Industria y Comercio

SUPERINTENDENCIA

Delegatura de propiedad Industrial

División de Nuevas Creaciones

01

PCT

SOLICITUD

PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 06-12170

54. **TÍTULO** DERIVADOS DE PIRROLOTRIAZINA UTILES PARA TRATAR TRASTORNOS HIPER-PROLIFERATIVOS Y ENFERMEDADES ASOCIADAS CON ANGIOGENESIS

51. **CLASIFICACIÓN INTERNACIONAL**

71. **SOLICITANTE** BAYER PHARMACEUTICALS CORPORATION

DOMICILIO CONNECTICUT 06516, ESTADOS UNDOS DE AMERICA

74. **APODERADO** EMILIO FERRERO

C.C. 438.019 de Usaquén

22. **BOGOTÁ, D. C.,**

(FORMA P-10)

SS

Industria y Comercio
SUPERINTENDENCIA

PETITORIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-121701- -00000-0000
Fec: 2006-12-01 17:37:35 Dep: 0000 NUECREACION09
Tra: 11 PATENTEIVII
Fol: 379 FASENACIONALII
Act: 411 PRESENTACION Folios: 634

FORMULARIO UNICO 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: **BAYER PHARMACEUTICALS CORPORATION**
sociedad constituida y existente bajo las leyes del Estado de Delaware, Estados Unidos de América.

Dirección: 400 Morgan Lane,
West Haven,
Connecticut 06516,
Estados Unidos de América

Domicilio: West Haven,
Connecticut 06516,
Estados Unidos de América

IDENTIFICACIÓN

C.C. ☐ NIT ☐
C.E. ☐ Otro ☐
Cual ____
Número ____

3 REPRESENTANTE O APODERADO

Nombre: EMILIO FERRERO
Dirección: Carrera 4ª. No. 72-35
Teléfono: 347 36 11
Fax: 211 86 50
E-mail: clientes@camyp.com.
Domicilio: Bogotá, Colombia.

IDENTIFICACIÓN

C.C. ☒ NIT ☐
C.E. ☐ Otro ☐
Cual ____
Número 438.019 T.P 31.929

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13. **Harold C. E. KLUENDER**
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Estados Unidos de América

(5) **PCT (86)**
Solicitud Internacional No. PCT/US2005/019472 Fecha: 3 de junio de 2005
Publicación Internacional No. WO 2005/121147 A1 Fecha: 22 de diciembre de 2005

(6) TÍTULO (54)
DERIVADOS DE PIRROLOTRIAZINA ÚTILES PARA TRATAR TRASTORNOS HIPER-PROLIFERATIVOS Y ENFERMEDADES ASOCIADAS CON ANGIOGÉNESIS

(7) **Clasificación Internacional (51)** C07D 487/004 C07D 519/00
A61K 31/53 A61P 35/00

(8) **Prioridad** SI☒ NO☐

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	3 de junio de 2004	60/576,652
US	9 de noviembre de 2004	60/626,531

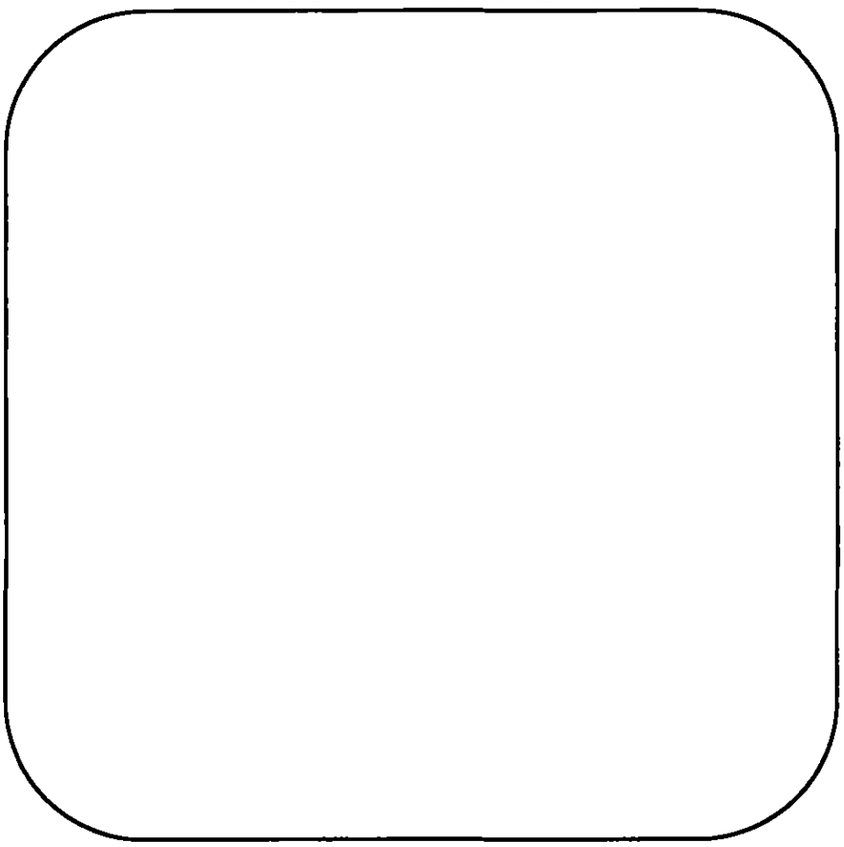
(9) **Comprobante de pago No.:** 06-86,289 **Fecha:** 8 de noviembre de 2006

(10) **Anexos:**

- ☒ Comprobante de pago de la tasa de presentación de la solicitud por $ 463.000.oo.
- ☐ Comprobante de pago por reivindicación de prioridad.
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso.
- ☐ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones.
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ 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.
- ☒ Otros: VER HOJA DE DOCUMENTOS ANEXOS

5' 3

(11) **FIGURA CARACTERÍSTICA**



(12) **Solicito la concesión de la patente,**

NOMBRE: EMILIO FERRERO

FIRMA : _____

C.C. 438.019 de Usaquén T.P. 31.929

NNJ

DOCUMENTOS ANEXOS

1. ☒ Publicación Internacional WO 2005/121147 A1
   Descripción:
   Páginas 344 en el idioma original
   Páginas 299 en español
   Reivindicaciones: Número (s) 13
   Figuras: Número (s)

2. ☒ **Forma PCT/ISA/210.** Informe de Búsqueda Internacional.

3. ☒ Extracto de publicación.

NO SE REALIZARON MODIFICACIONES EN LA FASE INTERNACIONAL

CAVELIER
ABOGADOS
EDIFICIO SISKI
CARRERA 4a N° 72-35
BOGOTA, 8 – COLOMBIA

181

Representación y Poder con autenticación notarial y Apostille para patentes, modelos de utilidad, diseños industriales, marcas de fábrica, nombres comerciales, enseñas, nombres de dominio, lemas comerciales, licencias.

Representation and Power-of-Attorney with notarial authentication and Apostille for patents, utility models, industrial designs, trademarks, commercial names, trade emblems, domain names, slogans, licenses.

REPRESENTACION Y PODER

REPRESENTATION AND POWER-OF-ATTORNEY

14125
5829

Yo (nosotros), abajo firmado (s)/I (we), the undersigned

BAYER PHARMACEUTICALS CORPORATION

400 Morgan Lane
domiciliado (s) en/of West Haven, CT 06516
United States of America

por el presente nombramos a EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 23555 y GERMAN CAVELIER, tpa. 832, domiciliados en la Carrera 4a N° 72-35, Bogotá, Colombia, en obedecimiento a lo dispuesto en el parágrafo 1o del Artículo 543 del Código de Comercio, el primero como principal y los demás como suplentes, en su orden, como mis (nuestros) representantes en todos los asuntos de propiedad industrial con facultad para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales. El primer representante suplente reemplazará al principal en caso de ausencia o impedimento temporal o definitivo de aquél. La misma regla se aplicará cuando el segundo representante suplente haya de reemplazar al primero, o el tercero al segundo. En tales casos, el representante principal, o el primero, o segundo suplente, en su caso, o ambos, declararán su intención de no ejercer la representación mediante declaración autenticada por Notario Público en Colombia, o por Notario u otro Funcionario Público, o Cónsul de Colombia, en el extranjero; y si se tratare de impedimento, con el certificado respectivo. Si alguno de los nombrados faltare nitivamente, el siguiente tomará su lugar. Cuando cesare la ausencia o impedimento del representante principal, o de su primero o segundo suplentes, en su caso, podrán ejercer la representación, en su orden, uno u otros según el caso, asumiéndola por el solo hecho de ejercerla, cesando en ese momento el ejercicio de la representación por el primero, segundo o tercer suplente en su caso.

Además, confiero (confierimos) poder a los abogados arriba nombrados, para obtener la protección de mi (nuestra) propiedad industrial y contra la competencia desleal, a cuyo efecto autorizo (amos) a los dichos apoderados para que me (nos) representen ante cualesquiera entidades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso- administrativo y judicial, así como los tribunales de arbitramento, en todo lo concerniente a los siguientes asuntos: a) Obtención de patentes de invención, modelos de utilidad y diseños industriales; el registro de marcas de fábrica, colectivas, defensivas, de servicio, lemas comerciales, nombres comerciales, enseñas, nombres de dominio, variedades vegetales y denominaciones de origen; su renovación, traspaso, cambio de nombre o domicilio, cancelación voluntaria; y el registro de licencias de uso de esos derechos; b) Las acciones de competencia desleal, protección del consumidor, oposiciones u observaciones, cancelación administrativa y judicial, nulidad, medidas cautelares, concesión de licencias, la tutela,

in due compliance with the terms of paragraph 1st. of article 543 of the Commercial Code, do hereby appoint EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 23555 and GERMAN CAVELIER, tpa. 832, domiciled at Carrera 4a N° 72□35, Bogotá, Colombia, the first as principal and the others as alternates, in the order of their appointment, as our representatives for all industrial property matters with faculty to receive notifications and to appoint attorneys in and out of Court. The first alternate shall replace the principal in case of his absence or of temporal or definitive impediment. The same rule will apply when the second alternate representative is to replace the first one, or when the third is to replace the first or second alternates in their turn, or both of them, second. In such cases, the principal representative, or the first or second alternates in their turn, or both of them, shall state their intention not to act as representatives through a declaration given before a Notary Public in Colombia, or before a Notary or another Public Official or a Colombian Consul abroad; and in case of impediment, the corresponding certificate shall suffice. If any of the aforementioned were to be definitely absent, the following alternate shall take his place. When the absence or impediment of the principal representative or of the first or second alternate in their turn ceases, the representation can be taken again in their sequence, by the principal, the first or second alternate depending on case, and the mere fact of its exercise will suffice. The exercise of the representation by the first, second or third alternates in their turn shall end at such time. In addition, we grant a Power of Attorney in favor of the above□named attorneys□at□law so that they may obtain the protection of my (our) industrial property and against the unfair competition, for which purpose I (we) authorize the said attorneys to represent me (us) before any authorities or persons, with or without jurisdiction, specially those administrative, administrative contentious and judicial, as well as before Arbitration Court, in all matters concerning the following: a) Obtainment of patents, utility models and industrial designs; the registration of trademarks, collective, defensive and service marks, slogans, commercial names, trade emblems, domain names, vegetal varieties and denominations of origin; its renewal, assignment, change of name or domicile, voluntary cancellation; and the registration of licenses of use of the above rights; b) Actions of unfair competition, protection to the consumer, oppositions or observations, administrative or Court cancellation, nullity, infringement, granting of licenses, the action for writ

6

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country: The United States of America

THIS PUBLIC DOCUMENT

2. has been signed by **ELAINE PORTER**

3. acting in the capacity of **NOTARY PUBLIC**

4. in the State of Connecticut for the term of **July 1, 2001 to June 30, 2006**

CERTIFIED

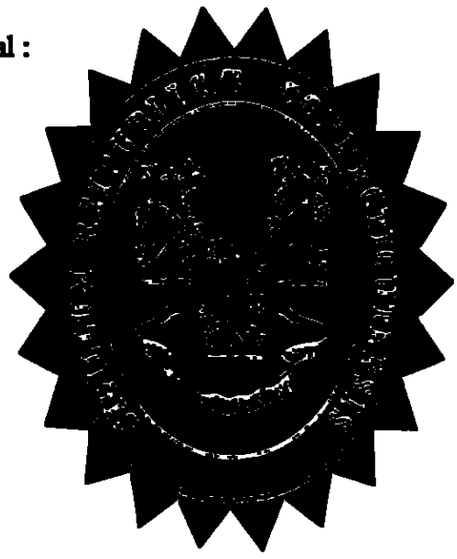
5. at Hartford, Connecticut

6. on **February 5, 2004**

7. by **SUSAN BYSIEWICZ** Secretary of the State of Connecticut

8. Number : **2004-1177**

9. Seal :



COMO NOTARIO SEXTO (6) DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA

24 NOV 2006

10. Signature

Susan Bysiewicz

Secretary of the State

ia protección de secretos industriales, y en general los juicios civiles, penales, administrativos o contencioso□administrativos relacionados con estos derechos; acciones y procesos que promovamos o se nos promuevan. Y para que en todos los asuntos arriba determinados, puedan sustituir este mandato, transigir, conciliar, admitir los hechos del proceso, desistir, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos.

mandamus, the protection of trade secrets, and in general the civil, penal, and administrative suits relating to those rights; actions and suits instituted by me (us) or against me (us). And that in all the above matters they may substitute this Power of Attorney, compromise, conciliate, admit the facts of the case, desist, cancel, receive, resign, and ratify acts done by representatives without a power of attorney.

Dado y firmado hoy/Given and signed this 30 January 2004

en/in West Haven, Connecticut, United States of America

por/by Jeffrey M. Greenman

Assistant Secretary of Bayer Pharmaceuticals Corporation

Firma/Signature

COMO NOTARIO SEXTO (E) DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA

24 NOV 2006

PABLO [illegible] JARAMILLO
NOTARIO (E)

— NOTARIO PÚBLICO O FUNCIONARIO AUTORIZADO — NOTARY PUBLIC OR ATTESTING OFICIAL —

CERTIFICACIÓN NOTARIAL (SOCIEDAD)

A los 30 días del mes de Enero de 2004 compareció(eron) ante mí, Jeffrey M. Greenman Secretario Assistente de Bayer Pharmaceuticals Corporation Quien(es) conozco personalmente y que firma(n) este documento en representación de la Sociedad/compañía denominada Bayer Pharmaceuticals Corporation

Certifico:

1. Que he visto los siguientes documentos:*
1. Certificado de Constitucion de Bayer Pharmaceuticals Corporation fechado 14 Nov. 2002;
2. Resolucion de la Junta Directiva fechado 1 Enero, 2003
3. Consentimiento escrito deffundador Único de Bayer Pharmaceuticals Corporation fechado 14 Noviembre 2002, eligiendo la Junta Directiva

2. Que dichos documentos prueban lo siguiente:

2.1. Que Bayer Pharmaceuticals Corporation es una Sociedad/Compañía legalmente constituida y existente de acuerdo con las leyes de l Estado de Delaware Estados Unidos de America

2.2. Que el domicilio de dicha Sociedad/Compañía es 400 Morgan Lane, West Haven, Connecticut 06516, Estados Unidos de America

2.3. Que el objeto u objetos para los cuales se otorga el presente poder están comprendidos dentro del objeto social de la mencionada Sociedad/Compañía.

2.4. Que el(los) Sr.(Sres.) Jeffrey M. Greenman está(n) autorizado(s) para otorgar el presente Poder.

Ciudad West Haven

Estado Connecticut, Estados Unidos de America

Hoy 30 Enero de 2004

NOTARIAL CERTIFICATION (CORPORATION)

On this 30th day of January 200 4 appeared before me *Jeffrey M. Greenman* *Assistant Secretary of Bayer Pharmaceuticals Corporation* who(m) I know personally and who(m) signed this document as representative(s) of the Corporation/Company named *Bayer Pharmaceuticals Corporation* .

I certify:

1. That I have seen the following documents:*

1) Certificate of Incorporation of Bayer Pharmaceuticals Corporation dated 14 November 2002;
2) Resolution of the Board of Directors dated 1 January 2003;
3) Written Consent of the Sole Incorporator of Bayer Pharmaceuticals Corporation dated 14 November 2002 electing the Board of Directors;

2. That the above documents duly prove the following:

2.1. That *Bayer Pharmaceuticals Corporation* is a Corporation/Company legally constituted and in existence in accordance with the laws *of the State of Delaware, United States of America*

2.2. That the domicile of said Corporation/Company is *400 Morgan Lane, West Haven, Connecticut 06516 United States of America*

2.3. That the purpose or purposes for which the present Power of Attorney is granted are comprised within the corporation purposes set forth in the charter of the mentioned Company.

2.4. That Mr.(Messrs.) *Jeffrey M. Greenman* is(are) authorized to grant the present Power.

City *West Haven*

State *Connecticut, United States of America*

This *30th* day of *January* 200 4

COPIA NOTARIAL DE COPIA. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA

By: .....
Paul R. Berry
Vice President, General Counsel and Secretary of Bayer Pharmaceuticals Corporation

NOTARIAL CERTIFICATE

United States of America
State of Connecticut
County of New Haven
City of West Haven

On this the 30th day of the month of January 2004, before me, Notary Public practicing in this locality, appeared Paul R. Berry, known to me to be the person whose name is subscribed to the foregoing instrument, who acknowledged himself to be Vice President, General Counsel and Secretary of Bayer Pharmaceuticals Corporation, and that acting in such capacity and with authorization, he executed the foregoing instrument on behalf of Bayer Pharmaceuticals Corporation for the purposes therein contained.

In witness thereof I set my hand.

NOTARY PUBLIC
My Commission Expires

[NOTARIAL SEAL]

Elaine Porter
Notary Public
My Commission Expires June 30, 2008

CAVELIER ABOGADOS
WPPODE01-181 (MINUTA N°12.1.1.2.6 USA)

TRADUCCIÓN OFICIAL 031/2004 DE UN DOCUMENTO ESCRITO EN INGLÉS Y EN ESPAÑOL, REALIZADA POR EDUARDO CALADO NOGUERA, TRADUCTOR OFICIAL APROBADO POR RESOLUCIÓN 541 DEL 27 DE FEBRERO DE 1976 POR EL MINISTERIO DE JUSTICIA Y DEBIDAMENTE REGISTRADO ANTE EL MINISTERIO DE RELACIONES EXTERIORES DE LA REPÚBLICA DE COLOMBIA Y MEDIANTE EL CUAL **BAYER PHARMACEUTICALS CORPORATION** EMPRESA DOMICILIADA EN **400 MORGAN LANE, WEST HAVEN, CT 06516, ESTADOS UNIDOS DE AMÉRICA** OTORGA PODER A EMILIO FERRERO, TPA 31929, GONZALO PERDOMO, TPA 831; LUZ CLEMENCIA DE PAEZ TPA 23555 Y A GERMÁN CAVELIER, TPA 832. EXPEDIDO Y FIRMADO EL 30 DE ENERO DE 2004 EN WEST HAVEN, CONNECTICUT, ESTADOS UNIDOS DE AMÉRICA POR JEFFREY M. GREENMAN, SUBSECRETARIO DE BAYER PHARMACEUTICALS CORPORATION. FIRMA:(ILEGIBLE)

CERTIFICADO NOTARIAL EN INGLES Y EN ESPAÑOL DE FECHA 30 DE ENERO DE 2004 POR EL CUAL SE CERTIFICA LA COMPARECENCIA DE JEFFREY M GREENMAN A NOMBRE DE BAYER PHARMACEUTICALS CORPORATION PARA CERTIFICAR LA EXISTENCIA LEGAL, EL DOMICILIO DE DICHA EMPRESA Y LA CAPACIDAD DE M. GREENMAN PARA COMPROMETER A DICHA FIRMA. WEST HAVEN, CONNECTICUT, ESTADOS UNIDOS DE AMÉRICA, 30 DE ENERO DE 2004.

COTEJADO CON SU ORIGINAL QUE HE TENIDO A LA VISTA
DE BOGOTÁ, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL
24 NOV 2006
PAOLO MENDEZ BARAJAS
NOTARIA 73

POR: FIRMADO: PAUL R. BERRY, VICE PRESIDENTE, JEFE DE ASUNTOS JURÍDICOS Y SECRETARIO DE BAYER PHARMACEUTICALS CORPORATION.

CERTIFICADO NOTARIAL

ESTADOS UNIDOS DE AMÉRICA

ESTADO DE CONNECTICUT, CONDADO DE NEW HAVEN

CIUDAD DE WEST HAVEN

Hoy 30 de enero de 2004, ante mí, notario público practicante en esta localidad, compareció Paul R. Berry, conocido mío como la persona cuyo nombre aparece escrito en el documento precedente, y quien reconoció ser el vicepresidente, jefe de asuntos jurídicos y secretario de Bayer Pharmaceuticals Corporation y que actuando en calidad de tal y con autorización, firmó el documento precedente a nombre de Bayer Pharmaceuticals Corporation para los objetivos allí contenidos. En testimonio de lo anterior, firmo: ELAINE PORTER, notario público. Sello: ELAINE PORTER, notario público. Mi cargo vence el 30 de junio de 2006.

APOSTILLA:

(Convención de La Haya del 5 de octubre de 1961)

1. Estados Unidos de América

Este documento público

2. ha sido firmado por ELAINE PORTER

3. quien actúa en su calidad de NOTARIO PÚBLICO

4. del estado de Connecticut para el período entre el primero de julio de 2001 y el 30 de junio de 2006

CERTIFICADO

5. en Hartford, Connecticut

6. el 5 de febrero de 2004

7. por Susan Bysiewicz Secretario del estado de Connecticut

8. Número 2004-1177

9. Sello:

El sello del estado de Connecticut

10. Firma: Susan Bysiewicz, secretario de estado.

COLO-14125-841-001-0; WPCL002G. ID 5326

Bog tá, 16 de febrero de 2004.

COMO NOTARIO SEXTO (6) DEL CIRCULO DE BOGOTÁ, HAGO CONSTAR QUE LA FOTOCOPIA CONCUERDA CON EL ORIGINAL QUE HE TENIDO A LA VISTA
24 NOV 2006
NOTARIO (E)

Eduardo Calvete Noguera
TRADUCTOR OFICIAL
Res. 541 Febrero de 1994

COMO NOTARIO SEXTO DEL CIRCULO DE SANTAFE DE
BOGOTA, HAGO CONSTAR QUE LA(S) FIRMA(S)

CORRESPONDE CON LA FIRMA REGISTRADA POR
EL(LOS) EN ESTA NOTARIA

SANTAFE DE BOGOTA D.C. 16 FEB. 2004

NOTARIA SEXTA

PABLO MENDEZ
BARAJAS

Notario Sexto Encargado

MINISTERIO DE RELACIONES
EXTERIORES

NO SE ASUME
RESPONSABILIDAD DEL TEXTO

16 FEB 04

12914

JEFE OFICINA DE LEGALIZACIONES
MINISTERIO DE RELACIONES EXTERIORES
SANTAFE DE BOGOTA D.C.

COMO NOTARIO SEXTO (E) DEL CIRCULO
DE BOGOTA, HAGO CONSTAR QUE LA
FOTOCOPIA CONCUERDA CON EL ORIGINAL
QUE HE TENIDO A LA VISTA

24 NOV 2006

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 December 2005 (22.12.2005)

PCT

(10) International Publication Number
WO 2005/121147 A1

(51) International Patent Classification[7]: C07D 487/04, 519/00, A61K 31/53

(21) International Application Number: PCT/US2005/019472

(22) International Filing Date: 3 June 2005 (03.06.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/576,652 3 June 2004 (03.06.2004) US
60/626,531 9 November 2004 (09.11.2004) US

(71) Applicant (*for all designated States except US*): BAYER PHARMACEUTICALS CORPORATION [US/US]; 400 Morgan Lane, West Haven, Connecticut 06516 (US).

(72) Inventors; and

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(54) Title: PYRROLOTRIAZINE DERIVATIVES USEFUL FOR TREATING HYPER-PROLIFERATIVE DISORDERS AND DISEASES ASSOCIATED WITH ANGIOGENESIS

(57) Abstract: This invention relates to pyrrozolotriazine compounds, pharmaceutical compositions containing such compounds and the use of those compounds and compositions for the prevention and/or treatment of hyper-proliferative disorders and diseases associated with angiogenesis.

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Pyrrolotriazine Derivatives Useful for Treating Hyper-Proliferative Disorders and Diseases Associated with Angiogenesis

This invention relates to novel pyrrozolotriazine compounds, pharmaceutical compositions containing such compounds and the use of those compounds and compositions for the prevention and/or treatment of hyper-proliferative disorders and diseases associated with angiogenesis.

Background of the Invention

To support progressive tumor growth beyond the size of 1-2 mm^3, it is recognized that tumor cells require a functional stroma, a support structure consisting of fibroblast, smooth muscle cells, endothelial cells, extracellular matrix proteins, and soluble factors (Folkman, J., *Semin Oncol*, **2002**. 29(6 Suppl 16), 15-8). Tumors induce the formation of stromal tissues through the secretion of soluble growth factors such as PDGF and transforming growth factor-beta (TGF-beta), which in turn stimulate the secretion of complimentary factors by host cells such as fibroblast growth factor (FGF), epidermal growth factor (EGF), and vascular endothelial growth factor (VEGF). These stimulatory factors induce the formation of new blood vessels, or angiogenesis, which brings oxygen and nutrients to the tumor and allows it to grow and provides a route for metastasis. It is believed some therapies directed at inhibiting stroma formation will inhibit the growth of epithelial tumors from a wide variety of histological types. (George, D. *Semin Oncol*, **2001**. 28(5 Suppl 17), 27-33; Shaheen, R.M., et al., *Cancer Res*, **2001**. 61(4), 1464-8; Shaheen, R.M., et al. *Cancer Res*, **1999**. 59(21), 5412-6). However, because of the complex nature and the multiple growth factors involved in angiogenesis process and tumor progression, an agent targeting a single pathway may have limited efficacy. It is desirable to provide treatment against a number of key signaling pathways utilized by tumors to induce angiogenesis in the host stroma. These include PDGF, a potent stimulator of stroma formation (Ostman, A. and C.H. Heldin, *Adv Cancer Res*, **2001**, 80, 1-38), FGF, a chemo-attractant and mitogen for fibroblasts and endothelial cells, and VEGF, a potent regulator of vascularization.

A major regulator of angiogenesis and vasculogenesis in both embryonic development and some angiogenic-dependent diseases is vascular endothelial growth factor (VEGF; also called vascular permeability factor, VPF). VEGF represents a family of isoforms of mitogens existing in homodimeric forms due to alternative RNA splicing. The VEGF isoforms are reported to be highly specific for vascular endothelial cells (for reviews, see: Farrara et al. *Endocr. Rev.* 1992, *13*, 18; Neufield et al. *FASEB J.* 1999, *13*, 9).

VEGF expression is reported to be induced by hypoxia (Shweiki et al. *Nature* 1992, *359*, 843), as well as by a variety of cytokines and growth factors, such as interleukin-1, interleukin-6, epidermal growth factor and transforming growth factor. To date, VEGF and the VEGF family members have been reported to bind to one or more of three transmembrane receptor tyrosine kinases (Mustonen et al. *J. Cell Biol.*, 1995, *129*, 895), VEGF receptor-1 (also known as flt-1 (fms-like tyrosine kinase-1)), VEGFR-2 (also known as kinase insert domain containing receptor (KDR); the murine analogue of KDR is known as fetal liver kinase-1 (flk-1)), and VEGFR-3 (also known as flt-4). KDR and flt-1 have been shown to have different signal transduction properties (Waltenberger et al. *J. Biol. Chem.* 1994, *269*, 26988); Park et al. *Oncogene* 1995, *10*, 135). Thus, KDR undergoes strong ligand-dependant tyrosine phosphorylation in intact cells, whereas flt-1 displays a weak response. Thus, binding to KDR is believed to be a critical requirement for induction of the full spectrum of VEGF-mediated biological responses.

In vivo, VEGF plays a central role in vasculogenesis, and induces angiogenesis and permeabilization of blood vessels. Deregulated VEGF expression contributes to the development of a number of diseases that are characterized by abnormal angiogenesis and/or hyperpermeability processes. It is believed regulation of the VEGF-mediated signal transduction cascade by some agents can provide a useful mode for control of abnormal angiogenesis and/or hyperpermeability processes.

The vascular endothelial growth factors (VEGF, VEGF-C, VEGF-D) and their receptors (VEGFR2, VEGFR3) are not only key regulators of tumor angiogenesis, but also lymphangiogenesis. VEGF, VEGF-C and VEGF-D are expressed in most tumors, primarily during periods of tumor growth and, often at substantially increased levels. VEGF expression is stimulated by hypoxia, cytokines, oncogenes

such as *ras*, or by inactivation of tumor suppressor genes (McMahon, G. *Oncologist* 2000, *5(Suppl. 1)*, 3-10; McDonald, N.Q.; Hendrickson, W.A. *Cell* 1993, *73*, 421-424)

The biological activities of the VEGFs are mediated through binding to their receptors. VEGFR3 (also called Flt-4) is predominantly expressed on lymphatic endothelium in normal adult tissues. VEGFR3 function is needed for new lymphatic vessel formation, but not for maintenance of the pre-existing lymphatics. VEGFR3 is also upregulated on blood vessel endothelium in tumors. Recently VEGF-C and VEGF-D, ligands for VEGFR3, have been identified as regulators of lymphangiogenesis in mammals. Lymphangiogenesis induced by tumor-associated lymphangiogenic factors could promote the growth of new vessels into the tumor, providing tumor cells access to systemic circulation. Cells that invade the lymphatics could find their way into the bloodstream via the thoracic duct. Tumor expression studies have allowed a direct comparison of VEGF-C, VEGF-D and VEGFR3 expression with clinicopathological factors that relate directly to the ability of primary tumors to spread (e.g., lymph node involvement, lymphatic invasion, secondary metastases, and disease-free survival). In many instances, these studies demonstrate a statistical correlation between the expression of lymphangiogenic factors and the ability of a primary solid tumor to metastasize (Skobe, M. et al. *Nature Med.* 2001, *7(2)*, 192-198; Stacker, S.A. et al.. *Nature Med.* 2001, *7(2)*, 186-191; Makinen, T. et al. *Nature Med.* 2001, *7(2)*, 199-205; Mandriota, S.J. et al. *EMBO J.* 2001, *20(4)*, 672-82; Karpanen, T. et al. *Cancer Res.* 2001, *61(5)*, 1786-90; Kubo, H. et al. *Blood* 2000, *96(2)*, 546-53).

Hypoxia appears to be an important stimulus for VEGF production in malignant cells. Activation of p38 MAP kinase is required for VEGF induction by tumor cells in response to hypoxia (Blaschke, F. et al. *Biochem. Biophys. Res. Commun.* 2002, *296*, 890-896; Shemirani, B. et al. *Oral Oncology* 2002, *38*, 251-257). In addition to its involvement in angiogenesis through regulation of VEGF secretion, p38 MAP kinase promotes malignant cell invasion, and migration of different tumor types through regulation of collagenase activity and urokinase plasminogen activator expression (Laferriere, J. et al. *J. Biol. Chem.* 2001, *276*, 33762–33772; Westermarck, J. et al. *Cancer Res.* 2000, *60*, 7156–7162; Huang, S. et al. *J. Biol.*

Chem. 2000, *275*, 12266-12272; Simon, C. et al. *Exp. Cell Res.* 2001, *271*, 344-355). Moreover, VEGF activates the extracellular signal-regulated protein kinase (ERK) in human umbilical vein endothelial cells (HUVEC) (Yu, Y.; Sato, D. *J. Cell Physiol* 1999, *178*, 235-246).

