea-trifluoroacético

(23 mg, 47% de rendimiento) después de purificación por HPLC preparativa. RMN-^{1}H (DMSO-d_6) δ 11.20 (s, 1H), 10.77 (s, 1H), 8.23 (m, 1H), 7.94 (d, 1H. J = 6.5 Hz). 7.70 (s, 2H), 7.45 (m, 1H), 7.35 (m, 2H), 7.16 (m, 3H), 6.64 (d, 1H. J = 2.5 Hz), 6.11 (s, 1H), 3.75 (s, 2H); MS (ESI$^+$) : m/z 399.12 $(M + H)^+$.

Ejemplo 97



1-(4-(2-Aminopiridin-4-iloxi)-2,3-difluorofenil)-3-(2-(4-fluorofenil)acetil)urea, sal del ácido 'trifluoroacético

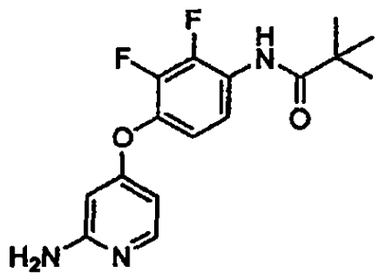


A) 4-Amino-2,3-difluorofenol

A una solución de 1,2,3-trifluoro-4-nitrobenceno (Aldrich, 15.0 g, 84.7 mmol) en DMF (25.0 mL) se agregaron K_2CO_3 (17.6 g. 127.8 mmol) y bencilalcohol (8.8 mL. 85.0 mmol). La suspensión se agitó toda la noche. A la mezcla de reacción se agregó luego H_2O (100 mL) y la solución se mantuvo a 4 °C toda la noche. El precipitado fue luego

recolectado y se lavó con H_2O para dar una mezcla de dos isómeros (22.4 g) [1-(benciloxi)-2,3-difluoro-4-nitrobenceno y 2-(benciloxi)-3,4-difluoro-1-nitrobenceno en una proporción de 1:1].

A una solución de [1-(benciloxi)-2,3-difluoro-4-nitrobenceno y 2-(benciloxi)-3,4-difluoro-1-nitrobenceno] (22.4 g, 84.5 mmol) en EtOAc (20.0 mL) y McOH (100.0 mL) se agregó 10% de Pd/C (1.0 g). La suspensión se agitó bajo atmósfera de hidrógeno por 12 h. La suspensión se filtró luego y se concentró a vacío para dar una mezcla de dos isómeros (12.6 g) [4-amino-2,3-difluorofenol y 6-amino-2,3-difluorofenol en una proporción de 1:1]. MS(ESI$^+$): m/z 146.00 $(M + H)^+$.



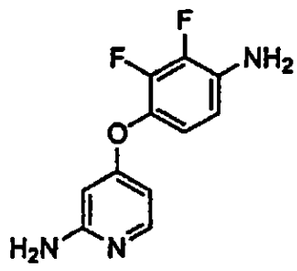
B) N-(4-(2-Aminopiridin-4-iloxi)-2,3-difluorofenil)pivalamida

Preparada de una manera similar a aquella que se describe en el Paso A del Ejemplo 90. Una mezcla de 4-amino-2,3-difluorofenol y 6-amino-2,3-difluorofenol (580 mg, 4.0 mmol) en DMF (3.0 mL) se convirtió a una mezcla de 4-(4-

amino-2,3-difluorofenoxi)picolinamida y 4-(6-amino-2,3-difluorofenoxi)picolinamida (300 mg). MS(ESI$^+$): m/z 266.13 (M + H)$^+$.

Preparado de una manera similar a aquella que se describe en el Paso A del Ejemplo 96. Una mezcla de 4-(4-amino-2,3-difluorofenoxi)picolinamida y 4-(6-amino-2,3-difluorofenoxi)picolinamida (300 mg, 1.13 mmol) se convirtió a una mezcla de 4-(2,3-difluoro-4-pivalamidofenoxi)picolinamida y 4-(2,3-difluoro-6-pivalamidofenoxi)picolinamida (406 mg). MS(ESI$^+$): m/z 350.20 (M + H)$^+$.

Preparado de una manera similar a aquella que se describe en el Paso A del Ejemplo 91. Una mezcla de 4-(2,3-difluoro-4-pivalamidofenoxi)picolinamida y 4-(2,3-difluoro-6-pivalamidofenoxi)picolinamida (400 mg) se hizo reaccionar con bis(trifluoroacetoxi)yodobenzeno para dar N-(4-(2-aminopiridin-4-iloxi)-2,3-difluorofenil)pivalamida, sal del ácido trifluoroacético (120 mg, 24% de rendimiento) después de la purificación por HPLC preparativa. MS(ESI+): m/z 322.23 (M + H)$^+$.



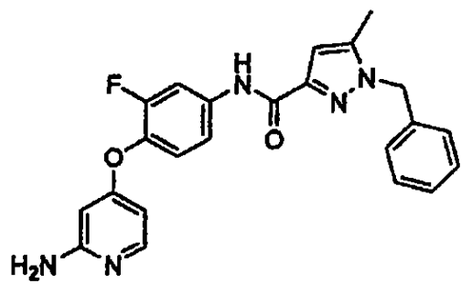
C) 4-(4-Amino-2,3-difluorofenoxi)piridin-2-amina

Preparada de una manera similar a aquella que se describe en el Paso C del Ejemplo 96. N-(4-(2-aminopiridin-4-iloxi)-2.3-difluorofenil)pivalamida, sal del ácido trifluoroacético (120 mg, 0.27 mmol) se convirtió a 4-(4-amino-2,3-difluorofenoxi)piridin-2-amina (52 mg, 81% de rendimiento). MS(ESI$^+$): m/z 238.11 $(M + H)^+$.

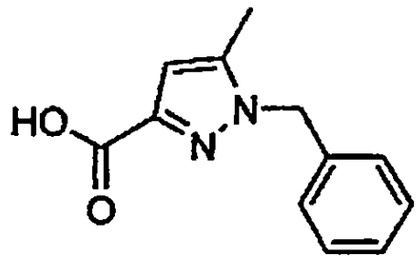
D) 1-(4-(2-Aminopiridin-4-iloxi)-2, 3-difluorofenil)-3-(2-(4-fluorofenil)acetil)urea, sal del ácido trifluoroacético

Preparada de una manera similar a aquella que se describe en el Paso F del Ejemplo 87. La 4-(4-Amino-2,3-difluorofenoxi)piridin-2-amina (24 mg, 0.10 mmol) en THE (3.0 mL) se convirtió a 1-(4-(2-aminopiridin-4-iloxi)-2,3-difluorofenil)-3-(2-(4-fluorofenil)acetil)urea, ácido trifluoroacético (21 mg, 40% de rendimiento). RMN-^{1}H (DMSO-d_6) δ 11.27 (s, 1H), 10.84 (s, 1H), 8.02 (m, 1H), 7.96 (d, 1H. J = 8.5 Hz), 7.73 (s, 2H), 7.34 (m, 3H), 7.17 (m, 2H), 6.70 (m, 1H), 6.20 (d, 1H, J = 2.0 Hz), 3.75 (s, 2H); MS (ESI$^+$) : m/z 417.10 $(M + H)^+$.

Ejemplo 98



N-(4-(2-Aminopiridin-4-iloxi)-3-fluorofenil)-1-bencil-5-metil-^{1}H-pirazol-3-carboxamida, sal de clorhidrato



A) ácido 1-bencil-5-metil-^{1}H-pirazol-3-carboxílico

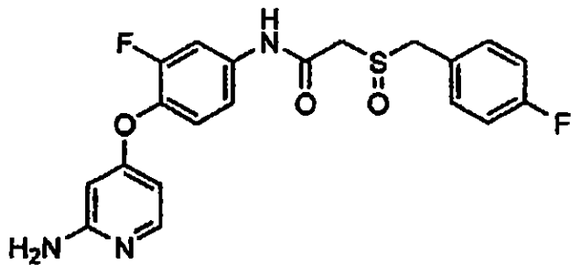
A una solución del diclorhidrato de 1-bencilhidrazina (Aldrich, 0.98 g. 5.0 mmol) en EtOH (30 mL) se agregaron DIEA (2.0 mL) y 2,4-dioxopentanoato de etilo (0.70 mL, 5.0 mmol). La mezcla se agitó a temperatura ambiente por 12 h y se concentró a vacío. El residuo se disolvió en NaOH 1 N (10 mL). La solución se calentó a 60°C por 1 h. Después de enfriar, la solución se extrajo con DCM (3 x 50 mL). La capa acuosa se neutralizó a pH 2.0 y luego se extrajo con EtOAc. La capa orgánica se lavó con salmuera y se secó sobre sulfato de magnesio. Se filtró y se concentró para dar el ácido 1-bencil-5-metil-^{1}H-pirazol-3-carboxílico (1.0 g, 92% de rendimiento). MS(ESI$^+$): m/z 217.12 $(M + H)^+$.

B) N-(4-(2-Aminopiridin-4-iloxi)-3-fluorofenil)-1-bencil-5-metil-^{1}H-pirazol-3-carboxamida, sal de clorhidrato

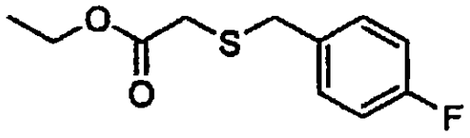
La 4-(4-Amino-2-fluorofenoxi)piridin-2-amina (Compuesto B del Ejemplo 24, 25 mg, 0.11 mmol) se acopló con el ácido 1-bencil-5-metil-^{1}H-pirazol-3-carboxílico (25 mg, 0.11 mmol) de

una manera similar a aquella que se describe en el Paso C del Ejemplo 1 para dar el clorhidrato de N-(4-(2- aminopiridin-4-iloxi)-3-fluorofenil)-1-bencil-5-metil-^{1}H-pirazol-3-carboxamida (10 mg, 20% de rendimiento) después de purificación por HPLC preparativa. RMN-^{1}H (DMSO-d_6) δ 10.64 (s, 1H), 7.8-7.98 (m, 3H), 7.00-7.65 (m, 9H), 6.71 (m, 1H), 6.15 (s, 1H), 5.65 (s, 2H), 2.24 (s, 3H); m/z 418.21 $(M + H)^+$.

Ejemplo 99



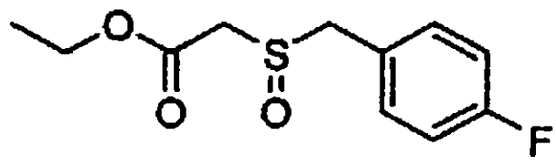
2-(4-Fluorobencilsulfinil)-N-(4-(2-aminopiridin-4-iloxi)-3-fluorofenil)acetamida, sal de clorhidrato



A) 2-(4-fluorobenciltio)acetato de etilo

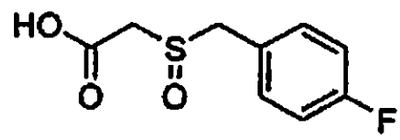
A una solución de 2-mercaptoacetato de etilo (Aldrich, 1.0 mL, 9.1 mmol) en acetonitrilo (10.0 mL) se agregaron K_2CO_3 (2.76 g, 20.0 mmol) y 1-(bromometil)-4-fluorobenceno

(2.27 g, 12.0 mmol). La mezcla se agitó a temperatura ambiente por 12 h. Después de la filtración y concentración, el residuo se purificó mediante cromatografía instantánea en columna sobre SiO_2 para dar el 2-(4-fluorobenciltio)acetato de etilo (1.89 g, 91% de rendimiento). MS (ESI^+) : m/z 251.08 $(M + H)^+$.



B) 2-(4-fluorobencilsulfinil)acetato de etilo

A una solución de 2-(4-fluorobenciltio)acetato de etilo (1.89 g, 8.29 mmol) en DCM (20.0 mL) a -40 °C se agregó una solución de m-CPBA (77%, 1.86 g, 8.29 mmol) en DCM (20.0 mL) gota a gota. La solución se agitó desde -40 °C hasta la temperatura ambiente toda la noche. La solución se apagó luego con dietilentriamina enlazada al polímero. Después de la filtración y concentración, el residuo se purificó mediante cromatografía instantánea sobre SiO_2 para dar el 2-(4-fluorobencilsulfinil)acetato de etilo (2.0 g, 98% de rendimiento). MS(ESI^+): m/z 267.09 $(M + H)^+$.



C) ácido 2-(4-fluorobencilsulfínil)acético

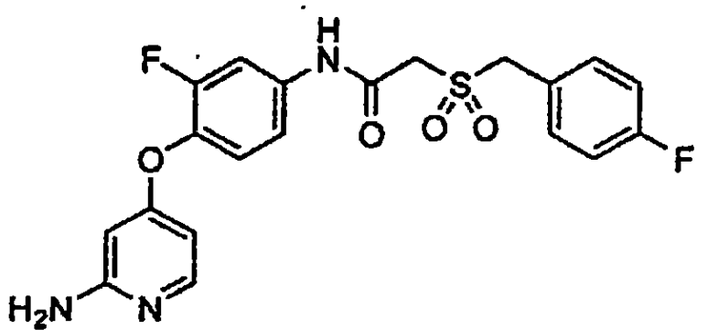
A una solución de 2-(4-fluorobencilsulfinil)acetato de etilo (1 .60 g, 6.55 mmol) en THF (10.0 mL) y MeOH (20.0 mL) se agregó 1 N NaOH (20.0 mmol). La mezcla se agitó a temperatura ambiente por 2 h. Después de la eliminación del solvente orgánico bajo presión reducida, la solución acuosa remanente se neutralizó con HCl 1N (25.0 mL). Se extrajo con EtOAc (3 x 100 mL) y la capa orgánica combinada se secó sobre sulfato de magnesio. La solución se filtró luego y se concentró a vacío para dar el ácido 2-(4-fluorobencilsulfínil)acético (1.25 g, 88% de rendimiento). MS (ESI^+):

D) 2-(4-Fluorobencilsulfinil)-N-(4-(2-aminopiridin-4-iloxi)-3-fluorofenil)acetamida, sal de clorhidrato

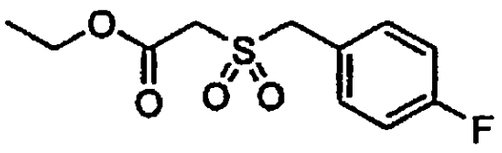
El diclorhidrato de la 4-(4-Amino-2-fluorofenoxi)piridin-2-amina (Compuesto B del Ejemplo 24, 29 mg, 0.10 mmol) se acopló con el ácido 2-(4-fluorobencilsulfinil)acético (22 mg, 0.1 mmol) de una manera similar a aquella que se describe en el Paso C del Ejemplo 1 para dar la 2-(4-fluorobencilsulfinil)-N-(4-(2-aminopiridin-4-iloxi)-3-fluorofenil)acetamida, sal de clorhidrato (17 mg, 37% de rendimiento). RMN-^{1}H (DMSO-d_6) δ 10.94 (s, 1H), 7.97 (d, 1H, J = 7.5 Hz), 7.85 (m, 3H), 7.39-7.45 (m, 4H), 7.23 (t, 2H, J = 7.5 Hz), 6.70 (m, 1H), 6.13 (d, 1H, J = 2.5 Hz), 4.32 (d, 1H, J = 1 1.0 Hz), 4.11 (d, 1H, J = 11.0 Hz), 3.98

(d, 1H, J = 13.0 Hz), 3.65 (d, 1H, J = 13.0 Hz); MS(ESI+): m/z 418.26 $(M + H)^+$.

Ejemplo 100



2-(4-Fluorobencilsulfonil)-N-(4-(2-aminopiridin-4-iloxi)-3-fluorofenil)acetamida, sal de clorhidrato

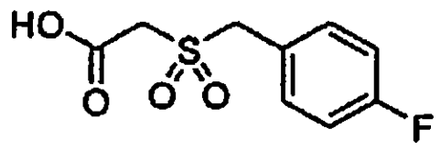


A) 2-(4-fluorobencilsulfonil)acetato de etilo

A una solución de 2-(4-fluorobencilsulfinil)acetato de etilo (370 mg, 1.52 mmol) en DCM (5.0 mL) se agregó m-CPBA (77%, 450 mg, 2.0 mmol).

La mezcla se agitó a temperatura ambiente por 2 h y se apagó luego con dietilentriamina enlazada al polímero (1.5 g).

La mezcla de reacción se filtró y se concentró a vacío para dar el 2-(4-fluorobencilsulfonil)acetato de etilo (360 mg, 91% de rendimiento). MS(ESI^+): m/z 283.10 $(M + H)^+$.



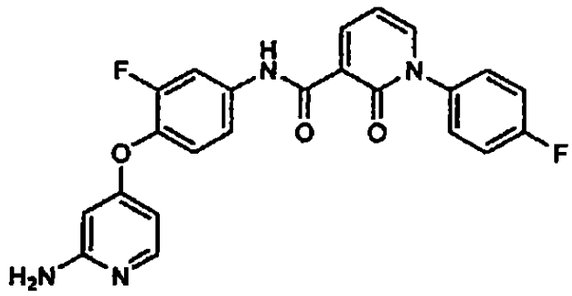
B) ácido 2-(4-fluorobencilsulfonil)acético

Preparado de una manera similar a aquella que se describe en, el Paso C del Ejemplo 99. El 2-(4-fluorobencilsulfonil)acetato de etilo (340 mg, 1.31 mmol) se convirtió a 2-(4-fluorobencilsulfonil)ácido acético (270 mg. 81% de rendimiento). MS(ESI$^+$): m/= 255.05 $(M + H)^+$.

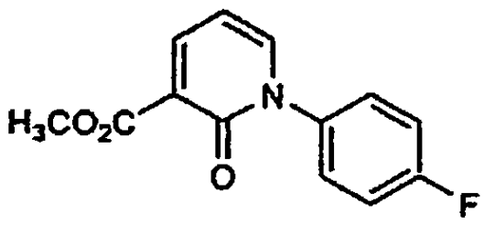
C) 2-(4-Fluorobencilsulfonil)-N-(4-(2-aminopiridin-4-iloxi)-3-fluorofenil)acetamida, sal de clorhidrato

4-(4-Amino-2-fluorofenoxi)piridin-2-amina diclorhidrato de (50 mg, 0.17 mmol) se acopló con el ácido 2-(4-fluorobencilsulfonil)acético (33 mg, 0.14 mmol) de una manera similar a aquella que se describe en el Paso C del Ejemplo 1 para dar la 2-(4-fluorobencilsulfonil)-N-(4-(2- aminopiridin-4-iloxi)-3-fluorofenil)acetamida, sal de clorhidrato (30 mg, 45% de rendimiento). RMN-^{1}H (DMSO-d_6) δ 13.40 (s, 1H), 11.15 (s, 1H), 7.97 (d, 1H. J = 7.0 Hz), 7.80- 7.90 (m, 3H), 7.47 (m, 4H), 7.26 (t 2H. J = 8.5 Hz), 6.72 (d, 1H. J = 7.0 Hz), 6.14 (d, 1H, J = 2.0 Hz), 4.69 (s, 2H), 4.27 (s, 2H); MS(ESI$^+$): m/z 434.15 $(M + H)^+$.

Ejemplo 101



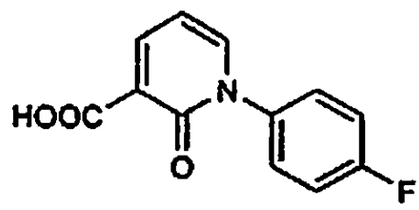
N-(4-(2-Aminopiridin-4-iloxi)-3-fluorofenil)-1-(4-fliiorofenil)-2-oxo-1,2-dihidropiridin-3-carboxamida, sal de clorhidrato



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 (Aldrich, 2.31 g, 15 mmol) en THF (40 mL) y DMF (10 mL) a temperatura ambiente se agregó 4-fluoroanilina (1.67 g, 15 mmol), y la mezcla de reacción se agitó por 2.5 h. Se observó precipitación de sólidos. Al aducto intermediario de 4-fluoroanilina formado vía la adición de Michael, obtenido en situ, se agregó EDCI.HCl (3.85 g, 20 mmol) y DMAP (120 mg) a

temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente toda la noche. A la mezcla de reacción se agregaron en aq HCl 1N (50 mL) y EtOAc (150 mL), la capa de EtOAc se separó, y la capa acuosa se lavó con EtOAc (150 mL), la capa combinada de EtOAc se secó sobre sulfato de magnesio y se concentró a vacío para obtener a material semi-sólido (~4.4 g). A este producto crudo se agregaron éter (100 mL) y metanol (15 mL), se agito, y el sólido se filtró para obtener el producto sólido no deseado (870 mg). La solución filtrada se concentró para obtener un producto crudo semi-sólido, deseado (2.95 g, crudo 80 %) el cual fue lo suficientemente puro para usarse en el siguiente paso sin purificación adicional. RMN-^{1}H (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) 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

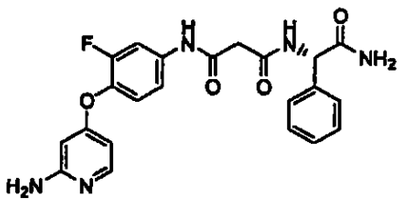
mmol) y 6 N aq NaOH (2.5 mL) en metanol (60 mL) se agitó a temperatura ambiente por 4 h. A la mezcla de reacción se agregó HCl conc. (1 mL) lentamente con agitación a temperatura ambiente, y el precipitado sólido se filtró, se lavó con una pequeña cantidad agua, se secó para obtener el producto ácido deseado (2.1 g) como un sólido amarillo. La solución filtrada se concentró a vacío. El residuo se mezcló con agua (50 mL) y se lavó con EtOAc (2 x 130 mL). Las capas de EtOAc se secaron sobre sulfato de magnesio y se concentraron a vacío. El residuo se trituró con una pequeña cantidad de éter para obtener la 2ª cosecha del producto (195 mg, total 2.30 g, 82 %). RMN-^{1}H (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-(2-Aminopiridin-4-iloxi)-3-fluorofenil)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridin-3-carboxamida, sal de clorhidrato

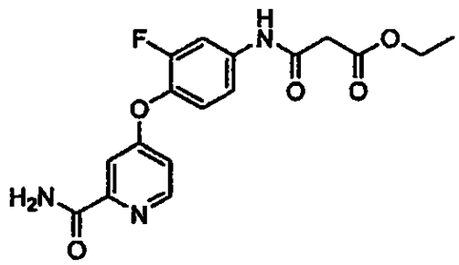
La 4-(4-amino-2-fluorofenoxi)piridin-2-amina (Compuesto B del Ejemplo 24, 58 mg, 0.20 mmol) se acopló con el ácido 1-(4-fluorofenil)-2-oxo-1,2-dihidropiridin-3-carboxílico (47 mg, 0.20 mmol) de una manera similar a aquella que se describe en el Paso C del Ejemplo 1 para dar N-(4-(2-aminopiridin-4-iloxi)-3-fluorofenil)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridin-3-carboxamida, sal de clorhidrato (22 mg,

23% de rendimiento). RMN-^{1}H (DMSO-d_6) δ 13.40 (s, 1H), 12.13 (s, 1H), 8.58 (d, 1H, J = 5.0 Hz), 8.13 (d, 1H, J = 5.0 Hz), 8.07 (d, 1H, J = 10.0 Hz), 7.98 (d, 1H. J = 7.5 Hz), 7.89 (s, 2H), 7.40-7.60 (m, 6H), 6.72 (m, 2H), 6.17 (d, 1H, J = 2.5 Hz) : MS (ESI$^+$) m/z 435.18 $(M + H)^+$.

Ejemplo 102



(S)-N^1-(2-Amino-2-oxo-1-feniletil)-N^3-(4-(2-aminopiridin-4-iloxi)-3-fluorofenil)malonamida, sal de clorhidrato

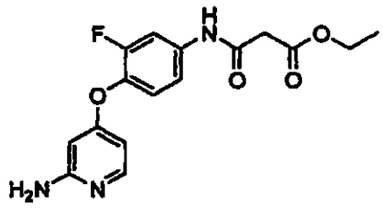


A) 3-(4-(2-carbamoilpiridin-4-iloxi)-3-fluorofenilamino)-3- oxopropanoato de etilo

A una solución de 4-(4-amino-2-fluorofenoxi)picolinamida (Compuesto B' del Ejemplo 24, 1.0 g, 4.0 mmol) en DMF (10.0 mL) se agregaron DIEA (2.0 mL) y 3- cloro-3-oxopropanoato de etilo (Aldrich, 0.75 mL, 6.0 mmol). La mezcla se agitó a temperatura ambiente por 12 h y se agregó más 3-cloro-3-

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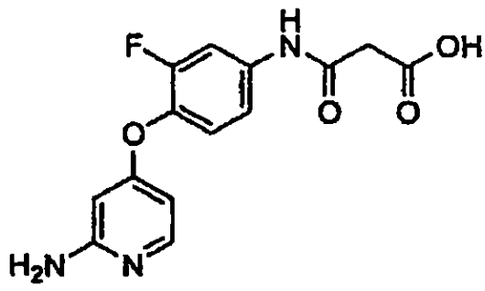
oxopropanoato de etilo (0.20 mL, 1.65 mmol). La mezcla se agitó por 2 h y luego se diluyó con EtOAc (200 mL). Se lavó con agua y salmuera y luego se secó sobre sulfato de magnesio. Después de filtración y concentración, el residuo se trituró con DCM y se filtró para dar 3-(4-(2-carbamoilpiridin-4-iloxi)-3-fluorofenilamino)-3-oxopropanoato de etilo (900 mg, 62% de rendimiento). MS(ESI+) m/z 362.28 $(M + H)^+$.



B) 3-(4-(2-aminopiridin-4-iloxi)-3-fluorofenilamino)-3-oxopropanoato de etilo

Preparado de una manera similar a aquella que se describe en el Paso A del Ejemplo 91. El 3-(4-(2-carbamoilpiridin-4-iloxi)-3-fluorofenilamino)-3-oxopropanoato de etilo (900 mg. 2.5 mmol) en DMF (10.0 mL) se convirtió a 3-(4-(2-aminopiridin-4-iloxi)-3-fluorofenilamino)-3-oxopropanoato de etilo (710 mg, 86% de rendimiento). MS(ESI+) m/z 334.26 $(M + H)^+$.

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C) ácido 3-(4-(2-aminopiridin-4-iloxi)-3-fluorofenilamino)-3-oxopropanoico

Preparado de una manera similar a aquella que se describe en el Paso C del Ejemplo 99. El 3-(4-(2-aminopiridin-4-iloxi)-3-fluorofenilamino)-3-oxopropanoato de etilo (700 mg, 2.10 mmol) se convirtió a ácido 3-(4-(2-aminopiridin-4-iloxi)-3-fluorofenilamino)-3-oxopropanoico (630 mg, 98% de rendimiento). MS(ESI$^+$) m/z 306.20 $(M + H)^+$.

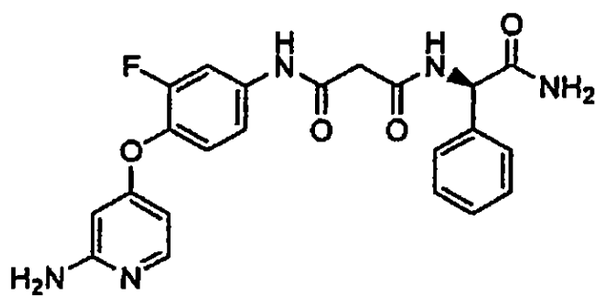
D) (S)-N^1-(2-amino-2-oxo-1-feniletil)-N^3-(4-(2-aminopiridin-4-iloxi)-3-fluorofenil)malonamida, sal de clorhidrato

El ácido 3-(4-(2-aminopiridin-4-iloxi)-3-fluorofenilamino)-3-oxopropanoico (30 mg, 0.10 mmol) se acopló con clorhidrato de (S)-2-amino-2-fenilacetamida (Acros, 28 mg, 0.15 mmol) de una manera similar a aquella que se describe en el Paso C del Ejemplo 1 para dar la (S)-N1-(2-amino-2-oxo-1-feniletil)-N^3-(4-(2-aminopiridin-4-iloxi)-3-fluorofenil)malonamida, sal de clorhidrato (25 mg 53% de rendimiento). RMN-^{1}H (DMSO-d_6) δ 10.68 (s, 1H), 8.80 (d, 1H, J = 8.0 Hz), 7.96 (d, 1H, J = 7.5 Hz). 7.77-7.90 (m, 4H), 7.20-7.45 (m, 8H), 6.70 (m, 1H), 6.12 (s, 1H), 5.39 (d, 1H, J =

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7.5 Hz), 3.48 (d, 1H, J = 15.0 Hz), 3.41 (d, 1H, J = 15.0 Hz); MS(ESI$^+$) m/z 438.26 $(M + H)^+$.

Ejemplo 103

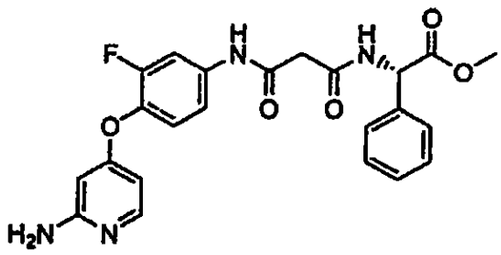


(R)-N^1-(2-Amino-2-oxo-1-feniletil)-N^3-(4-(2-aminopiridin-4-iloxi)-3-fluorofenil)malonamida, sal de clorhidrato

El ácido 3-(4-(2-aminopiridin-4-iloxi)-3-fluorofenilamino)-3-oxopropanoico (Compuesto C del Ejemplo 102, 30 mg, 0.10 mmol) se acopló con clorhidrato de (R)-2-amino-2-fenilacetamida (Bachem, 28 mg, 0.15 mmol) de una manera similar a aquella que se describe en el Paso C del Ejemplo 1, para dar la (R)-N^1-(2-amino-2-oxo-1-feniletil)-N^3-(4-(2-aminopiridin-4-iloxi)-3-fluorofenil)malonamida, sal de clorhidrato (14 mg, 30% de rendimiento).

RMN-^{1}H (DMSO-d_6) δ 10.65 (s, 1H), 8.76 (d, 1H, J = 8.0 Hz), 7.92 (d, 1H, J = 7.0 Hz), 7.75-7.88 (m, 4H), 7.20-7.43 (m, 8H), 6.66 (m, 1H), 6.09 (s, 1H), 5.35 (d, 1H, J = 8.0 Hz), 3.45 (d, 1H, J = 15.0 Hz), 3.37 (d, 1H, J = 15.0 Hz); MS (ESI$^+$) m/z 438.23 $(M + H)^+$.

Ejemplo 104

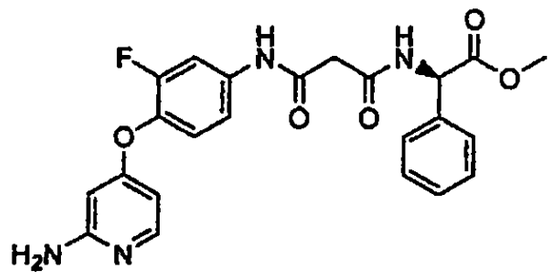


2-(3-(4-(2-aminopiridin-4-iloxi)-3-fluorofenilamino)-3-oxopropanamido)-2-fenilacetato de (S)-metilo, sal declorhidrato

El ácido 3-(4-(2-aminopiridin-4-iloxi)-3-fluorofenilamino)-3-oxopropanoico (Compuesto C del Ejemplo 102, 30 mg, 0.10 mmol) se acopló con clorhidrato de 2-amino-2-fenilacetato de (S)-metilo (Aldrich, 30 mg. 0.10 mmol) de una manera similar a aquella que se describe en el Paso C del Ejemplo 1, para dar (2-(3-(4-(2-aminopiridin-4-iloxi)-3-fluorofenilamino)-3-oxopropanamido)-2-fenilacetato de S)-metilo, sal de clorhidrato (21 mg, 43% de rendimiento). RMN-^{1}H (DMSO-d_6) δ 10.58 (s, 1H), 9.04 (d, 1H. J = 7.0 Hz), 7.97 (d, 1H, J = 7.0 Hz), 7.75-7.88 (m, 3H), 7.42 (m, 7H), 6.72 (d, 1H, J = 7.0 Hz), 6.12 (s, 1H), 5.45 (d, 1H, J = 7.0 Hz), 3.63 (s, 3H), 3.43-3.38 (m, 2H); MS(ESI$^+$) m/z 453.26 $(M + H)^+$.

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Ejemplo 105

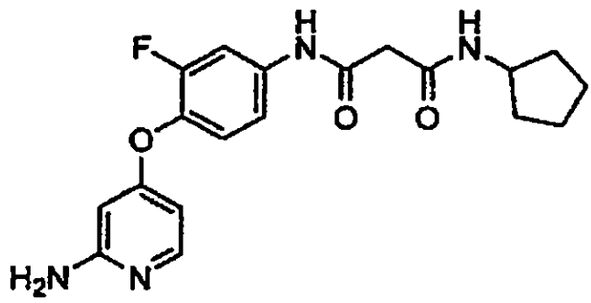


2-(3-(4-(2-aminopiridin-4-iloxi)-3-fluorofenilamino)-3-oxopropanamido)-2-fenilacetato de (R)-metilo, sal de clorhidrato

El ácido 3-(4-(2-aminopiridin-4-iloxi)-3-fluorofenilamino)-3-oxopropanoico (Compuesto C del Ejemplo 102, 30 mg, 0.10 mmol) se acopló con 2-amino-2-fenilacetato de (R)-metilo, sal de clorhidrato (Aldrich, 30 mg, 0.10 mmol) de una manera similar a aquella que se describe en el Paso C del Ejemplo 1 para dar 2-(3-(4-(2-aminopiridin-4-iloxi)-3-fluorofenilamino)-3-oxopropanamido)-2-fenilacetato de (R)-metilo, sal de clorhidrato (25 mg, 51% de rendimiento). RMN-^{1}H (DMSO-d_6) δ 10.58 (s, 1H), 9.03 (d, 1H. J = 7.0 Hz), 7.96 (d, 1H, J = 7.0 Hz), 7.77-7.88 (m, 3H), 7.42 (m, 7H), 6.71 (d, 1H, J = 7.5 Hz), 6.12 (s, 1H), 5.44 (d, 1H, J = 7.0 Hz), 3.63 (s, 3H), 3.44-3.38 (m, 2H); MS(ESI$^+$) m/z 453.29 $(M + H)^+$.