PDGF is another key regulator of stromal formation which is secreted by many tumors in a paracrine fashion and is believed to promote the growth of fibroblasts, smooth muscle and endothelial cells, promoting stroma formation and angiogenesis. PDGF was originally identified as the v-sis oncogene product of the simian sarcoma virus (Heldin, C.H., et al., *J Cell Sci Suppl*, 1985, 3, 65-76). The growth factor is made up of two peptide chains, referred to as A or B chains which share 60% homology in their primary amino acid sequence. The chains are disulfide cross linked to form the 30 kDa mature protein composed of either AA, BB or AB homo- or heterodimmers. PDGF is found at high levels in platelets, and is expressed by endothelial cells and vascular smooth muscle cells. In addition, the production of PDGF is up regulated under low oxygen conditions such as those found in poorly vascularized tumor tissue (Kourembanas, S., et al., *Kidney Int*, 1997, 51(2), 438-43). PDGF binds with high affinity to the PDGF receptor, a 1106 amino acid 124 kDa transmembrane tyrosine kinase receptor (Heldin, C.H., A. Ostman, and L. Ronnstrand, *Biochim Biophys Acta*, 1998. 1378(1), 79-113). PDGFR is found as homo- or heterodimer chains which have 30% homology overall in their amino acid sequence and 64% homology between their kinase domains (Heldin, C.H., et al.. *Embo J*, 1988, 7(5), 1387-93). PDGFR is a member of a family of tyrosine kinase receptors with split kinase domains that includes VEGFR2 (KDR), VEGFR3 (Flt4), c-Kit, and FLT3. The PDGF receptor is expressed primarily on fibroblast, smooth muscle cells, and pericytes and to a lesser extent on neurons, kidney mesangial, Leydig, and Schwann cells of the central nervous system. Upon binding to the receptor, PDGF induces receptor dimerization and undergoes auto- and trans-phosphorylation of tyrosine residues which increase the receptors' kinase activity and promotes the recruitment of downstream effectors through the activation of SH2 protein binding domains. A number of signaling molecules form complexes with activated PDGFR including PI-3-kinase, phospholipase C-gamma, src and GAP (GTPase activating protein for p21-ras) (Soskic, V., et al. *Biochemistry*, 1999, 38(6),

1757-64). Through the activation of PI-3-kinase, PDGF activates the Rho signaling pathway inducing cell motility and migration, and through the activation of GAP, induces mitogenesis through the activation of p21-ras and the MAPK signaling pathway.

In adults, it is believed the major function of PDGF is to facilitate and increase the rate of wound healing and to maintain blood vessel homeostasis (Baker, E.A. and D.J. Leaper, *Wound Repair Regen*, 2000. 8(5), 392-8; Yu, J., A. Moon, and H.R. Kim, *Biochem Biophys Res Commun*, 2001. 282(3), 697-700). PDGF is found at high concentrations in platelets and is a potent chemoattractant for fibroblast, smooth muscle cells, neutrophils and macrophages. In addition to its role in wound healing PDGF is known to help maintain vascular homeostasis. During the development of new blood vessels, PDGF recruits pericytes and smooth muscle cells that are needed for the structural integrity of the vessels. PDGF is thought to play a similar role during tumor neovascularization. As part of its role in angiogenesis PDGF controls interstitial fluid pressure, regulating the permeability of vessels through its regulation of the interaction between connective tissue cells and the extracellular matrix. Inhibiting PDGFR activity can lower interstitial preasure and facilitate the influx of cytotoxics into tumors improving the anti-tumor efficacy of these agents (Pietras, K., et al. *Cancer Res*, 2002. 62(19), 5476-84; Pietras, K., et al. *Cancer Res*, 2001. 61(7), 2929-34).

PDGF can promote tumor growth through either the paracrine or autocrine stimulation of PDGFR receptors on stromal cells or tumor cells directly, or through the amplification of the receptor or activation of the receptor by recombination. Over expressed PDGF can transform human melanoma cells and keratinocytes (Forsberg, K., et al. *Proc Natl Acad Sci U S A.*, 1993. 90(2), 393-7; Skobe, M. and N.E. Fusenig, *Proc Natl Acad Sci U S A*, 1998. 95(3), 1050-5), two cell types that do not express PDGF receptors, presumably by the direct effect of PDGF on stroma formation and induction of angiogenesis. This paracrine stimulation of tumor stroma is also observed in carcinomas of the colon, lung, breast, and prostate (Bhardwaj, B., et al. *Clin Cancer Res*, 1996, 2(4), 773-82; Nakanishi, K., et al. *Mod Pathol*, 1997, 10(4), 341-7; Sundberg, C., et al. *Am J Pathol*, 1997, 151(2), 479-92; Lindmark, G., et al. *Lab Invest*, 1993, 69(6), 682-9; Vignaud, J.M., et al, *Cancer Res*, 1994, 54(20),

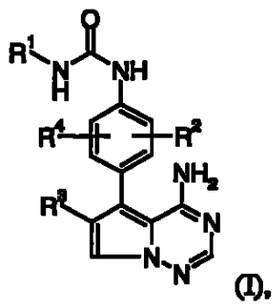
5455-63) where the tumors express PDGF, but not the receptor. The autocrine stimulation of tumor cell growth, where a large faction of tumors analyzed express both the ligand PDGF and the receptor, has been reported in glioblastomas (Fleming, T.P., et al. *Cancer Res*, 1992, 52(16), 4550-3), soft tissue sarcomas (Wang, J., M.D. Coltrera, and A.M. Gown, *Cancer Res*, 1994, 54(2), 560-4) and cancers of the ovary (Henriksen, R., et al. *Cancer Res*, 1993, 53(19), 4550-4), prostate (Fudge, K., C.Y. Wang, and M.E. Stearns, *Mod Pathol*, 1994, 7(5), 549-54), pancreas (Funa, K., et al. *Cancer Res*, 1990, 50(3), 748-53) and lung (Antoniades, H.N., et al., *Proc Natl Acad Sci U S A*, 1992, 89(9), 3942-6). Ligand independent activation of the receptor is found to a lesser extent but has been reported in chronic myelomonocytic leukemia (CMML) where the a chromosomal translocation event forms a fusion protein between the Ets-like transcription factor TEL and the PDGF receptor. In addition, activating mutations in PDGFR have been found in gastrointestinal stromal tumors in which c-Kit activation is not involved (Heinrich, M.C., et al., *Science*, 2003, 9, 9). Certain PDGFR inhibitors will interfere with tumor stromal development and are believed to inhibit tumor growth and metastasis.

The link between activity in tumor cell proliferation assays *in vitro* and anti-tumor activity in the clinical setting has been well established in the art. For example, the therapeutic utility of taxol (Silvestrini et al. *Stem Cells* 1993, 11(6), 528-35), taxotere (Bissery et al. *Anti Cancer Drugs* 1995, 6(3), 339), and topoisomerase inhibitors (Edelman et al. *Cancer Chemother.*

Cells protect their DNA by adopting a higher-order complex termed chromatin. Chromatin condensation is evident during mitosis and cell death induced by apoptosis while chromatin decondensation is necessary for replication, repair, recombination and transcription. Histones are among some of the DNA-binding proteins that are involved in the regulation of DNA condensation; and post-translational modifications of histone tails serve a critical role in the dynamic condensation/decondensation that occurs during the cell cycle. Phoshorylation of the tails of histone H3 is involved in both transcription and cell division (Prigent et al. *J. Cell Science* 2003, 116, 3677). A number of protein kinases have been reported to phosphorylate histone H3 and these kinases function both as signal transduction and mitotic kinases.

Pyrrolotriazine derivatives have been described as having kinase inhibitory activity in US application No. 10/289,010, US patent No. 6,670,357, WO 2001/19828, WO 2003/042172, WO 2004/009542, WO2004/009601, WO 2004/009784 and WO 2004/013145.

In one embodiment, the present invention provides a compound of formula (I)

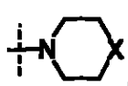


(I),

wherein

R^1 is selected from the group consisting of aryl, benzyl, and heteroaryl,

wherein aryl and heteroaryl can be optionally substituted with 0, 1, 2, 3 or 4 substituents independently selected from the group consisting of

- $(C_1\text{-}C_4)$alkyl, wherein $(C_1\text{-}C_4)$alkyl can be substituted with 0, 1, 2 or 3 halogen, 0 or 1 heterocyclyl, or 0 or 1 $(C_1\text{-}C_3)$alkoxy, wherein $(C_1\text{-}C_3)$alkoxy can be optionally substituted with $(C_1\text{-}C_3)$alkylamino,
- $(C_1\text{-}C_3)$alkoxy, wherein $(C_1\text{-}C_3)$alkoxy can be optionally substituted with $(C_1\text{-}C_3)$alkylamino,
- halogen,
- trifluoromethyl,
- trifluoromethoxy,
- $(C_3\text{-}C_6)$cycloalkyl,
- phenyl optionally substituted with 1 or 2 halogen,
-  , wherein X is CH_2, O, S or $NR^{1\text{-}1}$, and wherein $R^{1\text{-}1}$ is hydrogen or $(C_1\text{-}C_6)$alkyl,

- nitro,
- cyano,
- (C_1-C_3)alkylthio,
- trifluoromethylthio,
- (C_1-C_3)alkylcarbonyl,
- (C_1-C_6)alkoxycarbonyl, and
- phenoxy, wherein phenoxy can optionally be substituted with 0, 1 or 2 substituents independently selected from the group consisting of (C_1-C_6)alkyl, (C_1-C_6)alkoxy, trifluoromethoxy, and halogen,

and

wherein benzyl can be substituted with 0, 1, 2 or 3 groups selected from halogen, (C_1-C_3)alkyl, and (C_1-C_3)alkoxy;

R^2 is selected from the group consisting of hydrogen, halogen, (C_1-C_4)alkyl and (C_1-C_4)alkoxy;

R^3 is selected from the group consisting of

- carboxyl,
- formyl,
- (C_1-C_6)alkylcarbonyl optionally substituted with 0, 1, 2, or 3 groups selected from fluorine, chlorine, hydroxy, (C_1-C_6)alkoxy, and heterocycle,
- (C_3-C_6)cycloalkylcarbonyl,
- (C_1-C_6)alkoxycarbonyl optionally substituted with 0, 1, 2, or 3 groups selected from amino, and (C_1-C_6)alkoxycarbonyl,
- aminocarbonyl,
- (C_1-C_6)alkylaminocarbonyl, wherein (C_1-C_6)alkylaminocarbonyl can optionally be substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of (C_3-C_6)cycloalkyl, halogen, amino, (C_1-C_6)alkylamino, hydroxy, (C_1-C_6)alkoxy, (C_1-C_6)alkoxycarbonyl, (C_1-C_6)alkylthio, (C_1-C_6)alkoxycarbonylamino, and methylsulfonyl, and wherein (C_1-C_6)alkylaminocarbonyl can optionally be substituted with or

0 or 1 heterocyclyl, wherein heterocyclyl can optionally be substituted with 0 or 1 (C_1-C_6)alkyl, and wherein (C_1-C_6)alkylaminocarbonyl can optionally be substituted with 0 or 1 phenyl, wherein phenyl can optionally be substituted with 0 or 1 halogen, (C_1-C_6)alkyl, or (C_1-C_6)alkoxy,

- heterocyclylcarbonyl optionally substituted with 0 or 1 amino, (C_1-C_6)alkylamino, cycloalkyl, or (C_1-C_6)alkyl, wherein (C_1-C_6)alkyl can optionally be substituted with 0 or 1 amino or (C_1-C_6)alkylamino,
- (C_1-C_6)alkyl optionally substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of
  - a) hydroxyl,
  - b) amino,
  - c) (C_1-C_6)alkylamino, wherein (C_1-C_6)alkylamino can be substituted with 0, 1, 2, 3 or 4 substituents independently selected from the group consisting of halogen, amino, alkylamino, methoxy, methylthio, and methylsulfonyl,
  - d) arylamino, wherein arylamino can be substituted with 0, 1 or 2 substituents independently selected from the group consisting of (C_1-C_6)alkyl, (C_1-C_6)alkoxy, and trifluoromethyl,
  - e) heterocyclyl, wherein heterocyclyl can be substituted with 0, 1 or 2 (C_1-C_6)alkyl, wherein (C_1-C_6)alkyl can be substituted with 0, 1 or 2 hydroxy, methoxy or pyridyl,
  - f) imidazolyl,
  - g) pyridylamino,
  - h) (C_1-C_3)alkoxy optionally substituted by fluoro up to the perfluoro level, or by heterocycle, wherein heterocycle can optionally be substituted by 0 or 1 (C_1-C_6)alkyl,
  - i) (C_1-C_3)alkoxy(C_2-C_3)alkoxy, and
  - j) (C_1-C_6)alkoxycarbonyl,
  - k) (C_3-C_6)cycloalkyl,
  - l) cyano,
- (C_1-C_6)alkoxy optionally substituted with 1, 2 or 3 substituents

independently selected from the group consisting of amino, (C_1-C_6)alkylamino, and heterocyclyl, wherein heterocyclyl can be substituted with 0, 1, 2 or 3 (C_1-C_6)alkyl,

- (C_3-C_6)cycloalkylaminocarbonyl optionally substituted with (C_1-C_3)alkyl,
- cyano,
- heteroaryl, wherein heteroaryl can be substituted with 0, 1, 2, or 3 groups independently selected from the group consisting of
  a) (C_1-C_6)alkyl, wherein (C_1-C_6)alkyl can be subsituted with 0, 1, 2, or 3 halogen, 0 or 1 heterocyclyl, 0 or 1 alkylamino, or 0 or 1 hydroxy or methoxy,
  b) halogen,
  c) amino,
  d) alkylamino,
  e) (C_1-C_6)alkoxycarbonyl, and
  f) (C_3-C_6)cycloalkyl,
- heteroarylcarbonyl, which can be substituted with 0, 1, 2, or 3 groups independently selected from the group consisting of (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl and halogen,
- heterocyclyl, wherein heterocyclyl can be substituted with 0, 1, 2, or 3 groups independently selected from the group consisting of (C_1-C_6)alkyl and (C_1-C_6)alkoxycarbonyl; and

R^4 is selected from the group consisting of hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy and halogen;

or a pharmaceutically acceptable salt thereof.

Depending on their structure, the compounds according to the invention can exist in stereoisomeric forms (enantiomers, diastereomers). The invention therefore relates to the enantiomers or diastereomers and to their respective mixtures. Such mixtures of enantiomers and/or diastereomers can be separated into stereoisomerically unitary constituents in a known manner.

The invention also relates to tautomers of the compounds, depending on the structure of the compounds.

A salt for the purposes of the invention is a pharmaceutically acceptable salt of the compound according to the invention.

Pharmaceutically acceptable salts of the compounds (I) include acid addition salts of mineral acids, carboxylic acids and sulphonic acids, for example salts of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, ethanesulphonic acid, toluenesulphonic acid, benzenesulphonic acid, naphthalenedisulphonic acid, acetic acid, propionic acid, lactic acid, tartaric acid, malic acid, citric acid, fumaric acid, maleic acid and benzoic acid.

Pharmaceutically acceptable salts of the compounds (I) also include salts of customary bases, such as for example alkali metal salts (for example sodium and potassium salts, alkaline earth metal salts (for example calcium and magnesium salts) and ammonium salts derived from ammonia or organic amines having 1 to 16 carbon atoms, such as ethylamine, diethylamine, triethylamine, ethyldiisopropylamine, monoethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, dimethylaminoethanol, procaine, dibenzylamine, *N*-methylmorpholine, dihydroabietylamine, arginine, lysine, ethylenediamine and methylpiperidine.

Solvates for the purposes of the invention are those forms of the compounds that coordinate with solvent molecules to form a complex in the solid or liquid state. Hydrates are a specific form of solvates, where the coordination is with water.

For the purposes of the present invention, the substituents have the following meanings, unless otherwise specified:

Alkyl represents a linear or branched alkyl radical having generally 1 to 6, 1 to 4 or 1 to 3 carbon atoms, representing illustratively methyl, ethyl, n-propyl, isopropyl, *tert*-butyl, n-pentyl and n-hexyl.

Alkoxy in general represents a straight-chain or branched hydrocarbon radical having generally 1 to 6, 1 to 4 or 1 to 3 carbon atoms and bound via an oxygen atom. Non-limiting examples include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, pentoxy, isopentoxy, hexoxy, isohexoxy. The terms "alkoxy" and "alkyloxy" can be used synonymously.

Alkylamino represents an amino radical having one or two (independently selected) alkyl substituents, illustratively representing methylamino, ethylamino, n-propylamino, isopropylamino, *tert*-butylamino, n-pentylamino, n-hexylamino, *N,N*-dimethylamino, *N,N*-diethylamino, *N*-ethyl-*N*-methylamino, *N*-methyl-*N*-n-propylamino, *N*-isopropyl-*N*-n-propylamino, *N*-t-butyl-*N*-methylamino, *N*-ethyl-*N*-n-pentylamino and *N*-n-hexyl-*N*-methylamino.

Alkylthio in general represents a straight-chain or branched hydrocarbon radical having 1 to 6 carbon atoms and bound via an sulfur atom. Non-limiting examples include methylthio and ethylthio.

Arylamino represents an amino radical having one or two (independently selected) aryl substituents, illustratively representing phenylamino.

Aminoalkyl represents an alkyl radical substituted with an amino group. Non-limiting examples include aminomethyl and aminoethyl.

Aminocarbonyl represents a free amide group.

Alkylcarbonyl represents a carbonyl group having an alkyl substituent. Non-limiting examples include acetyl, propanoyl, butanoyl, 2-methylpropanoyl, and hexanoyl.

Alkylaminocarbonyl represents an aminocarbonyl radical (free amide) having one or two (independently selected) alkyl substituents, illustratively representing methylaminocarbonyl, ethylaminocarbonyl, n-propylaminocarbonyl, isopropylaminocarbonyl, *tert*-butylaminocarbonyl, n-pentylaminocarbonyl, n-hexylaminocarbonyl, *N,N*-dimethylaminocarbonyl, *N,N*-diethylaminocarbonyl, *N*-ethyl-*N*-methylaminocarbonyl, *N*-methyl-*N*-n-propylaminocarbonyl, *N*-isopropyl-*N*-n-propylaminocarbonyl, *N*-t-butyl-*N*-methylaminocarbonyl, *N*-ethyl-*N*-n-pentylaminocarbonyl and *N*-n-hexyl-*N*-methylaminocarbonyl.

Alkoxycarbonyl represents a carbonyl group having an alkoxy substituent. It illustratively represents methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, isopropoxycarbonyl, *tert*-butoxycarbonyl, n-pentoxycarbonyl and n-hexoxycarbonyl.

Cycloalkyl represents a monocyclic cycloalkyl radical having generally 3 to 8 or 5 to 7 carbon atoms, illustratively representing cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

Aryl represents a mono- to bicyclic carbocyclic radical, which is aromatic at least in one ring, having generally 6 to 10 carbon atoms, illustratively representing phenyl and naphthyl.

Heteroaryl represents an mono- or bicyclic radical having generally 5 to 10 or 5 or 6 ring atoms and up to 5, in another embodiment up to 4 hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur, which is aromatic at least in one ring. It can be attached via a ring carbon atom or a ring nitrogen atom. If it represents a bicycle, wherein one ring is aromatic and the other one is not, it can be attached at either ring. Illustrative examples are thienyl, furyl, pyrrolyl, pyrazolyl, thiazolyl, oxazolyl, imidazolyl, pyridyl, pyrimidyl, pyridazinyl, indolyl, indazolyl, benzofuryl, benzimidazolyl, benzothiophenyl, quinolinyl, isoquinolinyl, 1,3-benzodioxinyl, 1,4-benzodioxinyl, or benzodioxolyl.

Heteroarylcarbonyl represents a heteroaryl residue bonded via a carbonyl carbon atom.

Heterocyclyl represents a mono- or bicyclic, in another embodiment monocyclic, nonaromatic, i.e. saturated or partially unsaturated radical having generally 4 to 10 or 5 to 8 ring atoms and up to 3, in another embodiment up to 2 hetero atoms and/or hetero groups selected from the group consisting of nitrogen, oxygen and sulfur, CO, SO and SO_2. If bicyclic, it can be a fused or spiro-connected bicycle. It can be attached via a ring carbon atom or a ring nitrogen atom. Illustrative examples are tetrahydrofuran-2-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, pyrrolinyl, piperidinyl, morpholinyl, perhydroazepinyl.

Heterocyclylcarbonyl represents a heterocyclyl residue bonded via a carbonyl carbon atom.

Methylsulfonyl represents a $-S(O)_2CH_3$ residue.

Halogen or halo represents a substituent selected from the group consisting of fluoro, chloro, bromo and iodo, in another embodiment fluoro and chloro.

(C_1-C_3)alkoxy(C_2-C_3)alkoxy represents an 2 to 3 carbon alkoxy group substituted at the 2 or 3-positon with a 1 to 3 carbon alkoxy group , illustratively representing 2-methoxyethoxy (CH_3-O-CH_2CH_2-O-), 3-ethoxypropoxy (CH_3CH_2-O-$CH_2CH_2CH_2$-O-), 2-methoxypropoxy (CH_3-O(CH_3)$CHCH_2$-O-), 2-isopropoxyethoxy ($CH_3(CH_3)CH$-O-CH_2CH_2-O-) 2-methoxy-1-methylethoxy ($CH_3OCH_2(CH_3)CH$-O-) or 3-propoxyethoxy, ($CH_3CH_2CH_2$-O-CH_2CH_2-O-).

(C_3-C_6)cycloalkylaminocarbonyl optionally substituted by (C_1-C_3)alkyl represents an aminocarbonyl radical (free amide) having one (independently selected) cycloalkyl substituent, which may be optionally substituted on the nitrogen atom by a (C_1-C_3)alkyl group and independently substituted on any available carbon atom by 1 or 2 (C_1-C_3)alkyl groups, illustratively representing *N*-cyclopyropylaminocarbonyl,

N-cyclopyropyl-*N*-methylaminocarbonyl, *N*-(2-methylcyclopropyl)aminocarbonyl, *N*-cyclobutylaminocarbonyl, *N*-(2,2-dimethyl)cyclopropyl)aminocarbonyl, cylcopentylaminocarbonyl, *N*-(3-ethylcyclopentyl)aminocarbonyl, *N*-cyclohexylaminocarbonyl, *N*-cyclohexyl-*N*-ethylaminocarbonyl, *N*-(3-propylcyclohexyl)aminocarbonyl, and *N*-(4,4-dimethylcyclohexyl)aminocarbonyl.

A * symbol next to a bond denotes the point of attachment in the molecule. Alternatively, a dotted line (—) denotes the bond via a radical is attached to the rest of the molecule.

When prefixes such as (C_1-C_4) are used before substituents, they mean to indicate the respective number of carbon atoms, for example 1 to 4 in case of (C_1-C_4).

When more than one substituent is selected from a group, selection can be independent of each other. Unless a maximum number of substituents is indicated, substitution can take place up to the maximum number of available substitution locations, e.g. in case of halogenation to the perhalo level.

In another embodiment, the present invention provides a compound of formula (I), wherein

R^1 is selected from the group consisting of phenyl and monocyclic heteroaryl having 5 or 6 ring atoms,

wherein phenyl and heteroaryl can be optionally substituted with 0, 1, 2, 3 or 4 substituents independently selected from the group consisting of

- (C_1-C_4)alkyl, wherein (C_1-C_4)alkyl can be substituted with 0, 1, 2 or 3 halogen, 0 or 1 pyrrolidinyl, 0 or 1 morpholinyl, or 0 or 1 (C_1-C_3)alkoxy wherein

  (C_1-C_3)alkoxy can be optionally substituted with (C_1-C_3)alkylamino,

- (C_1-C_3)alkoxy, wherein (C_1-C_3)alkoxy can be optionally substituted with (C_1-C_3)alkylamino,
- halogen,
- trifluoromethyl,
- trifluoromethoxy,
- (C_3-C_6)cycloalkyl,
- phenyl optionally substituted with 1 or 2 halogen,
- trifluoromethylthio;

R^2 is selected from the group consisting of hydrogen, halogen, (C_1-C_4)alkyl and (C_1-C_4)alkoxy;

R^3 is selected from the group consisting of

- carboxyl,
- formyl,
- (C_1-C_6)alkylcarbonyl optionally substituted with 0, 1, 2, or 3 groups selected from fluorine, chlorine, hydroxy, (C_1-C_6)alkoxy, and monocyclic heterocycle having 5 or 6 ring atoms,
- (C_3-C_6)cycloalkylcarbonyl,
- (C_1-C_6)alkoxycarbonyl optionally substituted with 0, 1, 2, or 3 groups selected from amino, and (C_1-C_6)alkoxycarbonyl,
- aminocarbonyl,
- (C_1-C_6)alkylaminocarbonyl, wherein (C_1-C_6)alkylaminocarbonyl can optionally be substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of (C_3-C_6)cycloalkyl, halogen, amino, (C_1-C_6)alkylamino, hydroxy, (C_1-C_6)alkoxy, (C_1-C_6)alkoxycarbonyl, (C_1-C_6)alkylthio, (C_1-C_6)alkoxycarbonylamino, and methylsulfonyl, and wherein (C_1-C_6)alkylaminocarbonyl can optionally be substituted with 0 or 1 hydroxyl or 0 or 1 monocyclic heterocyclyl having 5 or 6 ring atoms, wherein heterocyclyl can optionally be substituted with 0 or 1 (C_1-C_6)alkyl, and wherein (C_1-C_6)alkylaminocarbonyl can optionally be

substituted with 0 or 1 phenyl, wherein phenyl can optionally be substituted with 0 or 1 halogen or (C_1-C_6)alkyl,

- monocyclic heterocyclylcarbonyl having 5 or 6 ring atoms, optionally substituted with 0 or 1 amino, (C_1-C_6)alkylamino, (C_3-C_6)cycloalkyl, or (C_1-C_6)alkyl, wherein (C_1-C_6)alkyl can optionally be substituted with 0 or 1 amino or (C_1-C_6)alkylamino,
- (C_1-C_6)alkyl optionally substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of

  a) hydroxyl,

  b) amino,

  c) (C_1-C_6)alkylamino, wherein (C_1-C_6)alkylamino can be substituted with 0, 1, 2, 3 or 4 substituents independently selected from the group consisting of halogen, amino, alkylamino, methoxy, methylthio, and methylsulfonyl,

  e) monocyclic heterocyclyl having 5 or 6 ring atoms, wherein heterocyclyl can be substituted with 0, 1 or 2 (C_1-C_6)alkyl, wherein (C_1-C_6)alkyl can be substituted with 0, 1 or 2 hydroxy, methoxy or pyridyl,

  f) imidazolyl,

  h) (C_1-C_3)alkoxy optionally substituted by fluoro up to the perfluoro level, or by monocyclic heterocycle having 5 or 6 ring atoms, wherein heterocycle can optionally be substituted by 0 or 1 (C_1-C_6)alkyl,

  i) (C_1-C_3)alkoxy(C_2-C_3)alkoxy, and

  j) (C_1-C_6)alkoxycarbonyl,

  k) (C_3-C_6)cycloalkyl,

  l) cyano,
- (C_3-C_6)cycloalkylaminocarbonyl optionally substituted with (C_1-C_3)alkyl,
- cyano,
- heteroaryl, wherein heteroaryl can be substituted with 0, 1, 2, or 3 groups independently selected from the group consisting of

a) (C_1-C_6)alkyl, wherein (C_1-C_6)alkyl can be subsituted with 0, 1, 2, or 3 halogen, 0 or 1 monocyclic heterocyclyl having 5 or 6 ring atoms, 0 or 1 alkylamino, or 0 or 1 hydroxy or methoxy,

b) halogen,

e) (C_1-C_6)alkoxycarbonyl, and

f) (C_3-C_6)cycloalkyl,

- monocyclic heteroarylcarbonyl having 5 or 6 ring atoms,
- monocyclic heterocyclyl having 5 or 6 ring atoms, wherein heterocyclyl can be substituted with 0, 1, 2, or 3 groups independently selected from the group consisting of (C_1-C_6)alkyl and (C_1-C_6)alkoxycarbonyl; and

R^4 is selected from the group consisting of hydrogen and halogen;

or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides a compound of formula (I), wherein

R^1 is selected from the group consisting of phenyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, pyridinyl, and pyrimidinyl,

wherein phenyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, pyridinyl, and pyrimidinyl can be optionally substituted with 0, 1, 2, 3 or 4 substituents independently selected from the group consisting of

- (C_1-C_4)alkyl, wherein (C_1-C_4)alkyl can be substituted with 0, 1, 2 or 3 halogen,
- (C_1-C_3)alkoxy, wherein (C_1-C_3)alkoxy can be optionally substituted with (C_1-C_3)alkylamino,
- halogen,
- trifluoromethyl,

- trifluoromethoxy,
- cyclopropyl,
- phenyl optionally substituted with 1 or 2 halogen;

R^2 is selected from the group consisting of hydrogen, fluoro and chloro;

R^3 is selected from the group consisting of

- (C_1-C_6)alkylcarbonyl optionally substituted with 0, 1, 2, or 3 groups selected from fluorine, chlorine, hydroxy, (C_1-C_6)alkoxy, piperazinyl, morpholinyl, pyrrolidinyl, and piperidinyl,
- cyclopropylcarbonyl,
- aminocarbonyl,
- (C_1-C_6)alkylaminocarbonyl, wherein (C_1-C_6)alkylaminocarbonyl can optionally be substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of (C_3-C_6)cycloalkyl, halogen, amino, (C_1-C_6)alkylamino, hydroxy, (C_1-C_6)alkoxy, (C_1-C_6)alkoxycarbonyl, (C_1-C_6)alkylthio, (C_1-C_6)alkoxycarbonylamino, and methylsulfonyl, and wherein (C_1-C_6)alkylaminocarbonyl can optionally be substituted with 0 or 1 hydroxyl, piperazinyl, morpholinyl, pyrrolidinyl or piperidinyl, wherein piperazinyl, morpholinyl, pyrrolidinyl or piperidinyl can optionally be substituted with 0 or 1 (C_1-C_6)alkyl, and wherein (C_1-C_6)alkylaminocarbonyl can optionally be substituted with 0 or 1 phenyl, wherein phenyl can optionally be substituted with 0 or 1 halogen or (C_1-C_6)alkyl,
- heterocyclylcarbonyl selected from piperazinylcarbonyl, morpholinylcarbonyl, pyrrolidinylcarbonyl or piperidinylcarbonyl, optionally substituted with 0 or 1 amino, (C_1-C_6)alkylamino, (C_3-C_6)cycloalkyl, or (C_1-C_6)alkyl, wherein (C_1-C_6)alkyl can optionally be substituted with 0 or 1 amino or (C_1-C_6)alkylamino,
- (C_1-C_6)alkyl optionally substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of

a) hydroxyl,

c) (C_1-C_6)alkylamino, wherein (C_1-C_6)alkylamino can be substituted with 0, 1, 2, 3 or 4 substituents independently selected from the group consisting of halogen, alkylamino, and methoxy,

e) piperazinyl, morpholinyl, pyrrolidinyl or piperidinyl, wherein piperazinyl, morpholinyl, pyrrolidinyl or piperidinyl can be substituted with 0, 1 or 2 (C_1-C_6)alkyl, wherein (C_1-C_6)alkyl can be substituted with 0, 1 or 2 hydroxy or methoxy,

f) imidazolyl,

h) (C_1-C_3)alkoxy optionally substituted by fluoro up to the perfluoro level, or by monocyclic heterocycle having 5 or 6 ring atoms, wherein heterocycle can optionally be substituted by 0 or 1 (C_1-C_6)alkyl,

i) (C_1-C_3)alkoxy(C_2-C_3)alkoxy, and

j) (C_1-C_6)alkoxycarbonyl,

k) (C_3-C_6)cycloalkyl,

l) cyano,

- (C_3-C_6)cycloalkylaminocarbonyl optionally substituted with (C_1-C_3)alkyl,
- cyano,
- pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, imidazolyl or pyrimidinyl, wherein pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, imidazolyl or pyrimidinyl can be substituted with 0, 1, 2, or 3 groups independently selected from the group consisting of
  - a) (C_1-C_6)alkyl, wherein (C_1-C_6)alkyl can be subsituted with 0, 1, 2, or 3 halogen, 0 or 1 alkylamino, or 0 or 1 methoxy,
  - b) halogen, and
  - f) (C_3-C_6)cycloalkyl,
- pyrazolylcarbonyl, oxazolylcarbonyl, isoxazolylcarbonyl, thiazolylcarbonyl, pyridinylcarbonyl or pyrimidinylcarbonyl; and

R^4 is selected from the group consisting of hydrogen and fluoro;

or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides a compound of formula (I), wherein

R^1 is selected from the group consisting of phenyl and monocyclic heteroaryl,

wherein aryl and heteroaryl can be optionally substituted with 0, 1, 2, 3 or 4 substituents independently selected from the group consisting of

- (C_1-C_4)alkyl, wherein (C_1-C_4)alkyl can be substituted with 0, 1, 2 or 3 halogen, 0 or 1 pyrrolidinyl or morpholinyl, or 0 or 1 (C_1-C_3)alkoxy wherein

  (C_1-C_3)alkoxy can be optionally substituted with (C_1-C_3)alkylamino,
- (C_1-C_3)alkoxy, wherein (C_1-C_3)alkoxy can be optionally substituted with (C_1-C_3)alkylamino,
- halogen,
- trifluoromethyl,
- trifluoromethoxy,
- (C_3-C_6)cycloalkyl,
- (C_1-C_3)alkylthio, and
- phenoxy, wherein phenoxy can optionally be substituted with 0, 1 or 2 substituents independently selected from the group consisting of (C_1-C_6)alkyl, (C_1-C_6)alkoxy, trifluoromethoxy, and halogen,

R^2 is selected from the group consisting of hydrogen, halogen, (C_1-C_4)alkyl and (C_1-C_4)alkoxy;

R^3 is selected from the group consisting of

- carboxyl,

- (C_1-C_6)alkylcarbonyl optionally substituted with 0, 1, 2, or 3 groups selected from fluorine, chlorine, hydroxy, (C_1-C_6)alkoxy, and heterocycle,
- (C_3-C_6)cycloalkylcarbonyl,
- (C_1-C_6)alkoxycarbonyl,
- aminocarbonyl,
- (C_1-C_6)alkylaminocarbonyl, wherein (C_1-C_6)alkylaminocarbonyl can optionally be substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of (C_3-C_6)cycloalkyl, halogen, (C_1-C_6)alkylamino, hydroxy and (C_1-C_6)alkoxy, and wherein (C_1-C_6)alkylaminocarbonyl can optionally be substituted with or 0 or 1 heterocyclyl, wherein heterocyclyl can optionally be substituted with 0 or 1 (C_1-C_6)alkyl, and wherein (C_1-C_6)alkylaminocarbonyl can optionally be substituted with 0 or 1 phenyl, wherein phenyl can optionally be substituted with 0 or 1 halogen, (C_1-C_6)alkyl, or (C_1-C_6)alkoxy,
- heterocyclylcarbonyl optionally substituted with 0 or 1 amino, (C_1-C_6)alkylamino, cycloalkyl, or (C_1-C_6)alkyl, wherein (C_1-C_6)alkyl can optionally be substituted with 0 or 1 amino or (C_1-C_6)alkylamino,
- (C_1-C_6)alkyl optionally substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of
  - a) hydroxyl,
  - c) (C_1-C_6)alkylamino, wherein (C_1-C_6)alkylamino can be substituted with 0, 1, 2, 3 or 4 substituents independently selected from the group consisting of halogen, amino, alkylamino, methoxy, methylthio, and methylsulfonyl,
  - e) heterocyclyl, wherein heterocyclyl can be substituted with 0, 1 or 2 (C_1-C_6)alkyl, wherein (C_1-C_6)alkyl can be substituted with 0, 1 or 2 hydroxy, methoxy or pyridyl,
  - f) imidazolyl,
  - h) (C_1-C_3)alkoxy optionally substituted by fluoro up to the perfluoro level, or by heterocycle, wherein heterocycle can optionally be substituted by 0 or 1 (C_1-C_6)alkyl,

i) (C_1-C_3)alkoxy(C_2-C_3)alkoxy, and
j) (C_1-C_6)alkoxycarbonyl,
k) (C_3-C_6)cycloalkyl,

- (C_3-C_6)cycloalkylaminocarbonyl optionally substituted with (C_1-C_3)alkyl,
- monocyclic heteroaryl having 5 or 6 ring atoms, wherein heteroaryl can be substituted with 0, 1, 2, or 3 groups independently selected from the group consisting of
  g) (C_1-C_6)alkyl, wherein (C_1-C_6)alkyl can be subsituted with 0, 1, 2, or 3 halogen, 0 or 1 heterocyclyl, 0 or 1 alkylamino, or 0 or 1 hydroxy or methoxy,
  h) halogen,
  i) amino,
  j) alkylamino,
  k) (C_1-C_6)alkoxycarbonyl, and
  l) (C_3-C_6)cycloalkyl,
- monocyclic heteroarylcarbonyl having 5 or 6 ring atoms,
- monocyclic heterocyclylcarbonyl having 5 or 6 ring atoms, wherein heterocyclyl can be substituted with 0, 1, 2, or 3 groups independently selected from the group consisting of (C_1-C_6)alkyl and (C_1-C_6)alkoxycarbonyl; and

R^4 is hydrogen or fluoro;

or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides a compound of formula (I), wherein

R^1 is selected from the group consisting of phenyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, pyridinyl, and pyrimidinyl,

wherein phenyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, pyridinyl, and pyrimidinyl can be optionally substituted with 0, 1, 2, 3 or 4 substituents independently selected from the group consisting of

- $(C_1$-$C_4)$alkyl, wherein $(C_1$-$C_4)$alkyl can be substituted with 0, 1, 2 or 3 halogen,
- $(C_1$-$C_3)$alkoxy,
- halogen,
- trifluoromethyl, and
- phenoxy, wherein phenoxy can optionally be substituted with 0, 1 or 2 substituents independently selected from the group consisting of alkyl, $(C_1$-$C_6)$alkoxy, trifluoromethoxy, and halogen;

R^2 is hydrogen, fluoro, chloro, methyl, ethyl or methoxy;

R^3 is selected from the group consisting of

- $(C_1$-$C_6)$alkoxcarbonyl,
- $(C_1$-$C_6)$alkylaminocarbonyl, wherein $(C_1$-$C_6)$alkylaminocarbonyl can optionally be substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of halogen, and
- $(C_3$-$C_6)$cycloalkylaminocarbonyl optionally substituted with $(C_1$-$C_3)$alkyl,
- piperazinylcarbonyl, morpholinylcarbonyl, pyrrolidinylcarbonyl or piperidinylcarbonyl; and

R^4 is hydrogen;

or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides a compound of formula (I), wherein

R^1 is selected from the group consisting of phenyl, pyrazolyl, thiazolyl, pyridinyl, and pyrimidinyl,

wherein phenyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, pyridinyl, and pyrimidinyl can be optionally substituted with 0, 1, 2, 3 or 4 substituents independently selected from the group consisting of

- methyl, ethyl, propyl or butyl, wherein methyl, ethyl, propyl or butyl can be substituted with 0, 1, 2 or 3 fluoro or chloro,
- fluoro or chloro,
- trifluoromethyl, and
- phenoxy, wherein phenoxy can optionally be substituted with 0, 1 or 2 substituents independently selected from the group consisting of methyl, ethyl, propyl or butyl, methoxy, ethoxy, propoxy, trifluoromethoxy, fluoro and chloro;

R^2 is hydrogen;

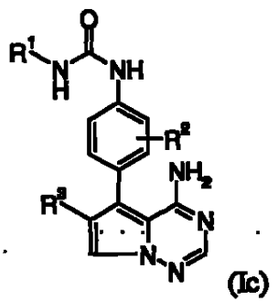
R^3 is selected from the group consisting of

- methoxcarbonyl, ethoxycarbonyl, propoxycarbonyl or butoxycarbonyl,
- $(C_1$-$C_4)$alkylaminocarbonyl, wherein $(C_1$-$C_4)$alkylaminocarbonyl can optionally be substituted with 0, 1, 2 or 3 fluoro, and
- cyclopropylaminocarbonyl optionally substituted with methyl, ethyl or propyl,
- pyrrolidinylcarbonyl or piperidinylcarbonyl; and

R^4 is hydrogen;

or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides a compound of formula (Ic)



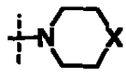
(Ic)

wherein

R^1 is selected from the group consisting of aryl, benzyl, and heteroaryl,

wherein aryl and heteroaryl can be optionally substituted with 1, 2, 3 or 4 substituents independently selected from the group consisting of

- (C_1-C_4)alkyl, wherein (C_1-C_4)alkyl can be substituted with 0, 1, 2 or 3 halogen, 0 or 1 pyrrolidinyl, 0 or 1 morpholinyl, or 0 or 1 (C_1-C_3)alkoxy wherein

  (C_1-C_3)alkoxy can be optionally substituted with (C_1-C_3)alkylamino,
- (C_1-C_3)alkoxy, wherein (C_1-C_3)alkoxy can be optionally substituted with (C_1-C_3)alkylamino,
- halogen,
- trifluoromethyl,
- trifluoromethoxy,
- (C_3-C_6)cycloalkyl,
- phenyl optionally substituted with 1 or 2 halogen,
-  , wherein X is CH_2, O, S or NR^{1-1}, and wherein R^{1-1} is hydrogen or (C_1-C_6)alkyl,
- nitro,
- cyano,
- (C_1-C_3)alkylthio,
- trifluoromethylthio,
- (C_1-C_3)alkylcarbonyl,

- (C_1-C_6)alkoxycarbonyl, and
- phenoxy

and

wherein benzyl can be substituted with 0, 1, 2 or 3 groups selected from halogen, (C_1-C_3)alkyl, and (C_1-C_3)alkoxy;

R^2 is selected from the group consisting of hydrogen, halogen, alkyl and alkoxy;

R^3 is selected from the group consisting of

- carboxyl,
- formyl,
- (C_1-C_6)alkylcarbonyl optionally substituted with 1, 2, or 3 fluorine,
- (C_1-C_6)alkoxycarbonyl,
- aminocarbonyl,
- (C_1-C_6)alkylaminocarbonyl, wherein (C_1-C_6)alkylaminocarbonyl can optionally be substituted with 1, 2 or 3 substituents independently selected from the group consisting of halogen, amino, alkylamino, methoxy, and methylsulfonyl, and wherein (C_1-C_6)alkylaminocarbonyl can be substituted with 0 or 1 hydroxyl or 0 or 1 heterocyclyl,
- heterocyclylcarbonyl,
- (C_1-C_6)alkyl optionally substituted with 1, 2 or 3 substituents independently selected from the group consisting of
  - a) hydroxyl,
  - b) amino,
  - c) (C_1-C_6)alkylamino, wherein (C_1-C_6)alkylamino can be substituted with 0, 1, 2, 3 or 4 substituents independently selected from the group consisting of halogen, amino, alkylamino, methoxy, methylthio, and methylsulfonyl,
  - d) arylamino, wherein arylamino can be substituted with 0, 1 or 2 substituents independently selected from the group consisting of (C_1-C_6)alkyl, (C_1-C_6)alkoxy, and trifluoromethyl,

e) heterocyclyl, wherein heterocyclyl can be substituted with 0, 1 or 2 (C_1-C_6)alkyl, wherein (C_1-C_6)alkyl can be substituted with 0, 1 or 2 methoxy or pyridyl,

f) imidazolyl,

g) pyridylamino,

h) (C_1-C_3)alkoxy optionally substituted by fluoro up to the perfluoro level,

i) (C_1-C_3)alkoxy(C_2-C_3)alkoxy, and

j) (C_1-C_6)alkoxycarbonyl,

- (C_1-C_6)alkoxy optionally substituted with 1, 2 or 3 substituents independently selected from the group consisting of amino, (C_1-C_6)alkylamino, and heterocyclyl, wherein heterocyclyl can be substituted with 0, 1, 2 or 3 (C_1-C_6)alkyl;
- (C_3-C_6)cycloalkylaminocarbonyl optionally substituted with (C_1-C_3)alkyl,
- cyano, and
- heteroaryl wherein heteroaryl can be substituted with 0, 1, 2, or 3 groups independently selected from the group consisting of

m) (C_1-C_6)alkyl, wherein (C_1-C_6)alkyl can be subsituted with 0, 1, 2, or 3 halogen, 0 or 1 heterocycyl, 0 or 1 alkylamino, or 0 or 1 methoxy,

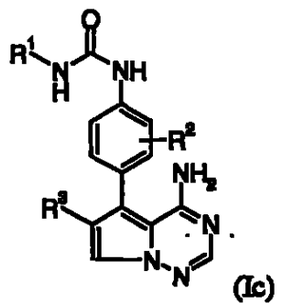
n) halogen,

o) amino, and

p) alkylamino;

or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides a compound of formula (Ic):



(Ic)

wherein

R^1 is selected from the group consisting of aryl and heteroaryl,

wherein aryl and heteroaryl can be substituted with 0, 1, 2, 3 or 4 substituents independently selected from the group consisting of

$(C_1\text{-}C_4)$alkyl,

$(C_1\text{-}C_3)$alkoxy,

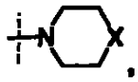
halogen,

trifluoromethyl,

trifluoromethoxy,

$(C_3\text{-}C_6)$cycloalkyl,

phenyl optionally substituted with 0, 1 or 2 halogen, and



, wherein X is CH_2, O, S or NR^{1-1}; and wherein R^{1-1} is hydrogen or $(C_1\text{-}C_6)$alkyl;

R^2 is selected from the group consisting of hydrogen, halogen, alkyl and alkoxy;

R^3 is selected from the group consisting of carboxyl, $(C_1\text{-}C_6)$alkoxycarbonyl, aminocarbonyl, $(C_1\text{-}C_6)$alkylaminocarbonyl, and heterocyclylcarbonyl,

wherein $(C_1\text{-}C_6)$alkylaminocarbonyl can optionally be substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of halogen, amino, alkylamino, methoxy and methylsulfonyl, or

R^3 is (C_1-C_6)alkyl optionally substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of hydroxyl, amino, (C_1-C_6)alkylamino, arylamino, heterocylcyl, pyridyl, and pyridylamino,
wherein (C_1-C_6)alkylamino can optionally be substituted with 0, 1, 2, 3 or 4 substituents independently selected from the group consisting of halogen, amino, alkylamino, methoxy, methylthio, and methylsulfonyl, and wherein heterocyclyl can optionally be substituted with 0, 1 or 2 (C_1-C_6)alkyl, wherein (C_1-C_6)alkyl can optionally be substituted with 1 or 2 methoxy or pyridyl,
and wherein arylamino can optionally be substituted with 0, 1 or 2 substituents independently selected from the group consisting of (C_1-C_6)alkyl, (C_1-C_6)alkoxy, and trifluromethyl, or

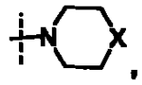
R^3 is (C_1-C_6)alkoxy optionally substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of amino, (C_1-C_6)alkylamino, and heterocyclyl, wherein heterocyclyl can optionally be substituted with 0, 1, 2 or 3 (C_1-C_6)alkyl;

or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides a compound of formula (I),

wherein

R^1 is selected from the group consisting of phenyl and meno- or bicyclic heteroaryl containing 5, 6, 9 or 10 ring atoms and up to 2 hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur,

wherein phenyl and heteroaryl can be substituted with 0, 1 or 2 substituents independently selected from the group consisting of (C_1-C_4)alkyl, C_1-C_3)alkoxy, halogen, trifluoromethyl, trifluoromethoxy, (C_3-C_6)cycloalkyl, phenyl optionally substituted with trifluoromethyl, and  , wherein X is CH_2, O, S or NR^{1-1};

wherein R^{1-1} is hydrogen or (C_1-C_6)alkyl;

R^2 is selected from the group consisting of hydrogen, fluoro, chloro, methyl, and methoxy;

R^3 is selected from the group consisting of carboxyl, (C_1-C_6)alkoxycarbonyl, aminocarbonyl, and (C_1-C_6)alkylaminocarbonyl,

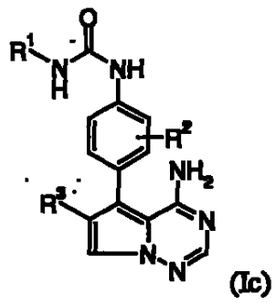
wherein (C_1-C_6)alkylaminocarbonyl can optionally be substituted with 0, 1 or 2 substituents independently selected from the group consisting of halogen, amino, alkylamino, methoxy and methylsulfonyl, or

R^3 is (C_1-C_6)alkyl substituted with amino, (C_1-C_6)alkylamino, pyridyl, or 5- to 6 membered heterocylcyl containing 1 or 2 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur,
wherein (C_1-C_6)alkylamino can optionally be substituted with 0, 1 or 2 substituents independently selected from the group consisting of halogen, amino, alkylamino, methoxy and methylsulfonyl, and wherein heterocyclyl can optionally be substituted with 0, 1 or 2 (C_1-C_6)alkyl, wherein (C_1-C_6)alkyl can optionally be substituted with 0 or 1 methoxy or pyridyl, or

R^3 is (C_1-C_6)alkoxy optionally substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of amino, (C_1-C_6)alkylamino, and a 5- to 6 membered heterocylcyl containing 1 or 2 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein heterocyclyl can optionally be substituted with 0, 1, 2 or 3 (C_1-C_6)alkyl;

or a pharmaceutically acceptable salt thererof.

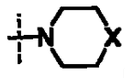
In another embodiment, the present invention provides a compound of formula (Ic),



(Ic)

wherein

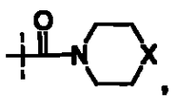
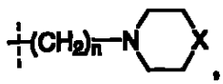
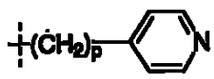
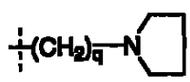
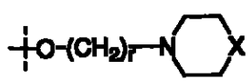
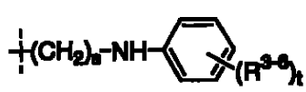
R^1 is selected from the group consisting of

- phenyl optionally substituted with 1-2 groups selected from halo, $(C_1\text{-}C_4)$alkyl, OCF_3, CF_3, and  , wherein X is CH_2, O, S or $NR^{1\text{-}1}$, wherein $R^{1\text{-}1}$ is hydrogen or $(C_1\text{-}C_6)$alkyl,
- pyridyl optionally substituted with CF_3,
- pyrazolyl option substituted with 1-2 groups selected from $(C_1\text{-}C_4)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, and phenyl optionally substituted with CF_3,
- isoxazolyl optionally substituted with $(C_1\text{-}C_4)$alkyl,
- pyrimid-4-yl optionally substituted with $(C_1\text{-}C_3)$alkoxy
- indazolyl, optionally substituted on N with $(C_1\text{-}C_4)$alkyl;

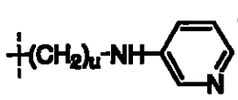
R^2 is hydrogen;

R^3 is selected from the group consisting of

- $CO_2R^{3\text{-}1}$
- $CONR^{3\text{-}2}R^{3\text{-}3}$
- $-(CH_2)_mNR^{3\text{-}4}R^{3\text{-}5}$

-  , wherein X is O or NH,
-  , wherein X is O or NH,
- 
- 
- 
- 

and

- 

m is 1,2 or 3

n is 1,2,or 3;

p is 1,2 or 3;

q is 2 or 3;

r is 2 or 3

s is 1,2 or 3;

t is 0, 1 or 2;

u is 1,2 or 3;

R^{3-1} is H or (C_1-C_6)alkyl;

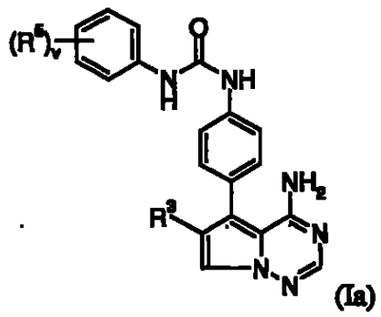
$R^{3-2}$and R^{3-3} are independently selected from H and (C_1-C_6)alkyl;

R^{3-4} and R^{3-5} are independently selected from H and (C_1-C_6)alkyl;

R^{3-6} is CF_3, (C_1-C_4)alkoxy or (C_1-C_4)alkyl;

or a pharmaceutically acceptable salt thereof.

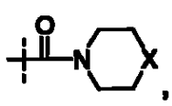
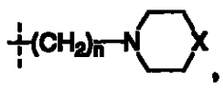
In another embodiment, the present invention provides a compound of the formula (Ia),



(Ia)

wherein

R^3 is selected from the group consisting of

-  , wherein X is O or NH,
-  , wherein X is O or NH, and
- aminocarbonyl or (C_1-C_6)alkylaminocarbonyl substituted as described above;

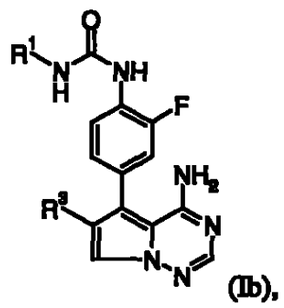
n is 1,2,or 3;

R^5 is independently selected from the group consisting of fluoro, chloro, methyl, ethyl, propyl, isopropyl, trifluoromethyl, trifluoromethoxy, and morpholino; and

v is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

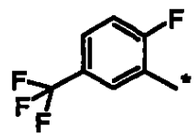
In another embodiment, the present invention provides a compound of the formula (Ib),



(Ib),

or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides a compound of the formula (Ic), wherein R^1 represents



In another embodiment, the present invention provides a compound of the formula (Ic), wherein R^3 represents ethoxycarbonyl.

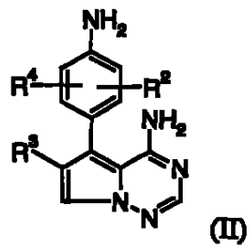
In another embodiment, the present invention provides a compound of the formula (Ic), wherein R^3 is $(C_1\text{-}C_6)$alkylaminocarbonyl,

wherein $(C_1\text{-}C_6)$alkylaminocarbonyl can optionally be substituted with 1 or 2 substituents independently selected from the group consisting of halogen, amino, alkylamino, methoxy and methylsulfonyl, and wherein arylamino can optionally be substituted with 1 or 2 methoxy or trifluoromethyl.

In another embodiment, the present invention provides a compound as described as an Operational Example Examples section of the present application.

In another embodiment, the present invention relates to a compound capable of being metabolized or hydrolyzed to a compound of formula (I) under physiological conditions. This includes e.g. ester and amide derivatives (which can be hydrolyzed to the respective acids, alcohols and amines) as well as orthoesters and aminal esters (which can be hydrolyzed to the respective acids), acetals and hemiacetals (which can be hydrolyzed to the respective keto derivatives, e.g. the oxo group of the 4-oxopyrimidine ring moiety).

In another embodiment, the present invention provides a process for preparing a compound of formula (I), wherein a compound of formula (II)



(II)

wherein R^2, R^3 and R^4 have the meaning indicated above,

is reacted with an isocyanate compound of formula (III)

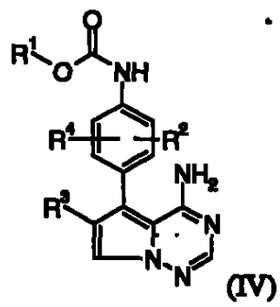
R^1-NCO (III)

or with an carbamate of formula (VI)

R^1-NH-C(O)-OPh (VI),

wherein R^1 has the meaning indicated above; or

a compound of formula (IV)



(IV)

wherein R^1, R^2, R^3 and R^4 have the meaning indicated above,

is reacted with an amine of formula (V)

R^1-NH_2 (V),

wherein R^1 has the meaning indicated above.

The preparation of the compounds according to the invention can be illustrated by means of the following synthetic schemes. Unless specifically defined otherwise, the substituent placeholders such as R^1 to R^3 have the meaning indicated above.

Methods for preparing pyrrolotriazines are also disclosed in published US application No. 10/289,010 (Publication No. US 2003-0186982 A1), US patent No. 6,670,357 (US application No. 10/036,293), as well as WO 2003/042172, WO 2004/009542, WO2004/009601, WO 2004/009784 and WO 2004/013145, all of which are hereby incorporated by reference in their entirety.

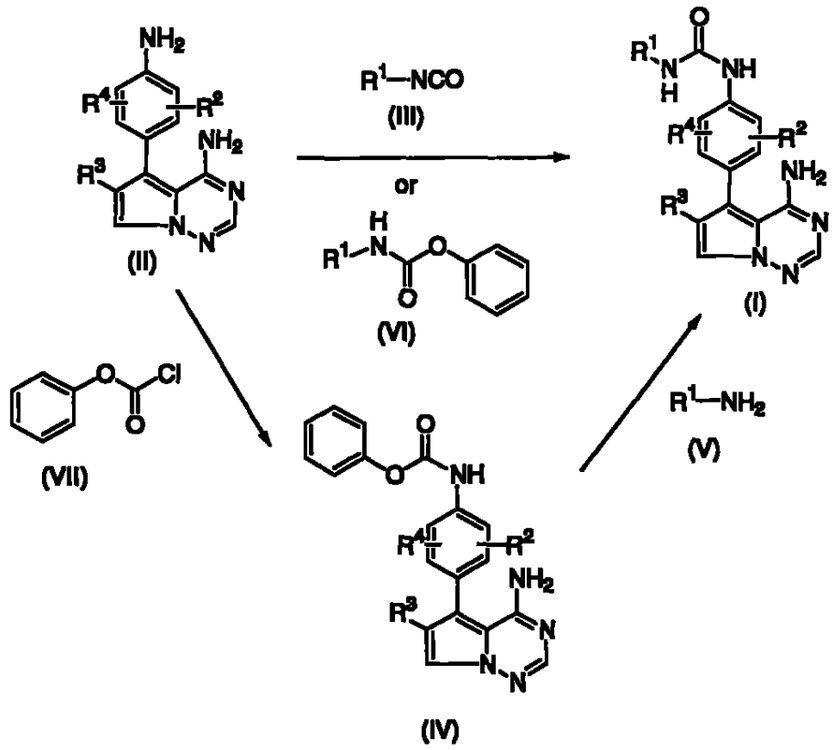
<u>General Methods of Preparation of Invention Compounds</u>

Compounds of the present invention of Formula (I) can be conveniently prepared from the corresponding amino compounds of Formula (II) by straightforward means as described in the Reaction Schemes below or by means well known to those skilled

in the art. In these Reaction Schemes, unless otherwise specifically defined, the meanings of R^1-R^3, R^{3-2}, R^{3-3}, R^{3-4}, R^4 and r are identical to those described above.

Reaction Scheme 1 illustrates the general method of preparing Formula (I) compounds from the corresponding amino compounds of Formula (II) by standard methods of urea formation. In this scheme, a Formula (II) compound is allowed to react with either an isocyanate of Formula (III), or more preferably a carbamate of Formula (VI), generally in an inert solvent, to give the compound of Formula (I) directly. Alternatively, the amine of Formula (II) can be treated first with a chloroformate of Formula (VII), in an inert solvent, to provide an intermediate carbamate of Formula (IV). The Formula (IV) compound is then allowed to react with an amine of Formula (V), in an inert solvent, to provide the compound of Formula (I).

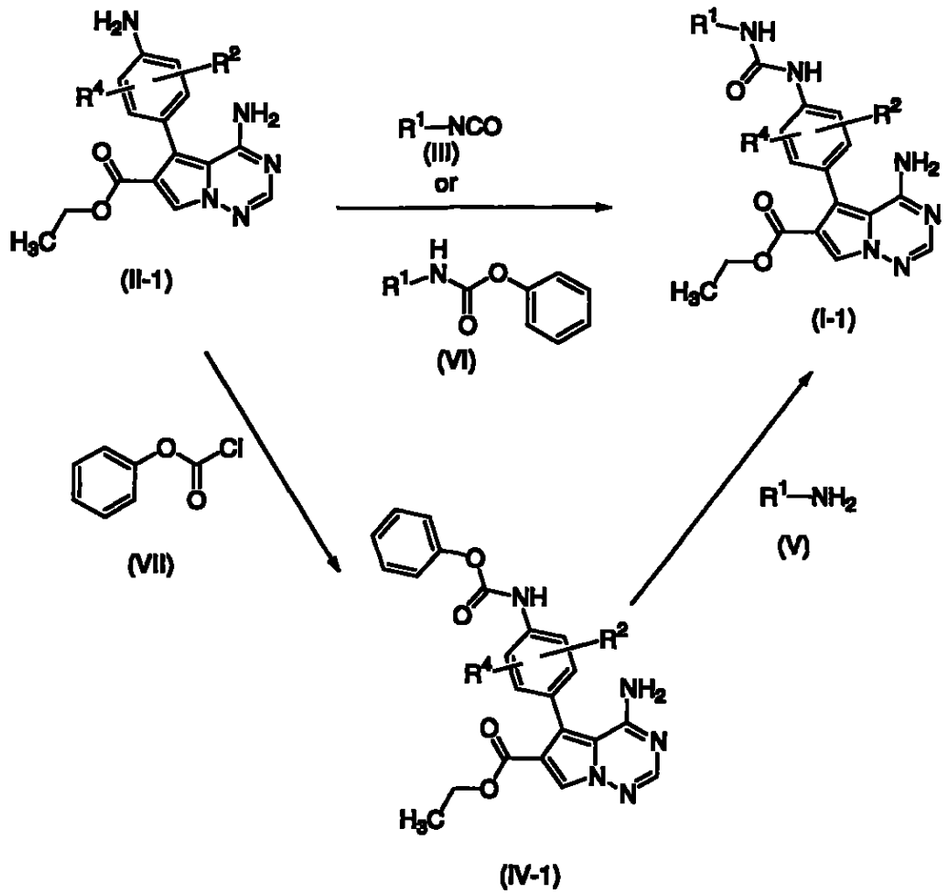
Reaction Scheme 1



A more specific example of the Reaction Scheme 1 method is illustrated in Reaction Scheme 2 below. In this scheme, the amine of Formula (II-1) [Formula (II), where

R^3 is CO_2Et], is used as the starting material, reacting with an isocyanate ((III), carbamate (VI), or in a two step sequence using (VII) followed by (V), to give the compound of Formula (I-1) [Formula (I) where R^3 is CO_2Et]. The Formula (I-1) compound can then be used as a starting material to prepare other compounds of Formula (I) as shown, for example, in Reaction Scheme 3 below.

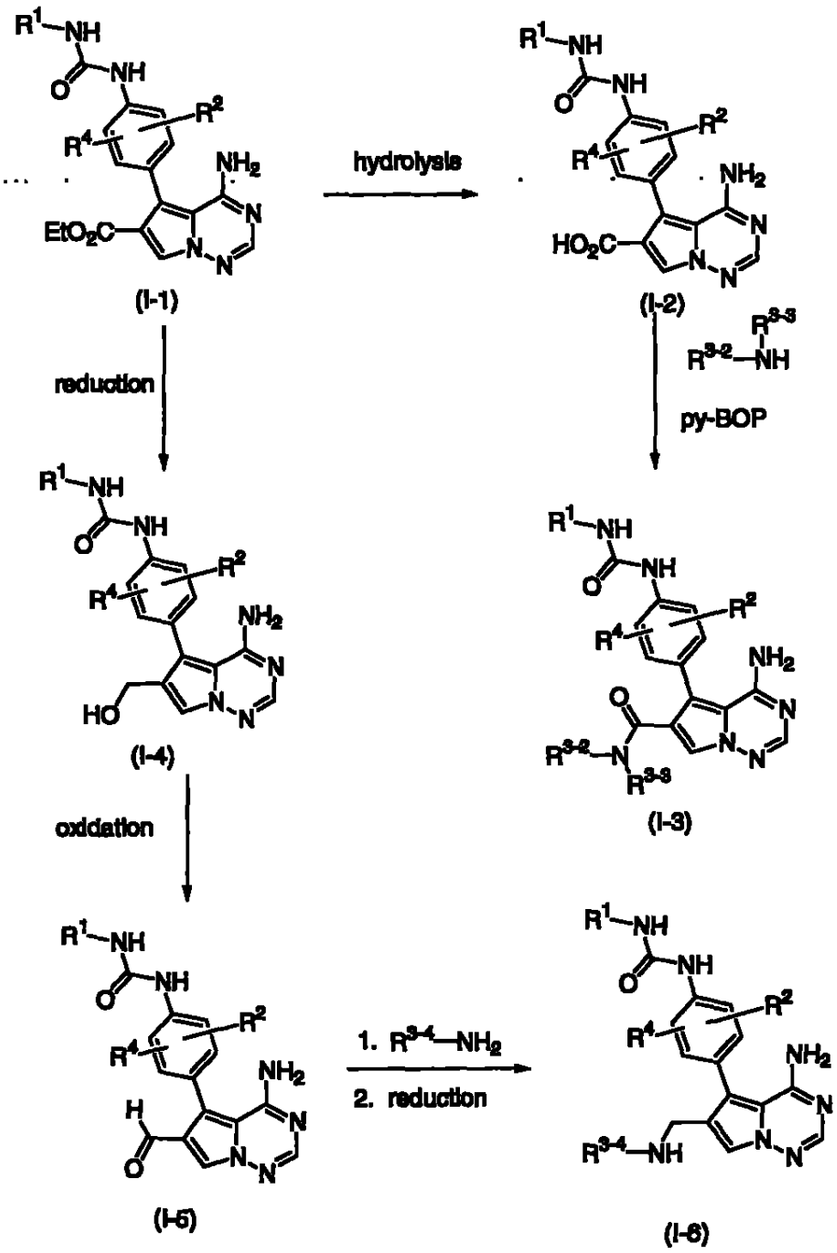
Reaction Scheme 2



Reaction Scheme 3 illustrates the preparation of compounds of Formula (I) in which R^3 is a variety of substituents, starting from the compound of Formula (I-1) in which R^3 is CO_2Et. For example, hydrolysis of (I-1), in either aqueous base or acid, provides the carboxylic acid compound of Formula (I-2). Coupling of this acid with an amine of Formula $(R^{3-2})(R^{3-3})NH$ gives amide compounds of Formula (I-3).