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Ejemplo 106

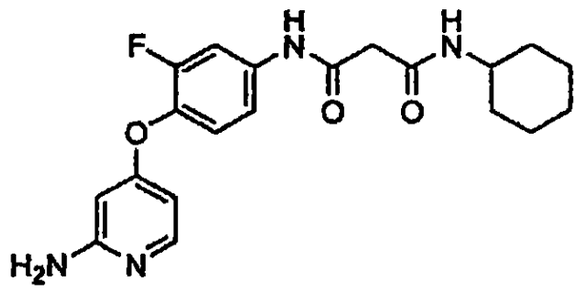


N^1-(4-(2-Aminopiridin-4-iloxi)-3-fluorofenil)-N^3-ciclopentilmalonamida, sal de clorhidrato

El ácido 3-(4-(2-aminopiridin-4-iloxi)-3-fluorofenilamino)-3-oxopropanoico (Compuesto C del Ejemplo 102, 30 mg, 0.10 mmol) se acopló con ciclopentanamina (Aldrich, 17 mg, 0.2 mmol) de una manera similar a aquella que se describe en el Paso C del Ejemplo 1 para dar N1-(4-(2-aminopiridin-4-iloxi)-3-fluorofenil)-N^3-ciclopentilmalonamida, sal de clorhidrato (18 mg, 44% de rendimiento). RMN-^{1}H (DMSO-d_6) δ 13.34(s, 1H), 10.66 (s, 1H), 8.15 (d, 1H, J = 7.0 Hz), 7.96 (d, 1H, J = 7.0 Hz). 7.77-7.88 (m, 3H), 7.42 (m, 2H), 6.70 (d, 1H, J = 7.5 Hz). 6.12 (s, 1H), 3.98 (m, 1H). 3.69 (s, 2H), 1.78 (m, 2H), 1.63 (m, 2H), 1.49 (m, 2H), 1.37 (m, 2H); MS (ESI^+) m/z 373.30 $(M + H)^+$

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Ejemplo 107

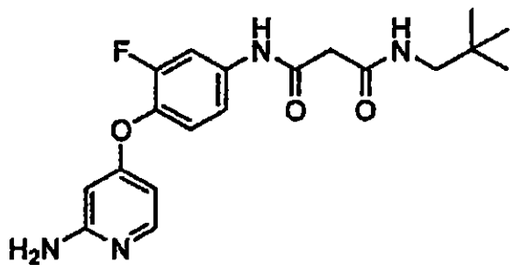


N^1-(4-(2-Aminopiridin-4-iloxi)-3-fluorofenil)-N^3-ciclohexilmalonamida, sal de clorhidrato

El ácido 3-(4-(2-aminopiridin-4-iloxi)-3-fluorofenilamino)-3-oxopropanoico (Compuesto C del Ejemplo 102, 30 mg, 0.10 mmol) se acopló con ciclohexanamina (Aldrich, 20 mg, 0.2 mmol) de una manera similar a aquella que se describe en el Paso C del Ejemplo 1 para dar N^1-(4-(2-aminopiridin-4-iloxi)-3-fluorofenil)-N3-ciclohexilmalonamida, sal de clorhidrato (22 mg, 52% de rendimiento). RMN-^{1}H (DMSO-d_6) δ 14.00 (s, 1H), 10.72 (s, 1H), 8.10 (d, 1H, J = 7.0 Hz), 7.97 (d, 1H, J = 7.0 Hz), 7.88 (m, 3H), 7.44 (m, 2H), 6.70 (m, 1H), 6.14 (d, 1H, J = 2.0 Hz), 3.54 (m, 1H), 3.27 (s, 2H), 1.66-1.75 (m, 4H). 1.52 (m, 1H), 1.15-1.25 (m, 5H); MS (ESI$^+$) m/z 387.32 $(M + H)^+$.

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Ejemplo 108

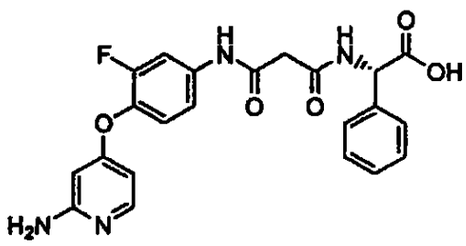


N^1-(4-(2-Aminopiridin-4-iloxi)-3-fluorofenil)-N^3-neopentilmalonamida, sal de clorhidrato

El ácido 3-(4-(2-aminopiridin-4-iloxi)-3-fluorofenilamino)-3-oxopropanoico (Compuesto C del Ejemplo 102, 30 mg, 0.10 mmol) se acopló con 2,2-dimetilpropan-1-amina (Aldrich, 12 mg, 0.2 mmol) de una manera similar a aquella que se describe en el Paso C del Ejemplo 1, para dar N^1-(4-(2-aminopiridin-4-iloxi)-3-fluorofenil-N^3-neopentilmalonamida, sal de clorhidrato (13 mg, 32% de rendimiento). RMN-^{1}H (DMSO-d_6) δ 13.34 (s, 1H), 10.69 (s, 1H), 8.08 (m, 1H), 7.96 (d, 1H, J = 7.0 Hz), 7.87 (m, 3H), 7.44 (m, 2H), 6.70 (m, 1H), 6.13 (d, 1H, J = 2.0 Hz), 3.34 (s, 2H), 2.91 (d, 2H. J = 6.5 Hz), 0.84 (s, 9H); MS (ESI^+) m/z 375.32 $(M + H)^+$.

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Ejemplo 109

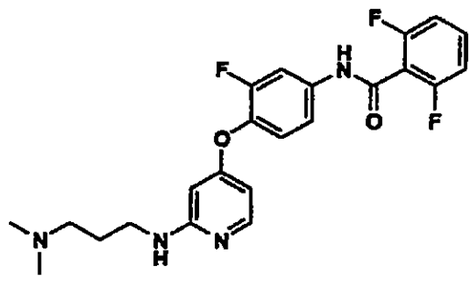


Ácido (S)-2-(3-(4-(2-aminopiridin-4-iloxi)-3-fluorofenilamino)-3-oxopropanamido)-2-fenilacético, sal de clorhidrato

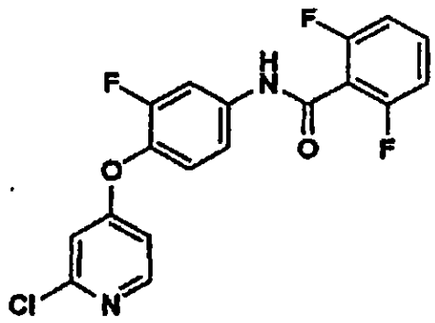
Siguiendo un procedimiento similar a aquel que se describe en el Paso C del Ejemplo 99, el 2-(3-(4-(2-aminopiridin-4-iloxi)-3-fluorofenilamino)-3-oxopropanamido)-2-fenilacetato de (S)-metilo, clorhidrato (Compuesto D del Ejemplo 102, 14 mg, 0.028 mmol) se hidrolizó para dar el ácido (S)-2-(3-(4-(2-aminopiridin-4-iloxi)-3-fluorofenilamino)-3-oxopropanamido)-2-fenilacético, sal de clorhidrato (13 mg, 97% de rendimiento). RMN-^{1}H (DMSO-d_6) δ 13.20 (s, 1H), 10.57 (s, 1H). 8.92 (d, 1H, J = 7.0 Hz), 7.95 (d, 1H, J = 7.0 Hz), 7.87 (d, 1H, J = 11.0 Hz), 7.70 (s, 2H), 7.41 (m, 8H). 6.69 (d, 1H. J = 7.5 Hz), 6.12 (d, 1H, J = 2.0 Hz), 5.35 (d, 1H, J = 7.5 Hz), 3.42 (s, 2H); MS(ESI$^+$) m/z 439.27 $(M + H)^+$.

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Ejemplo 110



N-(4-(2-(3-(Dimetilamino)propilamino)piridin-4-iloxi)-3-fluorofenil)-2,6-difluorobenzamida, sal de clorhidrato



A) N-(4-(2-Cloropiridin-4-iloxi)-3-fluorofenil)-2,6-difluorobenzamida

Una solución de 4-(2-cloropiridin-4-iloxi)-3-fluorobencenamina (Compuesto B del Ejemplo 20, 64 mg, 0.27 mmol), THF (1 ml), Et_3N (100 µL) se trató gota a gota con cloruro de 2,6-difluorobenzoilo (Aldrich, 33 µL, 0.27 mmol) y la mezcla se agitó a temperatura ambiente por 30 min. La mezcla se dividió entre EtOAc y solución acuosa saturada de carbonato ácido de sodio y la fase de EtOAc se separó, se secó (sulfato de magnesio) y se concentró a vacío para dar el compuesto del título (102 mg, 100 %) como un sólido blanco.

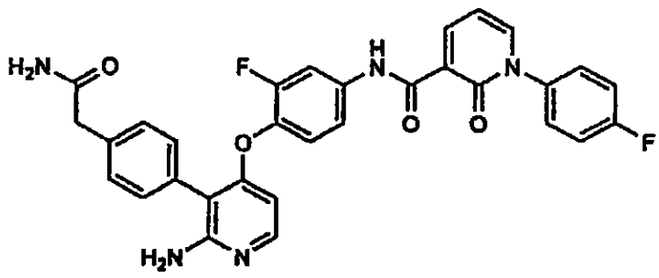
610

MS (ESI^+) : m/z 418.18 $(M + H)^+$.

B) N-(4-(2-(3-(Dimetilamino)propilamino)piridin-4-iloxi)-3-fluorofenil)-2,6-difluorobenzamida, sal de clorhidrato

Una mezcla de N-(4-(2-cloropiridin-4-iloxi)-3-fluorofenil)-2,6-difluorobenzamida (70 mg, 0.19 mmol), 3-(dimetilamino)propilamina (44 mL, 0.35 mmol), Cs_2CO_3 (85 mg, 0.26 mmol) y CuCl (17 mg, 0.17 mmol) en un frasco de tapa roscada se purgó con N2. Se agregaron NMP y 2,2,6,6,-tetrametil-3,5-heptanodiona (31 mg, 0.17 mmol) a la mezcla que se calentó luego a 120 °C por 4 h. La mezcla se enfrió, se dividió entre EtOAc y solución acuosa saturada de carbonato ácido de sodio y la fase de EtOAc se separó, se secó (sulfato de magnesio) y se concentró a vacío para dar el producto crudo. La purificación del residuo mediante HPLC preparativa (Columna C) y conversión a la sal de clorhidrato se llevó a cabo de una manera similar al Paso D del Ejemplo 33 para dar el compuesto del título (7 mg, 7 %) como un sólido blanquecino. MS (ESI^+) : m/z 517.37$(M + H)^+$.

Ejemplo 111



N-(4-(2-Amino-3-(4-(2-amino-2-oxoetil)fenil)piridin-4-iloxi)-

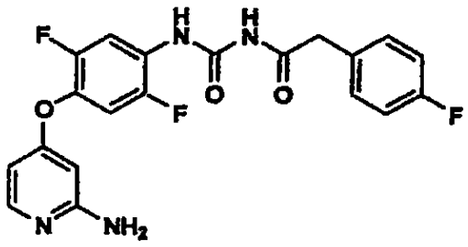
617

3-fluorofenil)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridin-3-carboxamida, sal de clorhidrato

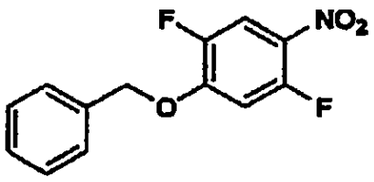
Una solución de 2-(4-(2-amino-4-(4-amino-2-fluorofenoxi)piridin-3-il)fenil)acetamida (Compuesto C del Ejemplo 78, 18 mg, 0.05 mmol) en DMF (1.5 mL) se trató con ácido 1-(4-fluorofenil)-2-oxo-1,2-dihidropiridin-3-carboxílico (Compuesto B del Ejemplo 101, 11 mg, 0.05 mmol), DIPEA (10 µL, 0.06 mmol) y TBTU (19 mg, 0.06 mmol). La mezcla se agitó a temperatura ambiente por 40 h. La mezcla se concentró a vacío y el residuo se purificó mediante HPLC preparativa (Columna A) para dar el compuesto del título como una sal de TFA. La sal de TFA se disolvió en MeOH anhidro y se trató con HCl 1 M/Et_2O a 0°C y se agitó por 5 min. La mezcla se concentró luego a vacío para dar el compuesto del título (15 mg, 47%) como un sólido amarillo. RMN-^{1}H (DMSO-d_6) δ 12.11 (s, 1H), 8.56 (dd, 1H. J = 2.2, 7.1 Hz), 8.13 (dd, 1H, J = 2.2, 6.7 Hz), 8.00 (dd, 1H, J = 2.2, 12.6 Hz), 7.96 (d, 1H, J = 7.7 Hz), 7.60 - 7.57 (m, 2H), 7.48 - 7.33 (m, 10H), 6.94 (s, 1H), 6.72 (dd, 1H, J = 7.2, 7.2 Hz), 6.38 (d, 1H, J = 7.2 Hz), 3.95 (s, 2H); MS(ESI$^+$): m/z 568.23 $(M + H)^+$,

612

Ejemplo 112



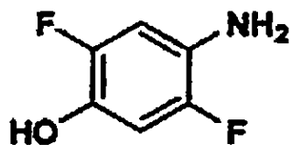
1-(4-(2-Aminopiridin-4-iloxi)-2,5-difluorofenil)-3-(2-(4-fluorofenil)-acetil)urea, sal del ácido clorhídrico



A) 1-((2,5-Difluoro-4-nitrofenoxi)metil)benceno

Una mezcla de 2,4,5-trifluoronitrobenceno (5.4 g, 30.8 mmol), bencilalcohol (3.2 mL, 30.8 mmol) y carbonato de potasio (6.4 g, 46.1 mmol), en DMF (20 mL), se agitó a temperatura ambiente por 72 h. Se agregó agua (60 mL) y la mezcla se enfrió a 4 °C por 24 h. El precipitado resultante se filtró, se enjuagó con agua y se secó a vacío para proporcionar el producto (7.5 g, 92%) como un sólido amarillo pálido. RMN-^{1}H (DMSO-d_6) δ 7.90-7.94 (m, 1H), 7.38-7.44 (m, 5H), 6.85-6.90 (m, 1H), 5.22 (s, 2H).

613



B) 4-Amino-2,5-difluorofenol

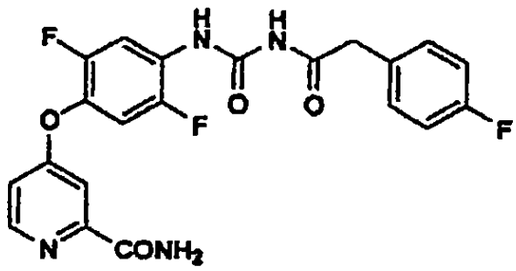
A un matraz se cargó 1-((2,5-difluoro-4-nitrofenoxi)metil)benceno (4.1 g. 15.6 mmol), que se evacuó secuencialmente y luego se purgó con nitrógeno tres veces, se agregó 10% de paladio sobre carbono (0.40 g). A los sólidos, bajo una atmósfera de nitrógeno, se agregó metanol anhidro (100 mL). La mezcla fue luego agitada bajo una atmósfera de hidrógeno 16 h. Se burbujeó nitrógeno a través de la mezcla de reacción por treinta minutos, antes de que la mezcla se filtrara a través de un lecho de Celite®, que se enjuagó luego con metanol. El filtrado se concentró a vacío, luego convirtió en azeótropo con tolueno para proporcionar el compuesto del título como un sólido café oscuro (2.2 g, 99%). RMN-^{1}H (DMSO-d_6) δ 9.05 (br s, 1H), 6.53-6.65 (m, 2H), 4.68 (s, 2H); MS (ESI^+) m/z 146 $(M+H)^+$.



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C) 4-(4-Amino-2,5-difluorofenoxi)picolinamida

A una mezcla de hidruro de potasio (30-35% dispersión en aceite mineral, 1.9 g, 13.9 mmol) en DMF (30 mL) se agregó 4-amino-2,5-difluorofenol (1.7 g, 11.6 mmol) como una solución en DMF (5 mL). Después de una hora de agitar a temperatura ambiente, se agregó 4-cloropicolinamida (1.8 g, 11.6 mmol) y la mezcla de reacción se calentó a 100 °C por 135 h. Una mezcla se enfrió a temperatura ambiente. se apagó con cloruro litio acuoso al 10% y luego se extrajo tres veces con EtOAc. Las capas orgánicas combinadas se secaron (MgSO,}), se filtró y se concentró a vacío. El sólido resultante se dividió entre cloroformo y agua. La capa orgánica se lavó con salmuera, se secó (sulfato de magnesio), se filtró y se concentró a vacío hasta obtener un sólido (3.0 g, 98%). RMN-^{1}H (DMSO-d_6) δ 8.51-8.57 (m, 1H), 8.14 (br s, 1H), 7.74 (br s, 1H), 7.37-7.38 (m, 1H), 7.17-7.30 (m, 2H), 6.74-6.80 (m, 1H), 5.62 (s, 2H); MS (ESI$^+$) m/z 266 $(M+H)^+$.



D) 1-(4-(2-Carbamoilpiridin-4-iloxi)-2,5-difluorofenol)-3-(2-(4-fluorofenil) acetil) urea

A mezcla homogénea de 4-(4-amino-2.5-

difluorofenoxi)picolinamida (0.15 g, 0.57 mmol) en THF (5 mL) se agregó diisopropiletilamina (0.10 mL, 0.57 mmol). La mezcla se agitó por dos minutos a temperatura ambiente antes que se agregara isocianato de 2-(4-fluorofenil)acetilo (Compuesto D del Ejemplo 11, 0.36 M en tolueno, 2.0 mL, 0.72 mmol). Después de 3.5 horas) se agregó a la mezcla de reacción isocianato de 2-(4-fluorofenil)acetilo (0.36 M en tolueno, 2.0 mL, 0.72 mmol. Después de dos horas adicionales, se agregó isocianato de 2-(4-fluorofenil)acetilo (0.36 M en tolueno, 2.0 mL, 0.72 mmol) a la mezcla de reacción. La mezcla fue luego agitada por 16 horas antes de concentrarse a vacío. El residuo se trató con Et_2O y sonicación y el sólido blanco resultante se retiró mediante filtración. El sólido se trató con Et_2O y sonicación dos veces más antes de la filtración a vacío proporcionó un sólido blanco (0.23 g, 91%). RMN-^{1}H (DMSO-d_6) δ 11.29(s, 1H), 10.92 (s, 1H), 8.56 (d, 1H, J = 5.6Hz), 8.21-8.26 (m, 1H), 8.16 (br s, 1H), 7.76 (br s. 1H), 7.66-7.71 (m, 1H), 7.12-7.44 (m, 6H). 3.77 (s, 2H); MS (ESI$^+$) m/z 445 $(M+H)^+$.

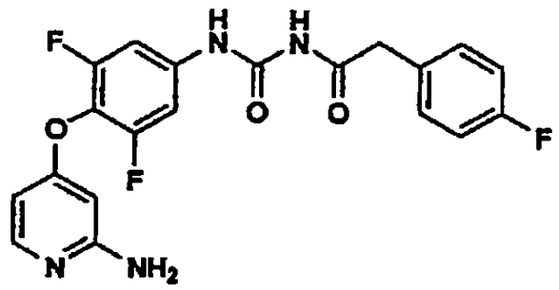
E) 1-(4-(2-Aminopiridin-4-iloxi)-2,5-difluorofenil)-3-(2-(4- fluorofenil)-acetil)urea, sal de ácido clorhídrico

Bis(trifluoroacetoxi)yodobenzeno (Aldrich, 0.18 g, 0.42 mmol) se agregó a una solución de 1-(4-(2- carbamoilpiridin-4-iloxi)-2,5-difluorofenil)-3-(2-(4-fluorofenil)-acetil)urea (0.13 g, 0.30 mmol), agua (0.01 mL, 0.60 mmol) y piridina

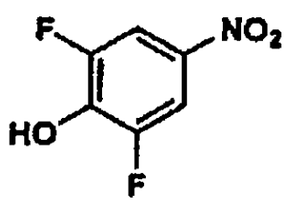
(0.05 mL, 0.66 mmol) en DMF (2 mL) a temperatura ambiente. Después de diez minutos se agregó, DMF adicional (2 mL). La mezcla de reacción fue luego agitada por 16 horas antes de concentrarse a vacío aproximadamente a la mitad del su volumen original. La mezcla resultante se dividió entre HCl 6 N y Et_2O, la solución acuosa se extrajo con Et_2O y las capas orgánicas combinadas se desecharon. La capa acuosa se neutralizó con carbonato ácido de sodio acuoso y se extrajo con EtOAc. Las capas orgánicas combinadas se secaron (sulfato de sodio), se filtró y se concentró a vacío. El residuo se purificó mediante cromatografía sobre gel de sílice (eluyendo con 0-5% de MeOH en $CHCl_3$) y Las fracciones apropiadas se concentraron a vacío. El residuo se disolvió en THF (1 mL), se enfrió a 0°C y se trató con HCl (4 N en dioxano, 0.5 mL, 2.0 mmol). La mezcla de reacción se dejó calentar a temperatura ambiente y se agitó por una hora, antes de liofilizarse para proporcionar el compuesto del título (73 mg, 53%) como un ólido blanco. RMN-^{1}H (DMSO-d_6) δ 13.54 (br s, 1H), 11.35 (s, 1H), 10.95 (s, 1H). 8.24-8.28 (m, 1H), 7.95-8.01 (m, 3H), 7.73-7.77 (m, 1H), 7.35-7.39 (m, 2H), 7.16-7.20 (m, 2H), 6.72-6.74 (m, 1H), 6.25 (s, 1H), 3.78 (s, 2H); HRMS (ESI$^+$) : 417.1175$(M+H)^+$calcd., 417.1187 $(M+H)^+$encontrado.

617

Ejemplo 113

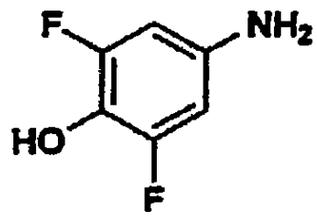


1-(4-(2-Aminopiridin-4-iloxi)-3,5-difluorofenol)-3-(2-(4-fluorofenil)-acetil)urea, sal del ácido trifluoroacético



A) 2,6-Difluoro-4-nitrofenol

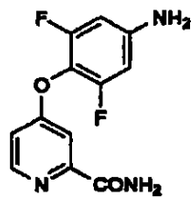
El 2,6-difluorofenol (10.0 g, 76.9 mmol) se convirtió al compuesto del título (12.7 g, 94%) de una manera similar a las condiciones descritas por Kark et al. J. Heterocyclic Chem. 1976, 13, 1253. RMN-^{1}H ($CDCl_3$) 6 12.15 (br s, 1H), 8.01-8.10 (m,2H).



B) 4-Amino-2,6-difluorofenol

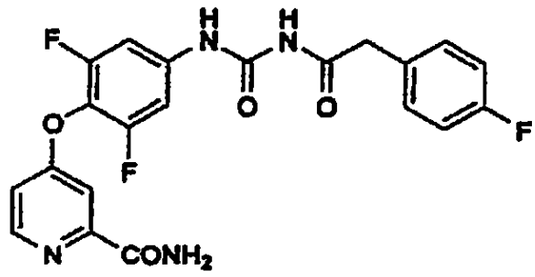
El 2,6-Difluoro-4-nitrofenol (2.1 g, 12.1 mmol) se

convirtió al compuesto del título (1.7 g, 99%) de una manera similar a aquella descrita por Demopoulos et al. J. Med. Chem. 2004. 47, 2706. MS (ESI^+) m/z 146 $(M+H)^+$.



C) 4-(4-Amino-2,6-difluorofenoxi)picolinamida

4-Cloropicolinamida (0.47 g, 3.0 mmol) se convirtió al compuesto del título (0.23 g, 29%) de una manera similar a la preparación del Compuesto C del Ejemplo 112, excepto que se utilizó 4-amino-2,6-difluorofenol (0.44 g, 3.0 mmol) en vez de 4-amino-2,5-difluorofenol. RMN-^{1}H (DMSO-d_6) δ 8.60 (d, 1H, J = 5.6 Hz), 8.22 (br s, 1H), 7.83 (br s, 1H), 7.45- 7.46 (m, 1H), 7.30-7.32 (m, 1H), 6.43-6.49 (m, 2H), 5.94 (s, 2H); MS (ESI^+) m/z 266 $(M+H)^+$.



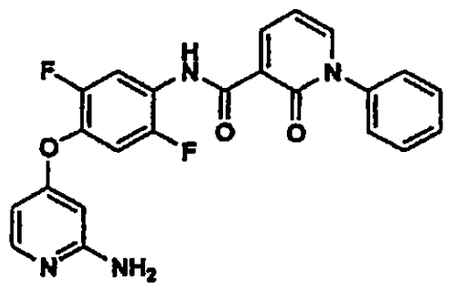
D) 1-(4-(2-Carbamoilpiridin-4-iloxi)-3,5-difluorofenil)-3-(2-(4-fluorofenil) acetil) urea

La 4-(4-amino-2,6-difluorofenoxi)picolinamida (104 mg, 0.39 mmol) se convirtió al compuesto del título (91 mg, 52%) de una manera similar a la preparación del Compuesto D del Ejemplo 112. RMN-^{1}H (DMSO-d_6) δ 11.07(s, 1H), 10.62 (s, 1H), 8.50 (d, 1H, J = 5.6 Hz), 8.11 (br s, 1H), 7.72 (br s, 1H), 7.61 (m, 2H), 7.36-7.37 (d, 1H, J = 2.3 Hz), 7.23-7.31 (m, 3H), 7.11 (m, 2H), 3.69 (s, 2H); HRMS (ESI^+), 445. 1124 $(M+H)^+$ calculado, 445.1117 $(M+H)^+$ encontrado.

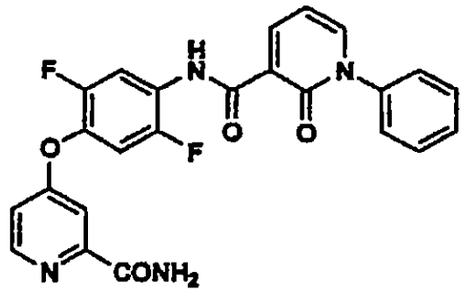
E) 1-(4-(2-Aminopiridin-4-iloxi)-3, 5-difluorofenil)-3-(2-(4-fluorofenil)-acetil)urea, sal del ácido trifluoroacético

1-(4-(2-Carbamoilpiridin-4-iloxi)-3,5-difluorofenil)-3-(2-(4-fluorofenil) acetil) urea (87 mg, 0.20 mmol) se convirtió al compuesto del título de una manera similar a la preparación del Compuesto E del Ejemplo 112, excepto que el producto crudo se purificó mediante HPLC preparativa (YMC S10 ODS, 30 x 500 mm, gradiente 30 minutos de 58% a 90 % metanol acuoso con 0.1% de TFA). Las fracciones apropiadas se combinaron y se liofilizó para proporcionar el compuesto del título (23 mg, 22%) como un sólido blanco. RMN-^{1}H (DMSO-d_6) δ 11.09 (s, 1H), 10.63 (s, 1H), 7.92 (d, 1H, J = 7.2 Hz), 7.62-7.72 (m, 4H), 7.27-7.31 (m, 2H), 7.09-7.14 (m, 2H), 6.68-6.70 (m, 1H), 6.17-6.18 (m, 1H), 3.69 (s, 2H); MS (ESI^+) m/z 417 $(M+H)^+$.

Ejemplo 114



N-(4-(2-Aminopiridin-4-iloxi)-2,5-difluorofenil)-2-oxo-1-fenil-1,2-dihidropiridin-3-carboxamida, sal de ácido clorhídrico



A) 4-(2,5-Difluoro-4-(2-oxo-1-fenil-1,2-dihidropiridin-3-carboxamido)-fenoxi)picolinamida

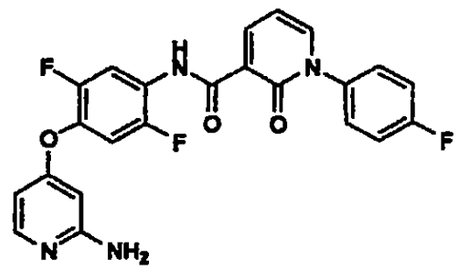
A una mezcla homogénea de ácido 2-oxo-1-fenil-1,2-dihidropiridin-3-carboxílico (Compuesto C del Ejemplo 57. 43 mg, 0.20 mmol) en DMF (4 mL) se agregó 1-hidroxi-benzotriazol hidratado (22 mg. 0.16 mmol). La mezcla se agitó hasta la homogeneidad antes de que se agregara clorhidrato de 1-(3-dimetilaminopropil)-3-etil-carbodiimida (102 mg, 0.53 mmol). Después de dos minutos, se agregó 4-(4-amino-2,5-

difluorofenoxi)picolinamida (Compuesto C del Ejemplo 112, 53 g, 0.20 mmol) y la mezcla de reacción se agitó a temperatura ambiente por 17 h. La mezcla de reacción se calentó luego a 40 °C y se agitó por 143 h adicionales. Después de enfriar a temperatura ambiente, la mezcla se dividió entre EtOAc y 10% de LiCl (acuoso). La capa orgánica se lavó dos veces con 10% de LiCl (acuoso), luego se concentró a vacío. El residuo se purificó mediante cromatografía sobre gel de sílice (eluyendo con hexano/EtOAc 1:3) y las fracciones apropiadas se concentraron a vacío para proporcionar el compuesto del título (45 mg, 49%). MS (ESI^+) m/z 463 $(M+H)^+$.

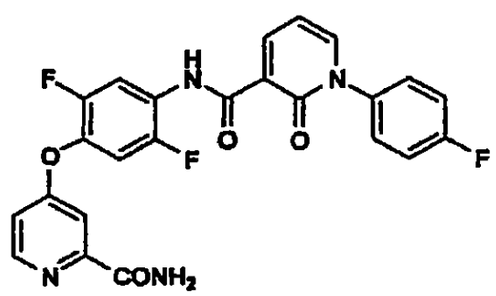
B) N-(4-(2-Aminopiridin-4-iloxi)-2,5-difluorofenil)-2-oxo-1-fenil-1,2-dihidropiridin-3-carboxamida, sal de ácido clorhídrico

4-(2,5-Difluoro-4-(2-oxo-1-fenil-1,2-dihidropiridin-3-carboxamido)-fenoxi)picolinamida (45 mg, 0.10 mmol) se convirtió al compuesto del título (19 mg. 40%) de una manera similar a la preparación del Compuesto E del Ejemplo 112. RMN-^1H (DMSO-d_6) δ 13.40 (br s, 1H), 12.47 (s, 1H), 8.53-8.57 (m, 2H), 8.12-8.13 (m, 1H), 7.92-7.93 (m, 1H), 7.83 (s, 2H), 7.66-7.71 (m, 1H), 7.46-7.53 (m, 5H), 6.66-6.72 (m, 2H), 6.19 (s, 1H); HRMS (ESI^+), 435.1269 $(M+H)^+$ calculado, 435.1258 $(M+H)^+$ encontrado.

Ejemplo 115



N-(4-(2-Aminopiridin-4-iloxi)-2,5-difluorofenil)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridin-3-carboxamida, sal de ácido clorhídrico



A) 4-(2,5-Difluoro-4-(1-(4-fluorofenil)-2-oxo-1,2-dihidropiridin-3-carboxamido)fenoxi)picolinamida

A una mezcla homogénea del ácido 1-(4-fluorofenil)-2-oxo-1,2-dihidropiridin-3-carboxílico (Compuesto B del Ejemplo 101, 50 mg, 0.21 mmol) y 4-(4-amino-2,5-difluorofenoxi)picolinamida (Compuesto C del Ejemplo 112, 69 mg, 0.26 mmol) en DMF (3 mL) se agregó DIPEA (0.05 mL, 0.26 mmol) y hexafluorofosfato de O-benzotriazol-1-il-N,N,N',N'-bis(tetrametilen)-uronio (TBTU) (83 mg. 0.26 mmol). La

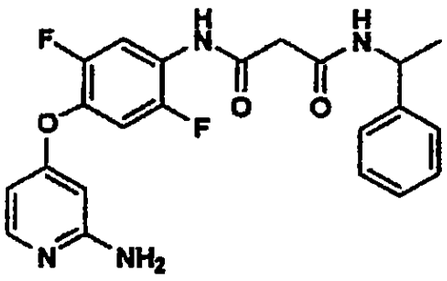
solución resultante se agitó por 18 horas antes de que se apagara con LiCl al 10% (acuoso). La mezcla se dividió entre EtOAc y LiCl al 10% (acuoso), las capas se separaron, y la capa acuosa se extrajo con EtOAc. Las capas orgánicas combinadas se lavaron dos veces con LiCl al 10% (acuoso), luego se concentró a vacío. El residuo se purificó mediante cromatografía sobre gel de sílice (eluyendo con hexano/EtOAc 1:3) y las fracciones apropiadas se concentraron a vacío para proporcionar el compuesto del título (22 mg, 22%). MS (ESI+) m/z 481 $(M+H)^+$.

B) N-(4-(2-Aminopiridin-4-iloxi)-2,5-difluorofenil)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridin-3-carboxamida, sal de ácido clorhídrico

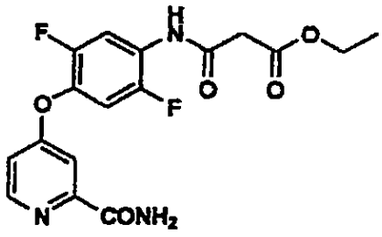
La 4-(2,5-difluoro-4-(1-(4-fluorofenil)-2-oxo-1,2-dihidropiridin-3-carboxamido)fenoxi)picolinamida (22 mg. 0.04 mmol) se convirtió al compuesto del título (21 mg. 95%) de una manera similar a la preparación del Compuesto E del Ejemplo 112. RMN-^{1}H (DMSO-d_6) δ 13.71 (br s, 1H), 12.43 (s, 1H). 8.48-8.57 (m, 2H), 8.10-8.13 (m, 1H). 7.93-7.95 (m, 3H), 7.61-7.70 (m, 1H), 7.53-7.56 (m, 2H), 7.29-7.39 (m, 2H), 6.64-6.72 (m, 2H), 6.10 (s, 1H); HRMS(ESI$^+$). 453.1175 $(M+H)^+$ calc., 453.1168 $(M+H)^+$ encontrado.

629

Ejemplo 116

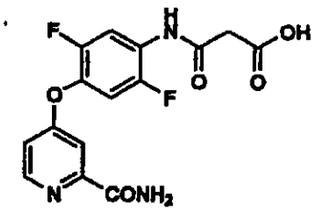


(±)-N^1-(4-(2-Aminopiridin-4-iloxi)-2,5-difluorofenil)-N^3-(1-feniletil)malonamida, sal de ácido clorhídrico



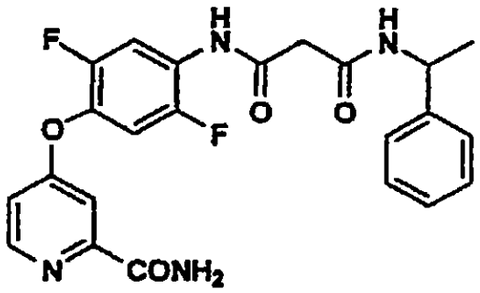
A) 3-(4-(2-carbamoilpiridin-4-iloxi)-2,5-difluorofenilamino)-3-oxopropanoato de etilo

4-(4-Amino-2,5-difluorofenoxi)picolinamida (Compuesto C del Ejemplo 112, 1.0 g, 3.9 mmol) se convirtió al compuesto del título (320 mg, 22%) de una manera similar a la preparación del Compuesto A del Ejemplo 102. RMN-^{1}H (DMSO-d^6) δ 10.32 (s, 1H), 8.54 (d, 1H, J = 5.5 Hz), 8.14- 8.37 (m, 2H), 7.75 (br s, 1H), 7.61-7.65 (m, 1H), 7.42-7.43 (m, 1H), 7.24-7.25 (m, 1H), 4.12 (q, 2H. J = 7.2 Hz), 3.60 (s, 2H), 1.20 (t, 3H, J = 7.2 Hz); MS (ESI+) m/z 380 (M+H)+.



B) ácido 3-(4-(2-carbamoilpiridin-4-iloxi)-2,5-difluorofenilamino)-3-oxopropanoico

A una mezcla heterogénea de 3-(4-(2- carbamoilpiridin-4-iloxi)-2,5-difluorofenilamino)-3-oxopropanoato de etilo (305 mg, 0.80 mmol) en MeOH (8 mL) se agregó solución acuosa de hidróxido de sodio 1 N (1.70 mL, 1.70 mmol). Después de una hora de agitación, la mezcla se acidificó con HCl acuoso IN (5 mL). La reacción se extrajo con EtOAc antes de que las capas orgánicas combinadas se secaran (sulfato de magnesio), se filtraran y se concentraran a vacío para proporcionar el compuesto del título (317 mg) que se utilizó sin purificación adicional. HRMS(ESI$^+$), 352.0745 (M+H)+ calculado, 352.0752 (M+H)+ encontrado.



C) (±)-4-(2,5-Difluoro-4-(3-oxo-3-(1-

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feniletilamino)propanamido)-fenoxi)picolinamida

A una mezcla homogénea de ácido 3-(4-(2-carbamoilpiridin-4-iloxi)-2,5-difluorofenilamino)-3-oxopropanoico (89 mg, 0.25 mmol) y (±)-1-fenil-etanamina (Aldrich, 0.05 mL, 0.38 mmol) en DMF (3 mL) se agregó DIPEA (0.07 mL, 0.38 mmol) y hexafluorofosfato de O-benzotriazol-1-il-N,N,N',N'-bis(tetrametilen)uronio (TBTU) (121 mg, 0.38 mmol). La solución resultante se agitó por 15 horas antes de que se apagara con LiCl al 10% (acuoso). La mezcla se dividió entre EtOAc y LiCl al 10% (acuoso), las capas se separaron, y la capa acuosa se extrajo con EtOAc. Las capas orgánicas combinadas se lavaron dos veces con LiCl al 10% (acuoso), luego se concentró a vacío. El residuo se purificó mediante cromatografía sobre gel de sílice (eluyendo con hexano/EtOAc 1:3) y las fracciones apropiadas se concentraron a vacío para proporcionar el compuesto del título (42 mg, 37%). HRMS (ESI^+), 455.1532 $(M+H)^+$ calculado, 455.1528 $(M+H)^+$ encontrado.

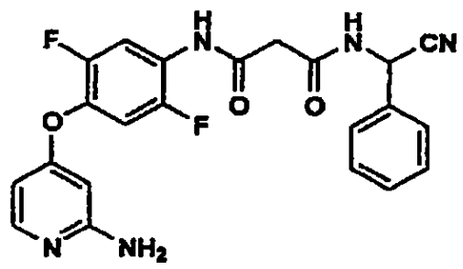
D) (±)-N^1-(4-(2-Aminopiridin-4-iloxi)-2, 5-difluorofenil)-N^3-(1-fenil-etil)malonamida, sal de ácido clorhídrico

La (±)-4-(2,5-difluoro-4-(3-oxo-3-(1-feniletilamino)propanamido)fenoxi)-picolinamida (41 mg, 0.09 mmol) se convirtió al compuesto del título (26 mg, 62%) de una manera similar a la preparación del Compuesto E del Ejemplo 112. RMN-^{1}H (DMSO-d_6) δ 10.46 (s, 1H), 8.70 (d, 1H, J = 7.8 Hz), 8.21-8.26 (m, 1H), 8.00 (d, 1H, J = 7.2 Hz), 7.89

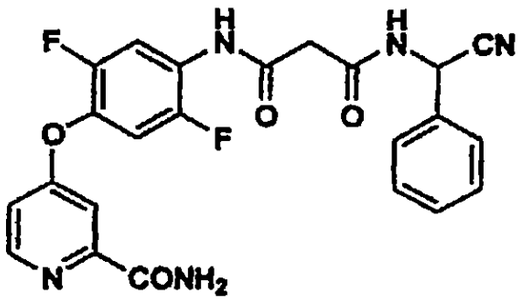
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(s, 2H), 7.67-7.72 (m, 1H), 7.22-7.36 (m, 5H), 6.73-6.76 (m, 1H), 6.21-6.22 (m, 1H), 4.93-4.96 (m, 1H), 3.57 (s, 2H), 1.35 (d, 3H, J = 7.0 Hz); HRMS(ESI$^+$), 427.1582 $(M+H)^+$ calculado, 427.1574$(M+H)^+$ encontrado.

Ejemplo 117



(±)-N^1-(4-(2-Aminopiridin-4-iloxi)-2,5-difluorofenil)-N^3-(ciano(fenil)-metil)malonamida, sal del ácido trifluoroacético



A) (±)-4-(4-(3-(ciano (fenil)metilamino)-3-oxopropanamido)-2,5-difluorofenoxi)picolinamida

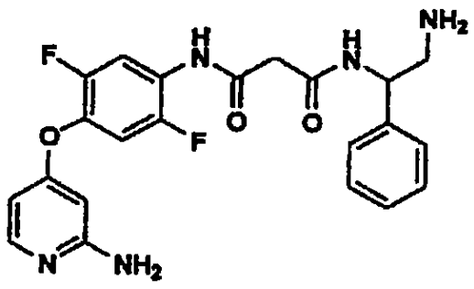
El ácido 3-(4-(2-carbamoilpiridin-4-iloxi)-2,5-difluorofenilamino)-3-oxopropanoico (Compuesto B del Ejemplo 116, 70 mg, 0.20 mmol) se convirtió al compuesto del título

(67 mg, 72%) de una manera similar a la preparación del Compuesto C del Ejemplo 116, excepto que se utilizó clorhidrato de (±)-2-amino-2-fenilacetonitrilo (Aldrich, 47 mg, 0.28 mmol) en vez de (±)-1-feniletanamina. MS(ESI$^+$) m/z 466 $(M+H)^+$.

B) (±)-N^1-(4-(2-aminopiridin-4-iloxi)-2,5-difluorofenil)-N^3-(ciano-(fenil)metil)malonamida, sal del ácido trifluoroacético

La (±)-4-(4-(3-(ciano(fenil)metilamino)-3-oxopropanamido)-2,5-difluoro-fenoxi)picolinamida (65 g, 0.14 mmol) se convirtió al compuesto del título de una manera similar a la preparación del Compuesto E del Ejemplo 112, excepto que el producto crudo se purificó mediante HPLC preparativa (YMC S10 ODS, 30 x 500mm, gradiente 30 minutos de 34% a 90% metano' acuoso con 0.1% de TFA). Las fracciones apropiadas se combinaron y se liofilizaron para proporcionar el compuesto del título (38 mg, 49%) como un sólido blanco.RMN-^{1}H (DMSO-d_6) δ 10.40 (s, 1H), 9.47 (d, 1H, J = 7.63 Hz), 8.21-8.26 (m, 1H), 7.99 (d, 1H, J = 7.2 Hz), 7.86 (br s, 2H), 7.68-7.73 (m, 1H), 7.43-7.54 (m, 5H), 6.74-6.77 (m, 1H), 6.20-6.22 (m, 2H), 3.55 (m, 2H); HRMS(ESI$^+$), 438.1378 $(M+H)^+$ calculado, 438.1374 $(M+H)^+$ encontrado.

Ejemplo 118

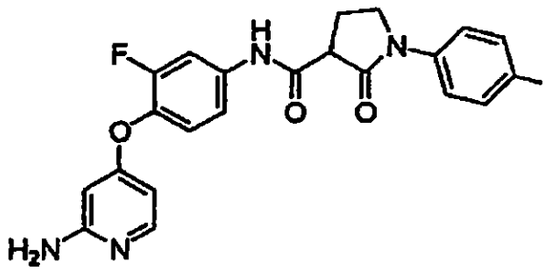


(±)-N^1-(2-Amino-1-feniletil)-N^3-(4-(2-aminopiridin-4-iloxi)-2,5-difluorofenil)malonamida, sal del ácido bis-trifluoroacético

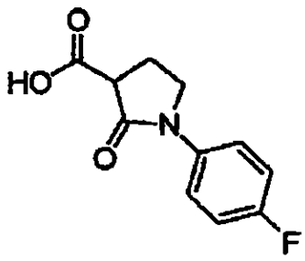
(±)-N-(4-(2-aminopiridin-4-iloxi)-2,5-difluorofenil)-N^3-(ciano(fenil)-metil)malonamida, sal del ácido trifluoroacético (Compuesto B del Ejemplo 117, 21 mg, 0.04 mmol) se convirtió al compuesto del título de una manera similar a las condiciones descritas por Campiani, et al. (Tetrahedron 2002, 58, 3689). El boruro de cobalto fue adquirido de Alfa Aesar. El producto crudo se purificó mediante HPLC preparativa (YMC S5 ODS, 10 x 250mm, gradiente 30 minutos de 10% a 90% metanol acuoso con 0.1 de %TFA). Las fracciones apropiadas se combinaron y se liofilizaron para proporcionar el compuesto del título (5 mg, 21%) como un sólido blanco. RMN-^{1}H (DMSO-d_6) δ 10.39 (s, 1H), 8.72 (d, 1H, J = 8.5 Hz), 8.12-8.17 (m, 1H), 7.90-7.94 (m, 3H). 7.59-7.63 (m, 2H), 7.27-7.34 (m, 4H), 6.60-6.62 (m, 1H), 6.09-6.10 (m, 1H), 5.09-5.10 (m, 1H), 3.10-3-50 (m, 6H); HRMS (ESI+),

442.1691 $(M+H)^+$ calculado, 442.1678 $(M+H)^+$ encontrado.

Ejemplo 119



N-(4-(2-Aminopiridin-4-iloxi)-3-fluorofenil)-1-(4-fluorofenil)-2-oxopirrolidin-3-carboxamida



A) ácido 1-(4-fluorofenil)-2-oxopirrolidin-3-carboxílico

A una solución de 6,6-dimetil-5,7-dioxaspiro[2.5]-octan-4,8-diona (Aldrich, 51 mg, 0.3 mmol) en DMF (0.5 mL) a temperatura ambiente se agregó 4-fluoroanilina (Aldrich, 33 mg, 0.3 mmol). La mezcla de reacción se calentó a 90 °C por 2 h, se enfrió a temperatura ambiente, y utilizada directamente en el siguiente paso.

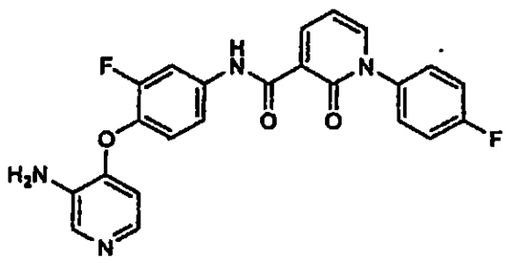
B) N-(4-(2-aminopiridin-4-iloxi)-3-fluorofenil)-1-(4-fluorofenil)-2-oxopirrolidin-3-carboxamida

A una mezcla de ácido 1-(4-fluorofenil)-2-oxopirrolidin-

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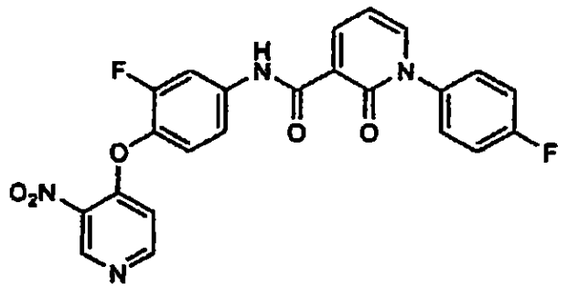
3-carboxílico (0.3 mol), 4-(4-amino-2-fluorofenoxi)piridin-2-amina (Compuesto B del Ejemplo 24, 21.9 mg, 0.1 mmol) en DMF (0.5 ml), se agregó HATU (76 mg, 0.2 mmol) y seguido por diisopropiletilamina (0.1 mL, 0.57 mmol). La mezcla de reacción se agitó a temperatura ambiente toda la noche y se apagó luego con 2 mL de metanol. La mezcla de reacción se purificó mediante HPLC preparativa. Las fracciones deseadas se combinaron, se neutralizaron con solución acuosa saturada de carbonato ácido de sodio, y se concentraron a vacío para proporcionar el compuesto del título (18 mg, 43%) como un sólido blanco. RMN-^{1}H (DMSO-d_6) δ 10.76 (brs, 1H). 7.95 (d, 1H, J = 7.2 Hz), 7.91 (m, 1H), 7.68 (m, 2H), 7.50(m, 1H), 7.44 (t, 1H, J = 10.0 Hz), 7.24 (m, 2H), 6.70 (m, 1H), 6.11 (d, 1H, J = 2.8 Hz), 3.91 (m, 2H), 3.78 (t, 1H, J = 5.0 Hz), 2.41 (m, 2H); MS(ESI$^+$) m/z 425.15 $(M + H)^+$.

Ejemplo 120



N-(4-(3-Aminopiridin-4-iloxi)-3-fluorofenil)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridin-3-carboxamida

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A) N-(3-Fluoro-4-(3-nitropiridin-4-iloxi)fenil)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridin-3-carboxamida

Preparada a partir de 3-fluoro-4-(3-nitropiridin-4-iloxi)bencenamina (Compuesto A del Ejemplo 72) de una manera similar a aquella del Ejemplo 62, para dar el compuesto deltítulo (89%) como un sólido tostado. RMN-^{1}H (CD_3OD) δ 9.13 (s, 1H), 8.72 (dd, 1H, J = 8, 4 Hz). 8.60 (d, 1H, J = 6 Hz), 8.07 (d, 1H, J = 12 Hz), 8.01-7.99 (m, 1H), 7.58-7.55 (m, 2H), 7.45 (t, 1H. J = 8 Hz), 7.40-7.32 (m, 3H), 6.99 (d, 1H, J = 4 Hz), 6.76 (t, 1H. J = 8 Hz); MS (ESI^+) m/z 465.18 $(M + H)^+$.

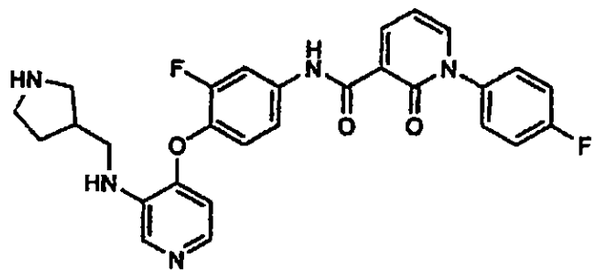
B) N-(4-(3-Aminopiridin-4-iloxi)-3-fluorofenil)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridin-3-carboxamida

Preparado de una manera similar al Paso C del Ejemplo 59. El producto crudo se purificó mediante cromatografía instantánea sobre gel de sílice (10% de McOH/EtOAc) para dar la sal de HCl del compuesto del título (58%) como un sólido blanquecino. RMN-^{1}H (DMSO-d_6) δ 12.07 (s, 1H), 8.59 (dd, 1H, J = 7.6, 2.4 Hz), 8.14 (dd, 1H, J = 6.4. 2 Hz), 8.04 (s, 1H). 7.99 (dd, IU, J = 13.2, 2.4 Hz), 7.66 (d, 1H. J = 5.2 Hz),

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7.63 - 7.60 (m, 2H), 7.46-7.41 (m, 3H), 7.22 (t, 1H, J = 9.2 Hz), 6.74 (t, 1H, J = 7.2 Hz), 6.46 (d, 1H, J = 5.2 Hz), 5.26 (br s. 2H); MS(ESI$^+$): m/z 435.26 $(M + H)^+$.

Ejemplo 121



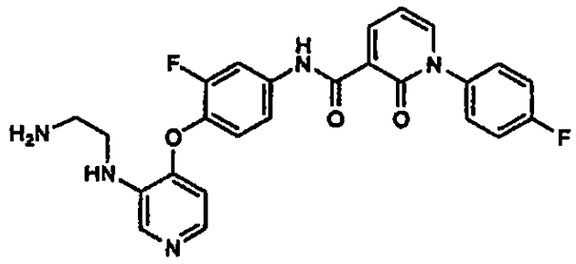
N-(3-Fluoro-4-(3-(pirrolidin-3-ilmetilamino)piridin-4-iloxi)fenil)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridin-3-carboxamida, sal de clorhidrato

A la N-(4-(3-aminopiridin-4-iloxi)-3-fluorofenil)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridin-3-carboxamida (Ejemplo 120, 30 mg, 0.07 mmol) en DCE (1 mL) se agregó éster terbutílico de ácido 3-formil-pirrolidin-1-carboxílico (CB Research & Development Inc.. 28 mg, 0.14 mmol), ácido acético (5 µL, 0.084 mmol), luego triacetoxiborohidruro de sodio (23 mg. 0.104 nmol). Después de agitar a temperatura ambiente por 6 h, se agregó una segunda porción (23 mg) de triacetoxiborohidruro de sodio. Después de agitar a temperatura ambiente por 2 h, la mezcla de reacción se cargó con HCl 4N en dioxano (5 mL) y se agitó una hora adicional a temperatura ambiente. La reacción se diluyó con 10% de

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McOH/EtOAc (10 mL) y se lavó con solución acuosa saturada de carbonato ácido de sodio (10 mL). La fase acuosa se volvió a extraer con 10 mL de 10% de McOH/EtOAc y las capas orgánicas combinadas se secaron sobre sulfato de sodio anhidro y luego se concentró a vacío. El producto crudo resultante se purificó mediante HPLC preparativa. Las fracciones apropiadas se concentraron para remover el metanol y luego se alcalinizó con solución acuosa saturada de carbonato ácido de sodio. La solución acuosa se extrajo con 10% de McOH/EtOAc (3 x 20 mL) y los extractos orgánicos combinados se secaron sobre anhidro Na_2SO_4 y luego se concentró a vacío. El residuo se liofilizó a partir de acetonitrilo (1 mL) /agua (3 mL) / HCl acuoso 1N (0.2 mL) para dar la sal de HCl del compuesto del título (25 mg, 60%) como un sólido blanco. RMN-^{1}H (DMSO-d_6) δ 12.17 (s, 1H), 8.59 (dd, 1H, J = 7.6, 2 Hz), 8.30 (s, 1H), 8.16 (dd, 1H, J = 6.4, 2 Hz), 8.10 (dd, 1H, J = 12.8, 2 Hz), 8.00 (d, 1H,7= 6.4 Hz), 7.64-7.58 (m, 3H), 7.52 (t, 1H, J = 9.2 Hz), 7.46-7.42 (m, 2H), 7.00 (d, 1H, J = 6 Hz), 6.75 (t, 1H, J = 7.2 Hz), 3.72-3.64 (m, 3H), 3.37-3.26 (m, 1H), 3.17-3.10 (m, 1H), 2.97-2.92 (m, 1H), 2.74-2.66 (m, 1H), 2.10-2.03 (m, 1H), 1.75-1.68 (m, 1 H); MS (ESI^+) m/z 518.29 $(M + H)^+$.

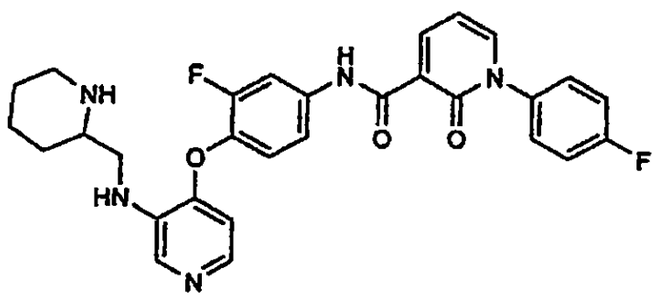
Ejemplo 122



N-(4-(3-(2-Aminoetilamino)piridin-4-iloxi)-3-fluorofenil)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridin-3-carboxamida, sal de clorhidrato

Preparado de una manera similar al Ejemplo 121 para dar la sal de HCl del compuesto del título (52%) como un sólido blanco. RMN-^{1}H (DMSO-d_6) δ 12.10 (s, 1H), 8.52 (dd, 1H, J = 7.6, 2.4 Hz), 8.25 (s, 1H), 8.09 (dd, 1H, J = 6.8, 2.4 Hz), 8.06-8.02 (m, 1H), 7.96 (d, 1H, J = 6.4 Hz), 7.56-3 7.52 (m, 3H), 7.42-7.34 (m, 3H), 6.92 (d, 1H, J = 6 Hz), 6.68 (t. 1H, J = 6.8 Hz), 3.50-3.48 (m, 2H), 3.00-2.99 (m, 2H); MS (ESI$^+$) m/z 478.29 $(M + H)^+$.

Ejemplo 123



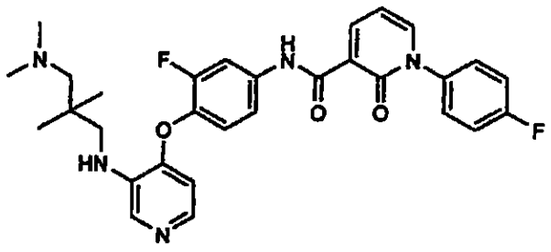
N-(3-Fluoro-4-(3-(piperidin-2-ilmetilamino)piridin-4-

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iloxi)fenil)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridin-3-carboxamida, sal de clorhidrato

Preparada de una manera similar al Ejemplo 121 para dar la sal de HCl del compuesto del título (71%) como un sólido amarillo. RMN-^{1}H (DMSO-d_6) δ 12.17 (s, 1H), 8.59 (dd, 1H, J = 7.2, 2 Hz), 8.51 (s, 1H), 8.16 (dd, 1H, J = 6.8, 2 Hz), 8.11 (dd, 1H, J = 13.2, 2.4 Hz), 8.02 (d, 1H, J = 6.4 Hz), 7.63-7.58 (m, 3H), 7.51 (t 1H, J = 8.8 Hz), 7.46-7.41 (m, 2H), 7.01 (d, 1H, J = 6 Hz), 6.75 (t, 1H, J = 6.8 Hz), 3.70-3.63 (m, 1H), 3.52-3.45 (m, 1H), 3.30-3.27 (m, 2H), 2.86-2.84 (m, 1H), 1.95-1.93 (m, 1H), 1.80-1.62 (m, 3H), 1.58-1.44 (m, 2H); MS (ESI$^+$) m/z 532.31 $(M + H)^+$.

Ejemplo 124

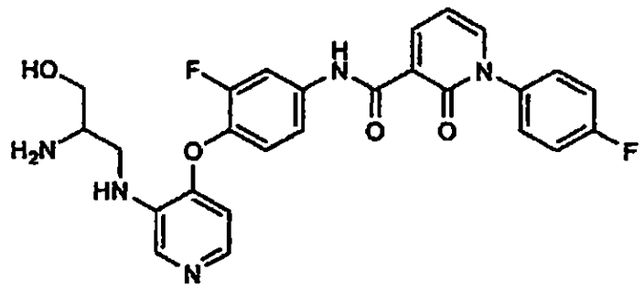


N-(4-(3-(3-(Dimetilamino)-2,2-dimetilpropilamino)piridin-4-iloxi)-3-fluorofenil)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridin-3-carboxamida, sal de clorhidrato

Preparado de una manera similar al Ejemplo 121 para dar la sal de HCl del compuesto del título (58%) como un sólido blanco. RMN-^{1}H (DMSO-d_6) δ 12.10 (s, 1H), 8.57 (s, 1H), 8.52 (dd, 1H, J = 7.6. 2 Hz), 8.09 (dd, 1H, J = 6.8, 2.4 Hz), 8.03

(dd, 1H, J = 13.2. 2.4 Hz), 7.90 (d, 1H, J = 6.4 Hz), 7.56-7.51 (m, 3H), 7.44 (t, 1H, J = 8.8 Hz), 7.39-7.35 (m, 2H), 6.92 (d, 1H, J = 6.4 Hz), 6.68 (t, 1H, J = 7.2 Hz), 3.33 (s, 2H), 3.10 (s, 2H), 2.77 (s, 3H), 2.76 (s, 3H), 1.07 (s, 6H); MS (ESI^+) m/z 548.34 $(M + H)^+$.

Ejemplo 125

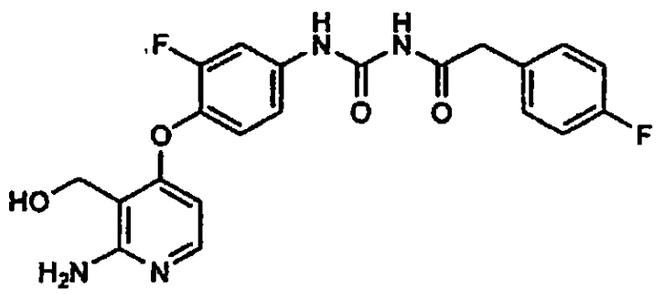


N-(4-(3-(2-Amino-3-hidroxipropilamino)piridin-4-iloxi)-3-fluorofenil)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridin-3-carboxamida, sal de clorhidrato

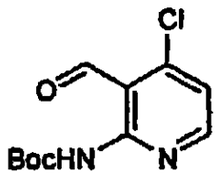
Preparado de una manera similar al Ejemplo 121 para dar la sal de HCl del compuesto del título (65%) como un sólido blanco. RMN-^{1}H (DMSO-d_6) δ 12.10 (s, 1H), 8.52 (dd, 1H. J = 7.2. 2 Hz), 8.30 (s, 1H), 8.09 (dd, 1H, J = 6. 8, 2.4 Hz), 8.03 (dd, 1H, J = 12.8, 2 Hz), 7.96 (d, 1H, J = 6.4 Hz), 7.56-7.52 (m, 3H), 7.43-7.35 (m, 3H), 6.93 (d, 1H. J = 6 Hz), 6.68 (t, 1H, J = 7.2 Hz), 3.65-3.56 (m, 2H), 3.48-3.45 (m, 3H); m/z 508.27 $(M + H)^+$.

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Ejemplo 126



1-(4-(2-Amino-3-(hidroximetil)piridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil) acetil) urea, sal de clorhidrato

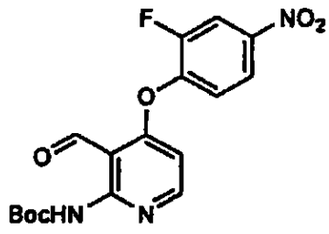


A) 4-cloro-3-formilpiridin-2-ilcarbamato de ter-butilo

Al éster ter-butílico del ácido (4-cloro-piridin-2-il)-carbámico (CB Research & Development Inc., 2.0 g, 8.75 mmol) en THE (18 mL) bajo nitrógeno a -78 °C, se agregó n-BuLi (13.7 mL, 21.9 mmol. 1.6 M en hexanos) gota a gota. Después de agitar a - 78 °C por 45 min, se agregó gota a gota una solución de DMF (1.93 mL) en THF (2 mL). La reacción se agitó a -78 °C por 30 min y luego se dejó calentar lentamente a temperatura ambiente. La reacción se apagó con HCl acuoso 1N y luego se alcalinizó con solución acuosa saturada de carbonato ácido de sodio (50 mL) y se extrajo con acetato de

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etilo (3 x 50 mL). Los extractos orgánicos combinados se secaron sobre sulfato de sodio anhidro y se concentraron a vacío. El producto crudo se purificó mediante cromatografía instantánea en columna sobre gel de sílice (EtOAc) para proporcionar el compuesto del título (0.95 g. 42%) como un sólido blanco. RMN-^{1}H (DMSO-d_6) δ 10.44 (s, 1H), 10.13 (s, 1H). 8.47 (d, 1H, J = 5.2Hz), 7.40 (d, 1H, J = 5.6Hz), 1.48 (s, 9H).

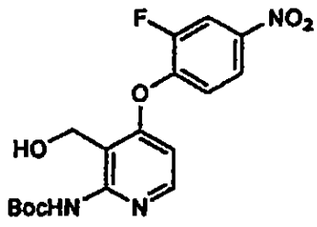


B) 4-(2-fluoro-4-nitrofenoxi)-3-formilpiridin-2-ilcarbamato de ter-butilo

Al 2-fluoro-nitrofenol (Aldrich, 700 mg, 4.44 mmol) en DMF (5 mL) se agregó hidruro de sodio (60%, 180 mg, 4.44 mmol). Después de agitar a temperatura ambiente por 5 min, se agregó a la mezcla una solución de 4-cloro-3-formilpiridin-2-ilcarbamato de ter-butilo (0.95 g, 3.7 mmol) en 5 mL de DMF. La mezcla de reacción se agitó a 60 °C por 20 h. Después de enfriar a temperatura ambiente, la reacción se diluyó con EtOAc (50 mL), se lavó con Licl al 10% (acuoso) (2 x 40 mL) seguido por solución acuosa saturada de carbonato ácido de

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sodio (40 mL), se secó sobre sulfato de sodio anhidro, y se concentró a vacío. El producto crudo se purificó mediante cromatografía instantánea sobre gel de sílice (50% de EtOAc/hexanos) para dar el compuesto del título (1.0 g, 72%) como un aceite amarillo. RMN-^{1}H (CD_3OD) δ 10.59 (s, 1H), 8.37-8.25 (m, 2H), 7.67 (t, 1H, J = 7.6 Hz), 6.60 (d, 1H, J = 6Hz), 1.59 (s. 9H).

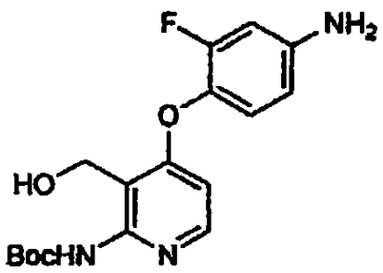


C) 4-(2-fluoro-4-nitrofenoxi)-3-(hidroximetil)piridin-2-ilcarbamato de ter-butilo

Al 4-(2-fluoro-4-nitrofenoxi)-3-formilpiridin-2-ilcarbamato de ter-butilo (75 mg, 0.2 mmol) en metanol (1 mL) a 0 °C se agregó borohidruro de sodio (7.6 mg, 0.20 mmol). Después de agitar a 0°C por 30 min, la reacción se apagó con solución acuosa saturada de cloruro de amonio (1 mL). La reacción se diluyó con EtOAc (5 mL) y las capas se separaron. La capa orgánica se secó sobre Na_2SO_4 nhidro y se concentró a vacío para dar el compuesto del título (65 mg, 86%) como un sólido blanco que se utilizó sin purificación adicional. RMN-^{1}H (CD_3OD) δ 8.28 (dd, 1H, J = 10.4, 2.8 Hz), 8.22-8.18 (m, 2H), 7.45 (t, 1H, J = 8.4 Hz), 6.68 (d, 1H, J = 6Hz), 4.81

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(s, 2H), 1. 57 (s, 9H); MS (ESI^+) m/z 380.27 $(M + H)^+$.



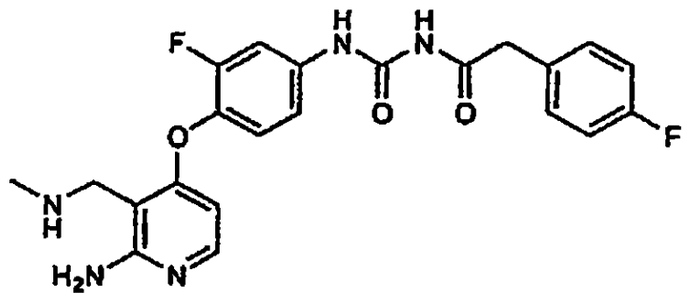
D) 4-(4-amino-2-fluorofenoxi)-3-(hidroximetil)piridin-2-ilcarbamato de ter-butilo

Preparado de una manera similar al Paso C del Ejemplo 59 para dar el compuesto del título como un sólido blanco. RMN-^1H (CD_3OD) δ 8.14 (d, 1H. J = 6 Hz), 6.97 (t, 1H, J = 8.8 Hz), 6.62-6.54 (m, 2H), 6.46 (d, 1H, J = 6.4 Hz), 4.64 (s, 2H), 1.55 (s, 9H); MS (ESI^+) m/z 350.11 $(M + H)^+$.