Reduction of the Formula (I-1) ester with a reducing agent such as DIBAL, provides the alcohol of Formula (I-4). Oxidation of the alcohol by standard means such as the Dess-Martin periodinane gives the aldehyde of Formula (I-5). Conversion of the aldehyde to an amine compound of Formula (I-6) is accomplished by a reductive amination sequence. In this sequence, a primary amine of Formula R^{3-4}-NH_2 is added to the compound of Formula (I-5) in the presence of acetic acid, and the intermediate imine compound is not isolated but is selectively reduced with a reagent such as sodium triacetoxyborohydride to give the amine of Formula (I-6).

Reaction Scheme 3

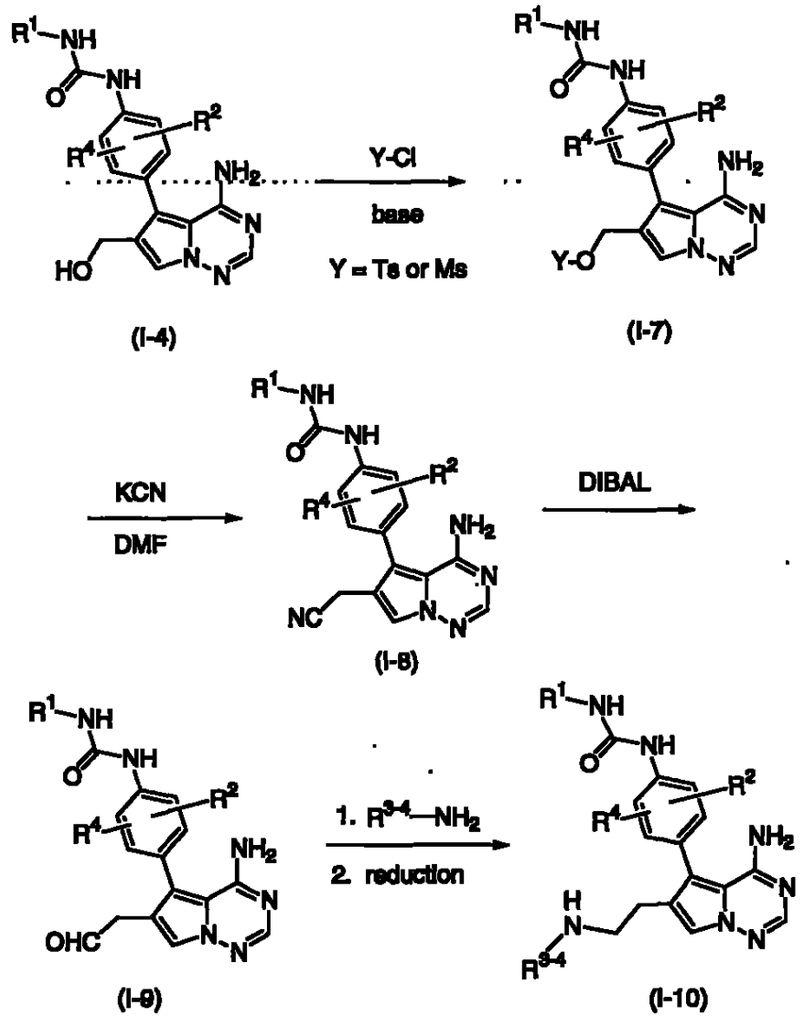


The alcohol of Formula (I-4) is further elaborated in Reaction Scheme 4, and the aldehyde of Formula (I-5) is further elaborated in Reaction Scheme 5, below.

In Reaction Scheme 4, the alcohol is converted to the homologous aldehyde by standard means, namely, conversion to a tosylate or mesylate with tosyl or mesyl

chloride, respectively, and a base such as pyridine or Et_3N, to give the intermediate of Formula (I-7). Reaction of (I-7) with a cyanide source, e.g., KCN or NaCN, in a polar solvent such as DMF gives the nitrile of Formula (I-8). Selective reduction with DIBAL with hydrolytic workup gives aldehyde of Formula (I-9). The Formula (I-9) aldehyde is converted to the compound of Formula (I-10) [(I) where R^3 is $(R^{3-4})NHCH_2CH_2$-] by the reductive amination sequence as described for preparation of (I-6) in Reaction Scheme 3.

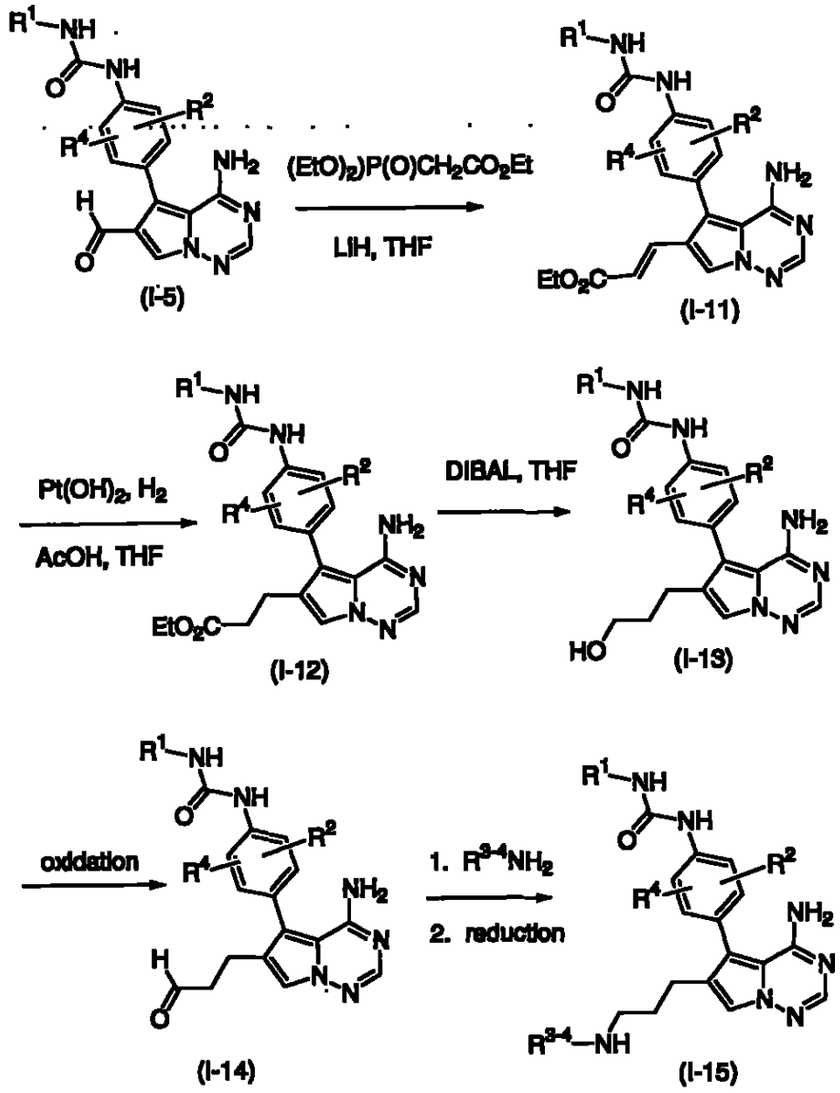
Reaction Scheme 4



(I-4) (I-7) (I-8) (I-9) (I-10)

The aldehyde of Formula (I-5) serves as the starting material for the preparation of additional Formula (I) compounds as shown below in Reaction Scheme 5. A Wadsworth-Emmons type reaction of (I-5) with a phosphonic ester and strong base such as LiH gives the unsaturated ester of Formula (I-11); reduction of this ester to the saturated compound of Formula (I-12) is accompliahed by hydrogenation using a platinum oxide catalyst in acetic acid. Reduction of the ester to the alcohol of Formula (I-13) is followed by oxidation to the compound of Formula (I-14), a 2-carbon homologue of the aldehyde of Formula (I-5). Reductive amination of (I-14), as previously described above in Reactions Schemes 3 and 4 provides the compound of Formula (I-15) [Formula (I) where R^3 is $(R^{3-4})NHCH_2CH_2CH_2$-].

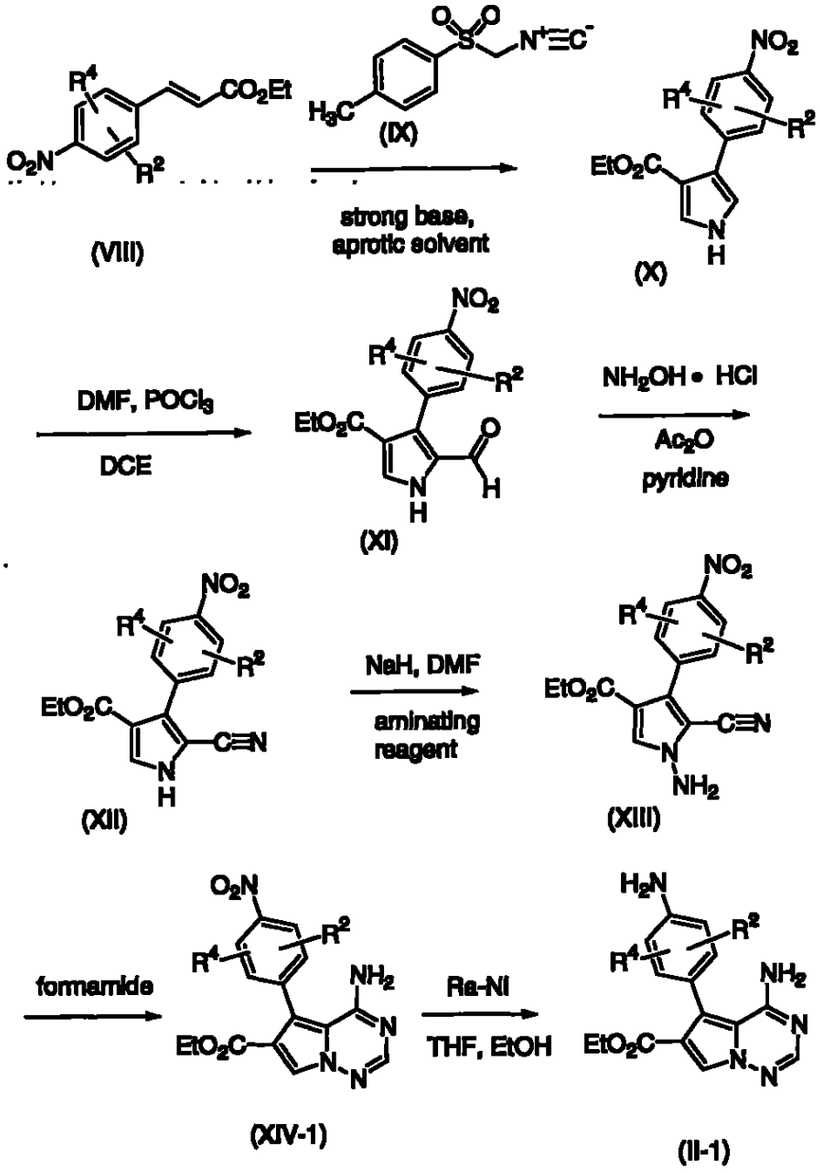
Reaction Scheme 5



General Methods of Preparation of Intermediates

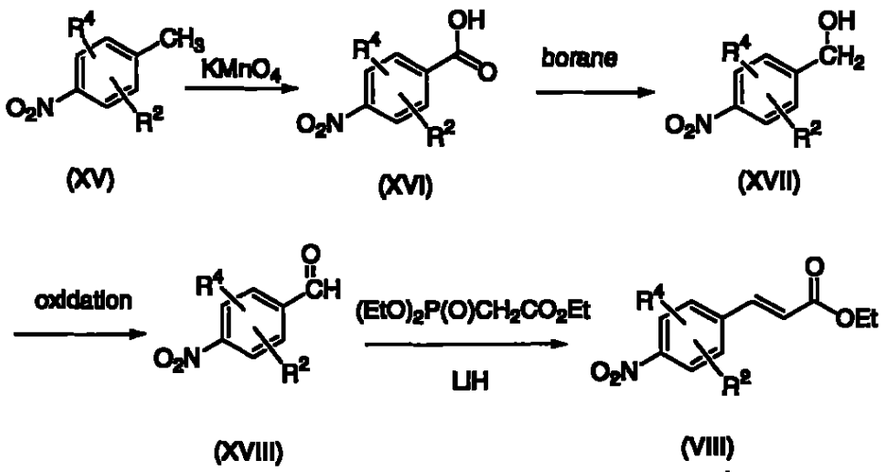
The preparation of key intermediate (II-1) shown above as starting material for Reaction Scheme 2, is prepared as illustrated below in Reaction Scheme 6. A 4-nitrocinnamate of Formula (VIII) is allowed to react with the isocyanide reagent of Formula (IX) in the presence of a strong base such as lithium hexamethyldisilazide (LHMDS) in an aprotic solvent such as THF, to give the substituted pyrrole of Formula (X). Formylation of (X) under Vilsmeier conditions (e.g., DMF, $POCl_3$) gives the 2-formylpyrrole of Formula (XI). The aldehyde (XI) is converted to the nitrile of Formula (XII) by reaction with hydroxylamine hydrochloride to form an intermediate oxime, which is dehydrated in situ to a nitrile of Formula (XII), using a reagent such as acetic anhydride. The nitrile of Formula (XII) is then *N*-aminated using a strong base such as NaH and an aminating reagent such as $(Ph)_2P(O)$-O-NH_2, to provide the *N*-amino nitrile of Formula (XIII). Reaction of (XIII) with formamide [$HC(O)NH_2$] gives the pyrrolotriazine intermediate of Formula (XIV-1). Selective reduction of the nitro substituent of the phenyl ring is accomplished in the final step using a catalyst such as Raney-Nickel in THF, providing the intermediate (II-1). These same reduction conditions are used to convert addition compounds of general formula (XIV), prepared as shown in Reaction Schemes 8-11 below, to the corresponding formula (II) intermediates.

Reaction Scheme 6



The cinnamates of Formula (VIII) are either commercially available or prepared as shown in Reaction Scheme 7. In this sequence, a substituted nitrotoluene of Formula (XV) is oxidized with a reagent such as potassium permanganate to give the corresponding acid of Formula (XVI); this acid is reduced to the alcohol of Formula (XVII) with a reducing agent such as borane and then oxidized to the aldehyde of Formula (XVIII) using a reagent such as the Dess-Martin periodinane. Wadsworth-Emmons type reaction of (XVIII) using $(EtO)_2P(O)CH_2CO_2Et$ and a strong base such as LiH gives the cinnamate of Formula (VIII).

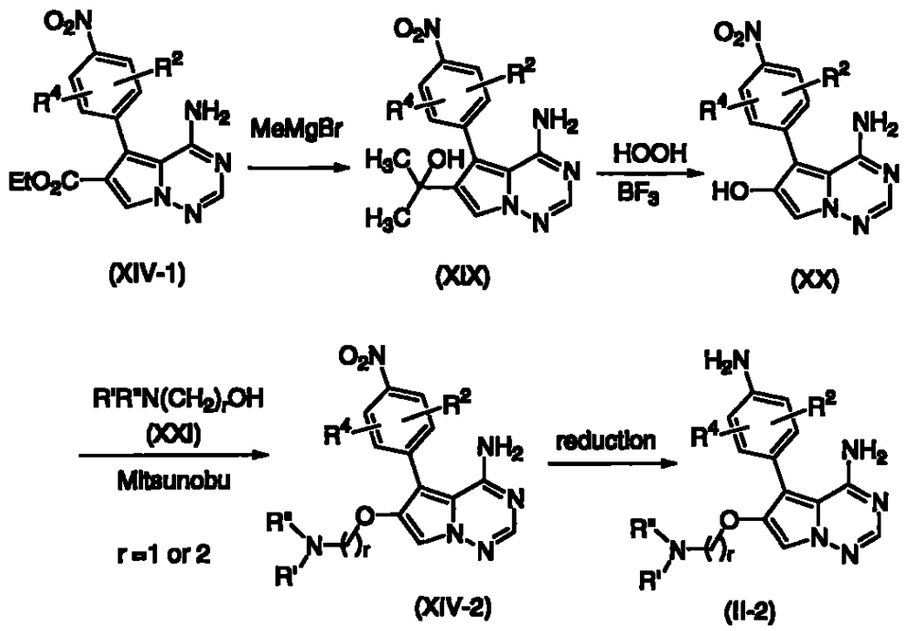
Reaction Scheme 7



The use of intermediate (XIV-1) for the preparation of the intermediate of Formula (II-2) is shown in Reaction Scheme 8 below. The Formula (XIV-1) compound is allowed to react with excess methyl Grignard reagent to give the tertiary alcohol of Formula (XIX). This compound is subjected to oxidative rearrangement and hydrolysis using hydrogen peroxide and a Lewis acid, such as BF_3, to give the hydroxy compound of Formula (XX). Reaction of (XX) with a substituted alcohol of Formula (XXI) under Mitsunobu conditions, e.g., DEAD, TPP, gives the intermediate of Formula (XIV-2). Reduction of the nitro group in Formula (XIV-2), as described for preparation of Formula (II-1) in Reaction Scheme 6, gives the intermediate of Formula (II-2) [Formula (II) where R^3 is $R'R''N(CH_2)_2O$- and R'' and R' are as described in Reaction Scheme 8].

The compound of Formula (II-2) can be used to prepare the compound of Formula (I) [where R^3 is a group of Formula R'R"N(CH$_2$)$_r$O-, and R" and R' are as described in Reaction Scheme 8] by the route outlined in Reaction Scheme 1.

Reaction Scheme 8

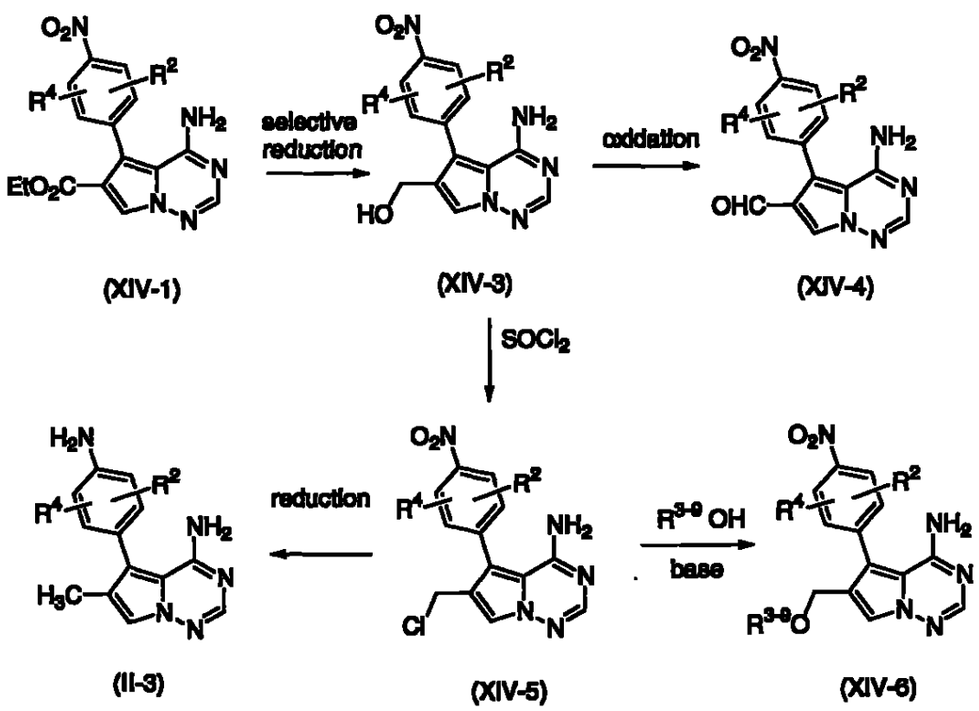


where
R', R" are independently selected from H and (C_1-C_8)alkyl
or
R' and R" may be joined together to form a 5- or 6-membered heterocyclic ring containing an additional N, O or S atom and may be optionally substituted with (C_1-C_8)alkyl

The compound of Formula (XIV-1), prepared as shown above in Reaction Scheme 6, is used to prepare a variety of other intermediates of Formula (IV-3) – (XIV-7) as shown below in Reaction Scheme 9. For example, selective reduction of the ester group in Formula (XIV-1) using, for example, DIBAL in THF, gives the compound of Formula (XIV-3). Oxidation of the alcohol (XIV-3) to the aldehyde of Formula (XIV-4) is accomplished using standard conditions such as the Dess-Martin periodinane reagent in methylene chloride. The Formula (XIV-3) compound may also be converted to the corresponding chloride of Formula (XIV-5) with, for example, thionyl chloride. Reduction of both the nitro group and the chlorine in

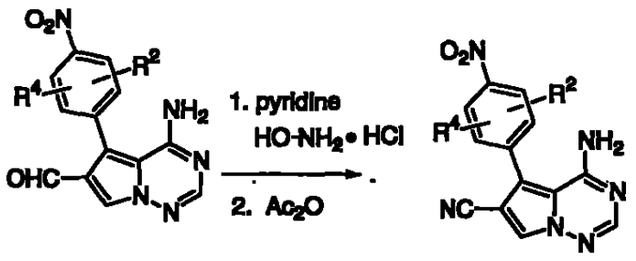
Formula (XIV-5) using Ra-Ni, provides the intermediate of Formula (II-3). Reaction of Formula (XIV-5) with an alcohol of Formula R^{3-9}-OH and base such as sodium hydride gives the ether of Formula (XIV-6).

Reaction Scheme 9

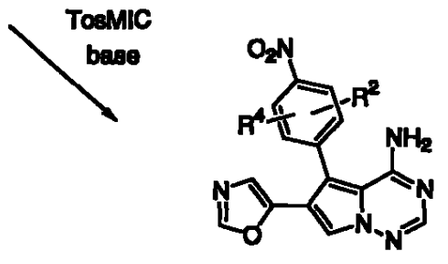


As shown below in Reaction Scheme 9, the compound of Formula (XIV-4) may also be used for the preparation of the nitrile of Formula (XIV-7), by a two step procedure: reaction with hydroxylamine hydrochloride and pyridine, followed by dehydration of the intermediate oxime using acetic anhydride. The Formula (XIV-4) aldehyde may also be converted to an isoxazole intermediate of Formula (XIV-8) by reaction with tosylmethylisocyanide (TosMIC) in the presence of a base such as potassium carbonate, in a protic solvent such as methanol.

Reaction Scheme 10



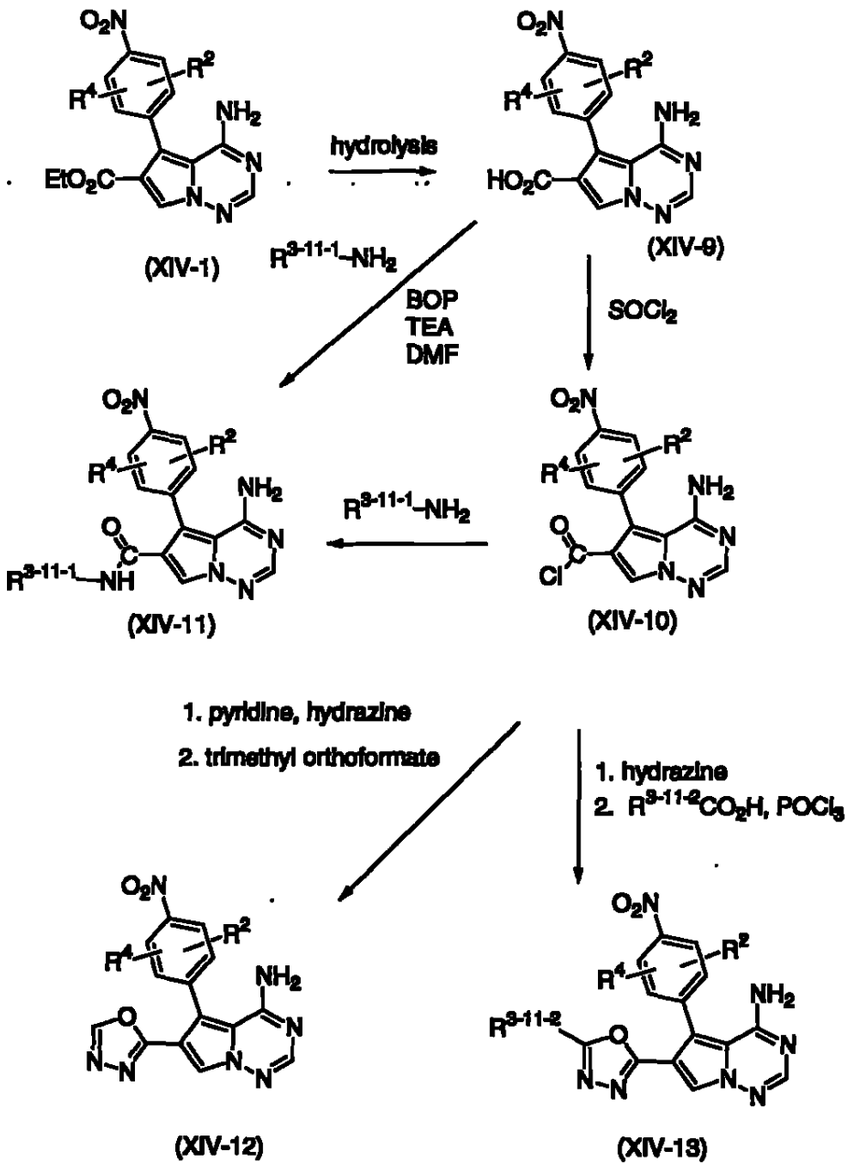
(XIV-4) (XIV-7)



(XIV-8)

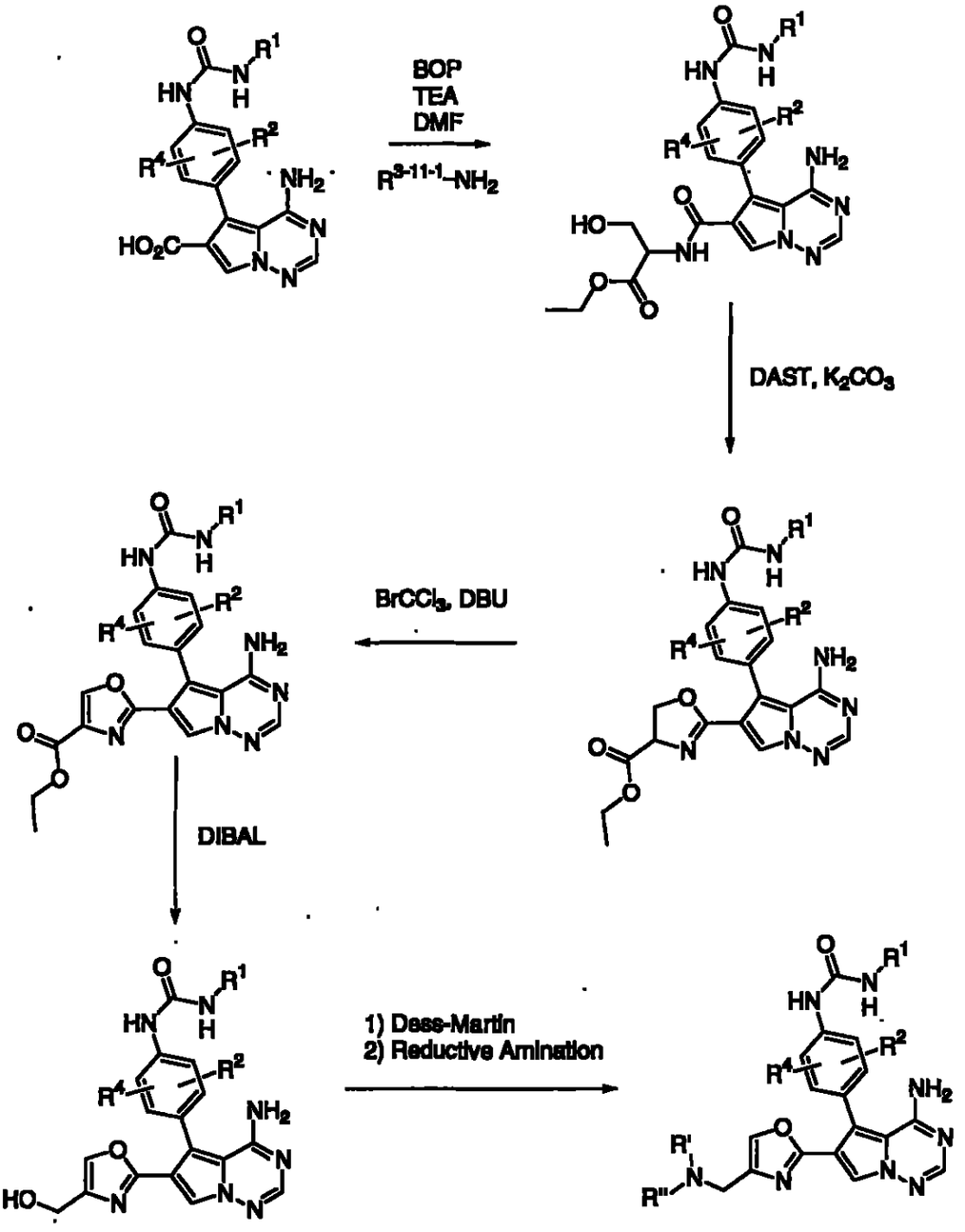
The intermediate of Formula (XIV-1) may also be used for the preparation of other amides and heterocycles as shown in Reaction Scheme 11. Hydrolysis of (XIV-1) under standard conditions to the corresponding acid of Formula (XIV-9) is followed by conversion to the amide of Formula (XIV-11), either directly using an amine of formula R^{3-11-1}-NH_2 , BOP, and a base such as TEA, or by prior conversion to the acid chloride of Formula (XIV-10), which is then allowed to react with the amine of formula R^{3-11-1}-NH_2. The acid chloride of Formula (XIV-10) is also used for the preparation of oxadiazoles of Formulae (XIV-12) and (XIV-13), by reaction with either 1) hydrazine and trimethyl orthoformate to give the oxadiazole of Formula (XIV-12), or 2) hydrazine, a carboxylic acid of formula R^{3-11-2}-CO_2H, and a dehydrating agent such as $POCl_3$, to give the substituted oxadiazole Formula (XIV-13).

Reaction Scheme 11



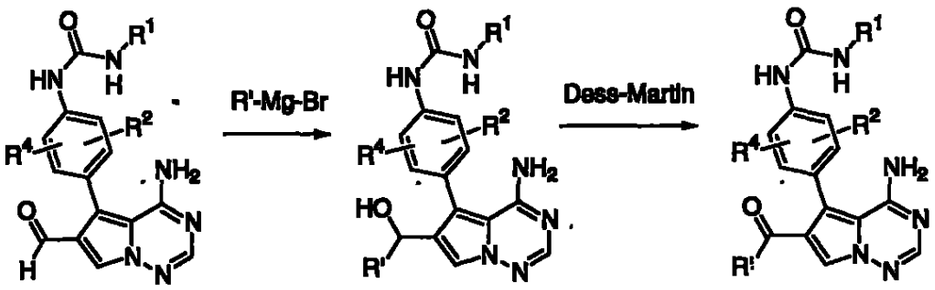
The intermediates of Formula (XIV-1) – (XIV-13) can then be reduced as desired to provide the corresponding amino compounds of Formula (II), and in turn the compounds of Formula (I).