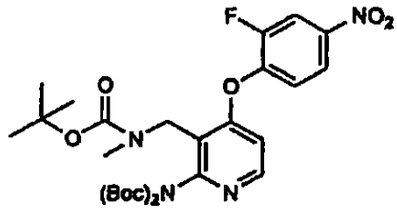
E) 1-(4-(2-mino-3-(hidroximetil)piridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil) acetil) urea, sal de clorhidrato

Preparado de una manera similar al Paso C del Ejemplo 59 para dar la sal de HCl del compuesto del título como un sólido blanco. RMN-^1H (DMSO-d_6) δ 10.99 (s, 1H), 10.56 (s, 1H), 7.82 (d, 1H, J = 7.2 Hz), 7.74 (dd, 1H, J = 13.6, 2.8 Hz), 7.31-26 (m, 3H), 7.19-7.02 (m, 3H), 6.16 (d, 1H. J = 7.2 Hz), 4.57 (s, 2H), 3.69 (s, 2H); MS(ESI^+) m/z 429.16$(M + H)^+$.

Ejemplo 127



1-(4-(2-Amino-3-((metilamino)metil)piridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil) acetil) urea, sal de clorhidrato



A) (2-bis-BOC-amino-4-(2-fluoro-4-nitrofenoxi)piridin-3-il)metil(metil)carbanato de ter-butilo

Al 4-(2-fluoro-4-nitrofenoxi)-3-formilpiridin-2-ilcarbamato de ter-butilo (Compuesto B del Ejemplo 126, 75 mg, 0.2 mmol) en dicloroetano (1 mL) a 0 °C se agregó metilamina (240 µL, 0.24 mmol, 2M en THF), ácido acético (14 µL, 0.24 mmol), seguido por triacetoxiborohidruro de sodio (400 mg, 1.89 mmol). Después de agitar a temperatura ambiente por 16 h, la mezcla de reacción se diluyó con EtOAc (5 mL), se lavó con solución acuosa saturada de carbonato ácido de sodio (5 mL), se secó sobre sulfato de sodio anhidro, y se

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concentró a vacío. El producto crudo se purificó mediante cromatografía instantánea en columna sobre gel de sílice (20% de McOH/EtOAc) para dar 4-(2-fluoro-4-nitrofenoxi)-3-((metilamino)metil)piridin-2-ilcarbamato de ter-butilo (37 mg, 47%) como un aceite amarillo.

Al 4-(2-fluoro-4-nitrofenoxi)-3-((metilamino)metil)piridin-2-ilcarbamato de ter-butilo (48 mg, 0.122 mmol) y DMAP (16 mg. 0.134 mmol) en diclorometano (1 mL) se agregó bicarbonato de di-ter-butilo (Aldrich, 32 mg. 0.15 mmol). Después de agitar a temperatura ambiente 30 min, se observó una mezcla de material bis- y tris-BOC (2:1). Se agregó una porción adicional de DMAP y dicarbonato di-ter-butilo. Después de agitar a temperatura ambiente por 30 min, la reacción se purificó directamente mediante cromatografía instantánea en columna sobre gel de sílice (EtOAc) para dar el compuesto del título (44 mg, 61%) como un aceite amarillo. RMN-^{1}H (CD_3OD) δ 8.50 (d, 1H, J = 5.2 Hz), 8.15-7.97 (m, 2H). 7.43 (d, 1H, J = 5.6 Hz), 7.07 (t, 1H, J = 8.4 Hz), 4.64 (s, 2H), 2.83 (s, 3H), 1.44 (s, 27H); MS (ESI$^+$) m/z 593.34 (M + H)1".

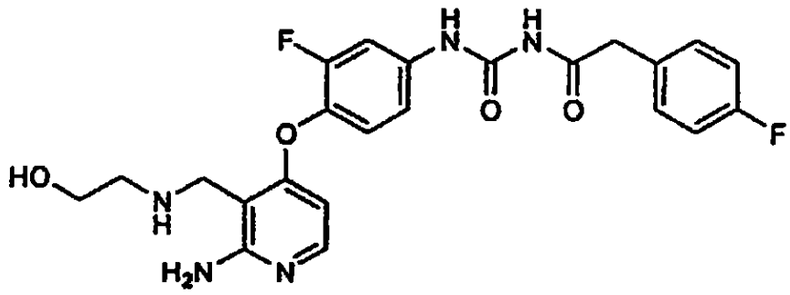
B) 1-(4-(2-Amino-3-((metilamino)metil)piridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea, sal de clorhidrato

Preparado de una manera similar al Paso C del Ejemplo 59 para dar la sal de HCl del compuesto del título (60%) como un

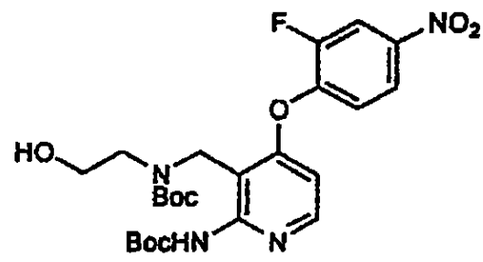
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sólido blanco. RMN-^{1}H (DMSO-d_6) δ 10.88 (s, 1H), 10.35 (s, 1H), 7.45-7.42 (m, 1H), 7.30 (m, 3H), 7.11-5 7.07 (m, 4H), 6.52 (d, 1H, J = 7.2 Hz), 4.02 (s, 2H), 3.66 (s, 2H), 2.54 (s, 3H); MS (ESI$^+$) m/z 442.30 $(M + H)^+$.

Ejemplo 128



1-(4-(2-Amino-3-((2-hidroxietilamino)metil)piridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea, sal del ácido trifluoroacético



A) (2-BOC-amino-4-(2-fluoro-4-nitrofenoxi)piridin-3-il)metil(2-hidroxietil)carbamato de ter-butilo

Preparado de una manera similar al Paso A del Ejemplo 127 para dar el compuesto del título (14%) como un aceite amarillo. RMN-^{1}H (CD_3OD) δ 8.30 (dd, 1H, J = 10.4, 2.8 Hz), 8.23-8.20 (m, 2H), 7.52 (t, 1H, J = 8.4 Hz), 6.64 (d, 1H, J =

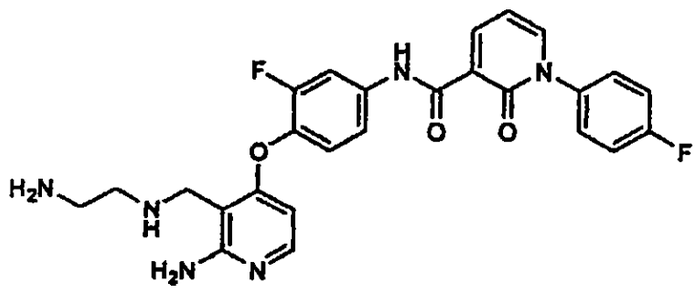
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7.2 Hz), 4.71 (s, 2H), 3.65 (t, 2H. J = 6 Hz), 3.40 (m, 2H), 1.57 (s, 18H); MS (ESI^+) m/z 523.32 $(M + H)^+$.

B) 1-(4-(2-Amino-3-((2-hidroxietilamino)metil)piridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil) acetil) urea, sal del ácido trifluoroacético

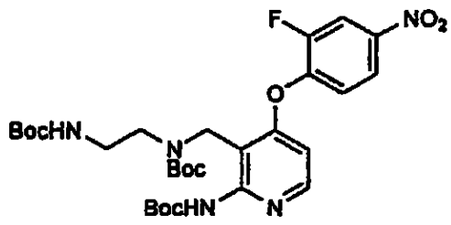
Preparado de una manera similar al Paso C del Ejemplo 59 para dar la sal de TFA del compuesto del título (45%) como un sólido blanco. RMN-^{1}H (DMSO-d_6) δ 11.12 (s, 1H), 10.69 (s, 1H), 8.01 (d, 1H./=6.8Hz), 7.87 (dd, 1H.J = 12.8. 2.4 Hz), 7.53-7.40 (m, 4H), 7.26-7.20 (m, 2H), 6.68 (d, 1H, J = 7.2 Hz), 4.34 (s, 2H), 3.81 (s, 2H), 3.75 (t, 2H. J = 7.2 Hz). 3.18 (m, 2H); MS (ESI^+) m/z 472.24 $(M + H)^+$.

Ejemplo 129



N-(4-(2-Amino-3-((2-aminoetilamino)metil)piridin-4-iloxi)-3-fluorofenil)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridin-3-carboxamida, sal del ácido trifluoroacético

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A) (2-BOC-amino-4-(2-fluoro-4-nitrofenoxi)piridin-3-il)metil(2-BOC-aminoetil)carbamato de ter-butilo

Preparado de una manera similar al Paso A del Ejemplo 127 para dar el compuesto del título (19%) como un aceite amarillo. RMN-^{1}H (CD_3OD) δ 8.30 (dd, 1H. J = 10, 2.4 Hz), 8.23-8.20 (m, 2H), 7.52 (t, 1H, J = 8.4 Hz), 6.61 (d, 1H, J = 7.2 Hz), 4.65 (s, 2H), 3.39 (m, 2H), 3.25 (m, 2H), 1.61 (s, 27H); MS(ESI$^+$) m/z 622.47 $(M + H)^+$.

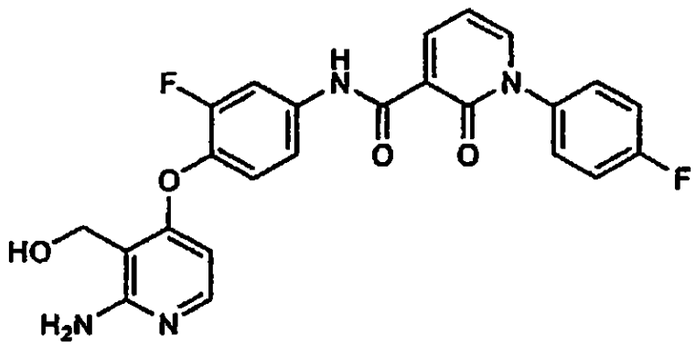
B) N-(4-(2-Amino-3-((2-aminoetilamino)metil)piridin-4-iloxi)-3-fluorofenil)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridin-3-carboxamida, sal del ácido trifluoroacético

El grupo nitro fue reducido de una manera similar al Paso C del Ejemplo 59 y luego la amida fue formada de una manera similar al Ejemplo 62, para dar la sal de TFA del compuesto del título (28%) como un sólido blanco. RMN-^{1}H (DMSO-d_6) δ 12.09 (s, 1H), 8.52 (dd, 1H, J = 7.2, 2 Hz), 8.09 (dd, 1H, J = 6.4, 2 Hz), 7.99 (dd, 1H, J = 12.8, 2.4 Hz), 7.89 (d, 1H. J = 6.4 Hz), 7.56-7.52 (m, 2H), 7.49-7.47 (m, 1H), 7.39-7.33 (m, 3H), 6.68 (t, 1H. J = 7.2 Hz), 6.07 (d, 1H, J = 7.2 Hz), 4.25 (s, 2H), 3.20 (m, 2H), 3.08 (m, 2H);

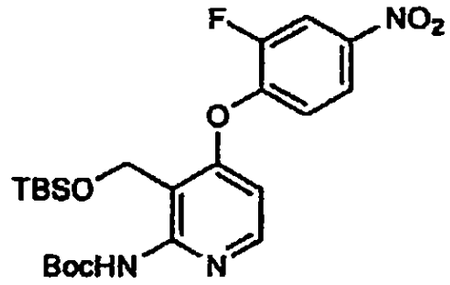
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MS(ESI$^+$) m/z 507.23 $(M + H)^+$.

Ejemplo 130



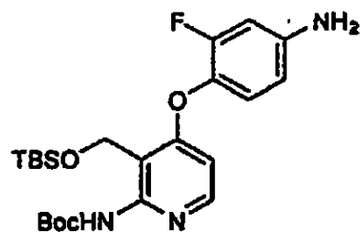
N-(4-(2-Amino-3-(hidroximetil)piridin-4-iloxi)-3-fluorofenil)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridin-3-carboxamida, sal del ácido trifluoroacético



A) 3-((ter-butildimetilsililoxi)metil)-4-(2-fluoro-4-nitrofenoxi) piridin-2-ilcarbamato de ter-butilo

Al 4-(2-fluoro-4-nitrofenoxi)-3-(hidroximetil)piridin-2-ilcarbamato de ter-butilo (Compuesto C del Ejemplo 126, 100 mg, 0.26 mmol) en diclorometano (3 mL) se agregó imidazol (21 mg, 0.31 mmol) seguido por cloruro de ter-butildimetilsililo (40 mg. 0.26 mmol). Después de agitar a temperatura ambiente

por 1 h, se agregó un segundo equivalente de cloruro de ter-butildimetilsililo (40 mg, 0.26 mmol). La reacción se agitó a temperatura ambiente por 3 h y luego se diluyó con diclorometano (10 mL), se lavó con agua (10 mL), se secó sobre Na_2SO_4 anhidro, y se concentró a vacío. El producto crudo se purificó mediante cromatografía instantánea en columna sobre gel de sílice (50% de EtOAc/hexanos) para dar el compuesto del título (102 mg, 79%) como un sólido blanco. RMN-^{1}H (CD_3OD) δ 8.16 (dd, 1H, J - 10.4, 2.8 Hz), 8.09-8.05 (m, 2H), 7.29 (t, 1H, J = 8.4 Hz). 6.53 (d, 1H. J = 5.6 Hz), 4.84 (s, 2H), 1.43 (s, 9H), 0.84 (s, 9H), 0.00 (s, 6H); MS (ESI^+) m/z 494.29 $(M + H)^+$.

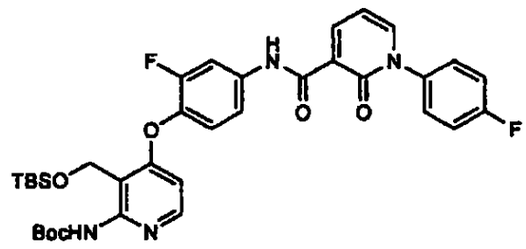


B) 4-(4-amino-2-fluorofenoxi)-3-((ter-butildimetilsililoxi)-metil)piridin-2-ilcarbamato de ter-butilo

Preparado de una manera similar al Paso C del Ejemplo 59 da el compuesto del título (95 mg, 98%) como un aceite amarillo. RMN-^{1}H (CD_3OD) δ 7.90 (d, 1H, J = 6 Hz), 6.76 (t, 1H, J = 8.8 Hz), 6.43 (dd, 1H, J = 12.8, 2.8 Hz), 6.39-6.37

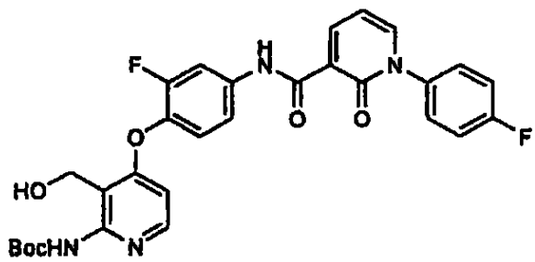
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(m, 1H), 6.21 (d, 1H, J = 5.6 Hz), 4.85 (s, 2H), 1.39 (s, 9H), 0.81 (s, 9H), 0.01 (s, 6H); MS(ESP) m/z 464.34 $(M + H)^+$.



C) 3-((tert-butildimetilsililoxi)metil)-4-(2-fluoro-4-(1-(4-fluorofenil)-2-oxo-1,2-dihidropiridin-3-carboxamido) fenoxi)piridin-2-ilcarbamato de ter-butilo

Preparado de una manera similar a aquella del Ejemplo 62, para dar el compuesto del título (86%) como un aceite incoloro. RMN-^{1}H (CD_3OD) δ 8.51 (dd, 1H, J = 7.6, 2.4 Hz), 7.93 (d, 1H. J = 6 Hz), 7.84-7.80 (m, 2H), 7.40-7.37 (m, 2H), 7.21-7.15 (m, 3H), 7.06 (t, 1H. J = 8.8 Hz), 6.57 (t, 1H, J = 6.8 Hz), 6.26 (d, 1H, J = 5.6 Hz), 4.86 (s, 2H), 1.40 (s, 9H), 0.82 (s, 9H), 0.00 (s, 6H); MS (ESI^+) m/z 679.34 $(M + H)^+$.



D) 4-(2-fluoro-4-(1-(4-fluorofenil)-2-oxo-1,2-dihidropiridin-3-carboxamido)fenoxi)-3-(hidroximetil)piridin-

2-ilcarbamato de ter-butilo

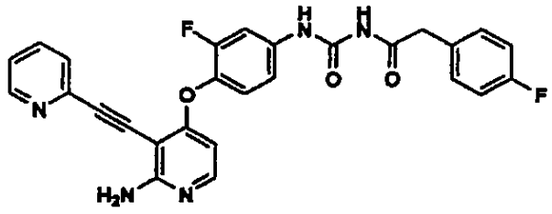
Al 3-((ter-butildimetilsililoxi)metil)-4-(2-fluoro-4-(1-(4-fluorofenil)-2-oxo-1,2-dihidropiridin-3-carboxamido)fenoxi)piridin-2-ilcarbamato de ter-butilo (119 mg, 0.176 mmol) en THF (2 mL) a temperatura ambiente se agregó floururo de tetrabutilamonio (260 µL, 0.264 mmol, 1 M en THF). Después de agitar a temperatura ambiente por 30 min, la reacción se diluyó con acetato de etilo (20 mL), se lavó con agua seguido por salmuera (10 mL cada uno), se secó sobre sulfato de magnesio anhidro, y se concentró a vacío. El producto crudo se purificó mediante cromatografía instantánea en columna sobre gel de sílice (5% de McOH / EtOAc) para dar el compuesto del título (66 mg, 66%) como un aceite amarillo. RMN-^{1}H (CD_3OD) δ 8.62 (dd, 1H, J = 7.2, 2 Hz), 8.04 (d, 1H, J = 6 Hz), 7.94-7.90 (m, 2H), 7.50-7.46 (m, 2H), 7.33-7.25 (m, 3H), 7.20 (t, 1H, J = 8.8 Hz), 6.67 (t, 1H, J = 6.8 Hz). 6.40 (d, 1H. J = 5.2 Hz), 4.78 (s, 2H). 1.49 (s, 9H) : MS (ESI^+) m/z 565.17 $(M+H)^+$.

E) N-(4-(2-Amino-3-(hidroximetil)piridin-4-iloxi)-3-fluorofenil)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridin-3-carboxamida, sal del ácido trifluoroacético

Al 4-(2-fluoro-4-(1-(4-fluorofenil)-2-oxo-1,2-dihidropiridin-3-carboxamido)fenoxi)-3-(hidroximetil)piridin-2-ilcarbamato de ter-butilo (33 mg 0.058 mmol) en THF (2 mL) a temperatura ambiente se agregó HCl 4N en dioxano (10 mL).

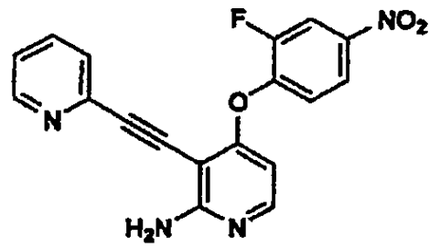
Después de la agitación a TA por 8 h. la reacción se concentró a vacío. El producto crudo resultante se purificó mediante HPLC preparativa. Las fracciones apropiadas se concentraron y se agregó tolueno (2x3 mL) y la mezcla resultante se concentró nuevamente. El residuo se liofilizó a partir de acetonitrilo (1 mL)/agua (3 mL) para dar la sal de TFA del compuesto del título (14 mg, 42%) como un sólido blanco. RMN-^{1}H (DMSO-d_6) δ 12.08 (s, 1H), 8.52 (dd, 1H. J = 7.2, 2 Hz), 8.09 (dd, 1H, J = 6.8, 2 Hz), 7.99 (dd, 1H, J = 12.8, 2.4 Hz), 7.81 (d, 1H, J = 7.2 Hz), 7.56-7.52 (m, 2H), 7.48-7.46 (m, 1H), 7.39-7.34 (m, 2H), 7.30 (t, 1 H. J = 9.2 Hz), 6.67 (t, 1H, J = 7.2 Hz), 6.21 (d, 1H, J = 7.2 Hz), 4.58 (s, 2H); MS (ESI$^+$) m/z 465.17 $(M + H)^+$.

Ejemplo 131



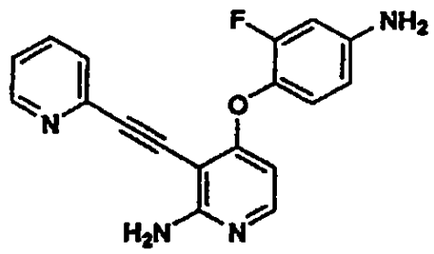
1-(4-(2-Amino-3-(2-(piridin-2-il)etinil)piridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea, sal de diclorhidrato

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A) 4-(2-Fluoro-4-nitrofenoxi)-3-(2-(piridin-2-il)etinil) piridin-2-amina

Una solución de 4-(2-fluoro-4-nitrofenoxi)-3-yodopiridin-2-amina (Compuesto C del Ejemplo 34, 100 mg, 0.27 mmol), 2-etinilpiridina (Aldrich, 56 µL, 0.54 mmol). Et_3N (2 mL), y THF (2 mL) se desgasificó mediante vacío/purga con argón y luego se trató con CuI (6 mg, 0.032 mmol) y (Ph_3P) 4Pd (20 mg, 0.017 mmol). La mezcla de reacción se calentó a 60 °C por 45 min, se enfrió a temperatura ambiente y se diluyó con EtOAc. La mezcla se lavó con solución acuosa saturada de carbonato ácido de sodio, salmuera, se secó (sulfato de magnesio) y se concentró a vacío. El producto crudo se purificó mediante cromatografía instantánea sobre SiO_2 utilizando 0-1.5 de McOH/cloruro de metileno para dar el compuesto del título (55 mg, 57%) como un sólido verde oliva. RMN-^{1}H (DMSO-d_6) δ 8.53 (d, 1H, J = 5.1 Hz), 8.42-8.37 (m, 1H), 8.19-8.12 (m, 1H), 7.96 (d, 1H, J = 5.6 Hz), 7.85-7.78 (m, 1H). 7.71 (d, 1H, J = 7.6 Hz), 7.52 (t, 1H, J = 8.6 Hz), 7.36 (ddd, 1H, J = 7. 6, 5. 1, 1.0 Hz), 6.71 (s, 2H), 6.21 (d, 1H, J = 5.6 Hz); MS (ESI^+) : m/z 351.25 $(M+H)^+$.



B) 4-(4-Amino-2-fluorofenoxi)-3-(2-(piridin-2-il)etinil)piridin-2-amina

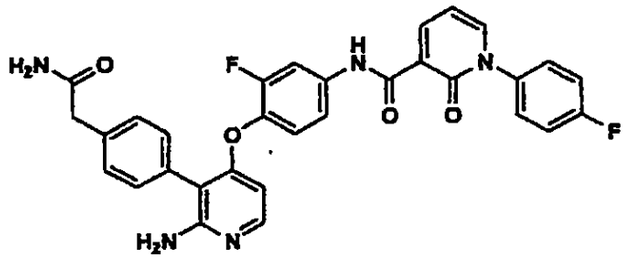
El compuesto del título se preparó a partir de la reducción de la 4-(2-fluoro-4-nitrofenoxi)-3-(2-(piridin-2-il)etinil)piridin-2-amina (35 mg, 0.10 mmol) utilizando polvo de zinc (65 mg, 1.0 mmol) y cloruro de amonio (53 mg, 1.0 mmol) de la misma manera que el Paso C del Ejemplo 11. Esto dio el compuesto del título (25 mg, 78%) como aceite café. MS (ESI^+) : m/z 321.25 $(M+H)^+$.

C) 1-(4-(2-Amino-3-(2-(piridin-2-il)etinil)piridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil) acetil) urea, sal de diclorhidrato

El compuesto del título se preparó a partir de 4-(4-amino-2-fluorofenoxi)-3-(2-(piridin-2-il)etinil)piridin-2-amina (25 mg, 0.078 mmol) y una solución 0.3 M de isocianato de 2-(4-fluorofenil)acetilo en tolueno (Compuesto D del Ejemplo 11, 0.26 mL, 0.078 mmol) de la misma manera que el Paso E del Ejemplo 11. El producto crudo se preparó mediante HPLC preparativa (Columna B). La sal de TFA se convirtió al clorhidrato de la misma manera que en el Paso E del Ejemplo 36, para dar el compuesto del título (18 mg, 40 %) como un

sólido café. RMN-^{1}H (DMSO-d_6) δ 11.06 (s, 1H), 10.63 (s, 1H), 8.62 (d, 1H, J = 4.6 Hz), 8.23 (s, 1H), 7.99 (d, 1H, J = 7.1 Hz), 7.94-7.84 (m, 3H), 7.87-7.76 (m, 1H), 7.51-7.42 (m, 3H), 7.39-7.32 (m, 2H), 7.21-7.13 (m, 2H), 6.30 (d, 1H, J = 7.1 Hz), 3.74 (s, 2H) MS (ESI$^+$) : m/z 498.11 $(M+H)^+$.

Ejemplo 132



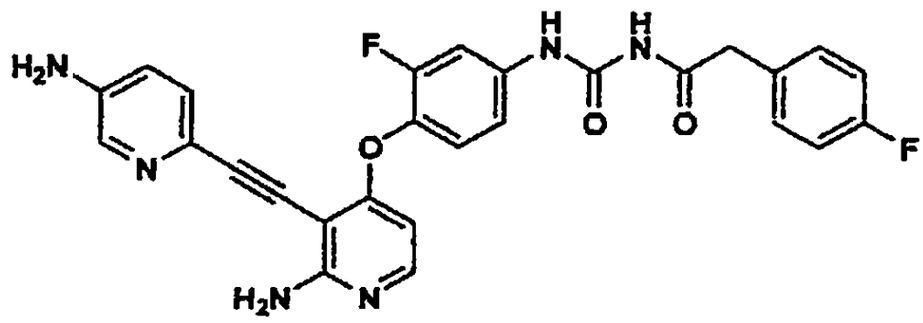
N-(4-(2-Amino-3-(4-(2-amino-2-oxoetil)fenil)piridin-4-iloxi)-3-fluorofenil)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridin-3-carboxamida, sal de clorhidrato

El compuesto del título se preparó a partir de 2-(4-(2-amino-4-(4-amino-2-fluorofenoxi)piridin-3-il)fenil)acetamida (Compuesto C del Ejemplo 78, 18 mg, 0.05 mmol) y ácido 1-(4-fluorofenil)-2-oxo-1,2-dihidropiridin-3-carboxílico (Compuesto B del Ejemplo 101, 11 mg, 0.05 mmol) de la misma manera que el Ejemplo 62. El producto crudo se preparó mediante HPLC preparativa (Columna B) seguido por conversión de la sal de TFA a la sal de clorhidrato (15 mg, 50 %). RMN-^{1}H (DMSO-d_6) δ 12.11 (s, 1H), 8.58-8.54 (m, 1H), 8.13 (dd, 1H, J = 6. 6, 2.2 Hz), 8.00 (dd, 1H, J = 12.6, 2.2 Hz), 7.96 (d, 1H, J = 7.7 Hz), 7.59 (dd, 2H, J = 8.8, 4.9 Hz), 7.47-7.41

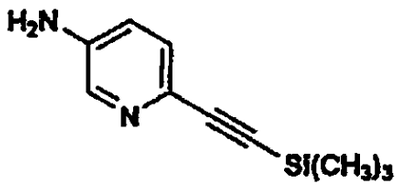
677 653

(m, 6H). 7.40-7.35 (m, 3H), 6.94 (s, 1H). 6.72 (t, 1H, J = 7.1 Hz), 6.38 (d, 1H, J = 7.1 Hz), 3.44 (s, 2H); MS (ESI^+) : m/z 568.23 $(M+H)^+$.

Ejemplo 133



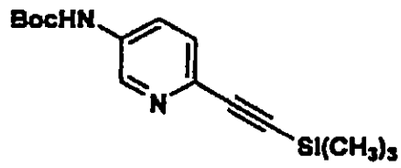
1-(4-(2-Amino-3-(2-(5-aminopiridin-2-il)etinil)piridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil) acetil) urea, sal de diclorhidrato



A) 6-(2-(Trimetilsilil)etinil) piridin-3-amina

Una mezcla de 3-amino-6-bromopiridina (Alfa Aesar, 1.0 g. 5.8 mmol), etiniltrimetilsilano (1.7 mL, 17.3 mmol). CH_3CN (3 mL), DMF (2 mL) y Et_3N (2 mL) se trató con CuI (60 mg, 0.32 mmol) y $(Ph_3P)_4Pd$ (114 mg, 0.10 mmol) y la mezcla se agitó a 45 °C por 1.5 h. Se agregó más etiniltrimetilsilano (1.7 mL, 17.3 mmol) a la reacción y la mezcla se agitó por 2

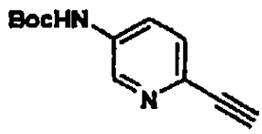
h. La mezcla se concentró a vacío y el residuo se dividió entre EtOAc y solución acuosa saturada de carbonato ácido de sodio. La fase de EtOAc se lavó con salmuera, se secó (sulfato de magnesio) y se concentró a vacío. El producto crudo se purificó mediante cromatografía instantánea sobre SiO_2 utilizando 0-6 de EtOAc/hexanos para dar el compuesto del título (0.75 g, 68 %) como un sólido café. RMN-^{1}H (DMSO-d_6) δ 7.85 (s, 1H), 7.15 (d, 1H, J = 8.1 Hz), 6.81 (d, 1H, J = 8.1 Hz), 5.76 (s, 2H), 0.19 (s, 9H); MS (ESI$^+$) : m/z 191.20 $(M+H)^+$.



B) 6-(2-(trimetilsilil)etinil)piridin-3-ilcarbamato de ter-butilo

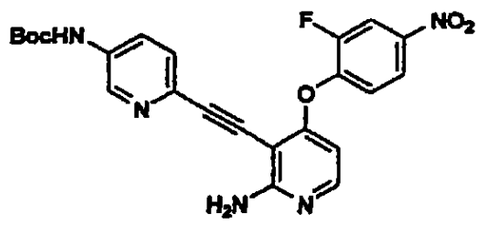
Una solución de 6-(2-(trimetilsilil)etinil)piridin-3-amina (0.5 g, 2.6 mmol) en THF se enfrió a -50 °C y se trató gota a gota con NaHMDS 1.0M en THF (5.3 mL, 5.5 mmol). La mezcla se calentó a -20 °C, se trató con anhídrido BOC en una porción y se dejó calentar a temperatura ambiente en 25 min. La mezcla se dividió entre EtOAc y solución acuosa saturada de carbonato ácido de sodio y la fase de EtOAc se separó y se lavó con salmuera. La solución de EtOAc se secó (sulfato de magnesio) y se concentró a vacío. El producto crudo se purificó mediante cromatografía instantánea sobre SiO_2

utilizando 0-25% de EtOAc/hexanos para dar el producto (0.5 g, 67%) como un sólido blanco. RMN-^{1}H (DMSO-d_6) δ 9.80 (s, 1H), 8.58 (d, 1H, J = 2.0 Hz), 7.86 (dd, J = 8.6, 2.5 Hz. 1 H), 7.44 (d, 1H, J = 8.6 Hz), 1.47 (s, 9H), 0.22 (s, 9H); MS (ESI$^+$) : m/z 291.34 $(M+H)^+$.



C) 6-etinilpiridin-3-ilcarbamato de ter-butilo

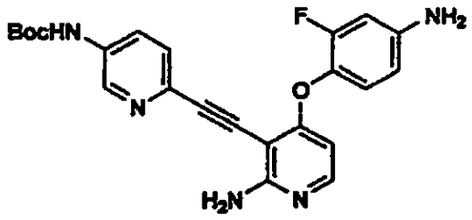
Una solución de 6-(2-(trimetilsilil) etinil) piridin-3-ilcarbamato de ter-butilo (62 mg, 0.21 mmol) en THE (5 mL) se enfrió a -15 °C y se trató con fluoruro de tetrabutilamonio 1.0 M (Aldrich, 0.25 mL, 0.25 mmol) y se agitó por 40 min. La mezcla se concentró a vacío y se dividió entre EtOAc y solución acuosa saturada de carbonato ácido de sodio. La fase de EtOAc se lavó con salmuera, se secó (sulfato de magnesio) y se concentró a vacío para dar el compuesto del título (45 mg, 100%) como un sólido blanquecino. RMN-^{1}H (DMSO-d_6) δ 9.78 (s, 1H), 8.58 (d, 1H, J = 2.5 Hz), 7.92-7.84 (m, 1H), 7.46 (d, 1H, J = 8.6 Hz), 4.17 (s, 1H), 1.47 (s, 9H); MS (ESI$^+$) : m/z 219.20 $(M+H)^+$.



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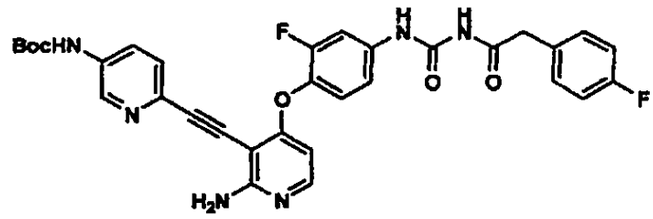
D) 6-(2-(2-amino-4-(2-fluoro-4-nitrofenoxi)piridin-3-il)etinil)piridin-3-ilcarbamato de ter-butilo

El compuesto del título se preparó a partir de 6-etinilpiridin-3-ilcarbamato de ter-butilo y 4-(2-fluoro-4-nitrofenoxi)-3-yodopiridin-2-amina (Compuesto C del Ejemplo 34) de la misma manera que el Paso A del Ejemplo 46 con 44% de rendimiento. RMN-^{1}H (DMSO-d_6) δ 9.77 (s, 1H), 8.56 (s, 1H), 8.40-8.36 (m, 1H), 8.14 (d, 1H, J = 8.8 Hz), 7.94 (d, 1H, J = 5.5 Hz), 7.89 (d, 1H, J = 8.2 Hz), 7.59 (d, 1H, J = 8.8 Hz), 7.53-7.47 (m, 1H), 6.63 (br s, 2H), 6.21 (d, 1H, J = 6.0 Hz), 1.47 (s, 9H); MS (ESI$^+$) : m/z 4



E) 6-(2-(2-amino-4-(4-amino-2-fluorofenoxi)piridin-3-il)etinil)piridin-3-ilcarbamato de ter-butilo

El compuesto del título se preparó a partir de 6-(2-(2-amino-4-(2-fluoro-4-nitrofenoxi)piridin-3-il)etinil)piridin-3-ilcarbamato de ter-butilo, de la misma manera que el Paso C del Ejemplo 11 con rendimiento cuantitativo. MS(ESI$^+$): m/z 436.29 $(M+H)^+$.



F) 6-(2-(2-amino-4-(2-fluoro-4-(3-(2-(4-fluorofenil)acetil)ureido)fenoxi)piridin-3-il)etinil)piridin-3-ilcarbamato de ter-butilo

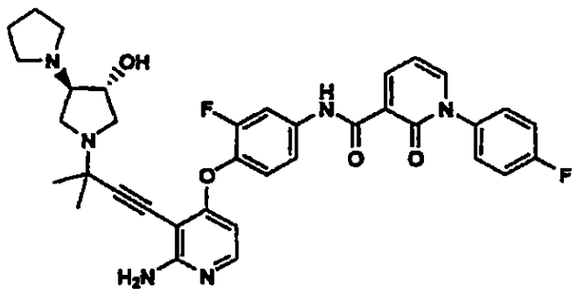
El compuesto del título se preparó a partir de 6-(2-(2-amino-4-(2-fluoro-4-nitrofenoxi)piridin-3-il)etinil)piridin-3-ilcarbamato de ter-butilo, de la misma manera que el Paso E del Ejemplo 11 con 80% de rendimiento. RMN-^{1}H (DMSO-d_6) δ 11.02 (s, 1H), 10.56 (s, 1H). 9.78 (s, 1H), 8.59 (d, 1H, J = 2.5 Hz), 7.91 (dd, 1H, J = 8.6, 2.5 Hz), 7.81 (d, 1H, J = 5.6 Hz), 7.75 (dd, 1H, J = 12.7, 2.5 Hz), 7.68 (d, 1H, J = 8.6 Hz,), 7.44-7.27 (m, 5H), 7.19-7.13 (m, 2H), 6.47 (s, 2H), 5.86-5.81 (m, 1H), 1.48 (s, 9H); MS (ESI^+) : m/z 615.34 $(M+H)^+$.

G) 1-(4-(2-Amino-3-(2-(5-aminopiridin-2-il)etinil)piridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea, sal de diclorhidrato

Una solución de 6-(2-(2-amino-4-(2-fluoro-4-(3-(2-(4-fluorofenil)acetil)ureido)fenoxi)piridin-3-il)etinil)piridin-3-ilcarbamato de ter-butilo (23 mg. 0.037 mmol) en cloruro de metileno (2 mL) y se trató con TFA (0.5 mL) y se agitó a temperatura ambiente por 1 h. La mezcla se concentró a vacío

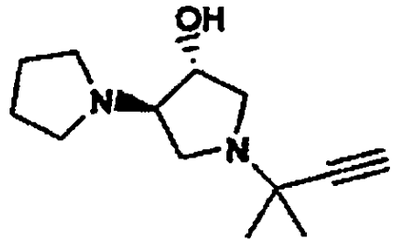
y el producto crudo se purificó mediante HPLC preparativa (Columna B) se convirtió a su sal de clorhidrato (11 mg, 52%) de la misma manera que el Paso E del Ejemplo 36. RMN-^{1}H (DMSO-d_6) δ 11.05 (s, 1H), 10.62 (s, 1H). 8.05 (s, 1H). 7.97 (d, 1H.J = 2.7 Hz), 7.94 (d, 1H, J = 7.1 Hz), 7.82 (d, 1H. J = 12.1 Hz). 7.66 (d, 1H, J = 8.8 Hz). 7.45-7.45 (m, 2H), 7.35 (dd, 2H, J = 8.2, 5.5 Hz). 7.20 (d, 1H, J = 6.6 Hz), 7.16 (t, 2H, J = 8.8 Hz), 6.24 (d, 1H, J = 6.6 Hz), 3.74 (s, 2H); MS (ESI$^+$) : m/z 515.19 $(M+H)^+$.

Ejemplo 134



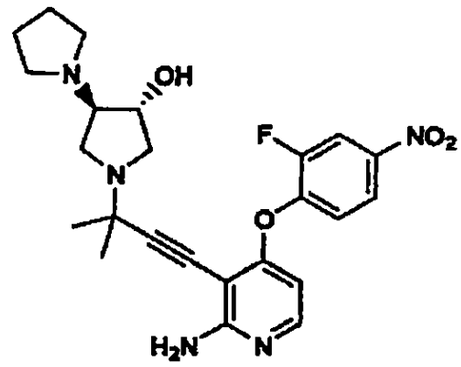
N-(4-(2-Amino-3-(3-((3R,4R)-3-hidroxi-4-(pirrolidin-1-il)pirrolidin-1-il)-3-metilbut-1-inil)piridin-4-iloxi)-3-fluorofenil)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridin-3-carboxamida, sal de triclorhidrato

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A) (3R,4R)-1-(2-metilbut-3-in-2-il)-4-(pirrolidin-1-il) pirrolidin-3-ol

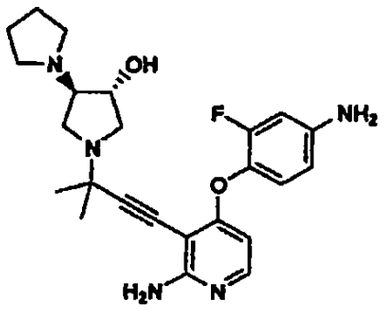
Una mezcla de (3R,4R)-4-(pirrolidin-1-il)pirrolidin-3-ol (Lexicon Pharma, 1.56 g. 10.0 mmol) y 3-cloro-3-metil-1-butino (GFS Chemical, Inc., 1.36 g, 13.2 mmol), THF (15 mL) y Et_3N (13.3 mmol) se trató con CuI (77 mg, 0.78 mmol). Sobrevino una reacción exotérmica con formación concomitante de un precipitado. Después de agitar a temperatura ambiente por 15 h. la mezcla se concentró a vacío y se dividió entre EtOAc y solución acuosa saturada de carbonato ácido de sodio. La fase acuosa se extrajo dos veces con EtOAc y las fases combinadas de EtOAc se secaron (sulfato de magnesio) y se concentró para dar un sólido café claro (1.0 g, 45%). RMN-^{1}H ($CDCl_3$) δ 4.20 (br s, 1H). 3.13- 3.04 (m, 1H), 2.95 (dd, 1H, J = 10.1, 6.6 Hz), 2.77 (dd, 1H, J = 10.1, 2.6 Hz). 2.64 (m, 3H). 2.61 (m, 2H), 2.55-2.46 (m, 1H). 2.26 (s, 1H), 1.85-1.74 (m, 4H), 1.38 (s, 3H), 1.36 (s, 3H); MS (ESI^+) : m/z 223.29 $(M+H)^+$.



B) (3R,4R)-1-(4-(2-Amino-4-(2-fluoro-4-nitrofenoxi)piridin-3-il)-2-metilbut-3-in-2-il)-4-(pirrolidin-1-il) pirrolidin-3-ol

El compuesto del título se preparó a partir de (3R,4R)-1-(2-metilbut-3-in-2-il)-4-(pirrolidin-1-il)pirrolidin-3-ol y 4-(2-fluoro-4-nitrofenoxi)-3-yodopiridin-2-amina (Compuesto C del Ejemplo 34), de la misma manera que el Paso D del Ejemplo 35 con 57% de rendimiento. RMN-^{1}H ($CDCl_3$) δ 8.10 (dd, 1H, J = 10.2, 2.5 Hz), 8.03 (d, 1H, J = 9.2 Hz), 7.99 (d, 1H, J = 5.6 Hz), 7.13-7.06 (m, 1H), 6.26 (d, 1H, J = 6.1 Hz), 5.18 (br s, 2H), 4.21 (m, 1H), 3.10-2.99 (m, 1H), 2.96 (s, 1H), 2.70 (dd, 2H, J = 9.7, 3.1 Hz), 2.66-1.15 (m, 2H), 1.87-1.76 (m, 5H), 133-1.32 (m, 2H), 1.32 (m, 3H); 1.34 (m, 3H); MS(ESI$^+$): m/z 470.20 $(M+H)^+$.

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C) (3R,4R)-1-(4-(2-Amino-4-(4-amino-2-fluorofenoxi)piridin-3-il)-2-metilbut-3-in-2-il)-4-(pirrolidin-1-il)pirrolidin-3-ol

El compuesto del título se preparó a partir de (3R,4R)-1-(4-(2-amino-4-(2-fluoro-4-nitrofenoxi)piridin-3-il)-2-metilbut-3-in-2-il)-4-(pirrolidin-1-il)pirrolidin-3-ol de la misma manera que el Paso C del Ejemplo 11 con 95% de rendimiento. MS(ESI$^+$): m/z 440.37 $(M+H)^+$.

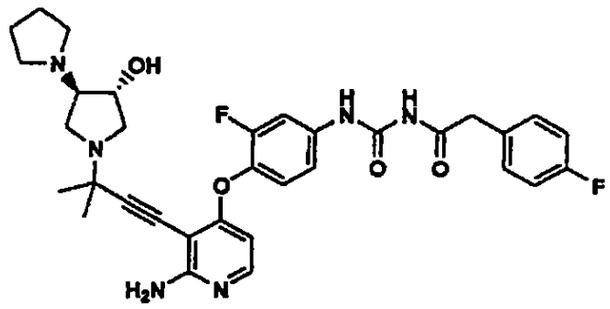
D) N-(4-(2-Amino-3-(3-((3R,4R)-3-hidroxi-4-(pirrolidin-1-il)pirrolidin-1-il)-3-metilbut-1-inil)piridin-4-iloxi)-3-fluorofenil)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridin-3-carboxamida, sal de triclorhidrato

El compuesto del título se preparó a partir de (3R,4R)-1-(4-(2-amino-4-(4-amino-2-fluorofenoxi)piridin-3-il)-2-metilbut-3-in-2-il)-4-(pirrolidin-1-il)pirrolidin-3-ol y ácido 1-(4-fluorofenil)-2-oxo-1,2-dihidropiridin-3-carboxílico (Compuesto B del Ejemplo 101), de la misma manera que el Ejemplo 62 con 50% de rendimiento. RMN-^{1}H (DMSO-d_6) δ 12.14 (s, 1H), 8.62-8.54 (m, 1H), 8.14 (dd, 3H, J = 6.6, 2.0 Hz), 8.05 (d, 1H, J = 13.2 Hz), 7.99 (d, 1H, J = 7.1 Hz),

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7.62-7.51 (m, 5H), 7.42 (t, 2H, J = 8.6 Hz), 6.78-6.70 (m, 1H), 6.32 (d, 1H, J = 7.1 Hz), 4.65 (br s, 1H), 3.94-3.84 (m, 1H), 3.71 (d, 2H, J = 16.8 Hz), 3.60 (m, 2 H), 3.52 (m, 1H), 3.22-3.08 (m, 2H), 2.00-1.91 (m, 2H), 1.88-1.78 (m, 2H), 1.70 (s, 6H); MS (ESI^+) : m/z 655.40 $(M+H)^+$.

Ejemplo 135



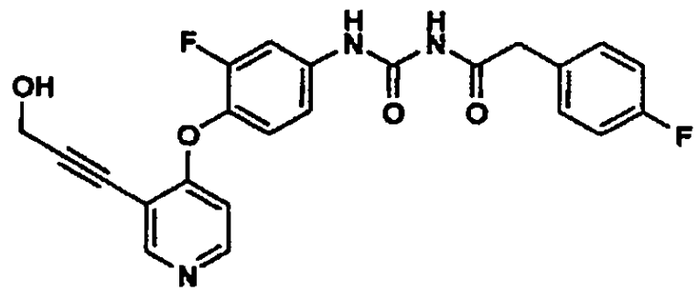
1-(4-(2-Amino-3-(3-((3R,4R)-3-hidroxi-4-(pirrolidin-1-il)pirrolidin-1-il)-3-metilbut-1-inil)piridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil) acetil) urea, sal de triclorhidrato

El compuesto del título se preparó a partir de (3R,4R)-1-(4-(2-amino-4-(4-amino-2-fluorofenoxi)piridin-3-il)-2-metilbut-3-in-2-il)-4-(pirrolidin-1-il)pirrolidin-3-ol con 40% de rendimiento, de la misma manera que el Paso E del Ejemplo 11. RMN-^{1}H (DMSO-d_6) δ 11.06 (s, 1H), 10.62 (s, 1H), 7.97(d, 2H, J = 6.6 Hz), 7.80 (d, 1H, J = 11.7 Hz), 7.51-7.40 (m, 2H), 7.38-7.32 (m, 2H), 7.16 (t, 2H, J = 8.6 Hz), 6.25 (d, 1H, J = 6.6 Hz), 4.63-4.53 (m, 1H), 3.79-3.68 (m, 1H), 3.74 (s, 2H), 3.68-3.56 (m, 2 H), 3.51-3.43 (m, 2H), 3.08-

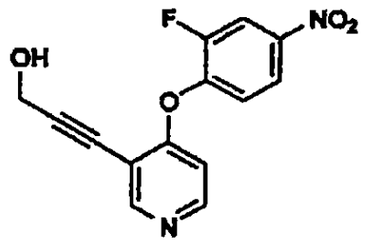
665

2.99 (m, 4H), 1.98-1.92 (m, 2H), 1.89-1.77 (m, 2H), 1.64 (s, 6H); MS (ESI^+) : m/z 619.41 $(M+H)^+$.

Ejemplo 136



1-(3-Fluoro-4-(3-(3-hidroxiprop-1-inil)piridin-4-iloxi)fenil)-3-(2-(4-fluorofenil) acetil) urea, sal de clorhidrato

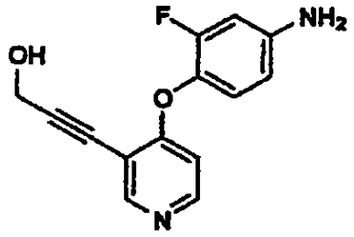


A) 3-(4-(2-Fluoro-4-nitrofenoxi)piridin-3-il)prop-2-in-1-ol

El compuesto del título se preparó a partir de 4-(2-fluoro-4-nitrofenoxi)-3-yodopiridina (Compuesto A del Ejemplo 33) y alcohol propargílico (Aldrich) con 77% de rendimiento, de la misma manera que el Paso A del Ejemplo 36. RMN-^{1}H (DMSO-d_6) δ 8.69 (s, 1H), 8.49 (d, 1H, J = 5.6 Hz), 8.43 (dd, 1H, J = 10.7, 2.5 Hz), 8.17 (d, 1H, J = 9.2 Hz). 7.57 (t, 1 H, J = 8.6 Hz), 7.04 (d, 1H, J = 5.6 Hz), 5.40 (t, 1H, J =

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6.1 Hz), 4.28 (d, 2H, J = 6.1 Hz); MS (ESI^+) : m/z 289.15 $(M+H)^+$.



B) 3-(4-(4-Amino-2-fluorofenoxi)piridin-3-il)prop-2-in-1-ol

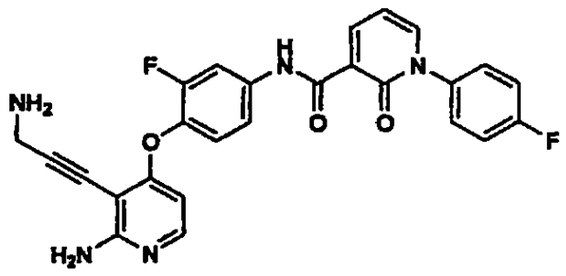
El compuesto del título se preparó a partir del 3-(4-(2-fluoro-4-nitrofenoxi)piridin-3-il)prop-2-in-1-ol con 95% de rendimiento de la misma manera que el Paso C del Ejemplo 11. MS (ESI^+) : m/z 259.21 $(M+H)^+$.

C) 1-(3-Fluoro-4-(3-(3-hidroxiprop-1-inil)piridin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)urea, sal de clorhidrato

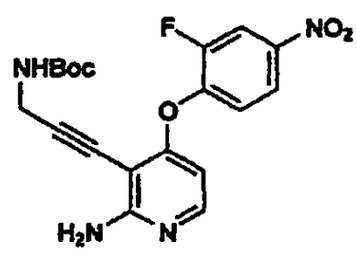
El compuesto del título se preparó a partir de 3-(4-(4-amino-2-fluorofenoxi)piridin-3-il)prop-2-in-1-ol con 36% de rendimiento, de la misma manera que el Paso E del Ejemplo 11. RMN-^{1}H (DMSO-d_6) δ 11.06(s, 1H), 10.63 (s, 1H), 8.79 (s, 1H), 8.49 (d, 1H, J = 6.1 Hz), 7.82 (d, 1H, J = 12.2 Hz), 7.45-7.40 (m, 2H), 7.38-7.33 (m, 2H), 7.23-7.13 (m, 2H), 6.89 (d, 1H, J = 6.1 Hz), 4.37 (s, 2H), 3.74 (s, 2H); MS (ESI^+) : m/z 438.23 $(M+H)^+$.

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Ejemplo 137



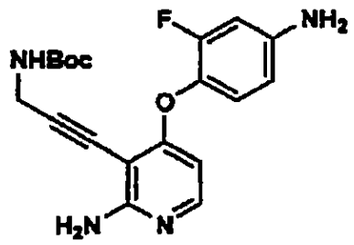
N-(4-(2-Amino-3-(3-aminoprop-1-inil)piridin-4-iloxi)-3-fluorofenil)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridin-3-carboxamida, sal de diclorhidrato



A) 3-(2-amino-4-(2-fluoro-4-nitrofenoxi)piridin-3-il)prop-2-inilcarbamato de ter-butilo

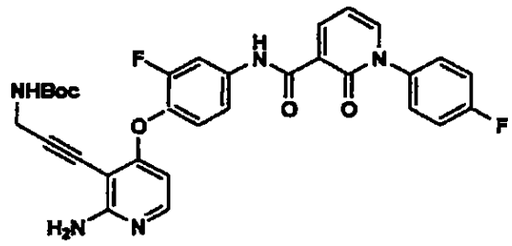
El compuesto del título se preparó a partir de N-Boc propargilamina (Compuesto A del Ejemplo 42) y 4-(2-fluoro-4-nitrofenoxi)-3-yodopiridin-2-amina (Compuesto C del Ejemplo 34) de la misma manera que el Paso A del Ejemplo 42 en 59% de rendimiento. RMN-^{1}H (DMSO-d_6) δ 8.35(dd, 1H, J = 10.7,2.5 Hz), 8.12 (d, 1H, J = 9.2 Hz), 7.88 (d, 1H. J = 5.6 Hz), 7.39 (t, 1H, J = 8.6 Hz), 7.31 (t, 1H, J = 5.1 Hz), 6.53 (s, 2H), 6.15

(d, 1H, J = 5.6 Hz), 3.92 (d, 2R, J = 5.6 Hz), 1.36 (s, 9H) : MS (ESI^+) : m/z 403.34 $(M+H)^+$.



B) 3-(2-amino-4-(4-amino-2-fluorofenoxi)piridin-3-il)prop-2-inilcarbamato de ter-butilo

El compuesto del título se preparó a partir de 3-(2-amino-4-(2-fluoro-4-nitrofenoxi)piridin-3-il)prop-2-inilcarbamato de ter-butilo con rendimiento cuantitativo, de la misma manera que el Paso C del Ejemplo 11. MS(ESI^+): m/z 373.35 $(M+H)^+$.



C) 3-(2-amino-4-(2-fluoro-4-(1-(4-fluorofenil)-2-oxo-1,2-dihidropiridin-3-carboxamido)fenoxi)piridin-3-il)prop-2-inilcarbamato de ter-butilo

El compuesto del título se preparó a partir de 3-(2-amino-4-(4-amino-2-fluorofenoxi)piridin-3-il)prop-2-inilcarbamato de ter-butilo y ácido 1-(4-fluorofenil)-2-oxo-

67 669

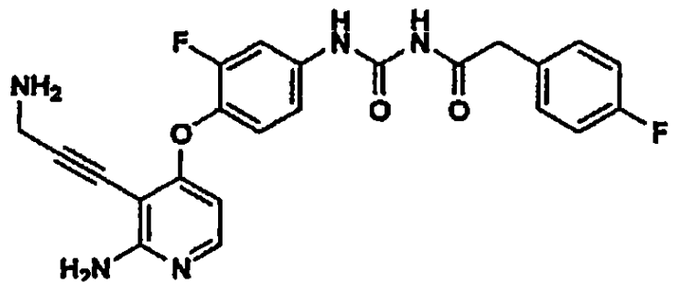
1,2-dihidropiridin-3-carboxílico (Compuesto B del Ejemplo 101), de la misma manera que el Ejemplo 62 en 48% de rendimiento. RMN-^{1}H (DMSO-d_6) δ 12.0.7 (s, 1H), 8.57 (dd, 1H, J = 7.1. 2.0 Hz). 8.12 (dd, 1H, J = 6.6, 2.0 Hz), 8.00- 7.93 (m, 1H), 7.75 (d, 1H. J = 6.1 Hz), 7.61 (d, 2H, J = 5.1 Hz), 7.59 (d, 1H, J = 4.6 Hz), 7.48-7.37 (m, 4 H), 7.30-7.25 (m, 1 H), 6.72 (t, 1H, J = 7.1 Hz), 6.37 (br s, 1H), 5.80 (d, 1H, J = 6.1 Hz), 4.00 (d, 2H. J = 5.1 Hz), 1.38 (s, 9H); MS (ESI$^+$): m/z 588.26 $(M+H)^+$.

D) N-(4-(2-Amino-3-(3-aminoprop-1-inil)piridin-4-iloxi)-3-fluorofenil)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridin-3-carboxamida, sal de diclorhidrato

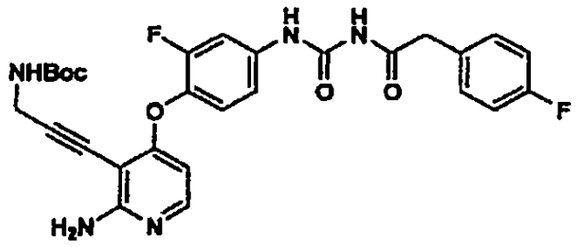
El compuesto del título se preparó a partir de 3-(2-amino-4-(2-fluoro-4-(1-(4-fluorofenil)-2-oxo-1,2-dihidropiridin-3-carboxamido)fenoxi)piridin-3-il)prop-2-inilcarbamato de ter-butilo con 80% de rendimiento, de la misma manera que el Paso E del Ejemplo 36. RMN-^{1}H (DMSO-d_6) δ 12.13 (s, 1H), 8.57 (dd, m, J = 7.1, 2.0 Hz), 8.51 (s, 2H), 8.14 (dd, 1H, J = 6.6, 2.0 Hz), 8.11-8.02 (m, 1H), 7.98-7.90 (m, 1H), 7.60 (dd, 2H, J = 9. 2, 5.1 Hz), 7.53 (d, 1H, J = 9.2 Hz), 7.46-7.37 (m, 3H), 6.76-6.71 (m, 1H), 6.20 (d, 1H, J = 6.6 Hz), 4.11-4.04 (m, 2H); MS(ESI$^+$): m/z 488.16 $(M+H)^+$.

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Ejemplo 138



1-(4-(2-Amino-3-(3-aminoprop-1-inil)piridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil) acetil) urea, sal de diclorhidrato



A) 3-(2-amino-4-(2-fluoro-4-(3-(2-(4-fluorofenil)acetil)ureido)fenoxi)piridin-3-il)prop-2-inilcarbamato de ter-butilo

El compuesto del título se preparó a partir de 3-(2-amino-4-(4-amino-2-fluorofenoxi)piridin-3-il)prop-2-inilcarbamato de ter-butilo con 38% de rendimiento, de la misma manera que el Paso E del Ejemplo 11. RMN-^{1}H (DMSO-d_6) δ 11.02 (s, 1H), 10.55 (s, 1H), 7.80-7.73-7.69 (m, 2H), 7.38-7.29 (m, 3H), 7.33 (d, 1H, J = 5.1 Hz), 7.30-7.21 (m, 1H), 7.21-7.13 (m, 2H), 6.37 (br s. 1H), 5.76 (d, 1H, J = 6.1 Hz),

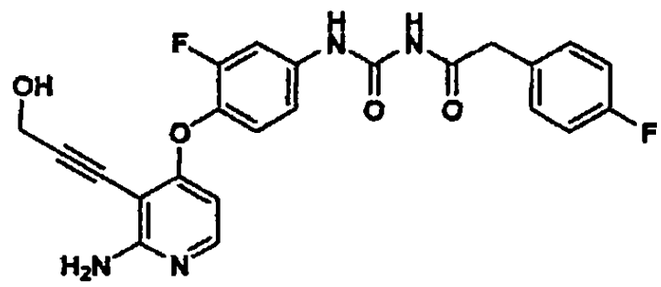
677 671

4.00 (s, 2H), 3.73 (s, 2H), 1.38 (s, 9H); MS (ESI^+) : m/2 552.24 $(M+H)^+$.

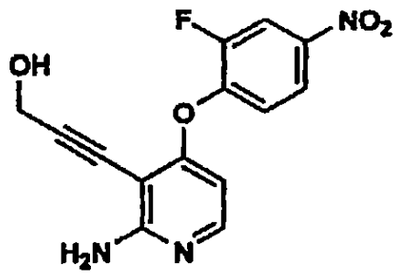
B) 1-(4-(2-Amino-3-(3-aminoprop-1-inil)piridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil)acetil)urea, sal de diclorhidrato

El compuesto del título se preparó a partir de 3-(2-amino-4-(2-fluoro-4-(3-(2-(4-fluorofenil)acetil)ureido)fenoxi)piridin-3-il)prop-2-inilcarbamato de ter-butilo con 65% de rendimiento, de la misma manera que el Paso E del Ejemplo 11. RMN-^{1}H (DMSO-d_6) δ 11.05(s, 1H), 10.61 (s, 1H), 8.48 (br s, 3H), 7.90 (d, 1H, J = 6.6 Hz), 7.84-7.76 (m, 2H), 7.45-7.39 (m, 1H), 7.39-7.32 (m, 3H), 7.20-7.13 (m, 2H), 6.11 (d, 1H, J = 6.1 Hz), 4.09-4.03 (m, 2H), 3.74 (s, 2H); MS (ESI^+) : m/z 452.12 $(M+H)^+$.

Ejemplo 139

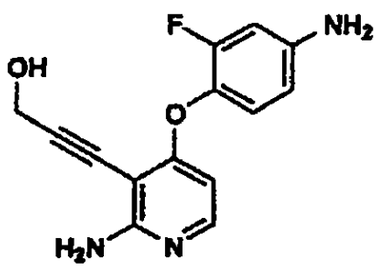


1-(4-(2-Amino-3-(3-hidroxiprop-1-inil)piridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil) acetil) urea, sal de clorhidrato



A) 3-(2-Amino-4-(2-fluoro-4-nitrofenoxi)piridin-3-il)prop-2-in-1-ol

El compuesto del título se preparó a partir de alcohol propargílico (Aldrich) y 4-(2-fluoro-4-nitrofenoxi)-3-yodopiridin-2-amina (Compuesto C del Ejemplo 34) con 46% de rendimiento de la misma manera que el Paso A del Ejemplo 36. RMN-^{1}H (DMSO-d_6) δ 8.40-8.34 (m, 1H), 8.13 (d, 1H, J = 8.6 Hz), 7.88 (d, 1H, J = 5.6 Hz), 7.42 (t, 1H, J = 8.6 Hz), 6.49 (s, 2H), 6.14 (d, 1H, J = 6.1 Hz), 5.26-5.20 (m, 1H), 4.26 (d, 2H, J = 6.1 Hz); MS (ESI$^+$) : m/z 304.23 $(M+H)^+$.



B) 3-(2-Amino-4-(4-amino-2-fluorofenoxi)piridin-3-il)prop-2-in-1-ol

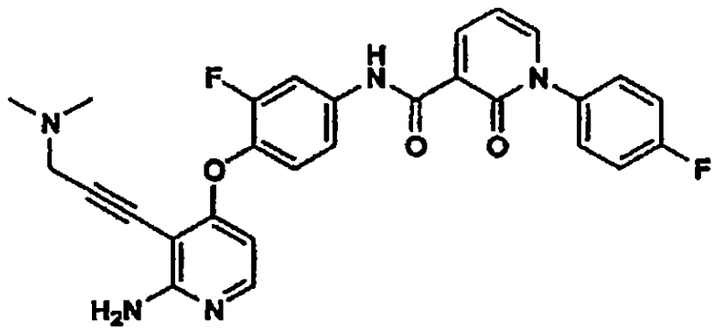
El compuesto del título se preparó a partir del 3-(2-amino-4-(2-fluoro-4-nitrofenoxi)piridin-3-il)prop-2-in-1-of

con 65% de rendimiento. MS(ESI$^+$): m/z 274.21.

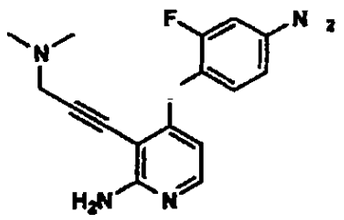
C) 1-(4-(2-Amino-3-(3-hidroxiprop-1-inil)piridin-4-iloxı)-3-fluorofenil)-3-(2-(4-fluorofenil) acetil) urea, sal de clorhidrato

El compuesto del título se preparó a partir de 3-(2-amino-4-(4-amino-2-fluorofenoxi)piridin-3-il)prop-2-in-1-ol con 48% de rendimiento. RMN-^{1}H (DMSO-d_6) δ 11.05 (s, 1H). 10.60 (s, 1H), 7.86 (d, 1H, J = 7.1 Hz). 7.83-7.77 (m, 1H), 7.44-7.37 (m, 2H), 7.37-7.32 (m, 3 H), 7.20-7.13 (m, 2H), 6.14 (d, J = 6.6 Hz, 1H), 4.37 (s, 2H), 3.74 (s, 2H); MS (ESI$^+$) : m/z 453.28 $(M+H)^+$.

Ejemplo 140

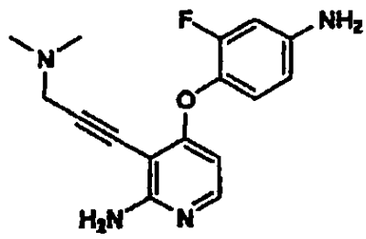


N-(4-(2-Amino-3-(3-(dimetilamino)prop-1-inil)piridin-4-iloxi)-3-fluorofenil)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridin-3-carboxamida, sal de diclorhidrato



A) 3-(3-(Dimetilamino)prop-1-inil)-4-(2-fluoro-4-nitrofenoxi)piridin-2-amina

El compuesto del título se preparó a partir de 1-dimetilamino-2-propino (Aldrich) y 4-(2-fluoro-4-nitrofenoxi)-3-yodopiridin-2-amina (Compuesto C del Ejemplo 34) con 64% de rendimiento, de la misma manera que el Paso A del Ejemplo 42. RMN-^{1}H (DMSO-d_6) δ 8.36 (dd, 1H, J = 10.7, 2.5 Hz), 8.11 (d, 1H, J = 8.6 Hz), 7.93 (d, 1H, J = 5.6 Hz), 7.30 (t, 1H, J = 8.6 Hz), 6.43 (br s, 2H), 6.28 (d, 1H, J = 6.1 Hz), 3.41 (s, 2H), 2.05 (s, 6H); MS (ESI$^+$) : m/z 331.28 $(M+H)^+$.



B) 4-(4-Amino-2-fluorofenoxi)-3-(3-(dimetilamino)prop-1-inil)piridin-2-amina

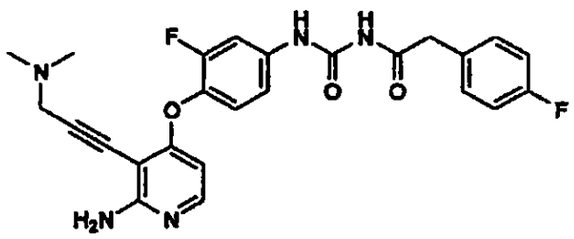
El compuesto del título se preparó a partir de 3-(3-(dimetilamino)prop-1-inil)-4-(2-fluoro-4-nitrofenoxi)piridin-2-amina con 77% de rendimiento, de la misma manera que el

Paso C del Ejemplo 11. MS(ESI$^+$): m/z 301.30 $(M+H)^+$.

C) N-(4-(2-Amino-3-(3-(dimetilamino)prop-1-inil)piridin-4-iloxi)-3-fluorofenil)-1-(4-fluorofenil)-2-oxo-1,2-dihidropiridin-3-carboxamida, sal de diclorhidrato

El compuesto del título se preparó a partir de 4-(4-amino-2-fluorofenoxi)-3-(3-(dimetilamino) prop-1-inil)piridin-2-amina y ácido 1-(4-fluorofenil)-2-oxo-1,2-dihidropiridin-3-carboxílico (Compuesto B del Ejemplo 101), de la misma manera que el Ejemplo 62 con 71% de rendimiento. RMN-^{1}H (DMSO-d_6) δ 12.14 (s, 1H), 11.39 (s, 1 H), 8.60-8.53 (m, 1H), 8.33 (s, 1H), 8.14 (dd, 1H, J = 6.6, 2.2 Hz), 8.05 (dd, 1H, J = 12.7, 2.2 Hz), 7.98 (d, 1H, J = 7.0 Hz), 7.61 (d, 1H, J = 5.3 Hz), 7.58 (d, 1H, J = 4.8 Hz), 7.56-7.50 (m, 1H), 737-7.47 (m, 3H), 6.76-6.69 (m, 1H), 6.30 (d, 1H, J = 7.0 Hz), 4.39 (s, 2H), 2.84 (s, 6H); MS(ESI$^+$): m/z 480.28 $(M+H)^+$.