Reaction Scheme 12



where
R', R" are independently selected from H and (C_1-C_8)alkyl
or
R' and R" may be joined together to form a 5- or 6-membered heterocyclic ring containing an additional N, O or S atom and may be optionally substituted with (C_1-C_8)alkyl

Reaction Scheme 13



where
R', R" are independently selected from substituted (C_1-C_8)alkyl and (C_3-C_8)cycloalkyl

It is also to be understood that starting materials are commercially available or readily prepared by standard methods well known in the art. Such methods include, but are not limited to the transformations listed herein.

If not mentioned otherwise, the reactions are usually carried out in inert organic solvents which do not change under the reaction conditions. These include ethers, such as diethyl ether, 1,4-dioxane or tetrahydrofuran, halogenated hydrocarbons, such as dichloromethane, trichloromethane, carbon tetrachloride, 1,2-dichloroethane, trichloroethane or tetrachloroethane, hydrocarbons, such as benzene, toluene, xylene, hexane, cyclohexane or mineral oil fractions, alcohols, such as methanol, ethanol or iso-propanol, nitromethane, dimethylformamide or acetonitrile. It is also possible to use mixtures of the solvents.

The reactions are generally carried out in a temperature range of from 0°C to 150°C, preferably from 0°C to 70°C. The reactions can be carried out under atmospheric, elevated or under reduced pressure (for example from 0.5 to 5 bar). In general, they are carried out under atmospheric pressure of air or inert gas, typically nitrogen.

Pro-drugs of this invention in general may be made by conventional methods well known in the art. For example, hydroxyl groups may be converted to esters by reacting the compounds with carboxylic acid chlorides or anhydrides under standard

conditions. A hydroxyl group may also be converted to carbonates by reacting the compounds with chloroformates under standard conditions.

Salts of the compounds identified herein can be obtained by isolating the compounds as hydrochloride salts, prepared by treatment of the free base with anhydrous HCl in a suitable solvent such as THF. Generally, a desired salt of a compound of this invention can be prepared in situ during the final isolation and purification of a compound by means well known in the art. Or, a desired salt can be prepared by separately reacting the purified compound in its free base form with a suitable organic or inorganic acid and isolating the salt thus formed. These methods are conventional and would be readily apparent to one skilled in the art.

Additionally, sensitive or reactive groups on the compound of this invention may need to be protected and deprotected during any of the above methods. Protecting groups in general may be added and removed by conventional methods well known in the art (see, for example, T. W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis;* Wiley: New York, (1999).

If used as active compounds, the compounds according to the invention are preferably isolated in more or less pure form, that is more or less free from residues from the synthetic procedure. The degree of purity can be determined by methods known to the chemist or pharmacist (see especially Remington's Pharmaceutical Sciences, 18th ed. 1990, Mack Publishing Group, Enolo). Preferably the compounds are greater than 99% pure (w/w), while purities of greater than 95%, 90% or 85% can be employed if necessary.

The compounds according to the invention exhibit an unforeseeable, useful pharmacological and pharmacokinetic activity spectrum. They are therefore suitable for use as medicaments for the treatment and/or prophylaxis of disorders in humans and animals.

Because of their antiproliferative properties, the compounds according to the invention are useful alone or in combination with other active components for treating and/or preventing mammalian hyper-proliferative disorders. Indications mediated by hyperproliferative disorders means diseases or conditions whose progression proceeds, at least in part, via proliferation.

The present invention also relates to a method of using the compounds or compositions described herein for the treatment or prevention of, or in the manufacture of a medicament for treating or preventing, mammalian hyper-proliferative disorders. This method comprises administering to a patient (or a mammal) in need thereof, including a human, an amount of a compound, a pharmaceutically acceptable salt or ester thereof, or a composition of this invention which is effective to treat or prevent the disorder.

The present invention also relates to a method for using the compounds of this invention as prophylactic or chemopreventive agents for prevention of the mammalian hyper-proliferative disorders described herein. This method comprises administering to a mammal in need thereof, including a human, an amount of a compound of this invention, or a pharmaceutically acceptable salt or ester thereof, which is effective to delay or diminish the onset of the disorder.

Hyper-proliferative disorders include but are not limited to solid tumors, such as cancers of the breast, respiratory tract, brain, reproductive organs, digestive tract, urinary tract, eye, liver, skin, head and neck, thyroid, parathyroid and their distant metastases. Those disorders also include lymphomas, sarcomas, and leukemias.

The present invention also relates to a method for using the compounds of this invention as prophylactic or chemopreventive agents for prevention of the mammalian hyper-proliferative disorders described herein. This method comprises administering to a mammal in need thereof, including a human, an amount of a compound of this invention, or a pharmaceutically acceptable salt or ester thereof, which is effective to delay or diminish the onset of the disorder.

Examples of breast cancer include, but are not limited to invasive ductal carcinoma, invasive lobular carcinoma, ductal carcinoma in situ, and lobular carcinoma in situ.

Examples of cancers of the respiratory tract include, but are not limited to small-cell and non-small-cell lung carcinoma, as well as bronchial adenoma and pleuropulmonary blastoma.

Examples of brain cancers include, but are not limited to brain stem and hypophthalmic glioma, cerebellar and cerebral astrocytoma, medulloblastoma, ependymoma, as well as neuroectodermal and pineal tumor.

Tumors of the male reproductive organs include, but are not limited to prostate and testicular cancer. Tumors of the female reproductive organs include, but are not limited to endometrial, cervical, ovarian, vaginal, and vulvar cancer, as well as sarcoma of the uterus.

Tumors of the digestive tract include, but are not limited to anal, colon, colorectal, esophageal, gallbladder, gastric, pancreatic, rectal, small-intestine, and salivary gland cancers.

Tumors of the urinary tract include, but are not limited to bladder, penile, kidney, renal pelvis, ureter, and urethral cancers.

Eye cancers include, but are not limited to intraocular melanoma and retinoblastoma.

Examples of liver cancers include, but are not limited to hepatocellular carcinoma (liver cell carcinomas with or without fibrolamellar variant), cholangiocarcinoma (intrahepatic bile duct carcinoma), and mixed hepatocellular cholangiocarcinoma.

Skin cancers include, but are not limited to squamous cell carcinoma, Kaposi's sarcoma, malignant melanoma, Merkel cell skin cancer, and non-melanoma skin cancer.

Head-and-neck cancers include, but are not limited to laryngeal / hypopharyngeal / nasopharyngeal / oropharyngeal cancer, and lip and oral cavity cancer.

Lymphomas include, but are not limited to AIDS-related lymphoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, Hodgkin's disease, and lymphoma of the central nervous system.

Sarcomas include, but are not limited to sarcoma of the soft tissue, osteosarcoma, malignant fibrous histiocytoma, lymphosarcoma, and rhabdomyosarcoma.

Leukemias include, but are not limited to acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, and hairy cell leukemia.

These disorders have been well characterized in humans, and also exist with a similar etiology in other mammals which can also be treated by the administration of the compounds and/or pharmaceutical compositions of the present invention.

The assay described in this application is one of the methods by which compound activity relating to treatment of the disorders identified herein can be determined.

In another embodiment, the present invention provides a medicament containing at least one compound according to the invention. In another embodiment, the present invention provides a medicament containing at least one compound according to the invention together with one or more pharmacologically safe excipient or carrier substances, for example hydroxypropylcellulose, and also their use for the abovementioned purposes.

The active component can act systemically and/or locally. For this purpose, it can be applied in a suitable manner, for example orally, parenterally, pulmonally, nasally, sublingually, lingually, buccally, rectally, transdermally, conjunctivally, otically or as an implant.

For these application routes, the active component can be administered in suitable application forms. An overview of application forms is given in Remington's Pharmaceutical Sciences, 18th ed. 1990, Mack Publishing Group, Enolo.

Useful oral application forms include application forms which release the active component rapidly and/or in modified form, such as for example tablets (non-coated and coated tablets, for example with an enteric coating), capsules, sugar-coated tablets, granules, pellets, powders, emulsions, suspensions, solutions and aerosols. Such sustained-release pharmaceutical compositions are described in Part 8, Chapter 91 of Remington's Pharmaceutical Sciences, 18th ed. 1990, Mack Publishing Group, Enolo.

Parenteral application can be carried out with avoidance of an absorption step (intravenously, intraarterially, intracardially, intraspinally or intralumbarly) or with inclusion of an absorption (intramuscularly, subcutaneously, intracutaneously, percutaneously or intraperitoneally). Useful parenteral application forms include injection and infusion preparations in the form of solutions, suspensions, emulsions, lyophilisates and sterile powders. Such parenteral pharmaceutical compositions are described in Part 8, Chapter 84 of Remington's Pharmaceutical Sciences, 18th ed. 1990, Mack Publishing Group, Enolo.

In one embodiment, the invention relates to intravenous (i.v.) application of the active compound, e.g. as bolus injection (that is as single dose, e.g. per syringe), infusion over a short period of time (e.g. for up to one hour) or infusion over a long period of time (e.g. for more than one hour). The application can also be done by intermittent dosing. The applied volume can vary dependent on the conditions and usually is 0,5 to 30, or 1 to 20 ml for bolus injection, 25 to 500, or 50 to 250 ml for infusion over a short period of time and 50 to 1000, or 100 to 500 ml for infusion over a long period of time.

The application forms have to be sterile and free of pyrogens. They can be based on aqueous solvents or mixtures of aqueous and organic solvents. Examples are ethanol, polyethyleneglycol (PEG) 300 or 400, aqueous solutions containing cyclodextrins or emulsifiers, such as lecithin, Pluronic F68®, Solutol HS15® or Cremophor®. Aqueous solutions are preferred.

For intravenous application the solutions are generally isotonic and euhydric, for example with a pH of 3 to 11, 6 to 8 or about 7.4.

Glass or plastic containers can be employed as packaging for i.v.-solutions, e.g. rubber seal vials. They can contain liquid volumes of 1 to 1000, or 5 to 50 ml. The solution can directly be withdrawn from the vial to be applied to the patient. For this purpose, it can be advantageous to provide the active compound in solid form (e.g. as lyophilisate) and dissolve by adding the solvent to the vial directly before administration.

Solutions for infusion can advantageously be packaged in containers made from glass or plastic, for example bottles or collapsible containers such as bags. They can contain liquid volumes of 1 to 1000, or 50 to 500 ml.

Forms suitable for other application routes include for example inhalatory pharmaceutical forms (including powder inhalers, nebulizers), nasal drops/solutions, sprays; tablets or capsules to be administered lingually, sublingually or buccally, suppositories, ear and eye preparations, vaginal capsules, aqueous suspensions (lotions, shake mixtures), lipophilic suspensions, ointments, creams, milk, pastes, dusting powders or implants.

The active components can be converted into the recited application forms in a manner known per se. This is carried out using inert non-toxic, pharmaceutically suitable excipients. These include *inter alia* carriers (for example microcrystalline cellulose), solvents (for example liquid polyethylene glycols), emulsifiers (for example sodium dodecyl sulphate), dispersing agents (for example polyvinylpyrrolidone), synthetic and natural biopolymers (for example albumin), stabilizers (for example antioxidants such as ascorbic acid), colorants (for example inorganic pigments such as iron oxides) or taste and/or odor corrigents.

For human use, in the case of oral administration, it is recommended to administer doses of from 0.001 to 100 mg/kg, or from 0.01 to 20 mg/kg. In the case of parenteral administration such as, for example, intravenously or via mucous membranes nasally, buccally or inhalationally, it is recommended to use doses of 0.001 to 0.60 mg/kg, in particular 0.01 to 30 mg/kg.

In spite of this, it can be necessary in certain circumstances to depart from the amounts mentioned, namely as a function of body weight, application route, individual behaviour towards the active component, manner of preparation and time or interval at which application takes place. It can for instance be sufficient in some cases to use less than the aforementioned minimum amount, while in other cases the upper limit mentioned will have to be exceeded. In the case of the application of

larger amounts, it can be advisable to divide them into a plurality of individual doses spread through the day.

The percentages in the tests and examples which follows are, unless otherwise stated, by weight; parts are by weight. Solvent ratios, dilution ratios and concentrations reported for liquid/liquid solutions are each based on the volume.

A. Examples

General Preparative Methods

Unless otherwise stated, the term 'concentrated under reduced pressure' refers to use of a Buchi rotary evaporator at approximately 15 mm of Hg.

Thin-layer chromatography (TLC) was performed on Whatman® pre-coated glass-backed silica gel 60A F-254 250 μm plates. Visualization of plates was effected by one or more of the following techniques: (a) ultraviolet illumination, (b) exposure to iodine vapor, (c) immersion of the plate in a 10% solution of phosphomolybdic acid in ethanol followed by heating, and/or (d) immersion of the plate in a cerium sulfate solution followed by heating. Column chromatography (flash chromatography) was performed using 230-400 mesh EM Science® silica gel.
"Shaker block" refers to the use of a shaker model BTS3000 from J-Kem Scientific at a speed of 150-180.

Proton (^{1}H) nuclear magnetic resonance (NMR) spectra were measured with a Varian 400 Mercury Plus (400 MHz) spectrometer with either Me_4Si (δ 0.00) or residual protonated solvent ($CHCl_3$ δ 7.26; MeOH δ 3.30; DMSO δ 2.49) as standard. Carbon (^{13}C) NMR spectra were measured with a Varian 400 Mercury Plus (400 MHz) (100 MHz) spectrometer with solvent ($CDCl_3$ δ 77.0; d_3-MeOD; δ 49.0; d_6-DMSO δ 39.5) as standard.

HPLC - electrospray mass spectra (HPLC ES-MS) for characterization were obtained using a Gilson HPLC system equipped with a variable wavelength detector set at 254 nm, a YMC pro C-18 column (2 x 23 mm, 120A), and a Finnigan LCQ ion trap mass spectrometer with electrospray ionization. Spectra were scanned from 120-1200 amu using a variable ion time according to the number of ions in the source. The eluants were A: 2% acetonitrile in water with 0.02% TFA and B: 2% water in acetonitrile with 0.018% TFA. Gradient elution from 10% B to 95% over 3.5 minutes at a flow rate of 1.0 mL/min was used with an initial hold of 0.5 minutes and a final hold at 95% B of 0.5 minutes. Total run time was 6.5 minutes.

Preparative high performance liquid chromatography (HPLC), when needed, was run using either a Gilson 215 Liquid Handler with a Gilson 322 pump and a Gilson UV-VIS-155 detector set at 254 nm or a Shimadzu LC-8A pump with a Shimadzu SPD-10A detector set at 220 nM both equipped with a YMC Pac ProC18 column (150 x 20 mm). Eluant A is acetonitrile with 0.01% of trifluoroacetic acid and Eluant B is water with 0.01% trifluoroacetic acid. Typically, a gradient was run from 10% A / 90% B to 90%A / 10% B over a period of 15-25 min. The fractions of interest were collected and the solvent removed *in vacuo* to give the final compound as a trifluoroacetic acid salt.

HPLC using a chiral column may be used to separate enantiomers. Analytical conditions used a Chiralcel OD-H® (4.6 x 150 mm) column on a Shimadzu HPLC. 30% Eluent A = Hexane (0.1 % Et_3N) and 70% eluent B = 1:1 MeOH-EtOH (0.1 % Et_3N) for 15 min. with a flowrate of 1.0 mL/min, detection by UV at 235 nm. Preparative conditions used a Chiralcel OD® (20 x 150 mm) column on a Gilson 215 HPLC. 30% Eluent A = Hexane (0.1 % Et_3N) and 70% eluent B = 1:1 MeOH-EtOH (0.1 % Et_3N) for 15 min. with a flowrate of 1.0 mL/min, detection by UV at 235 nm using approximately 75 mg material per injection.

RPMI growth media was obtained from GIBCO®.

The IUPAC names were generated using ACD/Name Version 7.0 from Advanced Chemistry Development (U.S.A.).

Abbreviations and Acronyms

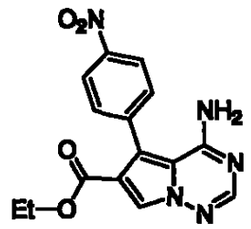
^{1}H-NMR	proton nuclear magnetic resonance spectroscopy
^{31}P-NMR	phophorus-31 nuclear magnetic resonance spectroscopy
AcOH	acetic acid
$(Ac)_2O$	acetic anhydride
abs	absolute
aq	aqueous
ap	approximate
atm	atmosphere
br	broad
BOP	benzotriazole-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate
Bu	butyl
ACN	acetonitrile
Ac_2O	acetic anhydride
AcOH	acetic acid
Celite®	brand of diatomaceous earth from Celite Corp.
CD_3CN	acetonitrile-d_3
CD_3OD	methanol-d_4
d	doublet
DCE	dichloroethane
DCM	dichloromethane
dd	double doublet
DIBAL	diisobutylaluminum hydride
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
DMSO-d_6	dimethyldsulfoxide-d_6
equiv	equivalent(s)
ES-MS	electrospray mass spectrometry
Et_3N	triethylamine
Et_2O	diethyl ether
EtOAc	ethyl acetate

EtOH	ethanol
FBS	fetal bovine serum
g	gram(s)
h	hour(s)
HPLC	high performance liquid chromatography
Hz	hertz
J	NMR coupling constant
L	liter(s)
LCMS	liquid chromatography-mass spectrometry
LHMDS	lithium hexamethyldisilazide
M	molar
Me	methyl
MeOH	methanol
mg	milligram(s)
MHz	megahertz
min	minute(s)
mL	milliliter
mmol	millimole
MPLC	medium pressure liquid chromatography
MS	mass spectrometry
Ms	methanesulfonyl
N	normal
nM	nanomolar
Pr	propyl
py-BOP	benzotriazol-1-yl-oxytripyrrolidineophosponium hexafluorophosphate
q	quartet
Ra-Ni	Raney-Nickel
R_f	TLC retention factor
Rochelle's salt	potassium sodium tartrate
RPMI	Roswell Park Memorial Institute
RT	retention time

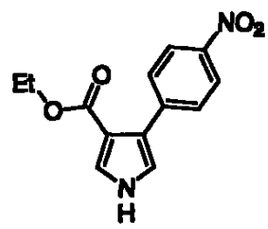
rt	room temperature
s	singlet
t	triplet
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TosMIC	Tosylmethyl isocyanide
TPP	triphenylphosphine
Ts	*p*-toluenesulfonyl
v/v	volume-to-volume proportion
v/v/v	volume-to-volume-to-volume proportion
µL	microliter
µm	micrometer

Preparation of Intermediates

Intermediate A: **Preparation of ethyl 4-amino-5-(4-nitrophenyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate**



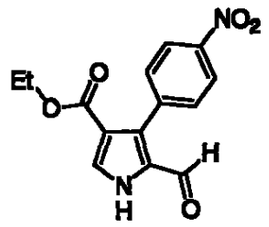
Step 1: Preparation of ethyl 4-(4-nitrophenyl)-1*H*-pyrrole-3-carboxylate



To a solution of 1M lithium hexamethyldisilazide in THF (102.4 mL, 102.4 mmol) cooled to –77 °C was added 1-[(isocyanomethyl)sulfonyl]-4-methylbenzene (20.0 g, 102.4 mmol) as a solution in THF (100 mL) dropwise over 30 min. The solution was allowed to stir an additional 15 min, and then ethyl (2E)-3-(4-nitrophenyl)acrylate was added dropwise (22.66 g, 102.4 mmol) as a solution in THF (250 mL) over 1 h. The reaction was allowed to warm to rt over 17 h. Aqueous saturated $NaHCO_3$ (200 mL) was added to the reaction mixture followed by EtOAc (500 mL). The solution was transferred to a separatory funnel, and the organic layer was isolated and washed with H_2O (100 mL). The aqueous layers were back extracted with EtOAc (2 x 150 mL). The combined organic layers were collected, dried ($MgSO_4$), concentrated onto silica gel, and purified by column chromatography (100% CH_2Cl_2 ramping to 95:5 v/v CH_2Cl_2-EtOAc) to afford 16.65 g of the above compound as an orange/yellow solid (63.98 mmol, yield 62%). ^{1}H-NMR (DMSO-d_6) δ 11.78 (br s, 1H), 8.19 to 8.15 (m, 2H), 7.76 to 7.73 (m, 2H), 7.57 to 7.56 (m,

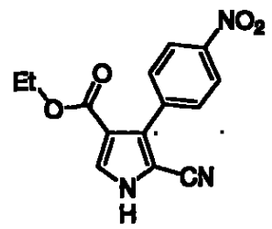
1H), 7.22 to 7.21 (m, 1H), 4.18 to 4.13 (q, J = 7.1 Hz, 2H), 1.21 (t, J = 7.1 Hz, 3H); LCMS RT = 2.90 min; TLC R_f = 0.47 (95:5 v/v CH_2Cl_2-EtOAc).

Step 2: Preparation of ethyl 5-formyl-4-(nitrophenyl)-1*H*-pyrrole-3-carboxylate ...



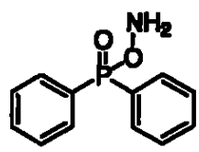
To a solution of DCE (100 mL) was added DMF (14.96 mL, 194.4 mmol), which was cooled in an ice-salt bath. As $POCl_3$ (18.12 mL, 194.4 mmol) was slowly added a white precipitate formed. The solution was allowed to warm to rt while vigorously stirring over 30 min. The slurry was again cooled in an ice-salt bath. Ethyl 4-(4-nitrophenyl)-1*H*-pyrrole-3-carboxylate (46.00 g, 176.8 mmol) was added as a suspension in DCE (500 mL). The reaction proceeded while cooling in an ice-salt bath for 1 h, and then was allowed to warm to rt over 17 h. Sodium Acetate (79.75 g, 972.2 mmol) in water (600 mL) was added to the reaction, and the solution was heated to 80 °C for 1 h. Upon cooling to rt the solution was transferred to a separatory funnel and the organic layer was isolated while the aqueous layer was back extracted with CH_2Cl_2 (2 x 150 mL). The combined organic layers were collected, dried ($MgSO_4$), filtered, and concentrated to dryness. The crude material was heated to reflux in toluene (2 L) and to the hot solution was added hexanes (200 mL). The solution was allowed to slowly cool, and over the following 2 days crystals formed. The crystals were collected, washed with Et_2O (500 mL), and dried under vacuum to afford 25.53 g of the above compound as golden needles (88.57 mmol, yield 50%). ^{1}H-NMR (DMSO-d_6) δ 12.94 (br s, 1H), 9.29 (d, J = 0.8 Hz, 1H), 8.25 to 8.22 (m, 2H), 7.81 (d, J = 2.7 Hz, 1H), 7.74 to 7.71 (m, 2H), 4.12 to 4.06 (q, J = 7.1 Hz, 2H), 1.15 to 1.11 (t, J = 7.0 Hz, 3H); LCMS RT = 2.75 min; TLC R_f = 0.16 (95:5 v/v CH_2Cl_2-EtOAc).

Step 3: Preparation of ethyl 5-cyano-4-(nitrophenyl)-1*H*-pyrrole-3-carboxylate



To a solution of pyridine (400 mL) was added ethyl 5-formyl-4-(nitrophenyl)-1*H*-pyrrole-3-carboxylate (24.55 g, 85.17 mmol) followed by hydroxylamine hydrochloride (6.51 g, 93.7 mmol). The solution was stirred at rt for 2 h, acetic anhydride (17.68 mL, 187.4 mmol) was added, and the solution was heated to 80 °C for 17 h. Upon cooling to rt the reaction mixture was partially concentrated in vacuo and then diluted with EtOAc (300 mL) and H_2O (300 mL). The solution was transferred to a separatory funnel, and the organic layer was isolated while the aqueous layers were back extracted with EtOAc (2 x 100 mL). The combined organic layers were collected, dried (Na_2SO_4), filtered, and concentrated to dryness. The crude material was then triturated with CH_2Cl_2–Et_2O (1:1 v/v, 300 mL). The solid was collected, washed with Et_2O (150 mL), and dried under vacuum to afford 18.94 g of the above compound as a fluffy white solid (66.40 mmol, yield 78%). ^{1}H-NMR (DMSO-d_6) δ 13.24 (br s, 1H), 8.30 to 8.27 (m, 2H), 7.92 (s, 1H), 7.74 to 7.71 (m, 2H), 4.16 to 4.10 (q, J = 7.2 Hz, 2H), 1.18 to 1.15 (t, J = 7.0 Hz, 3H); LCMS RT = 2.97 min; TLC R_f = 0.20 (95:5 v/v CH_2Cl_2-EtOAc).

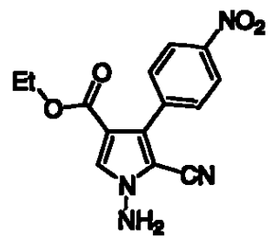
Step 4: Preparation of (aminooxy)(diphenyl)phosphine oxide



To hydroxylamine hydrochloride (15.86 g, 228.2 mmol) in H_2O (35 mL) cooled in an ice-salt bath was added 7.1 N NaOH (27.4 mL, 194.4 mmol) followed by 1,4-dioxane (100 mL). The solution was vigorously stirred for 15 min and then

chlorodiphenylphosphine oxide (20.00 g, 84.52 mmol) was added as a solution in 1,4-dioxane (100 mL). The solution was stirred an additional 15 min as a white precipitate formed which was filtered. The solid was suspended in 0.25 N NaOH (250mL) while stirring in an ice-salt bath for 1 h. The solid was then collected, washed with H_2O (100 mL), and thoroughly dried under vacuum to afford 7.09 g of the above compound as a white powder (30.4 mmol, yield 36%). ^{1}H-NMR (DMSO-d_6) δ 7.72 to 7.67 (m, 4H), 7.50 to 7.40 (m, 6H); ^{31}P-NMR (DMSO-d_6) δ 23.11 (br s, 1P).

Step 5: Preparation of ethyl 1-amino-5-cyano-4-(nitrophenyl)-1*H*-pyrrole-3-carboxylate



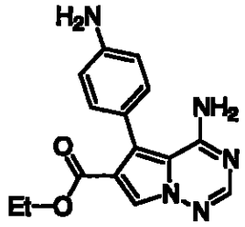
To a solution of DMF (625 mL) was added ethyl 5-cyano-4-(nitrophenyl)-1*H*-pyrrole-3-carboxylate (17.97 g, 63.00 mmol) followed by NaH, 60% dispersion in mineral oil (3.02 g, 75.59 mmol). The solution was stirred at rt for 15 min and then (aminooxy)(diphenyl)phosphine oxide (17.63 g, 75.59 mmol) was added, and the solution was heated to 80 °C for 17 h. Upon cooling to rt aqueous saturated $NaHCO_3$ (500 mL) was added followed by EtOAc (400 mL), which was transferred to a separatory funnel and the organic layer was isolated while the aqueous layer was back extracted with EtOAc (2 x 200mL). The combined organic layers were collected, dried (Na_2SO_4), filtered, and concentrated to dryness. The crude material was then triturated with CH_2Cl_2-hexanes (1:1 v/v 400 mL). The solid was collected, washed with hexanes (100 mL), dried under vacuum, suspended in EtOAc which was heated to reflux for 15 min, and then filtered. The filtrate was concentrated in vacuo and then dried under vacuum to afford 14.15 g of the above compound as a yellow powder (47.12 mmol, yield 75%). ^{1}H-NMR (DMSO-d_6) δ 8.29 to 8.27 (m, 2H), 7.73 (s, 1H), 7.71 to 7.69 (m, 2H), 6.71 (br s, 2H), 4.14 to 4.09 (q, J = 7.1 Hz, 2H),

1.17 to 1.14 (t, J = 7.1 Hz, 3H); LCMS RT = 2.91 min; TLC R_f = 0.30 (95:5 v/v CH_2Cl_2-EtOAc).

Step 6: Preparation of the title compound

To a solution of formamide (74.9 mL, 1.88 mol) was added ethyl 1-amino-5-cyano-4-(nitrophenyl)-1*H*-pyrrole-3-carboxylate (14.15 g, 47.12 mmol). The solution was heated to 195 °C for 2 h and was then allowed to cool to rt over 17 h. The crystalline solid was collected and washed with EtOAc (2 x 100mL) and then with H_2O (100mL). The solid was dried under vacuum to afford 10.20 g of the above compound as a bronze crystalline solid (31.16 mmol, yield 66%). ^{1}H-NMR (DMSO-d_6) δ 8.27 to 8.25 (m, 2H), 8.20 (s, 1H), 8.05 (br s, 1H), 7.97 (s, 1H), 7.66 to 7.64 (m, 2H), 5.52 (br s, 1H), 4.10 to 4.05 (q, J = 7.1 Hz, 2H), 1.11 to 1.07 (t, J = 7.1 Hz, 3H); MS $[M+H]^+$ = 328; LCMS RT = 2.51 min; TLC R_f = 0.20 (3:1 v/v CH_2Cl_2-EtOAc).

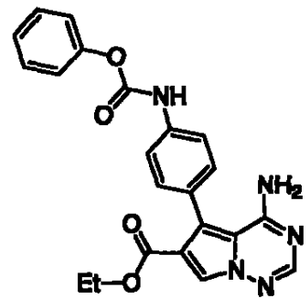
Intermediate B: Preparation of ethyl 4-amino-5-(4-aminophenyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate



Raney nickel was added to a flask containing 20 mL abs EtOH. The catalyst was triturated with abs EtOH (3 x 20 mL). A suspension of ethyl 4-amino-5-(4-nitrophenyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate (4.0 g, 12.2 mmol) in abs EtOH (600 mL)/THF (200 mL) was added to the flask with the catalyst. The flask was evacuated and refilled with hydrogen gas (3x) and the reaction was then placed under a hydrogen atmosphere (1 atm) and allowed to stir at rt overnight. The reaction was filtered through a Celite® pad and washed with copious amounts of EtOH/THF (3:1) to afford 3.60 g of the above compound as a brown solid (yield 96%) ^{1}H-NMR (DMSO-d_6) δ 8.05 (s, 1H), 8.04 (br s, 2H), 7.88 (s, 1H), 7.01 (d, J = 8.0 Hz, 2H), 6.61 (d, J = 8.0 Hz, 2H), 5.31 (br s, 2H), 4.07 (q, J = 7.4 Hz, 2H), 1.12

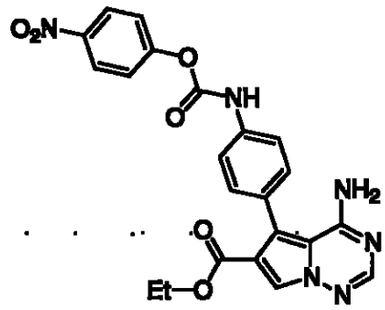
(t, J = 7.2 Hz, 3H); MS $[M+H]^+$ = 298; LCMS RT = 1.64 min; TLC R_f = 0.30 (Acetone/ CH_2Cl_2 1:3).

Intermediate C: Preparation of ethyl 4-amino-5-[4-[(phenoxycarbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate



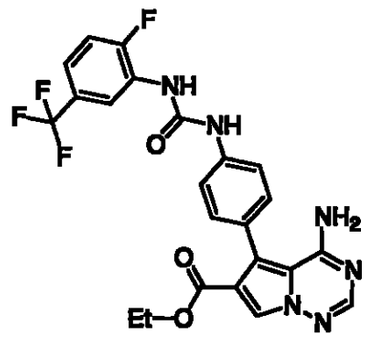
To a stirred solution of Intermediate B (1.0 g, 3.4 mmol) in THF (33 mL) was added pyridine (0.33 mL, 4.0 mmol), then phenyl chloroformate (0.42 mL, 3.4 mmol) at -40 °C. Some solid precipitated out. The mixture was stirred at rt for 2 h. Then more phenyl chloroformate (0.02 mL, 0.10 mmol) was added and the mixture was stirred at rt for another half hour. The reaction was filtered, washed with water (3 x 5 mL) and EtOAc-hexanes (9:1 v/v)(3 x 5 mL) to afford the above compound as a light yellow solid (600 mg, 43%). The filtrate was concentrated in vacuo and further purified by column chromatography (30:70:1 to 80:20:1 v/v/v EtOAc-hexanes-NH_4OH) to afford more of the title compound (570 mg, 40%). ^{1}H-NMR (DMSO-d_6) δ 10.42 (s, 1H), 8.13 (s, 1H), 8.06 (br s, 1H), 7.93 (s, 1H), 7.58 (d, J = 8.4 Hz, 2H), 7.46 to 7.39 (m, 2H), 7.35 (d, J = 8.5 Hz, 2H), 7.29 to 7.21 (m, 3H), 5.07 (br s, 1H), 4.06 (q, J = 7.2 Hz, 2H), 1.08 (t, J = 7.2 Hz, 3H); MS $[M+H]^+$ = 418; LCMS RT = 2.81 min.