Ejemplo 141

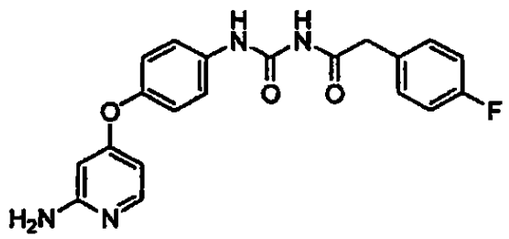


1-(4-(2-Amino-3-(3-(dimetilamino)prop-1-inil)piridin-4-iloxi)-3-fluorofenil)-3-(2-(4-fluorofenil) acetil) urea, sal de diclorhidrato

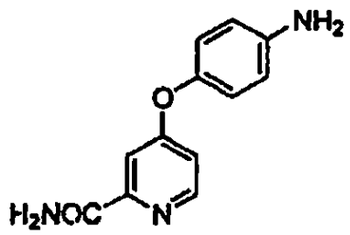
676 676

El compuesto del título se preparó a partir de 4-(4-amino-2-fluorofenoxi)-3-(3-(dimetilamino)prop-1-inil)piridin-2-amina, de una manera similar al Paso E del Ejemplo 11 con 70% de rendimiento. RMN-^{1}H (DMSO-d_6) δ 11.46 (br s, 1H), 11.07 (s, 1H), 10.64 (s, 1H), 8.37 br (s, 1H), 7.98 (t, 1H, J = 7.5 Hz), 7.81 (d, 1H, J = 13.6 Hz), 7.43- 7.32 (m, 4H), 7.20-7.09 (m, 2H), 6.27 (d, 1H, J = 7.0 Hz), 4.38 (s, 2H), 3.75 (s, 2H), 2.84 (s, 6H); MS(ESI$^+$): m/z 516.31 $(M+H)^+$.

Ejemplo 142



1-(4-(2-Aminopiridin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)urea, sal de clorhidrato

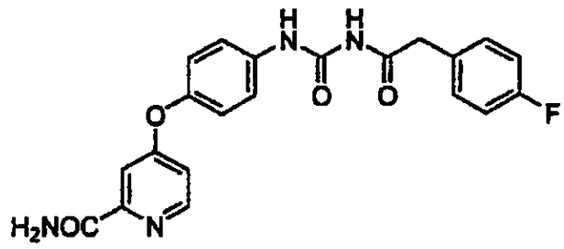


A) 4-(4-Aminofenoxi)picolinamida

El compuesto del título se preparó de una manera similar descrita en el Paso B' del Ejemplo 24, comenzando a partir

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del 4-aminofenol. Rendimiento: 85%. MS (ESI^+) m/z 230



B) 1-(4-(2-Carbamoilpiridin-4-iloxi)fenil)-3-(2-(4-fluorofenil) acetil) urea

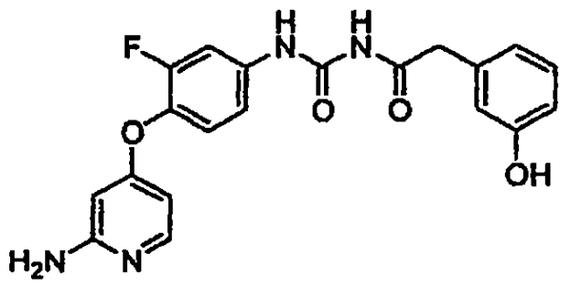
El compuesto del título se preparó de una manera similar a la descrita en el Paso C' del Ejemplo 24. Rendimiento: 95%. MS (ESI^4) m/z 409 $(M+H)^+$.

C) 1-(4-(2-Aminopiridin-4-iloxi)fenil)-3-(2-(4-fluorofenil)acetil)urea, sal de clorhidrato

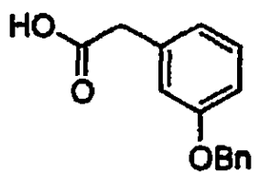
El compuesto del título se preparó de una manera similar a la descrita en el Paso D' del Ejemplo 24. Rendimiento: 58%. RMN-^{1}H (DMSO-d_6) δ 12.86 (s, 1H), 10.97 (s, 1H), 10.51 (s, 1H), 7.91 (d, 1H, J = 6.0 Hz), 7.67 (d, 3H, J = 9.0Hz), 7.34 (dd, 2H, J = 9.0, 5.0 Hz), 7.21 (d, 2H. J = 9.0 Hz), 7.16 (t, 2H, J = 9.0 Hz), 6.63 (dd, 1H, J = 9.5, 2.0 Hz), 6.05 (d, 1H. J = 2.0 Hz), 3.73 (s, 2H); MS (ESI^+) m/z 381 $(M+H)^+$.

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Ejemplo 143



1-(4-(2-Aminopiridin-4-iloxi)-3-fluorofenil)-3-(2-(3-hidroxifenil)acetil)urea



A) ácido 2-(3-(benciloxi) fenil) acético

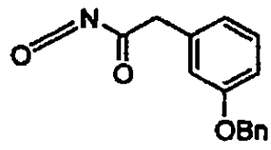
A una solución del ácido 3-hidroxifenilacético (Acros, 3.04 g. 20 mmol) en 20 mL de DMF se agregaron K_2CO_3 (6.90 g, 50 mmol) y bromuro de bencilo (4.75 mL. 40 mmol) a temperatura ambiente. La mezcla de reacción se agitó por 24 5 h. La suspensión se filtró y se lavó con éter dietílico. El filtrado luego se lavó con salmuera y se secó sobre sulfato de magnesio. La filtración, seguida por concentración, proporcionó el 2-(3-(Benciloxi)fenil)acetato de bencilo crudo, el cual se utilizó en el siguiente paso. MS (ESI^+) O m/z 355 $(M+Na)^+$.

El 2-(3-(benciloxi)fenil)acetato de bencilo crudo se

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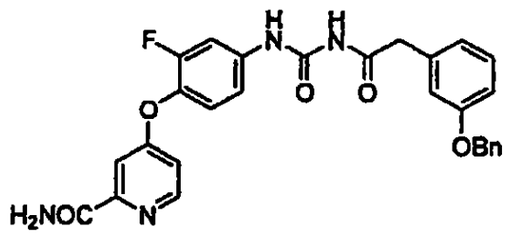
disolvió en una mezcla de McOH (20 mL) y THF (50 mL). A esta solución se agregó 40 mL de NaOH 1N (40 mmol). La mezcla de reacción se agitó a temperatura ambiente por 2 h.

El solvente orgánico se retiró a vacío. La solución acuosa remanente se extrajo con éter dietílico (2 x 50 mL). La solución acuosa se acidificó luego con HCl 1N (50 mL) y el compuesto del título precipitó. El sólido se recolectó mediante filtración (4.35 g, 90% dos pasos). MS(ESI+) m/z 0 265 $(M+Na)^+$.



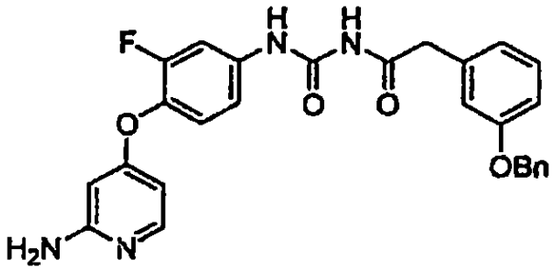
B) isocianato de 2-(3-(benciloxi)fenil) acetilo

A una solución de ácido 2-(3-(benciloxi)fenil)acético (484 mg, 2.0 mmol) en DCM (10 mL) a temperatura ambiente se agregó 1 gota de DMF y cloruro de tionilo (0.30 mL, 4 mmol). La mezcla de reacción se agitó a temperatura ambiente por 1 h y luego a 50 °C por 0.5 h. La mezcla se enfrió y el solvente se retiró a vacío. El residuo se disolvió en 5 mL de tolueno y se agregó AgOCN (600 mg, 4.0 mmol). La suspensión se agitó por 0.5 h y se filtró para proporcionar una solución de isocianato de 2-(3-(benciloxi)fenil)acetilo en tolueno (0.40 M).



C) 1-(2-(3-(benciloxi) fenil) acetil)-3-(4-(2-carbamoilpiridin-4-iloxi)-3-fluorofenil) urea

El compuesto del título se preparó de una manera similar a la descrita en el Paso C' del Ejemplo 24, utilizando la solución de Paso B de este Ejemplo. Rendimiento: 63%. MS(ESI$^+$) m/z 515(M+H)$^+$.



D) 1-(4-(2-Aminopiridin-4-iloxi)-3-fluorofenil)-3-(2-(3-(benciloxi)fenil)acetil)urea

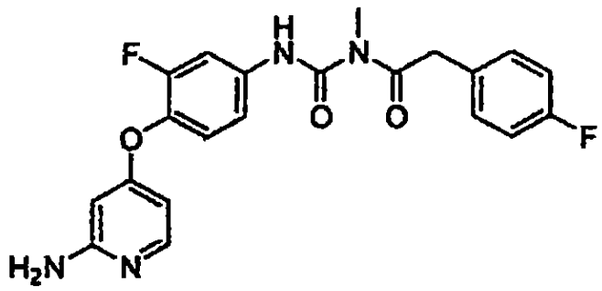
El compuesto del título se preparó de una manera similar a la descrita en el Paso D' del Ejemplo 24. Rendimiento: 61%. MS (ESI$^+$) m/z 487 (M+H)$^+$.

E) 1-(4-(2-Aminopiridin-4-iloxi)-3-fluorofenil)-3-(2-(3-hidroxifenil)acetil)urea

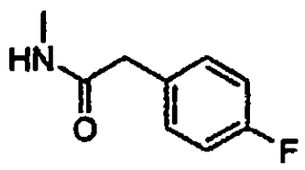
A una solución de 1-(4-(2-aminopiridin-4-iloxi)-3-

fluorofenil)-3-(2-(3-(benciloxi) fenil) acetil)urea (150 mg, 0.31 mmol) en una mezcla de 5 mL de EtOAc y 3 mL de MeOH, se agregó 10% de Pd/C (200 mg). La suspensión se agitó bajo atmósfera de hidrógeno por 1 h. La filtración, seguida por concentración, proporcionó el compuesto del título (77 mg, 63%). RMN-^{1}H (DMSO-d_6) δ 10.95 (s, 1H), 10.54 (s, 1H), 9.35 (s, 1H), 7.74 (d, 1H, J = 6.0 Hz), 7.68 (dd, 1H, J = 13.0, 2.0 Hz), 7.30 (dd, 1H, J = 9.0, 1.1 Hz), 7.23 (t, 1H, J = 9.0 Hz), 7.07 (t, 1H, J = 8.0 Hz), 6.69 (s, 1H), 6.68 (d, 1H, J = 7.0 Hz), 6.62 (dd, 1H, J = 7.0, 2.0 Hz), 6.10 (dd, 1H, J = 6.0, 2.0 Hz), 5.90 (s, 2H), 5.73 (d, 1H, J = 2.0 Hz), 3.27 (s, 2H); MS (ESI$^+$) m/z 397 $(M+H)^+$.

Ejemplo 144

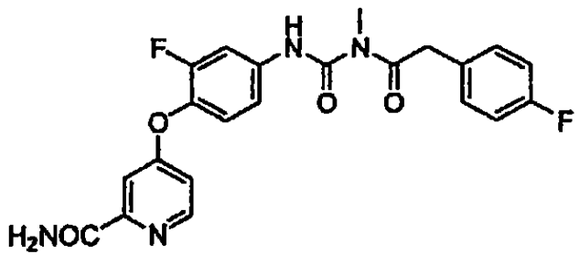


3-(4-(2-Aminopiridin-4-iloxi)-3-fluorofenil)-1-(2-(4-fluorofenil)acetil)-1-metilurea, sal de clorhidrato



A) 2-(4-Fluorofenil)-N-metilacetamida

A una solución de metilamina en THF (2.0 M, 5 mL, 10 mmol) se agregó 4-fluorofenilcloruro de acetilo (518 mg. 3.0 mmol) a -78 °C. La mezcla de reacción se agitó desde -78 °C hasta la temperatura ambiente por 1 h. La solución se diluyó con agua y se extrajo con EtOAc. La capa orgánica se lavó con salmuera y se secó sobre $MgSO_4$. La filtración, seguida por concentración, proporcionó el compuesto del título (490 mg, 98%). MS (ESI^+) m/z 168 $(M+H)^+$.



B) 3-(4-(2-Carbamoilpiridin-4-iloxi)-3-fluorofenil)-1-(2-(4-fluorofenil) acetil)-1-metilurea

A una solución de 2-(4-fluorofenil)-N-metilacetamida (89 mg, 0.53 mmol) en 2 mL de THF a -78 °C se agregó MeLi en Et_2O (1.6 M, 0.34 mL, 0.55 mmol). La solución se agitó a -78 °C por 5 min y luego se introdujo rápidamente fosgeno al 20% en tolueno (1.9 M, 0.29 mL, 0.55 mmol).

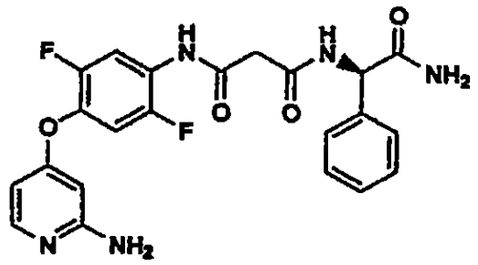
Después de 2 min, se agregó 4-(4-amino-2-fluorofenoxi)picolinamida (Compuesto B' del Ejemplo 24, 100 mg, 0.40 mmol), seguido por la adición de DMF (2 mL) y DIEA (0.4 mL). La mezcla de reacción se agitó a temperatura

ambiente por 1 h y se apagó con agua. La solución luego se extrajo con EtOAc y la capa orgánica se lavó con salmuera, se secó sobre sulfato de magnesio. Después de la filtración y concentraron, el residuo se purificó mediante cromatografía sobre gel de sílice para dar el compuesto del título (77 mg. 33%). MS (ESI^+) m/z 441 $(M+H)^+$.

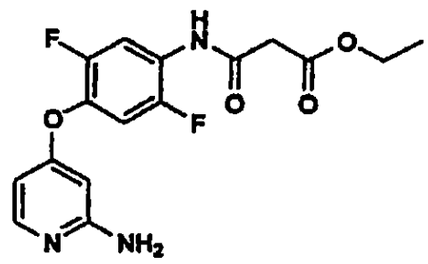
C) 3-(4-(2-Aminopiridin-4-iloxi)-3-fluorofenil)-1-(2-(4-fluorofenil)acetil)-1-metilurea, sal de clorhidrato

El compuesto del título se preparó de una manera similar a la descrita en el Paso D' del Ejemplo 24. Rendimiento: 24%. RMN-^{1}H (DMSO-d_6) δ 13.20 (s, 1H), 11.17 (s, 1H), 7.90 (d, 1H, J = 7.0 Hz), 7.78-7.74 (m, 3H), 7.39-7.34 (m, 2H), 7.23-7.21 (m, 2H), 7.10-7.05 (m, 2H), 6.63 (dd, 1H, J = 7.0, 2.0 Hz), 6.08 (d, 1H, .7 = 2.0 Hz), 4.00 (s, 2H), 3.24 (s, 3H); MS (ESI^+) m/z 413 $(M+H)^+$.

Ejemplo 145

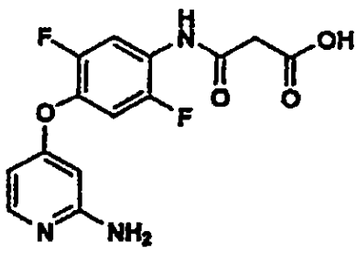


(R)-N^1-(2-Amino-2-oxo-1-feniletil)-N^3-(4-(2-aminopiridin-4-iloxi)-2,5-difluorofenil)malonamida, sal del ácido trifluoroacético



A) 3-(4-(2-aminopiridin-4-iloxi)-2,5-difluorofenilamino)-3-oxopropanoato de etilo

El 3-(4-(2-carbamoilpiridin-4-iloxi)-2,5-difluorofenilamino)-3-oxopropanoato de etilo (Compuesto A del Ejemplo 116, 0.73 g. 1.9 mmol) se convirtió al compuesto del título (0.24 g, 35%), de una manera similar a la preparación del Compuesto E del Ejemplo 112. MS(ESI$^+$) m/z 352 $(M+H)^+$.

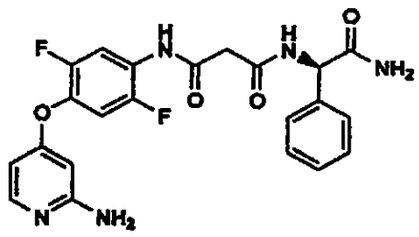


B) ácido 3-(4-(2-Aminopiridin-4-iloxi)-2,5-difluorofenilamino)-3-oxopropanoico

El 3-(4-(2-aminopiridin-4-iloxi)-2,5-difluorofenilamino)-3-oxopropanoato de etilo (0.24 g, 0.68 mmol) se convirtió al compuesto del título (0.039 mg, 18%), de una manera similar a la preparación del Compuesto B del Ejemplo 116. HRMS(ESI$^+$), Calculado: 324.0796 $(M+H)^+$,

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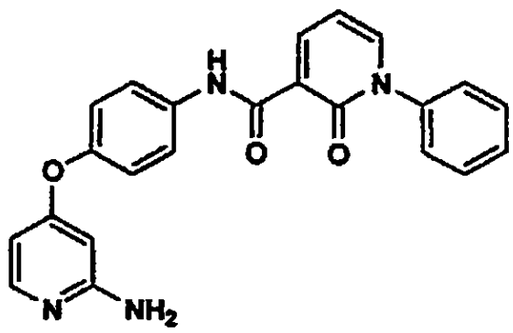
encontrado: 324.0795 $(M+H)^+$.



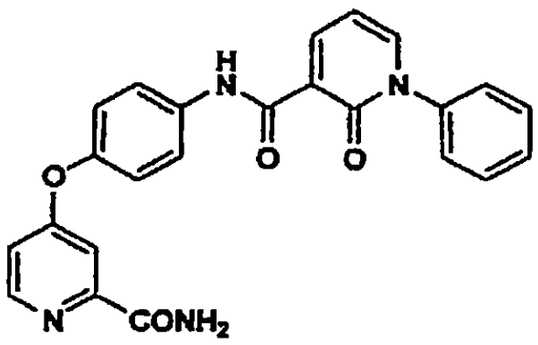
C) (R)-N^1-(2-amino-2-oxo-1-feniletil)-N^3-(4-(2-aminopiridin-4-iloxi)-2,5-difluorofenil)malonamida, sal del ácido trifluoroacético

El ácido 3-(4-(2-aminopiridin-4-iloxi)-2,5-difluorofenilamino)-3-oxopropanoico (0.039 g, 0.12 mmol) se acopló con clorhidrato de (R)-2-amino-2-fenilacetamida (Bachem, 0.023 g, 0.12 mmol), de una manera similar a la preparación del Ejemplo 103, para proporcionar el compuesto del título (0.0048 g, 7%). RMN-^{1}H (DMSO-d_6) δ 10.33 (s, 1H), 8.77 (d, 1H, J = 7.8 Hz), 8.10-8.19 (m, 1H),7.90(d, 1H, J = 7.2Hz), 7.60-7.75 (m, 4H), 7.17-7.39 (m, 6H), 6.66-6.69 (m, 1H), 6.11 (s, 1H), 5.35 (d, 1H, J = 7.8 Hz); HRMS(ESI+), Calculado: 456.1483 $(M+H)^+$, encontrado: 456.1487 $(M+H)^+$.

Ejemplo 146

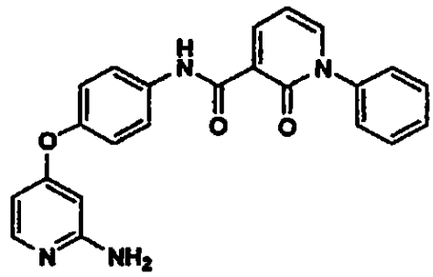


N-(4-(2-Aminopiridin-4-iloxi)fenil)-2-oxo-1-fenil-1,2-dihidropiridin-3-carboxamida, sal de clorhidrato



A) 4-(4-(2-oxo-1-fenil-1,2-dihidropiridin-3-carboxamido)fenoxi)picolinamida

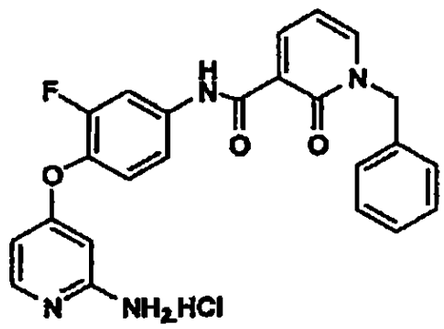
La 4-(4-aminofenoxi)picolinamida (Compuesto A del Ejemplo 142, 0.030 g. 0.13 mmol) se acopló con el Compuesto C del Ejemplo 57 (0.028 g, 0.13 mmol), de una manera similar a la preparación del Compuesto A del Ejemplo 115, para proporcionar el compuesto del título (0.057 g, 100%) el cual se utilizó sin purificación adicional. MS(ESI$^+$) m/z 427.



B) N-(4-(2-Aminopiridin-4-iloxi)fenil)-2-oxo-1-fenil-1,2-dihidropiridin-3-carboxamida, sal de clorhidrato

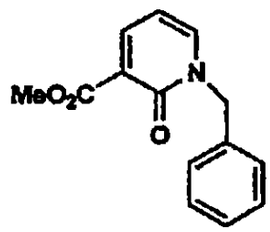
La 4-(4-(2-oxo-1-fenil-1,2-dihidropiridin-3-carboxamido)fenoxi)picolinamida (0.055, 0.13 mmol) se convirtió al compuesto del título (0.0093 g, 16%), de una manera similar a la preparación del Compuesto E del Ejemplo 112. RMN-^{1}H (CD_3OD) δ 12.10 (s, 1H), 8.59-8.61 (m, 1H), 7.88-7.90 (m, 1H), 7.69-7.76 (m, 3H), 7.39-7.53 (m, 5H), 7.10-7.13 (m, 2H), 6.66 (t, 1H, J = 6.9 Hz). 6.53-6.55 (m, 1H). 6.07-6.08 (m, 1H), 4.75 (br s, 2H); HRMS(ESI$^+$), Calculado: 399.1457 $(M+H)^+$, encontrado: 399.1453 $(M+H)^+$.

Ejemplo 147



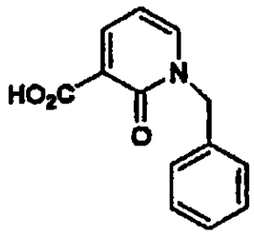
N-(4-(2-Aminopiridin-4-iloxi)-3-fluorofenil)-1-bencil-2-oxo-

1,2-dihidropiridin-3-carboxamida, sal de clorhidrato



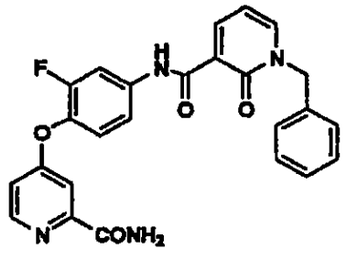
A) 1-bencil-2-oxo-1,2-dihidropiridin-3-carboxilato de metilo

Una mezcla heterogénea de 2-oxo-2H-piran-3-carboxilato de metilo (Aldrich, 2.0 g. 13 mmol, 1.0 eq) y 4-fluorobencilamina (1.5 mL, 13 mmol, 1.0 eq) en DMF (10 ml) se agitó a temperatura ambiente por 3 h. La mezcla de 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 por 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 al 10% (acuoso) (3 x 70 mL), se secó (sulfato de sodio), se filtró y el filtrado se concentró a vacío para proporcionar el producto (2.5 g, 73%) como un sólido, que se utilizó sin purificación adicional. RMN-^{1}H (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$^+$), Calculado: 262.0879, encontrado: 262.0885.



B) Ácido 1-bencil-2-oxo-1,2-dihidropiridin-3-carboxílico

Una solución de 1-bencil-2-oxo-1,2-dihidropiridin-3-carboxilato de metilo (2.4 g, 9.2 mmol. 1.0 eq) en McOH (25 mL) se trató con solución acuosa de hidróxido de sodio 5 N (4.6 mL, 24 mmol, 2.6 eq) a temperatura ambiente y la mezcla de reacción se agitó por 15 h. La mezcla de reacción se concentró luego a vacío, se diluyó con agua y la solución se extrajo con acetato de etilo, desechando 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 a vacío para proporcionar el producto (1.6 g, 70%), el cual se utilizó sin purificación adicional. RMN-^{1}H (DMSO-d_6) δ 8.39-8.44 (m, 2H), 7.42-7.46 (m, 2H), 7.18-7.24 (m, 2H), 6.78 (dd, 1H, J = 6.98 Hz). 5.31 (s, 2H); HRMS(ESI+), Calculado: 248.0723, encontrado: 248.0718.



C) 4-(4-(1-bencil-2-oxo-1,2-dihidropiridin-3-carboxamido)-

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2-fluorofenoxi)picolinamida

Una solución homogénea del ácido 1-bencil-2-oxo-1,2-dihidropiridin-3-carboxílico (0.10 g, 0.41 mmol, 1.0 eq), 4-(4-amino-2-fluorofenoxi)picolinamida (0.10 g, 0.41 mmol, 1.0 eq) y TBTU (0.17 g, 0.45 mmol, 1.1 eq) en DMF (2 mL), se trató con DIPEA (0.18 mL, 1.0 mmol. 2.5 eq) a temperatura ambiente y la mezcla de reacción se agitó por 12 h. La mezcla de reacción se apagó con Licl al 10% (acuoso) (15 mL) y la solución resultante se extrajo con acetato de etilo (4 x 40 mL). Los extractos orgánicos combinados se lavaron con Licl al 10% (acuoso) (4 x 50 mL), se secó (Na_2SO_4), se filtró y el filtrado se concentró a vacío. El residuo se purificó mediante cromatografía instantánea en columna (SiO_2 eluyendo con acetato de etilo) para proporcionar el producto (0.13 g, 67%) como un sólido. RMN-^{1}H (DMSO-d_6) 5 12.26 (s, 1H), 8.49-8.56 (m, 2H), 8.33-8.36 (m, 1H), 8.15 (br m, 1H). 8.03-8.07 (m, 1H), 7.74-7.75 (m, 1H), 7.51-7.54 (m, 1H), 7.41-7.46 (m, 4H), 7.20-7.24 (m, 3H), 6.71 (dd, 1H, J = 6.89 Hz), .5.32 (s, 2H) HRMS(ESI$^+$), Calculado: 477.1374, encontrado: 477.1378.

D) N-(4-(2-aminopiridin-4-iloxi)-3-fluorofenil)-1-bencil-2-oxo-1,2-dihidropiridin-3-carboxamida, sal de clorhidrato

Se agregó bis-(trifluoroacetoxi)yodobenzeno (0.12 g, 0.28 mmol, 1.1 eq) a una solución de 4-(4-(1-bencil-2-oxo-1,2-dihidropiridin-3-carboxamido)-2-fluorofenoxi)picolinamida (0.12 g, 0.26 mmol, 1.0 eq), y agua (0.01 mL, 0.51 mmol, 2 0

697 691

eq) en DMF (1 mL) a temperatura ambiente. Se agregó piridina (0.065 mL, 0.77 mmol, 3.0 eq) a la mezcla homogénea y la mezcla de reacción se agitó a temperatura ambiente por 12 h. La mezcla de reacción se apagó con HCl acuoso 1N (1 mL) y la solución resultante se extrajo con éter dietilico (3x5 mL), desechando la capa orgánica. La fracción acuosa se neutralizó con NaOH 1N acuoso y La solución resultante se extrajo con $CHCl_3$/MeOH 9/1 (4x10 mL). Los extractos orgánicos combinados se secaron (sulfato de sodio), se filtraron y el filtrado se concentró a vacío.

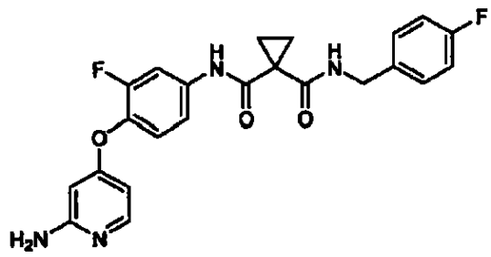
El residuo se purificó mediante cromatografía instantánea (SiO_2, eluyendo con 0-3% de McOH en $CHCl_3$) y Las fracciones apropiadas se concentraron a vacío. La base libre se disolvió en THF, se enfrió a 0°C y la solución homogénea se trató con HCl 4N anhidro en dioxano.

La mezcla de reacción se calentó a temperatura ambiente, se concentró a vacío y el residuo se trituró con éter dietílico, desechando el filtrado.

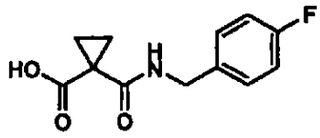
El sólido se secó a vacío para proporcionar el compuesto del título (0.082 g, 66%) como la sal de HCl. RMN-^{1}H (DMSO-d_6) δ 13.66 (br s, 1H), 8.49-8.51 (m, 1H), 8.39-8.49 (m, 1H), 8.37-8.39 (m, 1H), 8.00-8.09 (m, 3H), 7.54-7.56 (m, 1H), 7.43-7.48 (m, 3H), 7.19-7.24 (m, 2H), 6.69-6.72 (m, 2H), 6.21-6.22 (m, 1H), 5.32 (s, 2H); HRMS(ESI+), Calculado: 449.1425, encontrado: 449.1406.

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Ejemplo 148



N-(4-Fluorobencil)-N-(4-(2-aminopiridin-4-iloxi)-3-fluorofenil)ciclopropano-1,1-dicarboxamida

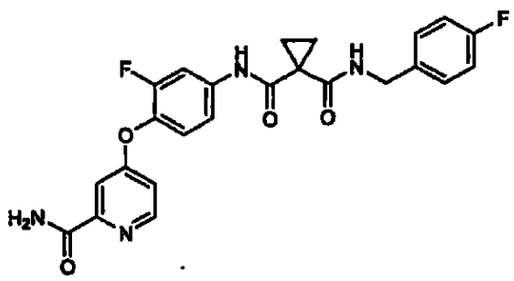


A) Ácido 1-((4-fluorobencil)carbamoil) ciclopropancarboxílico

A una solución del ácido 1,1-ciclopropancarboxílico (Aldrich, 390 mg, 3.0 mmol) en THF (5 ml) a 0°C, se agregó trietilamina (0.42 mmol, 3.0 mml). Después de agitar por 30 minutos, a 0°C, fue agregado cloruro de tionilo (0.219 ml, 3.0 mmol) a la mezcla de reacción. La mezcla fue agitada a 0°C por 30 minutos adicionales y fue agregada una solución de 4-fluorobencilamina (Aldrich, 375 mg, 3.0 mmol) en THF (2 ml). La mezcla de reacción fue agitada a 0°C por 2 h, diluida con acetato de etilo (100 ml) y extraída con NaOH 1 N (10 ml). La fase acuosa fue acidificada con HCl 1 N a pH 1-2. El sólido que se formó fue colectado por filtración (343 mg,

695 693

48%). EM(ESI$^+$), m/z 238.24 $(M + H)^+$.



B) N-(4-fluorobencil)-N-(4-(2-carbamoilpiridin-4-iloxi)-3-fluorofenil)ciclopropano-1,1-dicarboxamida

A una solución de 4-(4-amino-2-fluorofenoxi)picolinamida (Compuesto B' del Ejemplo 24, 49 mg, 0.2 mmol) en DMF (2 ml) a temperatura ambiente fue agregado ácido 1-((4-fluorobencil)carbamoil) ciclopropancarboxílico (47 mg, 0.2 mmol), HATU (Perseptive Biosystem, 114 mg, 0.3 mmol), y DIEA (0.2 ml, 1.1 mmol). La mezcla de reacción fue agitada a ta por 2 h, y luego enfriada rápidamente agregando 4 ml de metanol. La mezcla de reacción se purificó por HPLC prep. Las fracciones deseadas fueron combinadas, neutralizadas con K_2HPO ac., y concentradas in vacuo. El sólido que se formó fue colectado por filtración (29 mg, 31%). ^1H RMN (DMSO-d_6) δ 10.78 (br s, 1H), 8.53 (d, 1H, J = 5.5 Hz), 8.47 (1, 1H, J = 5.5 Hz), 8.11 (s, 1H), 7.88 (dd, 1H, J = 13.2, 2.3 Hz), 7.70 (s, 1H), 7.47 (d, 1H, J = 9.2 Hz), 7.38 (t, 1H, J = 9.21 Hz), 7.34-7.29 (m, 3H), 7.22 (dd, 1H, J = 5.5, 2.8 Hz), 7.13 (t, 2H, J = 8.8 Hz), 4.30 (d,

2H, J = 5.5 Hz), 1.37 (d, 4H, J = 10.6 Hz); EM(ESI$^+$) m/z 467.12 $(M+H)^+$.

C) N-(4-fluorobencil)-N-(4-(2-aminopiridin-4-iloxi)-3-fluorofenil)ciclopropano-1,1-dicarboxamida

A una solución de N-(4-fluorobencil)-N-(4-(2-carbamoilpiridin-4-iloxi)-3-fluorofenil)ciclopropano-1,1-dicarboxamida (25 mg, 0.05 mmol) en DMF (1 ml) a temperatura ambiente fue agregado piridina (0.2 ml), agua (0.1 ml), y [bis(trifluoroacetoxil)-yodo]benceno (Aldrich, 34 mg, 0.08 mmol).

La mezcla de reacción fue agitada a ta por 2 h, y entonces se enfrió rápidamente agregando 2 ml de metanol. La mezcla de reacción fue purificada por HPLC prep.

Las fracciones deseadas fueron combinadas, neutralizadas con K_2HPO_4 ac., concentradas y extraídas con acetato de etilo. Los extractos orgánicos fueron secados sobre $MgSO_4$ y se concentraron in vacuo.

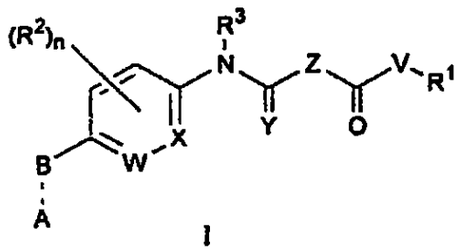
El residuo fue disuelto en una cantidad pequeña de CH_3CN/H_2O y liofilizado hasta sequedad para dar el compuesto del título (21 mg, 90%) como un sólido blanco.

^{1}H RMN (DMSO-d_6) δ 10.87 (br s, 1H), 8.44 (t, 1H, J = 6.0 Hz), 7.91 (d, 1H, J = 6.6Hz), 7.88 (d, 1H, J = 13.2 Hz), 7.37-7.29 (m, 6H), 7.13 (t, 2H, J = 8.8 Hz), 4.29 (d, 2H, J = 6.1 Hz), 1.38 (d, 4H, J = 2.2 Hz); EM(ESI$^+$) m/z 439.14 $(M+H)^+$.