Intermediate D: Preparation of ethyl 4-amino-5-(4-{[(4-nitrophenoxy)carbonyl]amino}phenyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate



The procedure used for the preparation of Intermediate C was used to prepare the title compound by substituting 4-nitrophenyl chloroformate for phenyl chloroformate. ^{1}H-NMR (DMSO-d_6) δ 10.66 (s, 1H), 8.32 (d, J = 9.3 Hz, 2H), 8.16 (s, 1H), 7.95 (s, 1H), 7.61 (d, J = 8.8 Hz, 2H), 7.56 (d, J = 8.9 Hz, 2H), 7.38 (d, J = 8.9 Hz, 2H), 4.07 (q, J = 7.2 Hz, 2H), 1.09 (t, J = 7.2 Hz, 3H); MS $[M+H]^+$ = 463; LCMS RT = 3.29 min.

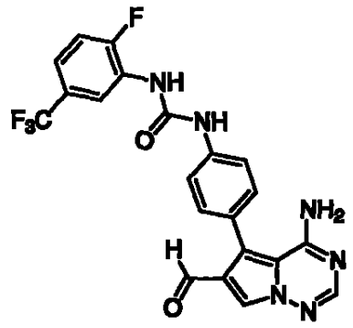
Intermediate E: Preparation of ethyl 4-amino-5-{4-[({[2-fluoro-5-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate



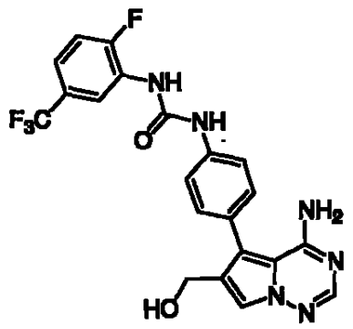
To a suspension of Intermediate C (210 mg, 0.45 mmol) in THF:DMF 4:1 (8 mL) was added Et_3N (0.20 mL, 1.4 mmol) and 2-fluoro-5-(trifluoromethyl)aniline (0.18 mL, 1.36 mmol). This was stirred at rt until reaction was complete upon which the reaction was evaporated to dryness and purified via HPLC (10-90% ACN/H_2O) to give the product as a yellow solid (80 mg, 35%). ^{1}H-NMR (DMSO-d_6) δ 9.33 (s, 1H), 8.97 (d, J = 4.0 Hz, 1H), 8.62 (d, J = 12.0 Hz, 1H), 8.12 (s, 1H), 8.11 (br s, 1H),

7.92 (s, 1H), 7.6-7.3 (m, 5H), 4.10 (q, J = 8.0 Hz, 2H), 1.11 (t, J = 8.0 Hz, 3H); MS $[M+H]^+$ = 503; LCMS RT = 3.50 min; TLC R_f = 0.40 (3:1 v/v CH_2Cl_2-Acetone).

Intermediate F: **Preparation of *N*-[4-(4-amino-6-formylpyrrolo[2,1-f][1,2,4]triazin-5-yl)phenyl]-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea**



Step 1: Preparation of *N*-{4-[4-amino-6-(hydroxymethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea



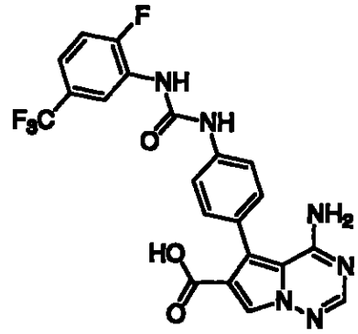
To a solution of THF (8.0 mL) was added Intermediate E (80.0 mg, 0.16 mmol) followed by DIBAL (0.8 mL, 0.8 mmol, 1.0M solution in THF). The reaction was stirred at rt with addition of DIBAL (2.4 mL, 2.4 mmol, 1.0M solution in THF) in three batches until HPLC indicated completion of reaction. The reaction was diluted with EtOAc and quenched with saturated aqueous Rochelle's salt. Reaction was extracted with EtOAc (4x). Organic was dried (Na_2SO_4) and evaporated to give a crude oil that was purified via HPLC (10-90% ACN/H_2O) yielding a yellow solid

(40.0 mg, 55%). ^{1}H-NMR (CD_3CN) δ 8.61 (d, *J*= 8.0 Hz, 1H), 7.80 (s, 1H), 7.66-7.60 (m, 3H), 7.42-7.32 (m, 4H), 4.50 (s, 2H); MS $[M+H]^+$ = 461; LCMS RT = 2.87 min.

Step 2: Preparation of the title compound

N-{4-[4-amino-6-(hydroxymethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea (40.0 mg, 0.09 mmol) was dissolved in THF (5.0 mL) and to it was added Dess-Martin Periodinane reagent (44.0 mg, 0.10 mmol). The reaction was stirred at rt until HPLC indicated completion of reaction. Reaction was diluted with EtOAc and washed with saturated aqueous $NaHCO_3/Na_2S_2O_3$ 1:1 (3x). The aqueous layer was back extracted with EtOAc (2x). Organic was dried (Na_2SO_4) and evaporated to give a crude oil that was purified via HPLC (10-90% ACN/H_2O) to give a yellow solid (35.0 mg, 88%). ^{1}H-NMR (CD_3OD) δ 9.76 (s, 1H), 8.61 (d, *J* = 8.0 Hz, 1H), 8.11 (s, 1H), 7.87 (s, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H); MS $[M+H]^+$ = 459; LCMS RT = 2.95 min.

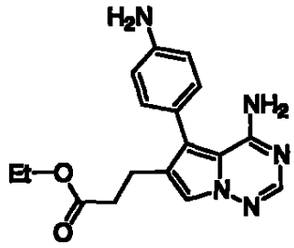
Intermediate G: Preparation of 4-amino-5-{4-[({[2-fluoro-5-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid



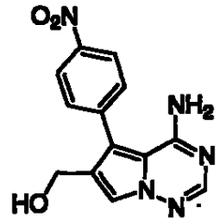
To a solution of Intermediate E (720.0 mg, 1.433 mmol) in 5 mL MeOH and 3 mL THF was added 1M NaOH (3.58 mL, 3.58 mmoL) and the reaction left to stir at 60 °C for 12 h. The reaction mixture was cooled and partitioned between $CHCl_3$ and pH 2 sulfate buffer. The organic layer was washed with brine, dried (Na_2SO_4)

and concentrated to yield a brown solid (623 mg, 92% yield). ^{1}H-NMR (DMSO-d_6) δ 12.17 (bs, 1H), 9.34 (s, 1H), 8.98 (d, J = 2 Hz, 1H), 8.62 (dd, J = 2 Hz, 8 Hz, 1H), 8.07 (3, 1H), 8.0 (bs, 1H), 7.91 (s, 1H), 7.53 (d, J = 8Hz, 2 H), 7.55-7.45 (m, 1H), 7.42-7.35 (m, 1H), 7.32 (d, J = 8 Hz, 2H), 5.0 (bs, 1H); MS $[M+H]^+$ = 475.2; LCMS RT = 2.56min; TLC R_f = 0.26 (1:1:0.02 v/v/v THF:CH_2Cl_2:MeOH).

Intermediate H: Preparation of ethyl 3-[4-amino-5-(4-aminophenyl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]propanoate

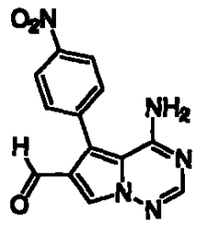


Step 1: Preparation of [4-amino-5-(4-nitrophenyl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methanol



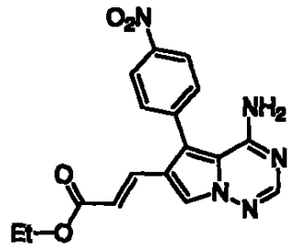
To a solution of THF (10 mL) was added Intermediate A (500 mg, 1.53 mmol) followed by DIBAL (3 mL, 3 mmol, 1.0M solution in toluene). The reaction was stirred at rt for 1 h. Additional DIBAL (1.5 mL, 1.5 mmol, 1.0M solution in toluene) was added and stirred at rt for another 1 h. The reaction was diluted with EtOAc and quenched with saturated aqueous Rochelle's salt. Reaction was extracted with EtOAc (4x). The organic was dried (Na_2SO_4) and evaporated to give a crude solid (435 mg, 100%) that was used directly in the next step without further purification. ^{1}H-NMR (DMSO-d_6) δ 8.29 (d, J= 9.2 Hz, 2H), 7.89 (s, 1H), 7.73 (s, 1H), 7.67 (d, J= 9.3 Hz, 2H), 5.07 (t, J= 5.5 Hz, 1H), 4.38 (d, J= 5.2 Hz, 2H); MS $[M+H]^+$ = 286; LCMS RT = 0.59 min.

Step 2: Preparation of 4-amino-5-(4-nitrophenyl)pyrrolo[2,1-f][1,2,4]triazine-6-carbaldehyde



To a solution of THF (80 mL) was added 4-amino-5-(4-nitrophenyl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methanol (435 mg, 1.53 mmol) followed by Dess-Martin Periodinane reagent (4 mL, 1.89 mmol, 15% wt in CH_2Cl_2). The reaction was stirred at rt until HPLC indicated completion of reaction (5 h). The reaction was diluted with EtOAc and washed with saturated aqueous $NaHCO_3/Na_2S_2O_3$ (1:1 v/v) (3x). The aqueous layer was back extracted with EtOAc (2x). The organic was dried (Na_2SO_4) and evaporated to give a crude yellow solid (433mg, 100%) that was used directly in the next step without further purification. ^{1}H-NMR (DMSO-d_6) δ 9.79 (s, 1H), 8.39 (s, 1H), 8.29 (d, J= 8.7 Hz, 2H), 8.00 (s, 1H), 7.73 (d, J= 8.8 Hz, 2H); MS $[M+H]^+ = 284$; LCMS RT = 2.48 min.

Step 3: Preparation of ethyl (2E)-3-[4-amino-5-(4-nitrophenyl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]acrylate



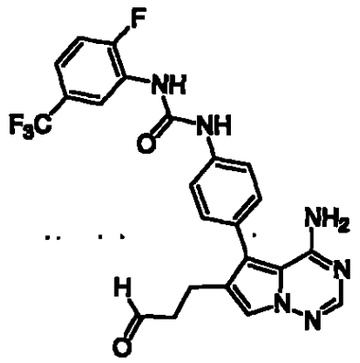
To a suspension of lithium hydride (68 mg, 4.0 mmol) in THF (5 mL) under N_2 atmosphere was added triethyl phosphonoacetate (498 mg, 2.22 mmol). The mixture was stirred at rt for 30 min and to the reaction mixture was added a slurry of 4-amino-5-(4-nitrophenyl)pyrrolo[2,1-f][1,2,4]triazine-6-carbaldehyde (433 mg, 1.53

mmol) in THF (15 ml). The mixture was heated at reflux for 2 h. After it was cooled to rt, aqueous $NaHCO_3$ was slowly added followed by EtOAc. The organic layer was collected and the aqueous layer was back extracted with EtOAc (2x). The combined organic layers were dried (Na_2SO_4) and evaporated to give a crude yellow solid that was purified by column chromatography (10:90 to 90:10 v/v EtOAc-hexanes) to afford the title compound (480 mg, 89%). ^{1}H-NMR (CD_3OD) δ 8.42 (d, J = 8.0 Hz, 2H), 8.17 (s, 1H), 7.88 (s, 1H), 7.68 (d, J = 8.0 Hz, 2H), 7.43 (d, J = 16 Hz, 1H), 6.36 (d, J = 16 Hz, 1H), 4.16 (q, J = 7.1 Hz, 2H), 1.23 (t, J = 7.1 Hz, 3H); MS $[M+H]^+$ = 354; LCMS RT = 3.12 min.

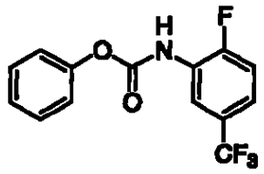
Step 4: Preparation of the title compound

A suspension of PtO_2 (16 mg, 0.070 mmol) in acetic acid (0.5 ml) was added to a suspension of ethyl (2E)-3-[4-amino-5-(4-nitrophenyl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]acrylate (144 mg, 0.408 mmol) in acetic acid (2 ml) under N_2 atmosphere. The flask was evacuated and refilled with hydrogen gas (3x) and the reaction proceeded under a hydrogen atmosphere (1 atm) for 1 d. Additional PtO_2 (50 mg, 0.22 mmol) in acetic acid (0.5 ml) was added and the reaction proceeded under H_2 atmosphere for an additional 1 d. The reaction was filtered through a Celite pad and washed with MeOH. It was evaporated to dryness, diluted with EtOAc and washed with aqueous Na_2CO_3. The aqueous layer was back extracted with EtOAc (2x). Organic was dried (Na_2SO_4), filtered, and evaporated to dryness to afford the above compound as a yellow solid (120 mg, yield 90%). ^{1}H-NMR (CD_3OD) δ 7.70 (s, 1H), 7.47 (s, 1H), 7.12 (d, J = 8.3 Hz, 2H), 6.84 (d, J = 8.3 Hz, 2H), 4.06 (q, J = 7.8 Hz, 2H), 2.82 (t, J = 7.8 Hz, 2H), 2.48 (t, J = 7.7 Hz, 2H), 1.18(t, J = 7.8 Hz, 3H); MS $[M+H]^+$ = 326; LCMS RT = 1.20 min.

Intermediate I: **Preparation of *N*-[4-[4-amino-6-(3-oxopropyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl]-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea**

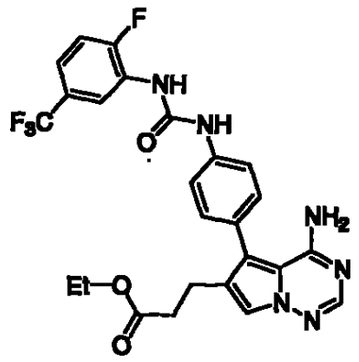


Step 1: Preparation of phenyl [2-fluoro-5-(trifluoromethyl)phenyl]carbamate



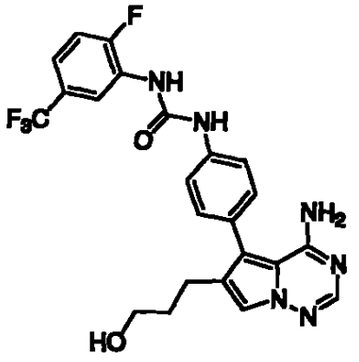
To a stirred solution of 2-fluoro-5-(trifluoromethyl)aniline (3.00 g, 16.7 mmol) in THF (80 mL) was added pyridine (2.71 mL, 33.5 mmol), followed by phenyl chloroformate (3.15 mL, 25.1 mmol) at rt. Some solid precipitated out. The mixture was stirred at rt overnight. Water was added to the reaction and it was extracted with EtOAc. The organic solution was washed with water (2x) and dried over $MgSO_4$ and then filtered. The filtrate was concentrated in vacuo and purified by column chromatography (10:90 to 30:70 v/v EtOAc-hexanes) to afford the title compound (3.1 g, 62%). ^{1}H-NMR (DMSO-d_6) δ 10.36 (br s, 1H), 8.15 (d, J = 7.1 Hz, 1H), 7.59 to 7.47 (m, 2H), 7.46 to 7.38 (m, 2H), 7.30 to 7.20 (m, 3H); TLC R_f = 0.39 (9:1 v/v hexanes-EtOAc).

Step 2: Preparation of ethyl 3-(4-amino-5-{4-[({[2-fluoro-5-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazin-6-yl)propanoate



To a solution of THF (2.0 mL) was added Intermediate H (80 mg, 0.25 mmol) followed by phenyl [2-fluoro-5-(trifluoromethyl)phenyl]carbamate (74 mg, 0.25 mmol) and triethylamine (34 μL, 0.25 mmol). The reaction was stirred at 0 °C and was allowed to slowly warm to rt overnight. The solution was concentrated in vacuo to dryness and then purified by column chromatography (5:95 to 50:50 v/v EtOAc-hexanes) to afford the title compound (66 mg, 50%). ^{1}H-NMR (CD_3OD) δ 8.62 (d, J = 7.4 Hz, 1H), 7.74 (s, 1H), 7.63 (d, J = 8.6 Hz, 2H), 7.52 (s, 1H), 7.40 to 7.31 (m, 4H), 4.06 (q, J = 7.0 Hz, 2H), 2.84 (t, J = 7.5 Hz, 2H), 2.50 (t, J = 7.4 Hz, 2H), 1.18 (t, J = 7.0 Hz, 3H); MS $[M+H]^+$ = 531; LCMS RT = 3.29 min.

Step 3: Preparation of *N*-{4-[4-amino-6-(3-hydroxypropyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea



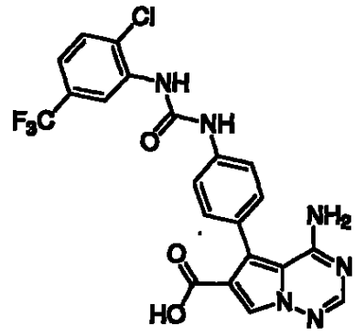
To a solution of THF (6 mL) was added ethyl 3-(4-amino-5-{4-[({[2-fluoro-5-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-

f][1,2,4]triazin-6-yl)propanoate (62 mg, 0.12 mmol) followed by DIBAL (0.6 mL, 0.6 mmol, 1.0M solution in toluene). The reaction was stirred at rt for 1 h. Additional DIBAL (1.2 mL, 1.2 mmol, 1.0M solution in toluene) was added and stirred at rt for an additional 1 h. The reaction was diluted with EtOAc and quenched with saturated aqueous Rochelle's salt. Reaction was extracted with EtOAc (4x). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated to dryness to afford a crude yellow solid (56 mg, 98%) that was used directly in the next step without further purification. ^{1}H-NMR (CD_3OD) δ 8.62 (d, J = 7.6 Hz, 1H), 7.74 (s, 1H), 7.61 (d, J = 7.6 Hz, 2H), 7.52 (s, 1H), 7.38 to 7.31 (m, 4H), 3.50 (t, J = 7.1 Hz, 2H), 2.61 (t, J = 7.8 Hz, 2H), 1.77 to 1.65 (m, 2H); MS $[M+H]^+$ = 489; LCMS RT = 2.50 min.

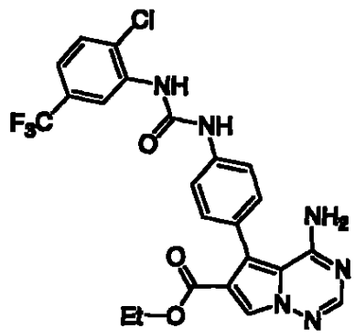
Step 4: Preparation of the title compound

To a solution of THF (5 mL) was added *N*-{4-[4-amino-6-(3-hydroxypropyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea (55 mg, 0.11 mmol) followed by Dess-Martin Periodinane reagent (0.29 mL, 0.14 mmol, 15% wt in CH_2Cl_2). The reaction was stirred until HPLC indicated completion of reaction (2 h). The reaction was diluted with EtOAc and washed with saturated aqueous $NaHCO_3/Na_2S_2O_3$ 1:1 (3x). The aqueous layer was back extracted with EtOAc (2x). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated to give a crude yellow solid (53mg, 96%) that was used without further purification. ^{1}H-NMR (DMSO-d_6) δ 9.35 (s, 1H), 8.98 (s, 1H), 8.62 (d, J = 7.2 Hz, 1H), 7.80 (s, 1H), 7.62 to 7.28 (m, 6H), 2.71 (t, J = 7.5 Hz, 2H), 2.41 (t, J = 7.4 Hz, 2H); MS $[M+H]^+$ = 487; LCMS RT = 2.62 min.

Intermediate J: Preparation of 4-amino-5-{4-[({[2-chloro-5-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid



Step 1: Preparation of ethyl 4-amino-5-{4-[({[2-chloro-5-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate



To a solution of DCE (5 mL) was added Intermediate B (300 mg, 1.01 mmol) followed by 2-chloro-1-isocyanato-4-(trifluoromethyl)benzene (0.32 mL, 2.12 mmol). The reaction was stirred under N_2 at rt for 1 h, and then aq 2N HCl (0.50 mL, 1.01 mmol) was added to the reaction followed by DMF (5 mL). The solution was heated at 80 °C for 1 h. Upon cooling to rt the solution was diluted with EtOAc, transferred to a separatory funnel, and washed with aq saturated $NaHCO_3$. The aq layer was back extracted with EtOAc. The combined organic layers were collected, dried, concentrated, and purified by column chromatography (95:5 v/v CH_2Cl_2-MeOH). The resulting fractions containing product were concentrated and triturated using CH_2Cl_2 and hexanes. The product was filtered and dried in vacuo to afford 408 mg of the above compound as a white solid (0.79 mmol, yield 78%). ^{1}H-NMR (DMSO-d_6) δ 9.72 (s, 1H), 8.67 (s, 1H), 8.64 (s, 1H), 8.13 (s, 1H), 8.08 (br s, 1H), 7.93 (s, 1H), 7.72 (d, J = 8.5 Hz, 1H), 7.56 (d, J = 8.8 Hz, 2H), 7.39 to 7.36 (m, 1H),

7.34 (d, J = 8.6 Hz, 2H), 5.10 (br s, 1H), 4.09 (q, J = 7.0 Hz, 2H), 1.12 (t, J = 7.1 Hz, 3H); MS $[M+H]^+$ = 519; LCMS RT = 3.58 min; TLC R_f = 0.26 (95:5 v/v CH_2Cl_2-MeOH).

Step 2: ... .. Preparation of the title compound

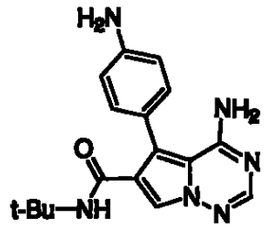
To a solution of MeOH (20 mL) and THF (50 mL) was added ethyl 4-amino-5-{4-[({[2-chloro-5-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate (381 mg, 0.73 mmol) followed by aq 1N NaOH (7.34 mL, 7.34 mmol). The reaction was then heated under N_2 at 60 °C for 17 h. Upon cooling to rt the solution was partially rotavapped and was then treated with 1N HCl (7.34 mL, 7.34 mmol). A precipitate formed which was collected and washed with water yielding 324 mg of the above compound as a white solid (0.66 mmol, yield 90%). ^{1}H-NMR (DMSO-d_6) δ 12.29 (br s, 1H), 9.75 (s, 1H), 8.69 (s, 1H), 8.63 (s, 1H), 8.08 (s, 1H), 8.03 (br s, 1H), 7.92 (s, 1H), 7.72 (d, J = 8.3 Hz, 1H), 7.55 (d, J = 8.4 Hz, 2H), 7.37 (m, 1H), 7.33 (d, J = 8.6 Hz, 2H), 5.05 (br s, 1H); MS $[M+H]^+$ = 491; LCMS RT = 3.15 min; TLC R_f < 0.1 (5:4:1 v/v/v CH_2Cl_2-EtOAc-MeOH).

Intermediate K: Preparation of 4-amino-5-(4-nitrophenyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid

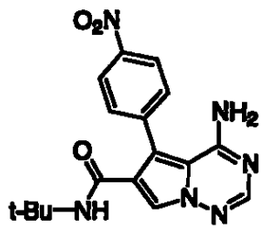


A suspension of Intermediate A (1.04 g, 3.18 mmol) in EtOH (10 mL), THF (5 mL) and 1N NaOH (5.56mL, 5.56 mmol) was stirred at 80 °C for 6 h. The homogeneous solution was cooled to rt and treated dropwise with 1N HCl (5.56 mL). The reaction was concentrated in vacuo and the resulting solid triturated with water to give the above compound as a tan solid. MS $[M+H]^+$ = 300.2; LCMS RT = 1.37 min.

Intermediate L: Preparation of 4-amino-5-(4-aminophenyl)-*N*-(*tert*-butyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



Step 1: Preparation of 4-amino-*N*-(*tert*-butyl)-5-(4-nitrophenyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide

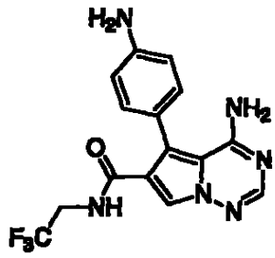


To a solution of toluene (10 mL) was added 2M trimethyl aluminum in hexanes (1.37 mL, 2.75 mmol) followed by 2-methylpropan-2-amine (0.14 mL, 1.37 mmol). The solution was stirred at rt for 15 min and then Intermediate A (300 mg, 0.92 mmol) was added. The solution was heated at 110 °C for 17 h. Upon cooling to rt 1N HCl was slowly added until bubbling ceased. EtOAc was added followed by careful addition of aq $NaHCO_3$. The solution was transferred to a separatory funnel, the organic was collected and the aqueous was back extracted with EtOAc (3 x 20 mL). The combined organics were dried ($MgSO_4$), concentrated, and purified by column chromatography (50:45:5 v/v/v CH_2Cl_2/EtOAc/MeOH) to afford 181 mg of the above compound (0.51 mmol, yield 56%). ^{1}H-NMR (DMSO-d_6) 8.25 (d, J = 8.9 Hz, 2H), 8.16 (s, 1H), 7.94 (s, 1H), 7.59 (d, J = 8.8 Hz, 2H), 7.39 (s, 1H) 1.25 (s, 9H); MS $[M+H]^+$ = 355; LCMS RT = 2.42 min.

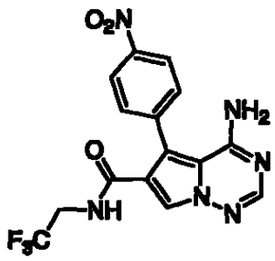
Step 2: Preparation of the title compound

The procedure used for the preparation of Intermediate B was used to prepare the title compound by substituting 4-amino-*N*-(*tert*-butyl)-5-(4-nitrophenyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide for Intermediate A. ^{1}H-NMR (DMSO-d_6) δ 7.91 (s, 1H), 7.89 (br s, 1H), 7.84 (s, 1H), 7.07 (d, J = 8.2 Hz, 2H), 6.69 (d, J = 8.3 Hz, 2H), 6.15 (s, 1H), 5.44 (s, 2H), 5.04 (br s, 1H), 1.14 (s, 9H); MS $[M+H]^+$ = 325; LCMS RT = 1.38 min; TLC R_f = 0.15 (95:5 v/v CH_2Cl_2-MeOH).

Intermediate M: Preparation of 4-amino-5-(4-aminophenyl)-*N*-(2,2,2-trifluoroethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



Step 1: Preparation of 4-amino-5-(4-nitrophenyl)-*N*-(2,2,2-trifluoroethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



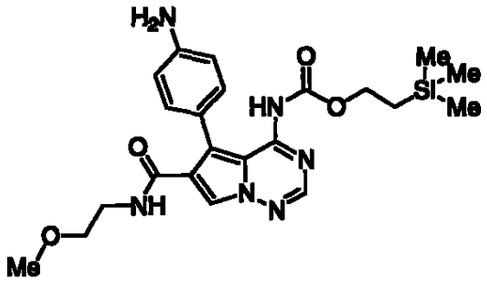
To a solution of thionyl chloride (15 mL) was added Intermediate K (495 mg, 1.73 mmol) which was heated at 50 °C for 3 h. Upon cooling to rt the reaction mixture was concentrated to dryness chasing with THF. The reaction mixture was then diluted with 2,2,2-trifluoro-ethylamine hydrochloride salt (587 mg, 4.33 mmol) and triethylamine (1.15 ml, 8.66 mmol) in THF (8 mL) and stirred at rt overnight.

The solution was rotavapped to dryness, diluted with EtOAc (50 mL), transferred to a separatory funnel, and washed with water (50 mL). The water layer was back extracted with EtOAc (4 x 20 mL), dried (Na_2SO_4), filtered, and concentrated to dryness. Then it was triturated with EtOAc/MeOH. The product was collected to afford 490 mg of the above compound as a yellow solid (yield 74%). ^{1}H-NMR (DMSO-d_6) δ 8.77 (t, J = 6.2 Hz, 1H), 8.29 (s, 1H), 8.23 (d, J = 8.9 Hz, 2H), 7.97 (s, 1H), 7.59 (d, J = 8.9 Hz, 2H), 3.97 to 3.91 (m, 2H); MS $[M+H]^+$ = 381.1; LCMS RT = 2.33 min).

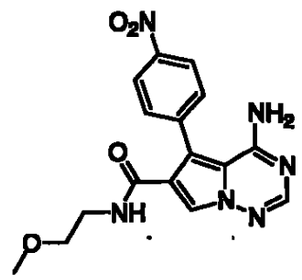
Step 2: Preparation of the title compound

The procedure used for the preparation of Intermediate B was used to prepare the title compound by substituting 4-amino-5-(4-nitrophenyl)-*N*-(2,2,2-trifluoroethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide for Intermediate A. ^{1}H-NMR (CD_3OD) δ 8.00 (s, 1H), 7.81 (s, 1H), 7.17 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 4.03 to 3.85 (m, 2H); MS $[M+H]^+$ = 351.2; LCMS RT = 1.14 min.

Intermediate N: **Preparation of 2-(trimethylsilyl)ethyl (5-(4-aminophenyl)-6-{[(2-methoxyethyl)amino]carbonyl}pyrrolo[2,1-f][1,2,4]triazin-4-yl)carbamate**

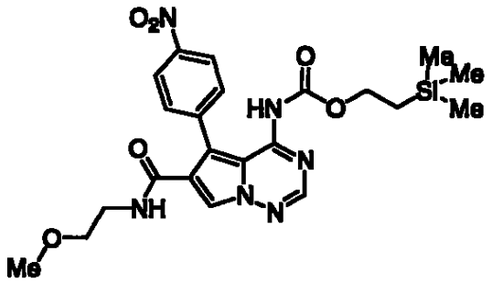


Step 1: Preparation of 4-amino-*N*-(2-methoxyethyl)-5-(4-nitrophenyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



The procedure used for the preparation of 4-amino-*N*-(*tert*-butyl)-5-(4-nitrophenyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide (Intermediate L Step 1) was used to prepare the title compound by substituting 2-methoxyethanamine for 2-methylpropan-2-amine. ^{1}H-NMR (DMSO-d_6) δ 8.22 (d, J = 8.7 Hz, 2H), 8.18 (s, 1H), 8.11 (t, J = 5.6 Hz, 1H), 7.93 (s, 1H), 7.58 (d, J = 8.9 Hz, 2H), 3.28 to 3.26 (m, 2H), 3.21 (s, 3H), 3.16 to 3.14 (m, 2H); MS $[M+H]^+$ = 357; LCMS RT = 1.83 min.

Step 2: Preparation of 2-(trimethylsilyl)ethyl [6-{[(2-methoxyethyl)amino]carbonyl}-5-(4-nitrophenyl)pyrrolo[2,1-f][1,2,4]triazin-4-yl]carbamate



To a solution of DMF (100 mL) was added 4-amino-*N*-(2-methoxyethyl)-5-(4-nitrophenyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide (4.03g, 11.3 mmol) followed by 60% NaH by weight in mineral oil (1.13g, 28.3 mmol). The solution was stirred for 15 min and then 4-nitrophenyl 2-(trimethylsilyl)ethyl carbonate (3.52 g, 12.4 mmol) was added. The solution was stirred under N_2 for 2 h. MeOH was added to the reaction until bubbling ceased and then EtOAc (50 mL) was added. The

solution was transferred to a separatory funnel and was washed with 1N NaOH (20 mL) and water (20 mL). The organic was collected, dried (Na_2SO_4), and purified by column chromatography to afford 3.60 g of the above compound (7.15 mmol, yield 63%). ^{1}H-NMR ($CDCl_3$) δ 8.38 (d, J = 8.5 Hz, 2H), 8.16 (s, 1H), 8.14 (s, 1H), 7.69 (d, J = 8.5 Hz, 2H), 5.87 to 5.86 (m, 1H), 4.17 (t, J = 8.3 Hz, 2H), 3.48 to 3.46 (m, 2H), 3.36 (t, J = 5.0 Hz 2H), 3.21 (s, 3H), 0.93 (t, J = 8.1 Hz 2H), -0.01 (s, 9H); MS $[M+H]^+$ = 501; LCMS RT = 3.17 min.