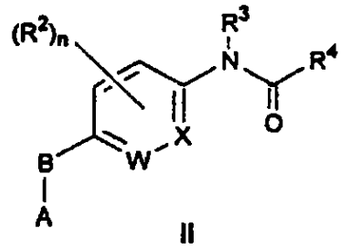
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REIVINDICACIONES

1. Compuesto que tiene la fórmula I o II:



I



II

o un enantiómero, diastereoisómero, hidrato, solvato o sal farmacéuticamente aceptable de los mismos caracterizado porque:

R^1 es hidrógeno, alquilo, alquilo sustituido, cicloalquilo, cicloalquilo sustituido, arilalquilo, arilalquilo sustituido, arilo, arilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, heteroarilo, heteroarilo sustituido, heterociclo, heterociclo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, heterocicloalquilo o heterocicloalquilo sustituido:

Cada R^2 es independientemente hidrógeno, halógeno, ciano, NO_2, ORS, NR^6R^7, alquilo, alquilo sustituido, cicloalquilo, cicloalquilo sustituido, arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, heterociclo, heterociclo sustituido, arilalquilo, arilalquilo sustituido, heterocicloalquilo, o heterocicloalquilo sustituido;

B es O, NR^8, NR^8CH_2, S, SO, SO_2 o CR^9R^{10};

V es NR^{11} o $-(CR^{37}R^{38})_p-$ con la condición de que cuando V sea nitrógeno, R^1 sea un alquilo o cicloalquilo;

W y X son cada uno independientemente carbono o nitrógeno;

Y se selecciona de oxígeno, azufre y NR^{12};

Z es $-CR^{13}R^{14}-$, o $-(CR^{13}R^{14})_1NR^{15}-$;

l es 0 a 2;

n es 0 a 4 si W y X son ambos carbono, 0 a 3 si uno de X o W es nitrógeno, y 0 a 2 si X y W son ambos nitrógeno;

p es 1 a 4;

R^3, R^5, R^6, R7, R^8, R^{11} y R^{15} son independientemente seleccionados de hidrógeno, alquilo, alquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, cicloalquilo, cicloalquilo sustituido, arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, heterociclo, heterociclo sustituido;

R^4 se selecciona de arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, heterocicloalquilo y heterocicloalquilo sustituido, con la condición de que:

(a) si R^4 es fenilo

(i) R^4 no está sustituido con hidroxilo y amido; y

(ii) R^4 no está sustituido con $-NRSO_2R-$ en donde R es alquilo o arilo;

(b) si R^4 es piridilo, R^4 no está sustituido con hidroxilo y metoxi;

y

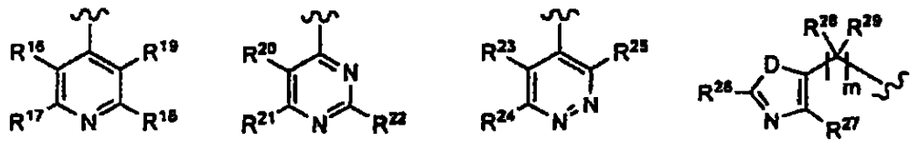
(c) si R^4 es pirimidinilo, éste no está sustituido con =O;

R^9 y R^{10} son independientemente seleccionados de hidrógeno, halógeno, alquilo, alquilo sustituido, cicloalquilo, cicloalquilo sustituido, arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, heterocicloalquilo o heterocicloalquilo sustituido;

R^{12} se selecciona de hidrógeno, alquilo, alquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, CN, NO_2 o SO_2NH_2;

R^{13} y R^{14} son independientemente seleccionados de hidrógeno, halógeno, alquilo, alquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, cicloalquilo, cicloalquilo sustituido, arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, heterocicloalquilo, heterocicloalquilo sustituido o tomados conjuntamente forman un anillo carbocíclico o heterocíclico de 3 a 8 átomos;

A se selecciona de uno de los siguientes:



en donde:

D es S u O;

m es 0 a 6;

R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26} y R^{27} son independientemente seleccionados de hidrógeno, halógeno, $NR^{30}R^{31}$, OR^{32}, CO_2R^{33}, $CONR^{34}R^{35}$, SO_2R^{36}, alquilo, alquilo sustituido, cicloalquilo, cicloalquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, -CN, arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, heterocicloalquilo, o heterocicloalquilo sustituido;

R^{28} y R^{29} son independientemente seleccionados de hidrógeno, alquilo, alquilo sustituido, cicloalquilo, cicloalquilo sustituido, arilo, arilo sustituido, o tomados conjuntamente forman un anillo carbocíclico o heterocíclico de 3 a 8 átomos;

R^{30}, R^{31}, R^{32}, R^{33} R^{34} R^{35} y R^{36} son independientemente seleccionados de hidrógeno, alquilo, alquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, cicloalquilo, cicloalquilo sustituido, alcoxicarbonilo, arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, heterociclo, heterociclo sustituido,

heterocicloalquilo, o heterocicloalquilo sustituido; y

R^{37} y R^{38} son cada uno independientemente hidrógeno, halógeno o alquilo.

2. Compuesto de conformidad con la reivindicación 1, caracterizado porque R^1 es un fenilo sustituido o no sustituido, un alquilo de 1 a 4 átomos de carbono sustituido o no sustituido, o un cicloalquilo de 3 a 8 átomos de carbono sustituido o no sustituido.

3. Compuesto de conformidad con la reivindicación 2, caracterizado porque R^1 es fluorofenilo, metilo sustituido, ciclohexilo o ciclopentilo.

4. Compuesto de conformidad con la reivindicación 1, caracterizado porque R^2 es alquilo de 1 a 4 átomos de carbono, halógeno o haloalquilo.

5. Compuesto de conformidad con la reivindicación 1, caracterizado porque R^4 es fenilo opcionalmente sustituido, piridilo, piridil-N-óxido, pirazolilo o pirrolidilo.

6. Compuesto de conformidad con la reivindicación 5, caracterizado porque R^4 está sustituido con oxígeno, fenilo, alquilo de 1 a 4 átomos de carbono, o halógeno.

7. Compuesto de conformidad con la reivindicación 1, caracterizado porque B es O, $NHCH_2$, CH_2 o CH (OH); Y es O ó S y Z es $-CR^{13}R^{14}$ o $-NR^{15}$ en donde R^{13}, R^{14} y R^{15} son cada uno hidrógeno.

8. Compuesto de conformidad con la reivindicación 1,

caracterizado porque A es una piridina o pirimidina opcionalmente sustituida.

9. Compuesto de conformidad con la reivindicación 8, caracterizado porque el sustituyente es alquilo, alquenilo, alquinilo, halógeno, cicloalquilo, heterocicloalquilo, $-NR^{39}COR^{40}$, $-NR^{39}C(O)_2R^{40}$, $-NR^{41}R^{42}$, o $-C(O)NR^{43}R^{44}$, en donde R^{39}, R^{40}, R^{41}, R^{42}, R^{43} y R^{44} son independientemente hidrógeno, alquilo inferior, alquilo inferior sustituido, hidroxialquilo, aminoalquilo, cicloalquilo, cicloalquilo sustituido, heterocicloalquilo, heterocicloalquilo sustituido, cicloalquenilo, cicloalquenilo sustituido, arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, o $NR^{43}R^{44}$ forman un heterocicloalquilo.

10. Compuesto de conformidad con la reivindicación 7, caracterizado porque A es una piridina sustituida con $-NR^{41}R^{42}$, $-NR^{39}COR^{40}$, $-C(O)NR^{43}R^{44}$, halógeno, alquilo de 1 a 4 átomos de carbono, $-C=C-R^{45}$, $-C\equiv C-R^{46}$, arilo o heteroarilo en donde R^{45} y R^{46} son alquilo, hidroxialquilo, aminoalquilo, cicloalquilo, heterocicloalquilo, $-C(O)R^{47}$, $-NR^{39}COR^{40}$, arilo, o heteroarilo.

11.- Compuesto de conformidad con la reivindicación 10, caracterizado porque el alquilo de 1 a 4 átomos de carbono es substituido con hidroxi, hidroxialquilamino, alquilamino, aminoalquilamino, o heteroarilalquilo.

12. Compuesto de conformidad con la reivindicación 8,

caracterizado porque R^{41} y R^{42} son cada uno independientemente hidrógeno, metilo, etilo, propilo, butilo, fenilo o bencilo, y R^{39} es hidrógeno y R^{40} es metilo, cicloalquilo, o heterocicloalquilo.

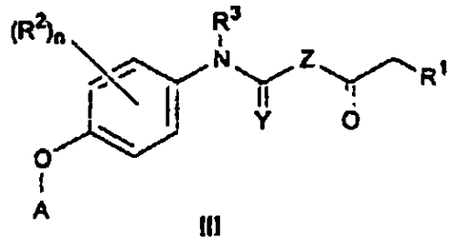
13. Compuesto de conformidad con la reivindicación 8, caracterizado porque R^{43} y R^{44} son hidrógeno y R^{45} y R^{46} son cada uno ciclohexeno, azetidina, piperazina, piperidina, pirrolidina, o piridina, opcionalmente sustituidos con alquilo de 1 a 4 átomos de carbono, $-CH_2NH_2$ $-NH_2$, o pirrolidina.

14. Compuesto de conformidad con la reivindicación 8, caracterizado porque la piridina está sustituida con un grupo fenilo, opcionalmente sustituido con $CONH_2$, metilo, aminoetilo, hidroxietilo, $-CONHCH_2CH_2NHCH_3$ o CH_2CONH_2; piridina o piperazina.

15. Compuesto de conformidad con la reivindicación 8, caracterizado porque A es pirimidina sustituida con $-NR^{41}R^{42}$, o $-NR^{39}CO_2R^{40}$.

16. Compuesto de conformidad con la reivindicación 15, caracterizado porque R^{41} y R^{42} son hidrógeno o metilo y R^{39} y R^{40} son independientemente hidrógeno o alquilo.

17. Compuesto de conformidad con la reivindicación 1, caracterizado porque tiene la fórmula III:



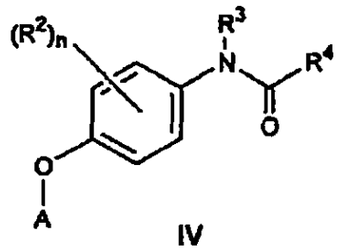
III

en donde

R^1 es alquilo o fenilo opcionalmente sustituido; Z es NH o NCH_3; R^2 es flúor, cloro, CH_3 o CF_3; R^3 es hidrógeno; e Y es oxígeno o azufre.

18. Compuesto de conformidad con la reivindicación 17, caracterizado porque R^1 es cicloalquilo de 3 a 7 átomos de carbono, fenilo sustituido o no sustituido, o $-(CH_2)_n-R^{50}$ en donde n es 1 a 3, R^{50} es hidrógeno, fenilo sustituido o no sustituido, amino, amido, CN, $-C(O)_2H$, o $-C(O)_2CH_3$.

19. Compuesto de conformidad con la reivindicación 1, que tiene la fórmula IV:

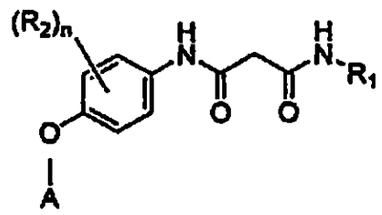


IV

caracterizado porque R^2 es halo o hidrógeno; R^3 es hidrógeno; R^4 es fenilo opcionalmente sustituido, pirazol opcionalmente sustituido, o piridilo opcionalmente sustituido; o una piridinona o un piridin N-óxido opcionalmente substituido y A es piridilo opcionalmente sustituido.

20. Compuesto de conformidad con la reivindicación 19, caracterizado porque R^4 es una piridinona opcionalmente sustituida o un piridin-N-óxido.

21. Compuesto de conformidad con la reivindicación 1, que tiene la fórmula V:



V

caracterizado porque R^1 es cicloalquilo o alquilo opcionalmente; A es pirimidina o piridina opcionalmente sustituidas; y R^2 es halo o hidrógeno y R13 Y R14 son ya sea hidrogeno o junto con el átomo de carbono al cuál están unidos para un ciclopropilo..

22. Compuesto de conformidad con la reivindicación 1, caracterizado porque tiene un valor de ICso menor de aproximadamente 1.0 µM.

23. Método para el tratamiento del cáncer en un paciente en necesidad del mismo, caracterizado porque comprende administrar al paciente una cantidad terapéuticamente efectiva de un compuesto de conformidad con la reivindicación 1.

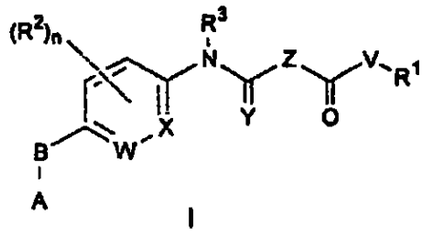
24.- Composición farmacéutica, caracterizada porque

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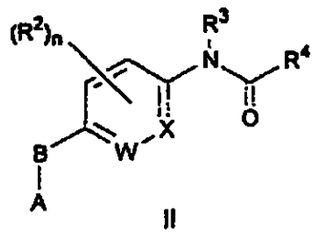
comprende una cantidad terapéuticamente efectiva de un compuesto de conformidad con la reivindicación 1 y un portador farmacéuticamente aceptable.

RESUMEN DE LA INVENCIÓN

La presente invención está dirigida a los compuestos que tienen la fórmula



I



II

y métodos para el uso de los mismos para el tratamiento del cáncer.

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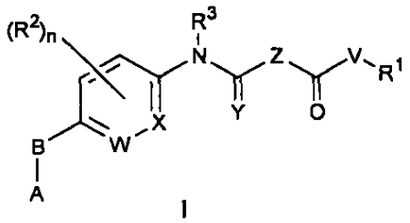
AMENDED

CLAIMS

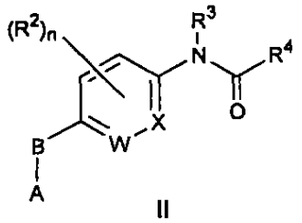
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WE CLAIM:

1. A compound having Formula I or II



I



II

or an enantiomer, diastereomer, hydrate, solvate or pharmaceutically acceptable salt 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, NR^8CH_2, S, SO, SO_2, or CR^9R^{10};

V is NR^{11} or $-(CR^{37}R^{38})_p-$ provided that when VR^{11} is N, R^1 is an alkyl or cycloalkyl,

W and X are each independently C or N;

Y is selected from O, S, and NR^{12},

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

l is 0 to 2,

n is 0 to 4 if W and X are both C, 0 to 3 if one of X or W is N, and 0 to 2 if X and W are both N;

p is 1 to 4,

R^3, R^5, R^6, R^7, R^8, R^{11} and R^{15} are independently selected from H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl,

substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclo, substituted heterocyclo;

R^4 is selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, and substituted heterocycloalkyl, provided that

(a) if R^4 is phenyl

(i) R^4 is not substituted with both hydroxy and amido, and

(ii) R^4 is not substituted with $-NRSO_2R-$ wherein R is alkyl or aryl;

(b) if R^4 is pyridyl, R^4 is not substituted with both hydroxy and methoxy, and

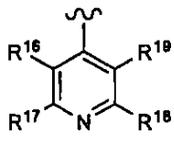
(c) if R^4 is pyrimidinyl, it is not substituted with =O;

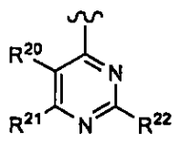
R^9 and R^{10} are independently selected from H, halogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, or substituted heterocycloalkyl;

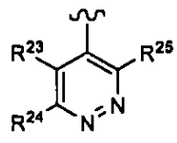
R^{12} is selected from H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, CN, NO_2 or SO_2NH_2;

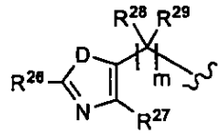
R^{13} and R^{14} are independently selected from H, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, substituted heterocycloalkyl or taken together to form a carbocyclic or heterocyclic ring of 3 to 8 atoms;

A is selected from one of the following.









wherein

D is S or O,

m is 0 to 6,

R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26} and R^{27} are independently selected from H, halogen, $NR^{30}R^{31}$, OR^{32}, CO_2R^{33}, $CONR^{34}R^{35}$, SO_2R^{36}, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, -CN, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, or substituted heterocycloalkyl;

R^{28} and R^{29} are independently selected from H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, or taken together to form a carbocyclic or heterocyclic ring of 3 to 8 atoms,

R^{30}, R^{31}, R^{32}, R^{33}, R^{34}, R^{35}, and R^{36} are independently selected from H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, alkoxycarbonyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclo, substituted heterocyclo, heterocycloalkyl, or substituted heterocycloalkyl, and

$R^{37}$and R^{38} are each independently H, halogen, or alkyl

2 The compound according to claim 1 wherein R^1 is a substituted or unsubstituted phenyl, a substituted or unsubstituted C_1 to C_4 alkyl, or a substituted or unsubstituted C_3 to C_8 cycloalkyl.

3 The compound according to claim 2 wherein R^1 is fluorophenyl, substituted methyl, cyclohexyl or cyclopentyl.

4. The compound according to claim 1 wherein R^2 is C_1 to C_4 alkyl, halogen, or haloalkyl.

5 The compound according to claim 1 wherein R^4 is optionally substituted phenyl, pyridinone, pyridyl, pyridyl-N-oxide, pyrazolyl, or pyrrolidyl.

6. The compound according to claim 5 wherein $R^4$is substituted with oxygen, phenyl, C_1 to C_4 alkyl, or halogen.

7. The compound according to claim 1 wherein B is O, $NHCH_2$, CH_2 or CH(OH), Y is O or S and Z is $-CR^{13}R^{14}$ or $-NR^{15}$ wherein R^{13}, R^{14}, and R^{15} are each H.

8 The compound according to claim 1 wherein A is an optionally substituted pyridine or pyrimidine

9 The compound according to claim 8 wherein the substituent is alkyl, alkenyl, alkynyl, halogen, cycloalkyl, heterocycloalkyl, $-NR^{39}COR^{40}$, $-NR^{39}C(O)_2R^{40}$, $-NR^{41}R^{42}$, or $-C(O)NR^{43}R^{44}$, wherein R^{39}, R^{40}, R^{41}, R^{42}, R^{43}, and R^{44} are independently H, lower alkyl, substituted lower alkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, or $-NR^{43}R^{44}$ form a heterocycloalkyl

10. The compound according to claim 7 wherein A is a pyridine substituted with $-NR^{41}R^{42}$, $-NR^{39}COR^{40}$, $-C(O)NR^{43}R^{44}$, halogen, C_1 to C_4 alkyl, $-C{=}C-R^{45}$, $-C{\equiv}C-R^{46}$, aryl, or heteroaryl wherein R^{45} and R^{46} are alkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, heterocycloalkyl, $-C(O)R^{47}$, $-NR^{39}COR^{40}$, aryl, or heteroaryl.

11 The compound according to claim 10 wherein said C_1 to C_4 alkyl is substituted with hydroxy, hydroxyalkylamino, alkylamino, aminoalkylamino, or heteroarylalkyl.

12. The compound according to claim 8 wherein R^{41} and R^{42} are each independently, H, methyl, ethyl, propyl, butyl, phenyl, or benzyl and R^{39} is H and R^{40} is methyl, cycloalkyl, or heterocycloalkyl

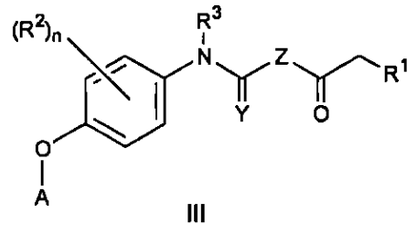
13 The compound according to claim 8 wherein R^{43} and R^{44} are H and R^{45} and R^{46} are each cyclohexene, azetidine, piperazine, piperidine, pyrrolidine, or pyridine, optionally substituted with C_1 to C_4 alkyl, $-CH_2NH_2$, $-NH_2$, or pyrrolidine.

14 The compound according to claim 8 wherein the pyridine is substituted with a phenyl group, optionally substituted with $CONH_2$, methyl, aminoethyl, hydroxyethyl, $-CONHCH_2CH_2NHCH_3$, or CH_2CONH_2, pyridine, or piperazine

15 The compound according to claim 8 wherein A is pyrimidine substituted with $-NR^{41}R^{42}$, or $-NR^{39}CO_2R^{40}$

16 The compound according to claim 15 wherein R^{41} and R^{42} are H or methyl and R^{39} and R^{40} are independently H or alkyl.

17 The compound according to claim 1 having the formula III.



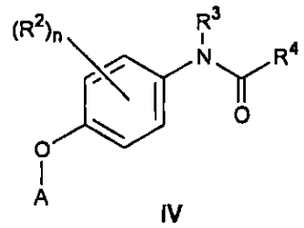
III

wherein

R^1 is optionally substituted phenyl or alkyl; Z is NH or NCH_3 , R^2 is F, Cl, CH_3 or CF_3, R^3 is H; and Y is O or S

18 The compound according to claim 17 wherein R^1 is C_3 to C_7 cycloalkyl, substituted or unsubstituted phenyl, or $-(CH_2)_n-R^{50}$ wherein n is 1 to 3, R^{50} is H, substituted or unsubstituted phenyl, amino, amido, CN, $-C(O)_2H$, or $-C(O)_2CH_3$

19 The compound according to claim 1 having Formula IV:

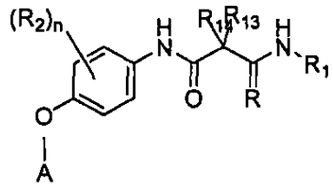


IV

wherein R^2 is halo or H, R^3 is H, R^4 is optionally substituted phenyl, optionally substituted pyrazole, or optionally substituted pyridyl or an optionally substituted pyridinone or a pyridine-N-oxide, and A is optionally substituted pyridyl.

20. The compound according to claim 19 wherein R^4 is an optionally substituted pyridinone or a pyridine-N-oxide.

21 The compound according to claim 1 having formula V



V

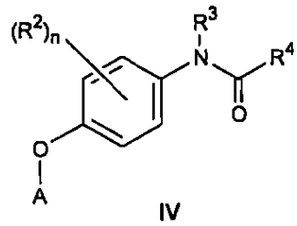
wherein R^1 is optionally alkyl or cycloalkyl; A is optionally substituted pyrimidine or pyridine, and R_2 is halo or H, and R^{13} and R^{14} are either H or together with the carbon to which they are attached for a cyclopropyl

22 A compound according to claim 1 having an IC_{50} value of less than about 1 0 μM

23 A method for treating cancer in a patient in need thereof comprising administering to the patient a therapeutically effective amount of a compound according to claim 1

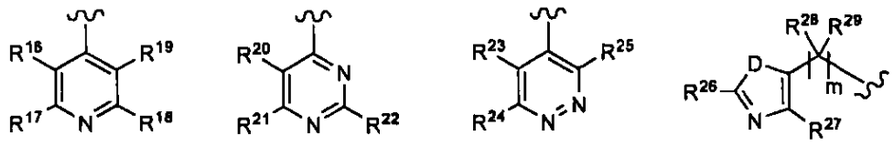
24 A pharmaceutical composition comprising a therapeutically effective amount of a compound according to claim 1 and a pharmaceutically acceptable carrier

25. A compound having the following Formula IV·



IV

wherein A is



wherein

R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26} and R^{27} are independently selected from H, halogen, $NR^{30}R^{31}$, OR^{32}, CO_2R^{33}, $CONR^{34}R^{35}$, SO_2R^{36}, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, -CN, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, or substituted heterocycloalkyl,

R^{28} and R^{29} are independently selected from H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, or taken together to form a carbocyclic or heterocyclic ring of 3 to 8 atoms,

R^2 is halo or H;

R^3 is H, and

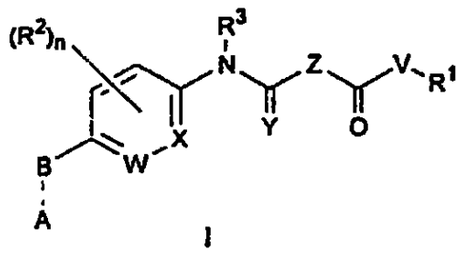
R^4 is optionally substituted phenyl, optionally substituted pyrazole, or optionally substituted pyridyl, pyridinone, or pyridine-N-oxide.

REIVINDICACIONES

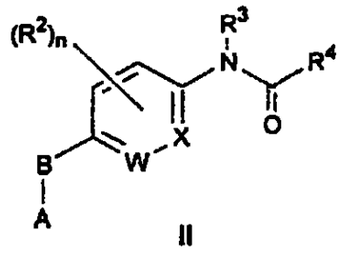
MODIFICADAS

REIVINDICACIONES

1. Compuesto que tiene la fórmula I o II:



I



II

o un enantiómero, diastereoisómero, hidrato, solvato o sal farmacéuticamente aceptable de los mismos caracterizado porque:

R^1 es hidrógeno, alquilo, alquilo sustituido, cicloalquilo, cicloalquilo sustituido, arilalquilo, arilalquilo sustituido, arilo, arilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, heteroarilo, heteroarilo sustituido, heterociclo, heterociclo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, heterocicloalquilo o heterocicloalquilo sustituido:

Cada R^2 es independientemente hidrógeno, halógeno, ciano, NO_2, ORS, NR^6R^7, alquilo, alquilo sustituido, cicloalquilo, cicloalquilo sustituido, arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, heterociclo, heterociclo sustituido, arilalquilo, arilalquilo sustituido, heterocicloalquilo, o heterocicloalquilo sustituido;

B es O, NR^8, NR^8CH_2, S, SO, SO_2 o CR^9R^{10};

V es NR^{11} o $-(CR^{37}R^{38})_p-$ con la condición de que cuando V sea nitrógeno, R^1 sea un alquilo o cicloalquilo;

W y X son cada uno independientemente carbono o nitrógeno;

Y se selecciona de oxígeno, azufre y NR^{12};

Z es $-CR^{13}R^{14}-$, o $-(CR^{13}R^{14})_1NR^{15}-$;

l es 0 a 2;

n es 0 a 4 si W y X son ambos carbono, 0 a 3 si uno de X o W es nitrógeno, y 0 a 2 si X y W son ambos nitrógeno;

p es 1 a 4;

R^3, R^5, R^6, R7, R^8, R^{11} y R^{15} son independientemente seleccionados de hidrógeno, alquilo, alquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, cicloalquilo, cicloalquilo sustituido, arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, heterociclo, heterociclo sustituido;

R^4 se selecciona de arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, heterocicloalquilo y heterocicloalquilo sustituido, con la condición de que:

(a) si R^4 es fenilo

(i) R^4 no está sustituido con hidroxilo y amido; y

(ii) R^4 no está sustituido con $-NRSO_2R-$ en donde R es alquilo o arilo;

(b) si R^4 es piridilo, R^4 no está sustituido con hidroxilo y metoxi;

Y

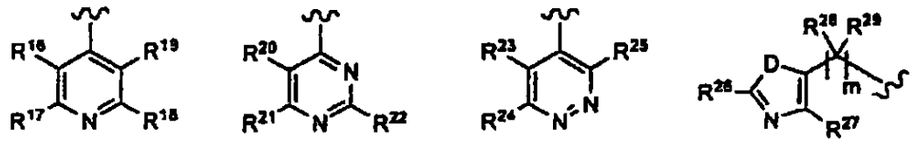
(c) si R^4 es pirimidinilo, éste no está sustituido con =O;

R^9 y R^{10} son independientemente seleccionados de hidrógeno, halógeno, alquilo, alquilo sustituido, cicloalquilo, cicloalquilo sustituido, arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, heterocicloalquilo o heterocicloalquilo sustituido;

R^{12} se selecciona de hidrógeno, alquilo, alquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, CN, NO_2 o SO_2NH_2;

R^{13} y R^{14} son independientemente seleccionados de hidrógeno, halógeno, alquilo, alquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, cicloalquilo, cicloalquilo sustituido, arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, heterocicloalquilo, heterocicloalquilo sustituido o tomados conjuntamente forman un anillo carbocíclico o heterocíclico de 3 a 8 átomos;

A se selecciona de uno de los siguientes:



en donde:

D es S u O;

m es 0 a 6;

R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26} y R^{27} son independientemente seleccionados de hidrógeno, halógeno, $NR^{30}R^{31}$, OR^{32}, CO_2R^{33}, $CONR^{34}R^{35}$, SO_2R^{36}, alquilo, alquilo sustituido, cicloalquilo, cicloalquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, -CN, arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, heterocicloalquilo, o heterocicloalquilo sustituido;

R^{28} y R^{29} son independientemente seleccionados de hidrógeno, alquilo, alquilo sustituido, cicloalquilo, cicloalquilo sustituido, arilo, arilo sustituido, o tomados conjuntamente forman un anillo carbocíclico o heterocíclico de 3 a 8 átomos;

R^{30}, R^{31}, R^{32}, R^{33} R^{34} R^{35} y R^{36} son independientemente seleccionados de hidrógeno, alquilo, alquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, cicloalquilo, cicloalquilo sustituido, alcoxicarbonilo, arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, heterociclo, heterociclo sustituido,

heterocicloalquilo, o heterocicloalquilo sustituido; y

R^{37} y R^{38} son cada uno independientemente hidrógeno, halógeno o alquilo.

2. Compuesto de conformidad con la reivindicación 1, caracterizado porque R^1 es un fenilo sustituido o no sustituido, un alquilo de 1 a 4 átomos de carbono sustituido o no sustituido, o un cicloalquilo de 3 a 8 átomos de carbono sustituido o no sustituido.

3. Compuesto de conformidad con la reivindicación 2, caracterizado porque R^1 es fluorofenilo, metilo sustituido, ciclohexilo o ciclopentilo.

4. Compuesto de conformidad con la reivindicación 1, caracterizado porque R^2 es alquilo de 1 a 4 átomos de carbono, halógeno o haloalquilo.

5. Compuesto de conformidad con la reivindicación 1, caracterizado porque R^4 es fenilo opcionalmente sustituido, piridilo, piridil-N-óxido, pirazolilo o pirrolidilo.

6. Compuesto de conformidad con la reivindicación 5, caracterizado porque R^4 está sustituido con oxígeno, fenilo, alquilo de 1 a 4 átomos de carbono, o halógeno.

7. Compuesto de conformidad con la reivindicación 1, caracterizado porque B es O, $NHCH_2$, CH_2 o CH (OH); Y es O ó S y Z es $-CR^{13}R^{14}$ o $-NR^{15}$ en donde R^{13}, R^{14} y R^{15} son cada uno hidrógeno.

8. Compuesto de conformidad con la reivindicación 1,

caracterizado porque A es una piridina o pirimidina opcionalmente sustituida.

9. Compuesto de conformidad con la reivindicación 8, caracterizado porque el sustituyente es alquilo, alquenilo, alquinilo, halógeno, cicloalquilo, heterocicloalquilo, $-NR^{39}COR^{40}$, $-NR^{39}C(O)_2R^{40}$, $-NR^{41}R^{42}$, o $-C(O)NR^{43}R^{44}$, en donde R^{39}, R^{40}, R^{41}, R^{42}, R^{43} y R^{44} son independientemente hidrógeno, alquilo inferior, alquilo inferior sustituido, hidroxialquilo, aminoalquilo, cicloalquilo, cicloalquilo sustituido, heterocicloalquilo, heterocicloalquilo sustituido, cicloalquenilo, cicloalquenilo sustituido, arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, o $NR^{43}R^{44}$ forman un heterocicloalquilo.

10. Compuesto de conformidad con la reivindicación 7, caracterizado porque A es una piridina sustituida con $-NR^{41}R^{42}$, $-NR^{39}COR^{40}$, $-C(O)NR^{43}R^{44}$, halógeno, alquilo de 1 a 4 átomos de carbono, $-C=C-R^{45}$, $-C\equiv C-R^{46}$, arilo o heteroarilo en donde R^{45} y R^{46} son alquilo, hidroxialquilo, aminoalquilo, cicloalquilo, heterocicloalquilo, $-C(O)R^{47}$, $-NR^{39}COR^{40}$, arilo, o heteroarilo.

11.- Compuesto de conformidad con la reivindicación 10, caracterizado porque el alquilo de 1 a 4 átomos de carbono es substituido con hidroxi, hidroxialquilamino, alquilamino, aminoalquilamino, o heteroarilalquilo.

12. Compuesto de conformidad con la reivindicación 8,

caracterizado porque R^{41} y R^{42} son cada uno independientemente hidrógeno, metilo, etilo, propilo, butilo, fenilo o bencilo, y R^{39} es hidrógeno y R^{40} es metilo, cicloalquilo, o heterocicloalquilo.

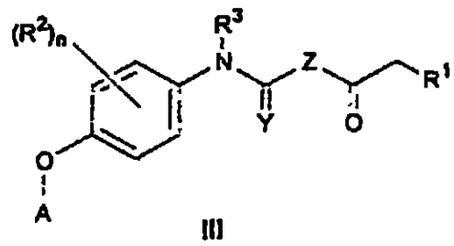
13. Compuesto de conformidad con la reivindicación 8, caracterizado porque R^{43} y R^{44} son hidrógeno y R^{45} y R^{46} son cada uno ciclohexeno, azetidina, piperazina, piperidina, pirrolidina, o piridina, opcionalmente sustituidos con alquilo de 1 a 4 átomos de carbono, $-CH_2NH_2$ $-NH_2$, o pirrolidina.

14. Compuesto de conformidad con la reivindicación 8, caracterizado porque la piridina está sustituida con un grupo fenilo, opcionalmente sustituido con $CONH_2$, metilo, aminoetilo, hidroxietilo, $-CONHCH_2CH_2NHCH_3$ o CH_2CONH_2; piridina o piperazina.

15. Compuesto de conformidad con la reivindicación 8, caracterizado porque A es pirimidina sustituida con $-NR^{41}R^{42}$, o $-NR^{39}CO_2R^{40}$.

16. Compuesto de conformidad con la reivindicación 15, caracterizado porque R^{41} y R^{42} son hidrógeno o metilo y R^{39} y R^{40} son independientemente hidrógeno o alquilo.

17. Compuesto de conformidad con la reivindicación 1, caracterizado porque tiene la fórmula III:



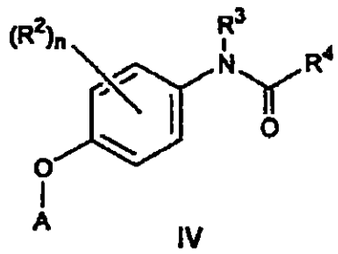
III

en donde

R^1 es alquilo o fenilo opcionalmente sustituido; Z es NH o NCH_3; R^2 es flúor, cloro, CH_3 o CF_3; R^3 es hidrógeno; e Y es oxígeno o azufre.