Step 3: Preparation of the title compound

The procedure used for the preparation of Intermediate B was used to prepare the title compound by substituting 2-(trimethylsilyl)ethyl [6-{[(2-methoxyethyl)amino]carbonyl}-5-(4-nitrophenyl)pyrrolo[2,1-f][1,2,4]triazin-4-yl]carbamate for Intermediate A. ^{1}H-NMR (DMSO-d_6) δ 8.26 (s, 1H), 8.23 (s, 1H), 8.16 (s, 1H), 7.42 (br s, 1H), 7.04 (d, J = 8.3 Hz, 2H), 6.61 (d, J = 8.3 Hz, 2H), 5.36 (br s, 2H), 3.99 (t, J = 8.3 Hz, 2H), 3.29 to 3.25 (m, 4H), 3.18 (s, 3H), 0.88 to 0.84, (m, 2H), -0.01 (s, 9H); MS $[M+H]^+$ = 471; LCMS RT = 3.04 min.

Intermediate O: **Preparation of 4-amino-5-(4-nitrophenyl)pyrrolo[2,1-f][1,2,4]triazine-6-carbonitrile**



To a solution of pyridine (8.75 mL) was added 4-amino-5-(4-nitrophenyl)pyrrolo[2,1-f][1,2,4]triazine-6-carbaldehyde (Intermediate H, Step 2) (500 mg, 1.77 mmol) followed by hydroxylamine hydrochloride (135 mg, 1.94 mmol). The solution was stirred at rt for 1 h, acetic anhydride (.366 mL, 3.88 mmol) was added, and the solution was heated to 80 °C for 17 h. Upon cooling to rt the reaction mixture was partially rotavapped and then diluted with EtOAc (50 mL) and H_2O (50 mL). The solution was transferred to a separatory funnel, and the organic

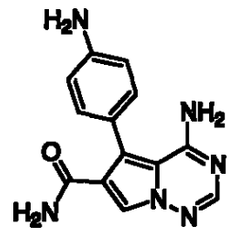
layer was isolated while the aqueous layers were back extracted with EtOAc (2 x 25 mL). The combined organic layers were collected, dried (Na_2SO_4), filtered, and concentrated to dryness to afford a brown solid. This proved to be a 1:1 ratio of the title compound and *N*-[6-cyano-5-(4-nitro-phenyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-acetamide. ^{1}H-NMR (DMSO-d_6) δ 10.67 (s, 1H), 8.96 (s, 1H), 8.62 (s, 1H), 8.57(s, 1H), 8.40 to 8.30 (m, 4H), 8.05 (s, 1H), 7.79 to 7.68 (m, 4H), 1.74 (s, 3H); MS $[M+H]^+$ = 281.2, 323.0; LCMS RT = 2.48 min.

Intermediate P: **Preparation of 4-amino-5-(4-aminophenyl)pyrrolo[2,1-f][1,2,4]triazine-6-carbonitrile**

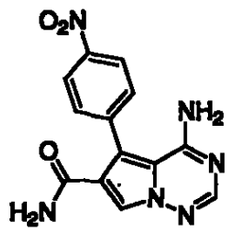


The procedure used for the preparation of Intermediate B was used to prepare the title compound by substituting Intermediate O for Intermediate A ^{1}H-NMR (CD_3OD) δ 8.29 (s, 1H), 7.98 (s, 1H), 7.57 (d, *J* = 9.0 Hz, 2H), 7.33 (d, *J* = 9.0 Hz, 2H); MS $[M+H]^+$ = 251.3; LCMS RT = 0.40 min.

Intermediate Q: **Preparation of 4-amino-5-(4-aminophenyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide**



Step 1: Preparation of 4-amino-5-(4-nitrophenyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide

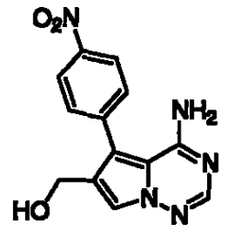


A mixture of Intermdediate O (80 mg, 0.29 mmol) in sulfuric acid (1 mL) was stirred at rt overnight. The reaction mixture was slowly quenched with saturated sodium bicarbonate solution until gas evolution ceased. The reaction mixture was then extracted with EtOAc (3 x 5 mL) and THF (3 x 5 mL), dried (Na_2SO_4), filtered, and concentrated to dryness to afford a brown solid. ^{1}H-NMR (CD_3OD) δ 8.22 (d, J = 9.0 Hz, 2H), 8.04 (s, 1H), 7.80 (s, 1H), 7.59 (d, J = 8.6 Hz, 2H); MS $[M+H]^+$ = 299.1; LCMS RT = 1.15 min.

Step 2: Preparation of the title compound

The procedure used for the preparation of Intermediate B was used to prepare the title compound by substituting 4-amino-5-(4-nitrophenyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide for Intermediate A. ^{1}H-NMR (CD_3OD) δ 8.26 (s, 1H), 8.02 (s, 1H), 7.98 (br s, 2H), 7.53 (d, J = 9.0 Hz, 2H), 7.33 (d, J = 9.0 Hz, 2H); MS $[M+H]^+$ = 269.3; LCMS RT = 0.19 min.

Intermediate R: **Preparation of [4-amino-5-(4-nitrophenyl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methanol**



To a solution of THF (10 mL) was added Intermediate A (500 mg, 1.53 mmol) followed by DIBAL (3 mL, 3 mmol, 1.0 M solution in toluene). The reaction

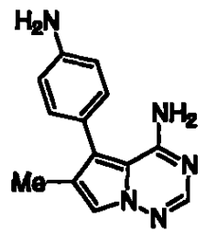
was stirred at rt for 1 h. Additional DIBAL (1.5 mL, 1.5 mmol, 1.0 M solution in toluene) was added and stirring continued at rt for another 1 h. The reaction was diluted with EtOAc and quenched with saturated aqueous Rochelle's salt. The reaction was extracted with EtOAc (4x). The organic was dried (Na_2SO_4) and evaporated to give a crude solid (435 mg, 100%) that was used directly in the next step without further purification. ^{1}H-NMR (DMSO-d_6) δ 8.29 (d, J= 9.2 Hz, 2H), 7.89 (s, 1H), 7.73 (s, 1H), 7.67 (d, J= 9.3 Hz, 2H), 5.07 (t, J= 5.5 Hz, 1H), 4.38 (d, J= 5.2 Hz, 2H); MS $[M+H]^+$ = 286; LCMS RT = 0.59 min.

Intermediate S: Preparation of 6-(chloromethyl)-5-(4-nitrophenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine



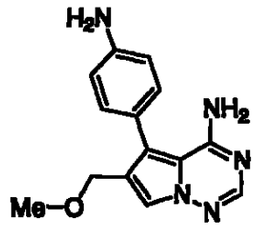
A mixture Intermediate R (522 mg, 1.83 mmol) in thionyl chloride (10 mL) was stirred at 50 °C for 1 h. It was then concentrated to dryness to afford a brown solid. ^{1}H-NMR (DMSO-d_6) δ 8.37 (d, J = 8.9 Hz, 2H), 8.19 (s, 1H), 8.16 (s, 1H), 7.74 (d, J = 8.9 Hz, 2H), 4.70 (s, 2H); MS $[M+H]^+$ = 304.3; LCMS RT = 2.44 min.

Intermediate T: Preparation of 5-(4-aminophenyl)-6-methylpyrrolo[2,1-f][1,2,4]triazin-4-amine

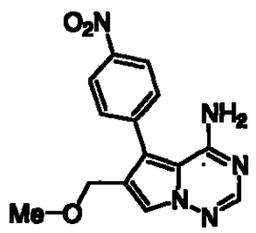


The procedure used for the preparation of Intermediate B was used to prepare the title compound by substituting Intermediate S for Intermediate A. ^{1}H-NMR (CD_3OD) δ 7.74 (s, 1H), 7.52 (s, 1H), 7.13 (d, J = 8.2 Hz, 2H), 6.86 (d, J = 8.5 Hz, 2H), 2.11 (s, 3H); MS $[M+H]^+$ = 240.3; LCMS RT = 1.06 min.

Intermediate U: **Preparation of 5-(4-aminophenyl)-6-(methoxymethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine**



Step 1: Preparation of 6-(methoxymethyl)-5-(4-nitrophenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine



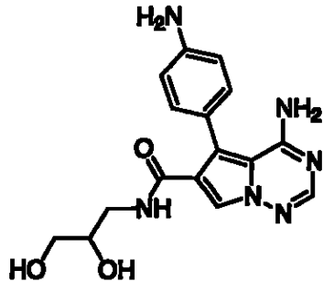
To a solution of thionyl chloride (20 mL) was added Intermediate R (873 mg, 3.06 mmol) which was heated to reflux under N_2 for 2 h. Upon cooling to rt the reaction mixture was rotavapped to dryness chasing with CH_2Cl_2. The reaction mixture was then diluted with MeOH (20 mL) and then 60% by weight NaH with mineral oil (489 mg, 12.2 mmol) was added. The solution was heated to reflux for 6 h. Upon cooling to rt the solution was rotavapped to dryness, diluted with EtOAc (50 mL), transferred to a separatory funnel, and washed with water (50 mL). The water layer was back extracted with EtOAc (4 x 20 mL), dried ($MgSO_4$), filtered, and purified by column chromatography (95:5 v/v CH_2CL_2:MeOH). The resulting clean

fractions were combined, evaporated, and triturated with CH_2Cl_2/diethyl ether. The product was collected to afford 470 mg of the above compound as a yellow solid (1.57 mmol, yield 51%). ^{1}H-NMR (DMSO-d_6) δ 8.30 (d, J = 8.9 Hz, 2H), 7.91 (s, 1H), 7.84 (s, 1H), 7.65 (d, J = 8.9 Hz, 2H), 4.29 (s, 2H), 3.21 (s, 3H); MS $[M+H]^+$ = 300; LCMS RT = 2.07 min; TLC R_f = 0.54 (95:5 v/v CH_2Cl_2-MeOH).

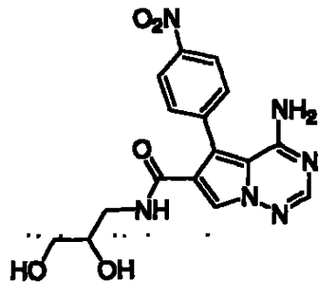
Step 2: Preparation of the title compound

The procedure used for the preparation of Intermediate B was used to prepare the title compound by substituting 6-(methoxymethyl)-5-(4-nitrophenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine for Intermediate A. ^{1}H-NMR (DMSO-d_6) δ 7.79 (s, 1H), 7.67 (s, 1H), 7.03 (d, J = 8.4 Hz, 2H), 6.64 (d, J = 8.7 Hz, 2H), 5.30 (s, 2H),), 4.24 (s, 2H), 3.19 (s, 3H); MS $[M+H]^+$ = 270; LCMS RT = 0.26 min; TLC R_f = 0.30 (95:5 v/v CH_2Cl_2-MeOH).

Intermediate V: **Preparation of 4-amino-5-(4-aminophenyl)-*N*-(2,3-dihydroxypropyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide**



Step 1: Preparation of 4-amino-*N*-(2,3-dihydroxypropyl)-5-(4-nitrophenyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide

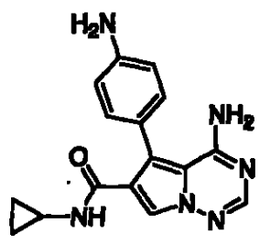


To a solution of Intermediate K (550 mg, 1.84 mmol), 3-amino-1,2-propanediol (251 mg, 2.76 mmol), triethylamine (1.0 mL, 7.4 mmol), and DMF (20 mL) was added py-BOP (1051 mg, 2.02 mmol) and the reaction was left to stir for 1 h. The reaction mixture was concentrated in vacuo and the residue triturated first with water and then with 30% aqueous ethanol to afford 318 mg of the above compound as an orange/yellow solid (yield 47%). MS $[M+H]^+ = 373.2$; LCMS RT = 1.21.

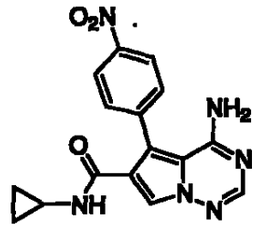
Step 2: Preparation of the title compound

The procedure used for the preparation of Intermediate B was used to prepare the title compound by 4-amino-*N*-(2,3-dihydroxypropyl)-5-(4-nitrophenyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide for Intermediate A. ^{1}H-NMR (DMSO-d_6) δ 8.02 (s, 1H), 7.84 (s, 1H), 7.28 (t, $J = 6$ Hz, 1H) 7.02 (d, $J = 8$ Hz, 2H), 5.34 (s, 2H), 5.05 (bs, 1H), 4.75 (bs, 1H), 4.52 (bs, 1H), 4.38 to 3.43 (m. 1H), 3.36 to 3.16 (m, 3H), 3.03 to 2.85 (m, 1H). MS $[M+H]^+ = 343.2$; LCMS RT = 1.02 min.

Intermediate W: Preparation of 4-amino-5-(4-aminophenyl)-*N*-cyclopropylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



Step 1: Preparation of 4-amino-*N*-cyclopropyl-5-(4-nitrophenyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide

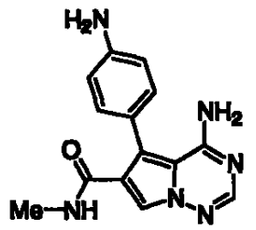


The procedure used for the preparation of 4-amino-*N*-(*tert*-butyl)-5-(4-nitrophenyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide (Intermediate L Step 1) was used to prepare the title compound by substituting cyclopropylamine for 2-methylpropan-2-amine. ^{1}H-NMR (DMSO-d_6) δ 8.23 (d, J = 8.8 Hz, 2H), 8.14 (s, 1H), 8.13 (br s, 1H), 7.93 (d, J = 8.4 Hz, 2H), 7.58 (s, 1H), 2.67 to 2.59 (m, 1H), 0.62 to 0.54 (m, 2H), 0.46 to 0.41 (m, 2H); MS $[M+H]^+$ = 339.2; LCMS RT = 1.40 min.

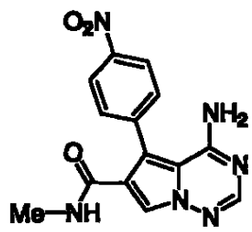
Step 2: Preparation of the title compound

The procedure used for the preparation of Intermediate B was used to prepare the title compound by substituting 4-amino-*N*-cyclopropyl-5-(4-nitrophenyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide for Intermediate A. ^{1}H-NMR (CD_3OD) δ 7.68 (s, 1H), 7.58 (s, 1H), 7.07 (s, 1H), 6.73 (d, J = 8.6 Hz, 2H), 6.33 (d, J = 8.3 Hz, 2H), 5.05 (s, 2H), 2.38 to 2.28 (m, 1H), 0.34 to 0.24 (m, 2H), 0.067 to -0.032 (m, 2H); MS $[M+H]^+$ = 309.3; LCMS RT = 0.23 min.

Intermediate X: Preparation of 4-amino-5-(4-aminophenyl)-*N*-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



Step 1: Preparation of 4-amino-*N*-methyl-5-(4-nitrophenyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide

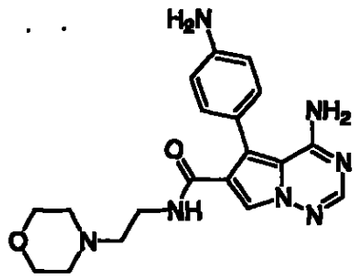


To a solution of thionyl chloride (10 mL) was added Intermediate K (300 mg, 1.00 mmol) which was heated at 50 °C for 3 h. Upon cooling to rt the reaction mixture was rotavapped to dryness chasing with THF. The reaction mixture was then diluted with 2M methylamine in THF (40 mL) and stirred at rt overnight. The solution was rotavapped to dryness, diluted with EtOAc (50 mL), transferred to a separatory funnel, and washed with water (50 mL). The water layer was back extracted with EtOAc (4 x 20 mL), dried (Na_2SO_4), filtered, and rotavapped to dryness. Then it was triturated with EtOAc/MeOH. The product was collected to afford 240 mg of the above compound as a yellow solid (240 mg, yield 76%). ^{1}H-NMR (DMSO-d_6) δ 8.22 (d, J = 8.9 Hz, 2H), 8.15 (s, 1H), 7.94 (s, 1H), 7.58 (d, J = 8.9 Hz, 2H), 3.60 to 3.55 (m, 1H), 2.62 (d, J = 4.6 Hz, 3H); MS $[M+H]^+$ = 313.2; LCMS RT = 0.58 min).

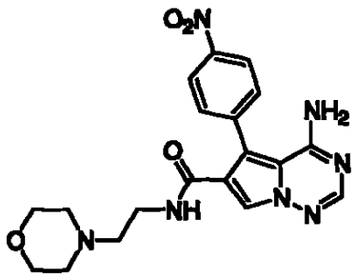
Step 2: Preparation of the title compound

The procedure used for the preparation of Intermediate B was used to prepare the title compound by substituting 4-amino-*N*-methyl-5-(4-nitrophenyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide for Intermediate A. ^{1}H-NMR (DMSO-d_6) δ 8.00 (s, 1H), 7.84 (s, 1H), 7.00 (d, J = 8.4 Hz, 2H), 6.61 (d, J = 8.5 Hz, 2H), 5.31 (s, 2H), 4.19 to 4.12 (m, 1H), 2.59 (d, J = 4.6 Hz, 3H); MS $[M+H]^+$ = 281.3; LCMS RT = 1.03 min

Intermediate Y: **Preparation of 4-amino-5-(4-aminophenyl)-*N*-(2-morpholin-4-ylethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide**



Step 1: Preparation of 4-amino-*N*-(2-morpholin-4-ylethyl)-5-(4-nitrophenyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



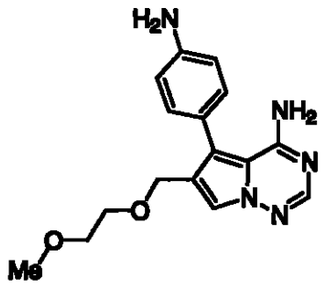
The procedure used for the preparation of 4-amino-*N*-methyl-5-(4-nitrophenyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide (Intermediate X Step 1) was used to prepare the title compound by substituting 2-morpholin-4-yl-ethylamine for methylamine. ^{1}H-NMR (CD_3OD) δ 8.34 (d, J = 8.8 Hz, 2H), 8.07 (s, 1H), 7.89 (s, 1H), 7.69 (d, J = 8.8 Hz, 2H), 3.66 to 3.61 (m, 4H), 3.39 (t, J = 6.6 Hz, 2H), 2.49 to 2.40 (m, 6H); MS $[M+H]^+$ = 412.2; LCMS RT = 0.28 min.

Step 2: Preparation of the title compound

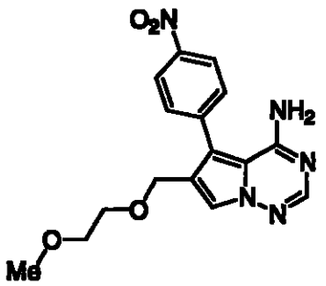
The procedure used for the preparation of Intermediate B was used to prepare the title compound by substituting 4-amino-*N*-(2-morpholin-4-ylethyl)-5-(4-

nitrophenyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide for Intermediate A. ^{1}H-NMR (CD_3OD) δ 8.04 (br s, 2H), 7.99 (s, 1H), 7.80 (s, 1H), 7.20 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 8.4 Hz, 2H), 3.64 to 3.57 (m, 4H), 3.42 to 3.36 (m, 2H), 2.35 to 2.27 (m, 6H); MS $[M+H]^+$ = 382.3; LCMS RT = 0.17 min.

Intermediate Z: Preparation of 5-(4-aminophenyl)-6-[(2-methoxyethoxy)methyl]pyrrolo[2,1-f][1,2,4]triazin-4-amine



Step 1: Preparation of 6-[(2-methoxyethoxy)methyl]-5-(4-nitrophenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine

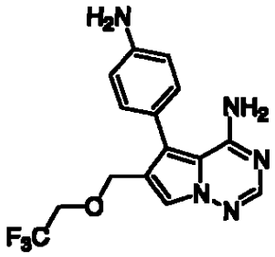


The procedure used for the preparation of 6-(methoxymethyl)-5-(4-nitrophenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine (Intermediate U Step 1) was used to prepare the title compound by substituting 2-methoxy-ethanol for methanol. ^{1}H-NMR (CD_3OD) δ 8.35 (d, J = 8.7 Hz, 2H), 7.85 (s, 1H), 7.77 (s, 1H), 7.75 (d, J = 8.7 Hz, 2H), 4.45 (s, 2H), 3.59 to 3.49 (m, 4H), 3.33 (s, 3H); MS $[M+H]^+$ = 344.1; LCMS RT = 2.14 min.

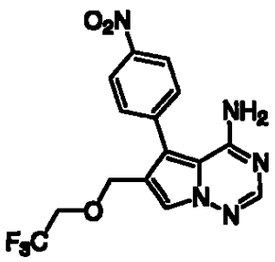
Step 2: Preparation of the title compound

The procedure used for the preparation of Intermediate B was used to prepare the title compound by substituting 6-[(2-methoxyethoxy)methyl]-5-(4-nitrophenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine for Intermediate A. ^{1}H-NMR (CD_3OD) δ 7.74 (s, 1H); 7.65 (s, 1H), 7.17 (d, J = 8.5 Hz, 2H), 6.81 (d, J = 8.5 Hz, 2H), 4.42 (s, 2H), 3.57 to 3.47 (m, 4H), 3.32 (s, 3H); MS $[M+H]^+$ = 314.3; LCMS RT = 0.25 min.

Intermediate AA: Preparation of 5-(4-aminophenyl)-6-[(2,2,2-trifluoroethoxy)methyl]pyrrolo[2,1-f][1,2,4]triazin-4-amine



Step 1: Preparation of 5-(4-nitrophenyl)-6-[(2,2,2-trifluoroethoxy)methyl]pyrrolo[2,1-f][1,2,4]triazin-4-amine



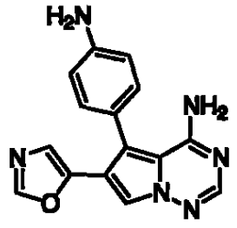
The procedure used for the preparation of 6-(methoxymethyl)-5-(4-nitrophenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine (Intermediate U Step 1) was used to prepare the title compound by substituting 2,2,2-trifluoro-ethanol for methanol. ^{1}H-NMR (Acetone-d_6) δ 8.36 (d, J = 8.6 Hz, 2H), 7.89 (s, 1H), 7.85 (s, 1H), 7.81 (d, J =

8.6 Hz, 2H), 4.68 (s, 2H), 4.04 to 3.94 (m, 2H); MS $[M+H]^+$ = 368.3; LCMS RT = 2.68 min.

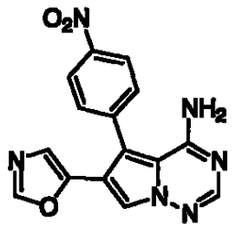
Step 2: Preparation of the title compound

The procedure used for the preparation of Intermediate B was used to prepare the title compound by 5-(4-nitrophenyl)-6-[(2,2,2-trifluoroethoxy)methyl]pyrrolo[2,1-f][1,2,4]triazin-4-amine for Intermediate A. ^{1}H-NMR (CD_3OD) δ 7.75 (s, 1H), 7.65 (s, 1H), 7.15 (d, J = 8.6 Hz, 2H), 6.81 (d, J = 8.6 Hz, 2H), 4.53 (s, 2H), 3.93 to 3.72 (m, 2H); MS $[M+H]^+$ = 338.2; LCMS RT = 1.69 min.

Intermediate AB: Preparation of 5-(4-aminophenyl)-6-(1,3-oxazol-5-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine



Step 1: Preparation of 5-(4-nitrophenyl)-6-(1,3-oxazol-5-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine



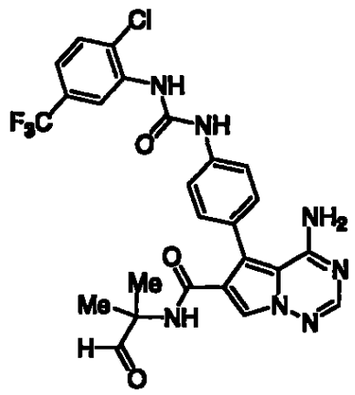
To a solution of 4-amino-5-(4-nitrophenyl)pyrrolo[2,1-f][1,2,4]triazine-6-carbaldehyde (Intermediate H, Step 2) (692 mg, 2.44 mmol) was added tosylmethyl isocyanide (477 mg, 2.44 mmol) and potassium carbonate (338 mg, 2.44 mmol) in

MeOH. The solution was allowed to stir at reflux overnight. The solution was dried and diluted with EtOAc (50 mL) and THF (50 mL). Water (50 mL) was added to the reaction mixture. The solution was transferred to a separatory funnel, and the organic layer was isolated and washed with brine (50 mL). The aqueous layers were back extracted with EtOAc (2 x 50 mL). The combined organic layers were collected, dried (Na_2SO_4), concentrated onto silica gel, and purified by column chromatography (100% CH_2Cl_2 ramping to 95:5 v/v CH_2Cl_2-EtOAc) to afford 310 mg of the above compound as an yellow solid (yield 39%). ^{1}H-NMR (DMSO-d_6) δ 11.70 (s, 1H), 8.31 (d, J = 8.5 Hz, 2H), 8.28 (s, 1H), 8.17 (s, 1H), 7.66 (d, J = 7.1 Hz, 2H), 6.75 (s, 1H); MS $[M+H]^+$ = 323.2; LCMS RT = 2.57 min.

Step 2: Preparation of the title compound

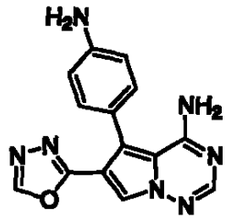
The procedure used for the preparation of Intermediate B was used to prepare the title compound by substituting 5-(4-nitrophenyl)-6-(1,3-oxazol-5-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine for Intermediate A. ^{1}H-NMR (CD_3OD) δ 8.11 (s, 1H), 7.91 (s, 1H), 7.79 (s, 1H), 7.15 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 6.45 (s, 1H); MS $[M+H]^+$ = 293.2; LCMS RT = 1.23 min.

Intermediate AC: Preparation of 4-amino-5-{4-[({[2-chloro-5-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}-*N*-(1,1-dimethyl-2-oxoethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide

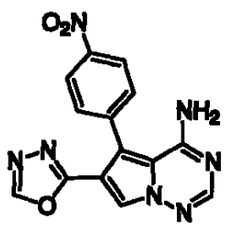


The procedure used for the preparation of Intermediate F (Step 2) was used to prepare the title compound by substituting 4-amino-5-{4-[({[2-chloro-5-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}-*N*-(2-hydroxy-1,1-dimethylethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carboxamide for *N*-{4-[4-amino-6-(hydroxymethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea. ^{1}H-NMR (DMSO-d_6) δ 9.69 (s, 1H), 9.21 (s, 1H), 8.65 (s, 1H), 8.62 (d, J = 2.1 Hz, 1H), 8.23 (s, 1H), 8.20 (s, 1H), 7.90 (s, 1H), 7.70 (d, J = 8.8 Hz, 1H), 7.53 (d, J = 9.1 Hz, 2H), 7.35 (dd, J = 8.8, 1.6 Hz, 1H), 7.30 (d, J = 8.6 Hz, 2H), 3.30 (s, 6H); MS $[M+H]^+$ = 560.1; LCMS RT = 3.36 min.

Intermediate AD: **Preparation of 5-(4-aminophenyl)-6-(1,3,4-oxadiazol-2-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine**



Step 1: Preparation of 5-(4-nitrophenyl)-6-(1,3,4-oxadiazol-2-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine



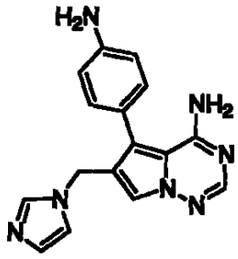
To a solution of thionyl chloride (5 mL) was added Intermediate K (183 mg, 0.613 mmol) which was heated at 50 °C for 3 h. Upon cooling to rt the reaction mixture was rotavapped to dryness chasing with THF. The reaction mixture was then diluted with pyridine (5 mL), added hydrazine (100 mg, 3.15 mmol), and stirred at rt

overnight. The solution was rotavapped to dryness, diluted with trimethoxy-methane (10 mL), and stirred at reflux for 5 h. The solution was rotavapped to dryness, and purified by HPLC to afford the title compound (27 mg, 14%); ^{1}H-NMR (CD_3OD) δ 8.71 (s, 1H), 8.24 (d, J = 9.1 Hz, 2H), 8.20 (s, 1H), 7.84 (s, 1H), 7.73 (d, J = 8.9 Hz, 2H); MS $[M+H]^+$ = 324.2; LCMS RT = 2.07 min.

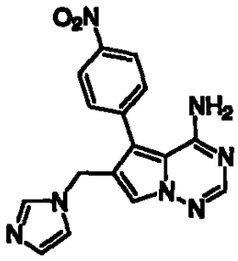
Step 2: Preparation of the title compound

The procedure used for the preparation of Intermediate B was used to prepare the title compound by substituting 5-(4-nitrophenyl)-6-(1,3,4-oxadiazol-2-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine for Intermediate A. ^{1}H-NMR (CD_3OD) δ 8.64 (s, 1H), 8.06 (s, 1H), 7.75 (s, 1H), 7.08 (d, J = 8.7 Hz, 2H), 6.66 (d, J = 8.9 Hz, 2H); MS $[M+H]^+$ = 294.2; LCMS RT = 0.21 min.

Intermediate AE: Preparation of 5-(4-Amino-phenyl)-6-imidazol-1-ylmethyl-pyrrolo[2,1-*f*][1,2,4]triazin-4-ylamine



Step 1: Preparation of 6-imidazol-1-ylmethyl-5-(4-nitro-phenyl)-pyrrolo[2,1-f][1,2,4]triazin-4-ylamine



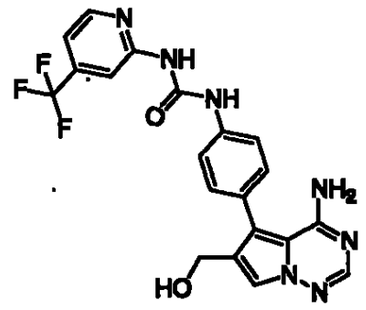
The procedure used for the preparation of 6-(methoxymethyl)-5-(4-nitrophenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine (Intermediate U Step 1) was used to

prepare the title compound by substituting imidazole for methanol. ^{1}H-NMR (Acetone-d_6) δ 8.22 (d, J = 8.8 Hz, 2H), 7.77 (s, 1H), 7.66 (s, 1H), 7.54 (d, J = 8.8 Hz, 2H), 7.27 (s, 1H), 6.82 (s, 1H), 6.73 (s, 1H), 5.14 (s, 2H); MS $[M+H]^+$ = 336.0; LCMS RT = 0.25 min.

Step 2: Preparation of the title compound

The procedure used for the preparation of Intermediate B was used to prepare the title compound by substituting 6-imidazol-1-ylmethyl-5-(4-nitro-phenyl)-pyrrolo[2,1-f][1,2,4]triazin-4-ylamine for Intermediate A. MS $[M+H]^+$ = 306.0; LCMS RT = 1.02 min.

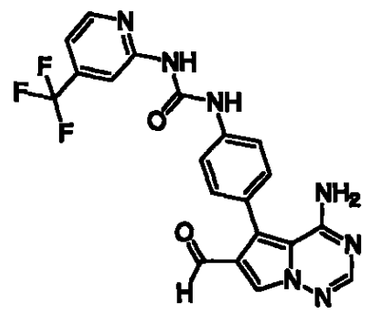
Intermediate AF: Preparation of N-{4-[4-amino-6-(hydroxymethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-[4-(trifluoromethyl)pyridin-2-yl]urea



Example 51 (0.25 g, 0.515 mmol) was suspended in THF (5 mL) and treated with 1M solution of DIBAL in THF (2 mL, 2.06 mmol). The resulting solution was stirred at room temperature for 3 hours and quenched with saturated NH_4Cl solution. The mixture was stirred for 1 hour. The mixture was transferred to a sep. funnel and the crude product was extracted with EtOAc. The organic layer was then washed with water and saturated NaCl solution. The organic layer was then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The remaining solid was then triturated with EtOAc and filtered providing 0.22 g of product as a tan solid (0.496 mmol, 96 % yield).. ^{1}H-NMR (DMSO) δ 11.66 (s, 1H), 9.86 (s, 1H), 9.73 (s, 1H), 8.53 (d, J = 8.7 Hz, 1H), 8.05 (s, 1H), 7.82 (s, 1H), 7.65 (s, 1H), 7.61 (d, J = 6.6

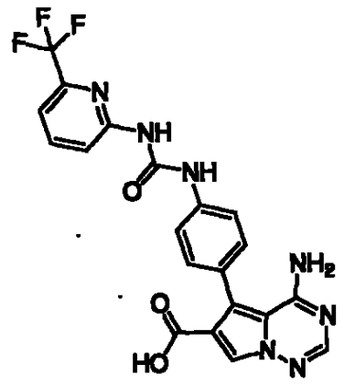
Hz, 2H), 7.38-7.35 (m, 3H), 4.95 (t, J = 5.2 Hz, 1H), 4.37 (d, J = 5.1 Hz, 2H); MS $[M+H]^+$ = 444.0; LCMS RT = 2.3 min.