18. Compuesto de conformidad con la reivindicación 17, caracterizado porque R^1 es cicloalquilo de 3 a 7 átomos de carbono, fenilo sustituido o no sustituido, o $-(CH_2)_n-R^{50}$ en donde n es 1 a 3, R^{50} es hidrógeno, fenilo sustituido o no sustituido, amino, amido, CN, $-C(O)_2H$, o $-C(O)_2CH_3$.

19. Compuesto de conformidad con la reivindicación 1, que tiene la fórmula IV:

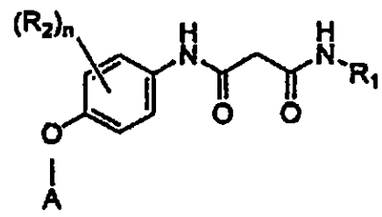


IV

caracterizado porque R^2 es halo o hidrógeno; R^3 es hidrógeno; R^4 es fenilo opcionalmente sustituido, pirazol opcionalmente sustituido, o piridilo opcionalmente sustituido; o una piridinona o un piridin N-óxido opcionalmente substituido y A es piridilo opcionalmente sustituido.

20. Compuesto de conformidad con la reivindicación 19, caracterizado porque R^4 es una piridinona opcionalmente sustituida o un piridin-N-óxido.

21. Compuesto de conformidad con la reivindicación 1, que tiene la fórmula V:



V

caracterizado porque R^1 es cicloalquilo o alquilo opcionalmente; A es pirimidina o piridina opcionalmente sustituidas; y R^2 es halo o hidrógeno.

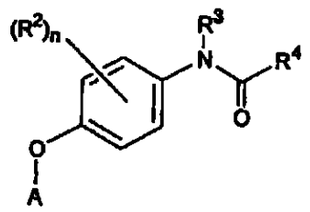
22. Compuesto de conformidad con la reivindicación 1, caracterizado porque tiene un valor de ICso menor de aproximadamente 1.0 µM.

23. Uso de un compuesto de conformidad con la reivindicación 1para la manufactura de un medicamento para tratamiento del cáncer en un paciente.

24.- Composición farmacéutica, caracterizada porque comprende una cantidad terapéuticamente efectiva de un compuesto de conformidad con la reivindicación 1 y un portador farmacéuticamente aceptable.

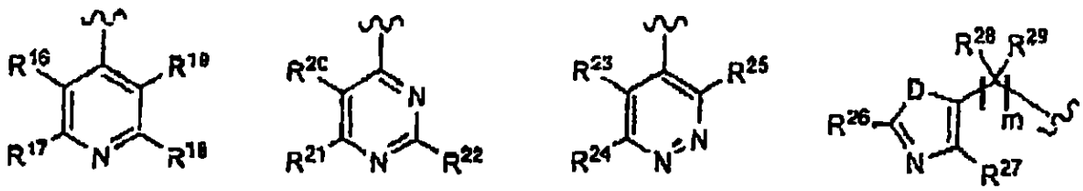
25. Compuesto, caracterizado porque tiene la Fórmula

IV:



IV

en donde A es



en donde

R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, y R^{27} son seleccionados independientemente de H, halógeno, $NR^{30}R^{31}$, OR^{32}, CO_2R^{33}, $CONR^{34}R^{35}$, SO_2R^{36}, alquilo, alquilo sustituido, cicloalquilo, cicloalquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, -CN, arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, heterocicloalquilo, heterocicloalquilo sustituido;

R^{28} y R^{29} son seleccionados independientemente de H, alquilo, alquilo sustituido, cicloalquilo, cicloalquilo sustituido, arilo, arilo sustituido, o tomados juntos forman un anillo carbocíclico o heterocíclico de 3 a 8 átomos;

R^2 es halo o H;

R^3 es H; y

R^4 es fenilo opcionalmente sustituido, pirazol opcionalmente sustituido, o piridilo opcionalmente sustituido, piridinona, o piridina-N-óxido.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below
10194 PCT		
International application No	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2005/014120	22/04/2005	23/04/2004
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 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report

1 **Basis of the report**

a With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23 1(b))

b [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No I

2 [ ] **Certain claims were found unsearchable** (See Box II)

3 [ ] **Unity of invention is lacking** (see Box III)

4 With regard to the **title**,

[X] the text is approved as submitted by the applicant

[ ] the text has been established by this Authority to read as follows

5 With regard to the **abstract**,

[X] the text is approved as submitted by the applicant

[ ] the text has been established, according to Rule 38 2(b), by this Authority as it appears in Box No. IV The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6 With regard to the **drawings**,

a the figure of the **drawings** to be published with the abstract is Figure No _____

[ ] as suggested by the applicant

[ ] as selected by this Authority, because the applicant failed to suggest a figure.

[ ] as selected by this Authority, because this figure better characterizes the invention

b [ ] none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/014120

A. CLASSIFICATION OF SUBJECT MATTER
A61K31/44 C07D213/68 C07D213/73 C07D213/74 C07D213/75
C07D239/34 C07D239/46 C07D401/04 C07D401/06 C07D401/12
C07D401/14 C07D417/12 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	DATABASE CROSSFIRE BEILSTEIN BEILSTEIN INSTITUT ZUR FOERDERUNG DER CHEMISCHEN WISSENSCHAFT, FRANKFURT AM MAIN, DE; XP002362294 Database accession no. BRN 667921 abstract -----	1
X	DATABASE CROSSFIRE BEILSTEIN BEILSTEIN INSTITUT ZUR FOERDERUNG DER CHEMISCHEN WISSENSCHAFT, FRANKFURT AM MAIN, DE; XP002362295 Database accession no. BRN 413351 abstract -----	1

-/--

[X] Further documents are listed in the continuation of box C

[X] Patent family members are listed in annex

* Special categories of cited documents

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 January 2006	25/01/2006

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	Bérillon, L

Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	DATABASE CROSSFIRE BEILSTEIN BEILSTEIN INSTITUT ZUR FOERDERUNG DER CHEMISCHEN WISSENSCHAFT, FRANKFURT AM MAIN, DE; XP002362296 Database accession no. BRN 450834 abstract	1
X	DATABASE CROSSFIRE BEILSTEIN BEILSTEIN INSTITUT ZUR FOERDERUNG DER CHEMISCHEN WISSENSCHAFT, FRANKFURT AM MAIN, DE; XP002362297 Database accession no. BRN 448780 abstract	1
P,X	WO 2005/005389 A (MERCK PATENT GMBH; BRUGE, DAVID; BUCHSTALLER, HANS-PETER; WIESNER, MAT) 20 January 2005 (2005-01-20) claims 4,7	1-24
A	EP 1 243 582 A (KIRIN BEER KABUSHIKI KAISHA) 25 September 2002 (2002-09-25) claims 1,32	1-24
A	EP 1 411 046 A (KIRIN BEER KABUSHIKI KAISHA) 21 April 2004 (2004-04-21) claims 1,18	1-24

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2005/014120

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
because they relate to subject matter not required to be searched by this Authority, namely

Although claim 23 is 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.

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US2005/014120

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005005389 A	20-01-2005	NONE	
EP 1243582 A	25-09-2002	AU 2223201 A	09-07-2001
		WO 0147890 A1	05-07-2001
		US 2004132727 A1	08-07-2004
EP 1411046 A	21-04-2004	CA 2454538 A1	03-01-2003
		CN 1553899 A	08-12-2004
		WO 03000660 A1	03-01-2003
		US 2004242603 A1	02-12-2004

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/US2005/014120	22 04 2005	23 04 2004

International Patent Classification (IPC) or both national classification and IPC
A61K31/44, C07D213/68, C07D213/73, C07D213/74, C07D213/75, C07D239/34, C07D239/46, C07D401/04,

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

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D-80298 Munich
Tel +49 89 2399 - 0 Tx 523656 epmu d
Fax +49 89 2399 - 4465

Authorized Officer

Bérillon, L

Telephone No +49 89 2399-7078

731 732

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No
PCT/US2005/014120

Box No. I Basis of the opinion

1 With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item

☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12 3 and 23 1(b)).

2 With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of

a type of material

☐ a sequence listing

☐ table(s) related to the sequence listing

b format of material

☐ in written format

☐ in computer readable form

c. time of filing/furnishing.

☐ contained in the international application as filed.

☐ filed together with the international application in computer readable form

☐ furnished subsequently to this Authority for the purposes of search.

3 ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished

4 Additional comments.

Box No. II Priority

1 ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis* 1 and 64.1) is the claimed priority date

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis* 1 and 64 1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date

3 Additional observations, if necessary.

~~735~~ 733

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No
PCT/US2005/014120

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application,

☒ claims Nos 1-20 (part), 21, 22 (part), 23

because.

☒ the said international application, or the said claims Nos. 23 relate to the following subject matter which does not require an international preliminary examination *(specify)*

see separate sheet

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 21 are so unclear that no meaningful opinion could be formed *(specify)*

see separate sheet

☐ the claims, or said claims Nos are so inadequately supported by the description that no meaningful opinion could be formed

☒ no international search report has been established for the whole application or for said claims Nos. 1-20 (part), 22 (part)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, d not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions

☐ See separate sheet for further details

736 739

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No
PCT/US2005/014120

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Statement

Novelty (N)	Yes	Claims	1-20 (part), 22 (part), 23 (part)
	No	Claims	1-20 (part), 22 (part), 23 (part)
Inventive step (IS)	Yes	Claims	1-20 (part), 22 (part), 23 (part)
	No:	Claims	
Industrial applicability (IA)	Yes	Claims	1-22, 24
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1 Certain published documents (Rules 43*bis* 1 and 70 10)

and / or

2 Non-written disclosures (Rules 43*bis* 1 and 70 9)

see form 210

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 II
Priority

The priority document pertaining to the present application was not available at the time of establishing this international preliminary examination report. Hence, it is based on the assumption that all claims enjoy priority rights from the filing date of the priority document. If it later turns out that this is not correct, the P-document cited in the international search report could become relevant to assess whether the claims satisfy the criteria set forth in Article 33(1) PCT.

Re Item III
Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1 The initial phase of the search revealed a very large number of documents relevant to the issue of novelty for claim 1, formula II (D1-D4 cited below are mere examples and do not represent an exhaustive list). So many documents were retrieved that it is impossible to determine which parts of claim 1, formula II may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, the search and hence present opinion were restricted to part of the application relating to compounds of formula (I).

2 In addition no search can be performed for claim 21 since no definition is present for the substituent R of formula V rendering the claimed subject-matter of claim 21 fully unclear. Hence, no opinion will be established for said claim 21

3 Claim 23 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67 1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(I) PCT).

Re Item V
Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No

PCT/US2005/014120

1 Prior art

Reference is made to the following documents.

D1: DATABASE CROSSFIRE BEILSTEIN, accession no. BRN 667921
D2: DATABASE CROSSFIRE BEILSTEIN, accession no. BRN 413351
D3: DATABASE CROSSFIRE BEILSTEIN, accession no. BRN 450834
D4: DATABASE CROSSFIRE BEILSTEIN, accession no. BRN 448780
D5: EP-A-1 243 582
D6: EP-A-1 411 046

2 Novelty (Article 33(2) PCT)

2.1 D1-D4 fall within the scope of formula II, claim 1 and hence are prejudicial to the novelty of said part of the present application (see also item III-1).

2.2 The present compounds of formula I differ from D5 and D6 in that they miss the quinoline/ quinoxaline ring present in the compounds disclosed in D6.

3 Inventive step (Article 33(3) PCT)

D6 which discloses quinoline and quinoxaline derivatives which are useful as antitumor agents represents the closest prior art.
The present compounds differ from the D6 compounds mainly in that they have a pyridine, pyrimidine, pyrazine or imidazole ring (see definition of A, in formula I, claim 1) instead of a quinoline or quinoxaline ring.
The technical problem underlying the present application is regarded as the provision of further antitumor agents.
No hint can be found in the prior art to replace the quinoline or quinoxaline ring of the D6 compounds by a pyridine, pyrimidine, pyridazine thiazole or oxazole ring. Hence, inventive step is acknowledged for the present compounds of formula I which are solutions of the posed technical problem.

4 Industrial applicability (Article 33(4) PCT)

For the assessment of the present claims 23 on the question whether it is 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 VIII
Certain observations on the international application

The proviso of claim 1 "when VR11 is N, R1 is an alkyl or cycloalkyl" is unclear.

TRATADO DE COOPERACION EN MATERIA DE PATENTES

PCT

REPORTE DE BUSQUEDA INTERNACIONAL
(Artículo 18 y Reglas 43 y 44 del PCT)

Referencia al expediente del solicitante o del mandatario 10194 PCT	**PARA ACCION ADICIONAL**	ver Notificación de la Transmisión del Reporte de Búsqueda Internacional (Forma PCT/ISA/220) así como, en donde aplique el inciso 5 posterior
No de solicitud internacional PCT/US2005/014120	Fecha de presentación internacional *(día/mes/año)* 22/04/2005	(Fecha de Prioridad) (La más cercana) *(día/mes/año)* 23/04/2004
Solicitante BRISTOL-MYERS SQUIBB COMPANY		

Este reporte de búsqueda internacional ha sido preparado por esta Autoridad de la Búsqueda Internacional y se transmite al solicitante de conformidad con el Artículo 18 Se transmite una copia a la Oficina Internacional

Este reporte de búsqueda internacional consiste de un total de 5 hojas

☒ También está acompañado de una copia de cada documento de la técnica anterior citado en este reporte

1 Bases del Reporte

a Con respecto al **lenguaje**, la búsqueda internacional se realizó en las bases de la solicitud internacional en el lenguaje en el cual sepresentó, a menos que se indique de otra manera bajo este punto

☐ La búsqueda internacional se realizó en base de una traducción de la solicitud internacional proporcionada a esta Autoridad (Regla 23 1(b))

b ☐ Con respecto a cualquier **secuencia de nucleótido y/o aminoácido** descrita en la solicitud internacional, la búsqueda internacional se realizó en las bases del listado de secuencia

2 ☐ **Se encontró que ciertas reivindicaciones no son localizables** (ver el Cuadro I)

3. ☐ **La unidad de la invención es deficiente** (ver el Cuadro II)

4 Con respecto al **título**,
☒ el texto se aprueba tal como lo presentó el solicitante,
☐ esta Autoridad ha establecido que el texto sea como sigue

5 Con respecto al **resumen**,
☒ el texto se aprueba tal como lo presentó el solicitante
☐ esta Autoridad ha establecido el texto, de acuerdo con la Regla 38 2(b), tal como aparece en el Cuadro III El solicitante puede, dentro de un mes a partir de la fecha de envío por correo de este reporte de búsqueda internacional, proporcionar comentarios a esta autoridad.

6 Con respecto a los dibujos,
a la figura de los **dibujos** que será publicada con el resumen es la Figura No _____
☐ como lo sugirió el solicitante
☐ como se selecciona por esta Autoridad, porque al solicitante le faltó sugerir una figura
☐ como se selecciona por esta Autoridad, porque esta figura caracteriza mejor la invención
b. ☐ ninguna de las figuras será publicada con el resumen

De la AUTORIDAD DE BUSQUEDA INTERNACIONAL

PCT

OPINION ESCRITA DE LA AUTORIDAD DE BUSQUEDA INTERNACIONAL

(Regla 43*bis*.1 del PCT)

Para. véase forma PCT/ISA/220	Fecha de envío *(día/mes/año)* véase forma PCT/ISA/210 (segunda hoja)
Referencia de archivo del solicitante o mandatario véase forma PCT/ISA/220	**PARA ACCION ADICIONAL** Véase párrafo 2 posterior

No de solicitud internacional	Fecha de presentación internacional *(día/mes/año)*	Fecha de Prioridad *(día/mes/año)*
PCT/US2005/014120	22.04.2005	23 04 2004

Clasificación de Patente Internacional (IPC) o Clasificación nacional e IPC

A61K31/44, C07D213/68, C07D213/73, C07D213/74, C07D213/75, C07D239/34, C07D239/46, C07DD401/04,

Solicitante

BRISTOL-MYERS SQUIBB COMPANY

1 Esta opinión contiene las indicaciones que están relacionadas con los siguientes puntos

- ☒ Recuadro No I Base de la opinión
- ☒ Recuadro No II Prioridad
- ☒ Recuadro No III Ningun establecimiento del reporte con respecto a la novedad, etapa inventiva, o aplicabilidad industrial
- ☐ Recuadro No IV Carencia de unidad de la invención
- ☒ Recuadro No V Declaración razonada bajo la Regla 43bis 1(a)(i) con respecto a la novedad, etapa inventiva o aplicabilidad Industrial, las citas y explicaciones que soportan tal declaración
- ☒ Recuadro No VI Ciertos documentos citados
- ☐ Recuadro No VII Ciertos defectos en la solicitud internacional
- ☒ Recuadro No VIII Ciertas observaciones en la solicitud internacional

2. ACCION ADICIONAL

Si se hace una solicitud para el examen preliminar internacional, esta opinión se considerará como una opinión escrita de la Autoridad de Examen Preliminar Internacional ("IPEA") excepto que esto no se aplica donde el solicitante elige una Autoridad diferente de esta para que sea la IPEA y la IPEA elegida ha notificado al Bureau Internacional bajo la Regla 66 1*bis(b)* que estas opiniones escritas de esta Autoridad de Búsqueda Internacional no será considerada

Si esta opinión es considerada, como se proporcionó anteriormente, para ser una opinión escrita de la IPEA, se invita al solicitante a presentar a la IPEA una respuesta escrita junto, donde sea apropiado, con enmiendas, antes de la expiración de 3 meses a partir de la fecha de envío de la Forma PCT/ISA/220 o antes de la expiración de 22 meses a partir de la fecha de prioridad, sea cual sea expira más tarde

Para opciones adicionales, véase Forma PCT/ISA/220

3 Para detalles adicionales, véase notas para la Forma PCT/ISA/220

Nombre y dirección de envío de la ISA	Oficial autorizado
European Patent Office D-80298 Munich Tel +49 89 2399 – O Tx 523656 epmu d Fax +49 89 2399 - 4465	Bérillon, L Teléfono No +49 89 2399-7078

OPINION ESCRITA DE LA AUTORIDAD DE BÚSQUEDA INTERNACIONAL

Solicitud Internacional No PCT/US2005/014120

Recuadro No. I Bases de la opinión

1 Con respecto al lenguaje, esta opinión se ha establecido en la base de la solicitud internacional en el lenguaje en el cual se presentó, a menos que se indique de otra forma bajo este ítem

☐ Esta opinión se ha establecido en la base de una traducción del lenguaje original en el siguiente lenguaje _____, el cual es el lenguaje de una traducción proporcionada para los propósitos de la búsqueda internacional (bajo Reglas 12 3 y 23 1(b))

2 Con respecto a cualquier **secuencia de nucleótido y/o aminoácido** descrita en la solicitud internacional y necesaria para la invención reivindicada, esta opinión se ha establecido en la base de

a tipo de material
- ☐ un listado de secuencia
- ☐ tabla(s) relacionadas al listado de secuencia

b formato de material
- ☐ en forma escrita
- ☐ en forma leíble por computadora

c tiempo de presentación/facilitado
- ☐ contenida en la solicitud internacional como se presentó
- ☐ presentada junto con la solicitud internacional en forma leíble por computadora
- ☐ provista posteriormente a esta Autoridad para los propósitos de búsqueda

3 ☐ Además, en el caso de que más de una versión o copia de un listado de secuencia y/o tabla relacionada con esto se ha presentado o provisto, las declaraciones requeridas que la información en las copias subsecuentes o adicionales es idéntico a aquella en la solicitud como se presentó o no va más allá de la solicitud como se presentó, cuando sea apropiado, donde sea provista

4 Observaciones adicionales

Recuadro No. II Prioridad

1 ☒ La validez de la reivindicación de prioridad no se ha considerado debido a que la Autoridad de Búsqueda Internacional no tiene en su posesión una copia de la solicitud anticipada cuya prioridad se ha reivindicado o, donde sea requerido, una traducción de la solicitud anticipada Esta opinión sin embargo se ha establecido en la suposición de que la fecha relevante (Reglas 43bis 1 y 64 1) es la fecha de prioridad reivindicada

2 ☐ Esta opinión se ha establecido como si ninguna prioridad se ha reivindicado debido al hecho que la reivindicación de prioridad se ha encontrado inválida (Regla 43bis 1 y 64 1) Por consiguiente, para los propósitos de esta opinión, la fecha de presentación internacional indicada anteriormente se considera que es la fecha relevante

3 Observaciones adicionales, si es necesario

Recuadro No. III. Sin establecimiento de opinión con respecto a la novedad, etapa inventiva y aplicabilidad industrial.

Las cuestiones de que si la invención reivindicada parece ser novedosa, involucra una etapa inventiva (que no es obvia), o es industrialmente aplicable no han sido examinadas con respecto de

☐ La solicitud internacional completa,

☒ Las reivindicaciones Nos 1-20 (PARTE), 21, 22 (PARTE), 23

porque

☒ La solicitud internacional, o las reivindicaciones Nos. 23 para aplicabilidad industrial se refieren al siguiente tema el cual no requiere un examen preliminar internacional (*especifique*).
véase hoja separada

☒ La descripción, reivindicaciones o dibujos (indicar los elementos particulares a continuación) o dichas reivindicaciones Nos 21 no son claras que ninguna opinión significativa se podría formar (*especifique*)
véase hoja separada

☐ Las reivindicaciones o dichas reivindicaciones Nos son inadecuadamente soportadas de este modo por la descripción que ninguna opinión significativa se podría formar

☒ No se ha establecido el reporte de búsqueda internacional para las reivindicaciones Nos 1-20

☐ el listado de secuencia de nucleótido y/o aminoácido no cumple con el estándar proporcionado en el Anexo C de las Instrucciones Administrativas porque

la forma escrita	☐ no se ha otorgado
	☐ no cumple con el estándar
la forma leible por computadora	☐ no se ha otorgado
	☐ no cumple con el estándar

☐ las tablas relacionadas al listado de secuencia de nucleótido y/o aminoácido, si en forma leible por computadora solamente, no cumple con los requerimientos técnicos proporcionados en el Anexo C-bis de las Instrucciones Administrativas

☐ Véase hoja separada para detalles adicionales

Recuadro No. V **Declaración razonada bajo la Regla 43bis.1(a)(i) con respecto a la novedad, etapa inventiva o aplicabilidad industrial; citas y explicaciones que soportan tal declaración.**

1. Declaración

Novedad (N)	Si	Reivindicaciones	1-20 (parte), 22 (parte), 23 (parte)
	No	Reivindicaciones	1-20 (parte), 22 (parte), 23 (parte)
Etapa Inventiva (EI)	Si	Reivindicaciones	1-20 (parte), 22 (parte), 23 (parte)
	No	Reivindicaciones	
Aplicabilidad industrial (AI)	Si	Reivindicaciones	1-22, 24
	No	Reivindicaciones	

2 Citas y explicaciones

ver hoja separada

VI. Ciertos documentos citados

1 Ciertos documentos publicados (Regla 43bis 1 y 70 10)

y/o

2 Descripciones no escritas (Regla 43bis.1 y 70 9)

Véase formulario 210

Recuadro No. VIII Ciertas observaciones en la solicitud internacional

Se hacen las siguientes observaciones en la claridad de las reivindicaciones, descripción, y dibujos o en la cuestión si las reivindicaciones están totalmente soportadas por la descripción

ver hoja separada

Referente al Punto II

Prioridad

El documento de prioridad que pertenece a la presente solicitud no estuvo disponible en el tiempo de establecimiento de este reporte de examen preliminar internacional. Por lo tanto, se basa en la suposición que todas las reivindicaciones gozan de derechos de prioridad desde la fecha de presentación del documento de prioridad. Si más tarde resulta que esto no es correcto, el documento P citado en el reporte de búsqueda internacional podrá llegar a ser relevante para valorar si las reivindicaciones satisfacen los criterios descritos en el Artículo 33(1) del PCT.

Referente al Punto III

Sin establecimiento de opinión con respecto a la novedad, etapa inventiva y aplicabilidad industrial

1. La fase inicial de la búsqueda reveló una número muy grande de documentos relevantes para la emisión de novedad para la reivindicación 1, fórmula II (D1-D4 citados posteriormente son solo ejemplos y no representan una lista exhaustiva). De este modo muchos documentos fueron recuperados que es imposible determinar cuales partes de la reivindicación 1, fórmula II

pueden ser las que definen el tema para el cual la protección puede legítimamente ser buscada (Artículo 6 del PCT). Por estas razones, la búsqueda y por lo tanto la presente opinión fueron restringidas para dividir la solicitud relacionada a los compuestos de la fórmula (I).

2 Además no se puede realizar ninguna búsqueda para la reivindicación 21 puesto que ninguna definición está presente para el sustituyente R de la fórmula V volviendo al tema reivindicado de la reivindicación 21 completamente no claro. Por lo tanto, no se establecerá opinión para la reivindicación 21.

3 La reivindicación 23 se refiere al tema considerado por esta Autoridad para ser cubierto por las estipulaciones de la Regla 67.1(iv) del PCT. En consecuencia, no se formulará opinión con respecto a la aplicabilidad industrial del tema de esta reivindicación (Artículo 34(4)(a)(1) del PCT).

Referente al Punto V

Declaración razonada con respecto a la novedad, etapa inventiva o aplicabilidad industrial; citas y explicaciones que soportan tal declaración

OPINION ESCRITA DE LA AUTORIDAD DE BÚSQUEDA INTERNACIONAL (HOJA SEPARADA)

Solicitud Internacional No. PCT/US2005/014120

1 Técnica previa

Se hace referencia a los siguientes documentos:

D1: DATABASE CROSSFIRE BEILSTEIN, no acceso BRN 667921

D2: DATABASE CROSSFIRE BEILSTEIN, no acceso BRN 413351

D3: DATABASE CROSSFIRE BEILSTEIN, no acceso BRN 450834

D4: DATABASE CROSSFIRE BEILSTEIN, no acceso BRN 448780

D5: EP-A-1 243 582

D6: EP-A-1 411 046

2 Novedad (Artículo 33(2) del PCT)

2.1 D1-D4 fallan dentro del alcance de la fórmula II, reivindicación 1 y por lo tanto son perjudiciales a la novedad de la parte de la presente solicitud (véase también punto III-1).

2.2 Los presentes compuestos de la fórmula I difieren de DD5 y D6 porque las reivindicaciones evitan el anillo de quinolina/quinoxalina presente en los compuestos descritos en D6.

3 Etapa inventiva (Artículo 33(3) del PCT)

D6 el cual describe derivados de quinolina y quinoxalina los cuales son útiles como agentes antitumorígenos representa la técnica previa más cercana.

Los presentes compuestos difieren de los compuestos de D6 principalmente porque tienen un anillo de piridina, pirimidina, pirazina o imidazol (véase definición de A, en fórmula I, reivindicación 1) en lugar de un anillo de quinolina o quinoxalina.

El problema técnico que fundamente la presente solicitud se considera como la provisión de agentes antitumorígenos adicionales.

Ninguna sugerencia se puede encontrar en la técnica previa para reemplazar el anillo de quinolina o quinoxalina de los compuestos de D6 por un anillo de piridina, pirimidina, piridazin tiazol u oxazol. Por lo tanto, la etapa inventiva se reconoce para los presentes compuestos de la fórmula I los cuales son soluciones del problema técnico propuesto.

4 Aplicabilidad industrial (Artículo 33(4) del PCT)

Para la valoración de las presentes reivindicaciones 23 en la pregunta si es industrialmente aplicable, no existen criterios unificados en los Estados Contratantes del PCT. La patentabilidad también puede ser dependiente de la formulación

de las reivindicaciones. La EPO, por ejemplo, no reconoce como aplicable industrialmente el tema de las reivindicaciones al uso de un compuesto en tratamiento médico, pero puede permitir, sin embargo, reivindicaciones a un compuesto conocido para el primer uso en tratamiento médico y el uso final de tal compuesto para la manufactura de un medicamento para un nuevo tratamiento médico.

Referente al Punto VIII

Ciertos observaciones sobre la solicitud internacional

La condición de la reivindicación 1 "cuando VR11 es N, R1 es un alquilo o cicloalquilo" no es clara.

10194-WO-PCT-748

PATENT COOPERATION TREATY

WO 2005117867
PCT/US2005/014120

102.328

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To

GIBBONS, Maureen, S.
Bristol-Myers Squibb Company
P O Box 4000
Princeton, New Jersey 08543-4000
ETATS-UNIS D'AMERIQUE

JAN 26 2006

Docketed
Due Date
Attorney

Date of mailing *(day/month/year)* 17 January 2006 (17.01.2006)	
Applicant's or agent's file reference 10194 PCT	IMPORTANT NOTIFICATION
International application No PCT/US2005/014120	International filing date *(day/month/year)* 22 April 2005 (22 04 2005)
International publication date *(day/month/year)* 15 December 2005 (15 12 2005)	Priority date *(day/month/year)* 23 April 2004 (23 04 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
23 April 2004 (23 04 2004)	60/564,842	US	19 September 2005 (19 09 2005)
23 December 2004 (23 12 2004)	60/639,178	US	19 September 2005 (19 09 2005)
21 April 2005 (21 04 2005)	11/111,144	US	09 January 2006 (09.01 2006)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

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Authorized officer
Alicia OLAIZ
Facsimile No (41-22) 338 71 30
Telephone No +41 22 338 9288

APOSTILLE

(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

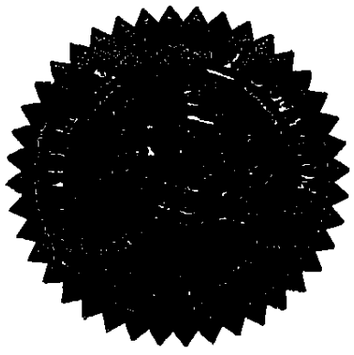
6. THE 13TH DAY OF JANUARY 2006

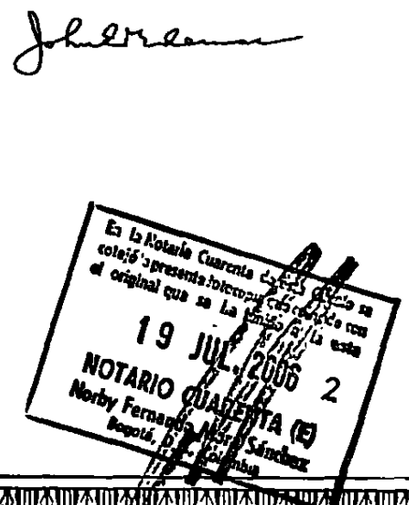
7. BY: John E McCormac, CPA, NEW JERSEY TREASURER

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 recebar 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 explotacion 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 o extrajudiciales.

Otorgado y firmado

hoy de 19 JUL. 2006 de 200_

Firma

Nombre

Cargo

En la Notaría Cuarenta de este Círculo se presentó para autenticar esta copia por ser fiel del original que se le tuvo a la vista

19 JUL. 2006

NOTARIO CUARENTA (E)

Norby Fernando Mora Díaz

Bogotá, D.C., Colombia

POWER OF ATTORNEY

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 to designate judicial and extrajudicial attorneys.

Granted and signed in

this 11th day Jan of 2006

Signature Suzanne E. Babajko

Name Suzanne E. Babajko

Title Senior Patent Counsel

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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 Publico (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)

En la Notaría Cuarenta de este Círculo fue cotejó la presente fotocopia con el original que se le tuvo a la vista
19 JUL. 2006
NOTARIO CUARENTA (E)
Harby Fernando Mora Sánchez
Bogotá, D.C. Colombia

LEGALIZACION POR APOSTILLA ES REQUERIDA.

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, 2008

Notary Public Seal

LEGALIZATION BY APOSTILLE IS REQUIRED.

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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)

PETITORIO

753

AS: 102.328

Industria y Comercio
SUPERINTENDENCIA

Rad. 05-107328- 00000-0000
PRESENTACION

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 Province Line 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, Lyndon A M. Cornelius, Robert J Schmidt, Gretchen M Schroeder, Kyoung S Kim. **Dirección:** 222 Riverwoods Drive, New Hope, PA 18938, US; 29 Mill Pond Road, Jackson, NJ 08527, US; 3 South Deer Place, Hainesport, New Jersey 08036, US, 82 Colleen Circle, Ewing, New Jersey 08638, US, 252 Forest Lane, North Brunswick, New Jersey 08902, Estados Unidos de América (Respectivamente). **Nacionalidad o Domicilio:** Estados Unidos de América	

5 PCT (86)
Solicitud Internacional No. PCT/US2005/014120 Fecha 22-04-2005
Publicación Internacional No. WO/2005/117867A2 Fecha 15-12-2005

6 Título (54): HETEROCICLOS MONOCICLICOS COMO INHIBIDORES DE CINASA

7 Clasificación Internacional (51) A61K 31/44 A 61P 35/00
C 07 D-/ 213/68

8 Prioridad SI ☒ NO ☐	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
	US	23-04-2004	60/564,842
	US	23-12-2004	60/639,178
	US	21-04-2005	11/111,144

9 Comprobante de pago No. 2006-76,627 Fecha 20-10-2006

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

2020-F06 (01-11-15)

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-107328- -00000-0000
Fec: 2006-10-23 17:06:17 Dop. 2020 NUECREACIONES
Tra 11 PATENTENII
Eva: 370 FASENACIONALI
Act 411 PRESENTACION Folios: 754
Industria y Comercio
SUPERINTENDENCIA

754

REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT

PATENTE DE INVENCION [X] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [X]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [X]
- Descripción de la invención [X]
- Dibujos de ser estos pertinentes [ ]
- Comprobante de pago de las tasas establecidas [X]

COMPLETA [X] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Firma Responsable

Fecha_____

Carrera 13 No. 27-00 Piso 5, 7 y 10
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E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
CADENA SARMIENTO JUAN PABLO
Apoderado(a) y/o Representante de
BRISTOL-MYERS SQUIBB COMPANY

REFERENCIA	Radicación No.	06 107328
	Solicitud internacional	PCT/US2005/014120
	Fecha inicio fase nacional	23/11/2006
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	0000 1862

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.

2. El solicitante debe presentar el resumen para efectos posteriores de publicacion.

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 09 FEB. 2007
lerazo