Intermediate AG: Preparation of N-[4-(4-amino-6-formylpyrrolo[2,1-f][1,2,4]triazin-5-yl)phenyl]-N'-[4-(trifluoromethyl)pyridin-2-yl]urea



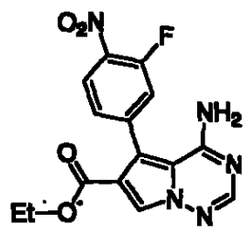
Intermediate AF (1.9 g, 4.29 mmol) was suspended in THF (20 mL) and treated with Dess-Martin periodinane (2.0 g , 4.71 mmol). The mixture was stirred at room temperature overnight and quenched with saturated $NHCO_3$ solution with $Na_2S_2O_3$. The mixture was stirred for 1 hour then transferred to a sep. funnel. The crude product was extracted with EtOAc and washed with water and saturated NaCl solution. The organic layer was then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The remaining solid was then triturated with EtOAc and filtered providing 1.8 g of product as a tan solid (4.08 mmol, 95 % yield). ^{1}H-NMR (DMSO) δ 10.05 (bs, 1H), 9.82 (s, 1H), 9.72 (s, 1H), 8.52 (d, J = 5.1 Hz, 1H), 8.26 (s, 1H), 8.07 (s, 1H), 7.95 (s, 1H), 7.64 (d, J = 8.6 Hz, 2H), 7.44 (d, J = 8.6 Hz, 2H), 7.35 (d, J = 5.8 Hz, 1H); MS $[M+H]^+$ = 442.0; LCMS RT = 2.81 min.

Intermediate AH: Preparation of 4-amino-5-{4-[({[6-(trifluoromethyl)pyridin-2-yl]amino}carbonyl) amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid

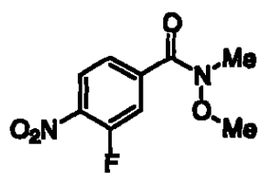


The procedure used for the preparation of Intermediate G was used to prepare the title compound by substituting Example 144 for Intermediate E. ^{1}H-NMR (DMSO) δ 10.29 (bs, 1H), 8.03 to 7.96 (m, 3H), 7.86 (s, 1H), 7.53 (d, J = 8.5 Hz, 2H), 7.45 (d, J = 7.0 Hz, 1H), 7.33 (d, J = 8.6 Hz, 2H); MS $[M+H]^+$ = 458.1; LCMS RT = 2.51 min.

Intermediate AI: Preparation of ethyl 4-amino-5-(3-fluoro-4-nitrophenyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate



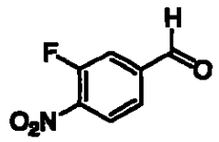
Step 1: Preparation of 3-fluoro-N-methoxy-N-methyl-4-nitrobenzamide



To a solution of CH_2Cl_2 (1L) was addded 3-fluoro-4-nitrobenzoic acid (100 g, 540 mmol) and EDCI (155.3 g, 810 mmol) followed by NMM (178 mL, 1.62 mol) and N-methoxymethanamine hydrochloride (79.0 g, 810 mmol). The solution was

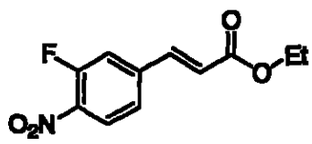
allowed to stir under N_2 at rt for 17h. The reaction mixture was then diluted with 1N HCl (1 L), transferred to separatory funnel, and separated. The organic phase was washed with 1N NaOH (2 x 500 mL) and water (250 mL). All aqueous layers were back extracted with EtOAc (2 x 500 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo. to afford 102.3 g of the above compound as a yellow solid (448 mmol, yield 83%). ^{1}H-NMR (DMSO-d_6) δ 8.22 to 8.18 (t, J = 8.0 Hz, 1H), 7.79 to 7.76 (d, J = 11.5 Hz, 1H), 7.60 to 7.58 (d, J = 8.3 Hz, 1H), 3.56 (s, 3H), 3.28 (s, 3H); MS $[M+H]^+$ = 229.1; LCMS RT = 2.27 min.

Step 2: Preparation of ethyl 3-fluoro-4-nitrobenzaldehyde



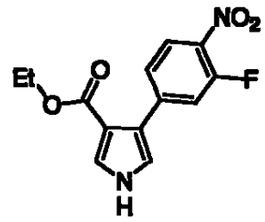
To a solution of THF (800 mL) cooled in an ice-salt/water bath was added 3-fluoro-N-methoxy-N-methyl-4-nitrobenzamide followed by addition of 1 M DIBAL in THF by addition funnel over 30 min. The solution was allowed to stir under N_2 for 1 h. The reaction mixture was then carefully diluted with 1N HCl (500 mL) and EtOAc (500 mL), transferred to separatory funnel, and separated. The organic phase was washed with 1N HCl (3 x 250 mL), 1N NaOH (2 x 250 mL), and water (250 mL). All aqueous layers were back extracted with EtOAc (2 x 250 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo to afford 67 g of the above compound (396 mmol, yield 88%). ^{1}H-NMR (DMSO-d_6) δ 10.06 (s, 1H), 8.36 to 8.32 (t, J = 7.8 Hz, 1H), 8.06 to 8.03(d, J = 11.2 Hz, 1H), 7.95 to 7.93 (d, J = 9.1 Hz, 1H).

Step 3: Preparation of ethyl (2E)-3-(3-fluoro-4-nitrophenyl)acrylate



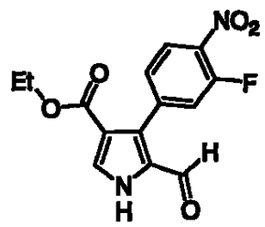
The procedure used for the preparation of Intermediate H Step 3 was used to prepare the title compound by substituting ethyl 3-fluoro-4-nitrobenzaldehyde for 4-amino-5-(4-nitrophenyl)pyrrolo[2,1-f][1,2,4]triazine-6-carbaldehyde. ^{1}H-NMR (DMSO-d_6) δ 8.17 to 8.13 (t, J = 8.2 Hz, 1H), 8.04 to 8.01 (d, J = 12.7 Hz, 1H), 7.79 to 7.77 (d, J = 8.4 Hz, 1H), 7.71 to 7.67 (d, J = 16.1 Hz, 1H), 6.93 to 6.87 (d, J = 15.9 Hz, 1H), 4.24 to 4.18 (q, J = 7.1 Hz, 2H), 1.29 to 1.25 (t, J = 7.1 Hz, 3H); **LCMS RT** = 3.18.

Step 4: Preparation of ethyl 4-(3-fluoro-4-nitrophenyl)-1H-pyrrole-3-carboxylate



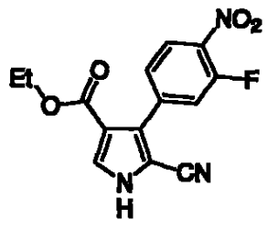
The procedure used for the preparation of Intermediate A Step 1 was used to prepare the title compound by substituting ethyl (2E)-3-(3-fluoro-4-nitrophenyl)acrylate for (2E)-3-(4-nitrophenyl)acrylate. ^{1}H-NMR (DMSO-d_6) δ 11.86 (s, 1H), 8.10 to 8.06 (t, J = 8.5 Hz, 1H), 7.74 to 7.71 (d, J = 13.5 Hz, 1H), 7.57 to 7.54 (m, 2H), 7.31 to 7.30 (m, 1H), 4.18 to 4.13 (q, J = 7.1 Hz, 2H), 1.25 to 1.21 (t, J = 7.0 Hz, 3H); **LCMS RT** = 3.05 min.

Step 5: Preparation of ethyl 4-(3-fluoro-4-nitrophenyl)-5-formyl-1H-pyrrole-3-carboxylate



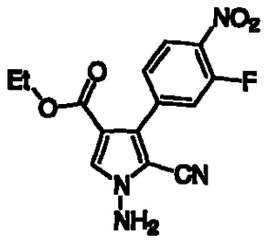
The procedure used for the preparation of Intermediate A Step 2 was used to prepare the title compound by substituting ethyl 4-(3-fluoro-4-nitrophenyl)-1H-pyrrole-3-carboxylate for ethyl 4-(4-nitrophenyl)-1*H*-pyrrole-3-carboxylate. ^{1}H-NMR (DMSO-d_6) δ 12.99 (s, 1H), 9.33 (s, 1H), 8.17 to 8.13 (t, J = 8.2 Hz, 1H), 7.81 to 7.74 (m, 2H), 7.52 to 7.50 (d, J = 6.6 Hz, 1H), 4.13 to 4.07 (q, J = 7.2 Hz, 2H), 1.16 to 1.13 (t, J = 7.0 Hz, 3H); **LCMS RT = 2.92.**

Step 6: Preparation of ethyl 5-cyano-4-(3-fluoro-4-nitrophenyl)-1H-pyrrole-3-carboxylate



The procedure used for the preparation of Intermediate A Step 3 was used to prepare the title compound by substituting of ethyl 4-(3-fluoro-4-nitrophenyl)-5-formyl-1H-pyrrole-3-carboxylate for 5-formyl-4-(nitrophenyl)-1*H*-pyrrole-3-carboxylate. ^{1}H-NMR (DMSO-d_6) δ 13.29 (s, 1H), 8.22 to 8.18 (t, J = 8.2 Hz, 1H), 7.91 (s, 1H), 7.74 to 7.71 (d, J = 10.9 Hz, 1H), 7.51 to 7.50 (d, J = 6.5 Hz, 1H), 4.16 to 4.10 (q, J = 7.0 Hz, 2H), 1.18 to 1.15 (t, J = 7.0 Hz, 3H).

Step 7: Preparation of ethyl 1-amino-5-cyano-4-(3-fluoro-4-nitrophenyl)-1H-pyrrole-3-carboxylate



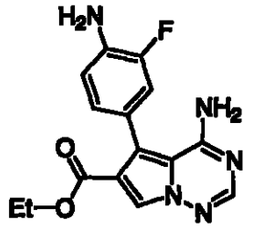
The procedure used for the preparation of Intermediate A Step 5 was used to prepare the title compound by substituting ethyl 5-cyano-4-(3-fluoro-4-nitrophenyl)-

1H-pyrrole-3-carboxylate for ethyl 5-cyano-4-(nitrophenyl)-1*H*-pyrrole-3-carboxylate. ^{1}H-NMR (DMSO-d_6) δ 8.23 8.21 (t, J = 8.3 Hz, 1H), 7.72 (s, 1H), 7.69 (d, J = 1.8 Hz, 1H), 7.49 to 7.47 (d, J = 8.5 Hz, 1H), 6.72 (s, 2H).

Step 8: Preparation of the title compound

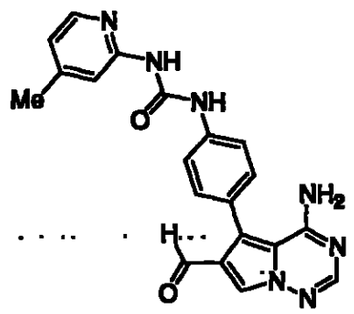
To a solution of EtOH (75 mL) was added ethyl 1-amino-5-cyano-4-(3-fluoro-4-nitrophenyl)-1H-pyrrole-3-carboxylate (1.68 g, 5.28 mmol) and formamidine acetate (5.49 g, 52.8 mmol). The solution was heated to 80 °C for 17 h. Upon cooling to rt the solution was treated with water and a precipitate formed which was filtered and washed with additional water. The solid was then suspended in DCM and Et_2O. The solid was collected and washed with Et_2O yielding 1.22 g of an orange-yellow solid (3.52 mmol, yield 67%). ^{1}H-NMR (DMSO-d_6) δ 8.20 (s, 1H), 8.18 to 8.14 (t, J = 8.2 Hz, 1H), 7.97 (s, 1H), 7.66 to 7.63 (d, J = 12.4 Hz, 1H), 7.41 to 7.39 (d, J = 8.4 Hz, 1H), 4.12 to 4.07 (q, J = 7.0 Hz, 2H), 1.13 to 1.10 (t, J = 7.0 Hz, 3H); MS $[M+H]^+$ = 346.2; LCMS RT = 2.77 min.

Intermediate AJ: Preparation of ethyl 4-amino-5-(4-amino-3-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate



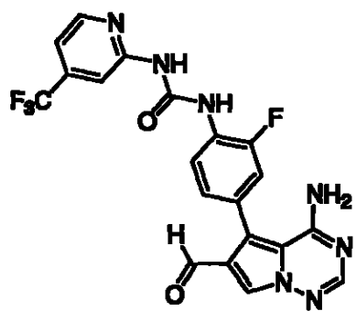
The procedure used for the preparation of Intermediate B was used to prepare the title compound by substituting Intermediate 2 for Intermediate A. ^{1}H-NMR (DMSO-d_6) δ 8.07 (s, 1H), 7.90 (s, 1H), 7.04 to 7.01 (d, J = 12.3 Hz, 1H), 6.88 to 6.85 (m, 2H), 6.81 to 6.77 (m, 1H), 5.36 (s, 2H), 4.11 to 4.06 (q, J = 7:1 Hz, 2H), 1.15 to 1.11 (t, J = 7.0 Hz, 3H); MS $[M+H]^+$ = 316.1; LCMS RT = 2.16 min.

Intermediate AK: Preparation of N-[4-(4-amino-6-formylpyrrolo[2,1-f][1,2,4]triazin-5-yl)phenyl]-N'-(4-methylpyridin-2-yl)urea



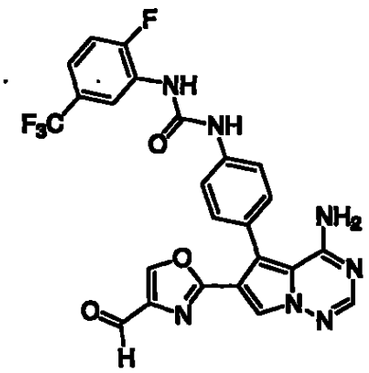
The procedure used for the preparation of Intermediate F was used to prepare the title compound by substituting Example 258 for Intermediate E. ^{1}H-NMR (DMSO-d_6) δ 10.90 (s, 1H), 9.74 (s, 1H), 9.48 (s, 1H), 8.26 (s, 1H), 8.15 to 8.14 (d, J = 5.2 Hz, 1H), 7.96 (s, 1H), 7.68 to 7.66 (d, J = 8.6 Hz, 2H), 7.45 to 7.43 (d, J = 8.4 Hz, 2H), 7.28 (s, 1H), 6.87 to 6.85 (m, 1H), 2.30 (s, 3H); MS $[M+H]^+$ = 388.1; LCMS RT = 2.09 min.

Intermediate AL: **Preparation of N-[4-(4-amino-6-formylpyrrolo[2,1-f][1,2,4]triazin-5-yl)-2-fluorophenyl]-N'-[4-(trifluoromethyl)pyridin-2-yl]urea**



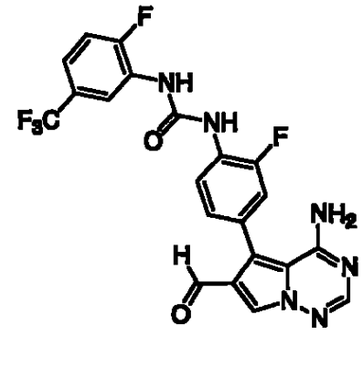
The procedure used for the preparation of Intermediate F was used to prepare the title compound by substituting Example 242 for Intermediate E. ^{1}H-NMR (DMSO-d_6) δ 10.16 (s, 1H), 10.13 to 10.08 (br s, 1H), 9.76 (s, 1H), 8.55 to 8.54 (d, J = 5.3 Hz, 1H), 8.34 to 8.29 (t, J = 8.6 Hz, 1H), 8.28 (s, 1H), 8.01 (s, 1H), 7.97 (s, 1H), 7.48 to 7.45 (d, J = 11.2 Hz, 1H), 7.39 to 7.38 (d, J = 5.7 Hz, 1H), 7.29 to 7.27 (d, J = 8.1 Hz, 1H); MS $[M+H]^+$ = 459.9; LCMS RT = 2.96 min.

Intermediate AM: **Preparation of N-[4-[4-amino-6-(4-formyl-1,3-oxazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-5-yl]phenyl}-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea**



The procedure used for the preparation of Intermediate F was used to prepare the title compound by substituting Example 237 for Intermediate E. ^{1}H-NMR (DMSO-d_6) δ 9.79 (s, 1H), 9.37 (s, 1H), 8.97 (s, 1H), 8.87 (s, 1H), 8.63 to 8.61 (d, J = 7.5 Hz, 1H), 8.34 (s, 1H), 7.96 (s, 1H), 7.60 to 7.58 (d, J = 8.6 Hz, 2H), 7.53 to 7.48 (m, 1H), 7.42 to 7.40 (m, 3H); MS $[M+H]^+$ = 526.1; LCMS RT = 2.93 min.

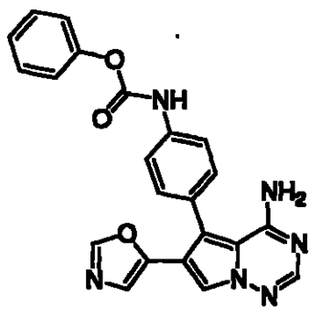
Intermediate AN: **Preparation of N-[4-(4-amino-6-formylpyrrolo[2,1-f][1,2,4]triazin-5-yl)-2-fluorophenyl]-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea**



The procedure used for the preparation of Intermediate F was used to prepare the title compound by substituting Example 249 for Intermediate E. ^{1}H-NMR (DMSO-d_6) δ 9.75 (s, 1H), 9.45 (s, 1H), 9.33 (s, 1H), 8.65 to 8.64 (d, J = 7.1 Hz,

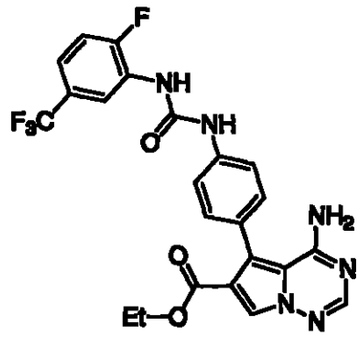
1H), 8.34 to 8.29 (m, 2H), 7.97 (s, 1H), 7.54 to 7.40 (m, 3H), 7.27 to 7.25 (d, J = 9.4 Hz, 1H); MS $[M+H]^+$ = 477.1; LCMS RT = 3.07 min.

Intermediate AO: Preparation of phenyl {4-[4-amino-6-(1,3-oxazol-5-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}carbamate



The procedure used for the preparation of Intermediate C was used to prepare the title compound by substituting Intermediate AB for Intermediate B. ^{1}H-NMR (DMSO-d_6) δ 10.48 (s, 1H), 8.29 (s, 1H), 8.09 (s, 1H), 7.90 (s, 1H), 7.67 to 7.65 (d, J = 8.4 Hz, 2H), 7.45 to 7.38 (m, 4H), 7.28 to 7.23 (m, 3H), 6.54 (s, 1H); MS $[M+H]^+$ = 413.1; LCMS RT = 2.51 min.

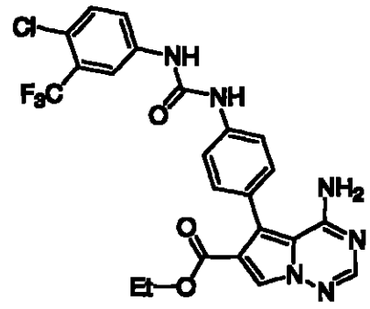
Example 1: Preparation of ethyl 4-amino-5-{4-[({[2-fluoro-5-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate



To a solution of DCE (2 mL) was added Intermediate B (75 mg, 0.25 mmol) followed by 1-fluoro-2-isocyanato-4-(trifluoromethyl)benzene (52 mg, 0.25 mmol). The reaction was stirred at rt for 2 h. The solution was concentrated in vacuo to

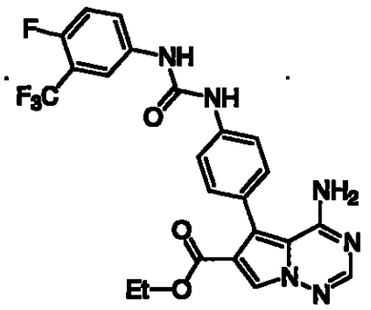
dryness and then purified by preparative HPLC (10-90% ACN/H_2O with 0.1% TFA). The resulting fractions were transferred to a separatory funnel, diluted with EtOAc (20 mL), washed with aqueous saturated $NaHCO_3$ (20 mL) and H_2O (20 mL). The organic layer was isolated, dried ($MgSO_4$), filtered, and concentrated to dryness to afford 30 mg of the above compound (0.060 mmol, yield 24%) ^{1}H-NMR (DMSO-d_6) δ 9.33 (s, 1H), 8.95 (d, J = 2.3 Hz, 1H), 8.63 to 8.61 (m, 1H), 8.13 (s, 1H), 8.07 (br s, 1H), 7.93 (s, 1H), 7.56 to 7.53 (m, 2H), 7.51 to 7.48 (m, 1H), 7.40 (br s, 1H), 7.34 to 7.32 (m, 2H), 5.09 (br s, 1H), 4.11 to 4.06 (q, J = 6.9 Hz, 2H), 1.13 to 1.10 (t, J = 7.1 Hz, 3H); MS $[M+H]^+$ = 503; LCMS RT = 3.22 min; TLC R_f = 0.15 (95:5 v/v CH_2Cl_2-MeOH).

Example 2: Preparation of ethyl 4-amino-5-{4-[({[4-chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate



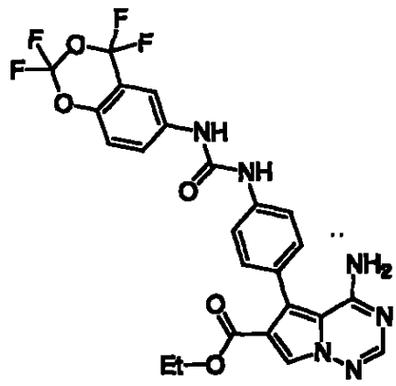
The procedure used for the preparation of Example 1 was used to prepare the title compound by substituting 1-chloro-4-isocyanato-2-(trifluoromethyl)benzene for 1-fluoro-2-isocyanato-4-(trifluoromethyl)benzene and purifying by column chromatography (5:4:1 v/v/v CH_2Cl_2-EtOAc-MeOH). ^{1}H-NMR (DMSO-d_6) δ 9.22 (br s, 1H), 9.02 (br s, 1H), 8.12 (s, 1H), 8.11 (d, J = 2.4 Hz, 1H), 7.92 (s, 1H), 7.63 (d, J = 2.3 Hz, 1H), 7.62 (s, 1H), 7.55 to 7.53 (m, 2H), 7.32 to 7.30 (m, 2H), 4.10 to 4.05 (q, J = 7.1 Hz, 2H), 1.12 to 1.09 (t, J = 7.0 Hz, 3H); MS $[M+H]^+$ = 519; LCMS RT = 3.06 min; TLC R_f = 0.48 (5:4:1 v/v/v CH_2Cl_2-EtOAc-MeOH).

Example 3: Preparation of ethyl 4-amino-5-{4-[({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate



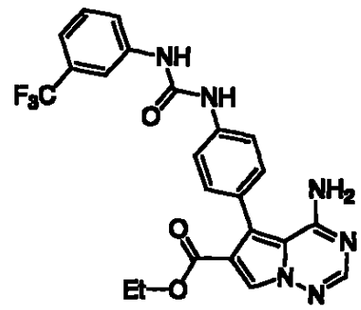
To a solution of THF (1 mL) was added Intermediate C (55 mg, 0.13 mmol) followed by 4-fluoro-3-(trifluoromethyl)aniline (30 μL, 0.24 mmol) and triethylamine (55 μL, 0.40 mmol). The reaction was stirred at 40 °C for 48 h. The solution was concentrated in vacuo to dryness and then purified by preparative HPLC (10-100% ACN/H_2O with 0.1% TFA). The resulting fractions were combined, concentrated in vacuo, diluted with EtOAc (5 mL), and washed with aqueous saturated Na_2CO_3 (5 mL). The aqueous layer was back extracted with EtOAc (5 mL). The organic layer was combined, dried (Na_2SO_4), filtered, and concentrated to dryness to afford 37 mg of the above compound (0.074 mmol, yield 56%). ^{1}H-NMR (CD_3OD) δ 8.08 (s, 1H), 7.92 (dd, J = 6.4, 2.7 Hz, 1H), 7.84 (s, 1H), 7.69 to 7.62 (m, 1H), 7.57 (d, J = 8.3 Hz, 2H), 7.36 (d, J = 8.7 Hz, 2H), 7.26 (t, J = 8.7 Hz, 1H), 4.10 (q, J = 7.1 Hz, 2H), 1.16 (t, J = 7.1 Hz, 3H); MS $[M+H]^+$ = 503; LCMS RT = 3.02 min.

Example 4: Preparation of ethyl 4-amino-5-[4-({[(2,2,4,4-tetrafluoro-4*H*-1,3-benzodioxin-6-yl)amino]carbonyl}amino)phenyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate



The procedure used for the preparation of Example 3 was used to prepare the title compound by substituting Intermediate D for Intermediate C, and 2,2,4,4-tetrafluoro-4*H*-1,3-benzodioxin-6-amine for 4-fluoro-3-(trifluoromethyl)aniline. ^{1}H-NMR (CD_3OD) δ 8.38 (s, 1H), 8.02 (s, 1H), 8.01 (d, J = 2.2 Hz, 1H), 7.67 (dd, J = 8.5, 2.2 Hz, 1H), 7.62 (d, J = 8.2 Hz, 2H), 7.42 (d, J = 8.2 Hz, 2H), 7.24 (d, J = 8.4 Hz, 1H), 4.17 (q, J = 7.2 Hz, 2H), 1.16 (t, J = 7.2 Hz, 3H); MS $[M+H]^+$ = 547; LCMS RT = 3.29 min.

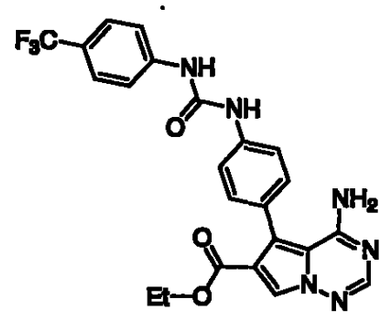
Example 5: Preparation of ethyl 4-amino-5-{4-[({[3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate



The procedure used for the preparation of Example 3 was used to prepare the title compound by substituting 3-(trifluoromethyl)aniline for 4-fluoro-3-(trifluoromethyl)aniline. ^{1}H-NMR (CD_3OD) δ 8.08 (s, 1H), 7.93 (br s, 1H), 7.84 (s, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.58 (d, J = 8.7 Hz, 2H), 7.48 (t, J = 8.0 Hz, 1H), 7.38

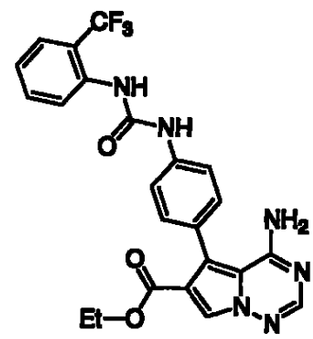
(d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.2 Hz, 1H), 4.10 (q, J = 7.3 Hz, 2H), 1.16 (t, J = 7.3 Hz, 3H); MS $[M+H]^+$ = 485; LCMS RT = 3.43 min.

Example 6: Preparation of ethyl 4-amino-5-{4-[({[4-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate



The procedure used for the preparation of Example 3 was used to prepare the title compound by substituting 4-(trifluoromethyl)aniline for 4-fluoro-3-(trifluoromethyl)aniline. ^{1}H-NMR (CD_3OD) δ 8.07 (s, 1H), 7.83 (s, 1H), 7.66 (d, J = 8.3 Hz, 2H), 7.60 to 7.55 (m, 4H), 7.36 (d, J = 8.6 Hz, 2H), 4.14 (q, J = 7.2 Hz, 2H), 1.16 (t, J = 7.2 Hz, 3H); MS $[M+H]^+$ = 485; LCMS RT = 3.47 min.

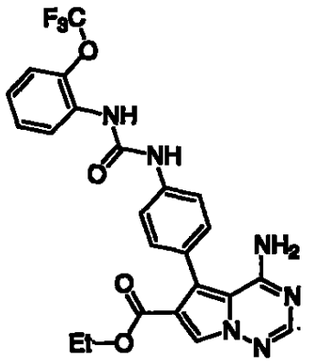
Example 7: Preparation of ethyl 4-amino-5-{4-[({[2-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate



The procedure used for the preparation of Example 3 was used to prepare the title compound by substituting 2-(trifluoromethyl)aniline for 4-fluoro-3-

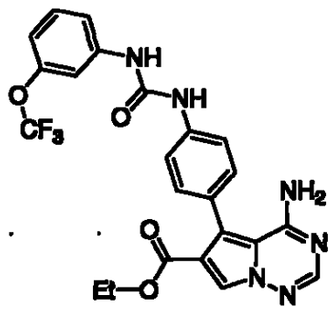
(trifluoromethyl)aniline. ^{1}H-NMR (CD_3OD) δ 8.07 (s, 1H), 7.96 (d, J = 8.7 Hz, 1H), 7.83 (s, 1H), 7.70 to 7.56 (m, 4H), 7.37 (d, J = 8.7 Hz, 2H), 7.30 (t, J = 7.9 Hz, 1H), 4.11 (q, J = 7.1 Hz, 2H), 1.16 (t, J = 7.1 Hz, 3H); MS $[M+H]^+$ = 485; LCMS RT = 2.80 min.

Example 8: **Preparation of ethyl 4-amino-5-{4-[({[2-(trifluoromethoxy)phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate**



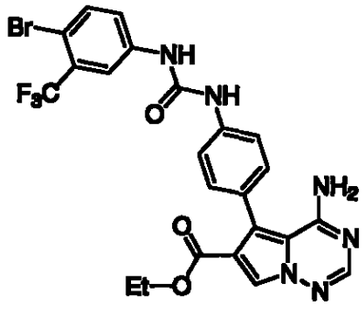
The procedure used for the preparation of Example 3 was used to prepare the title compound by substituting 2-(trifluoromethoxy)aniline for 4-fluoro-3-(trifluoromethyl)aniline. ^{1}H-NMR (CD_3OD) δ 8.26 (dd, J = 8.5, 2.1 Hz, 1H), 8.07 (s, 1H), 7.83 (s, 1H), 7.59 (d, J = 8.6 Hz, 2H), 7.40 to 7.28 (m, 4H), 7.14 to 7.07 (m, 1H), 4.08 (q, J = 7.2 Hz, 2H), 1.16 (t, J = 7.2 Hz, 3H); MS $[M+H]^+$ = 501; LCMS RT = 3.07 min.

Example 9: **Preparation of ethyl 4-amino-5-{4-[({[3-(trifluoromethoxy)phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate**



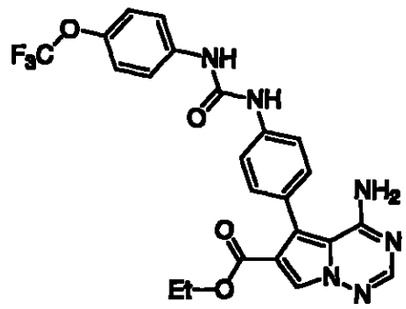
The procedure used for the preparation of Example 3 was used to prepare the title compound by substituting 3-(trifluoromethoxy)aniline for 4-fluoro-3-(trifluoromethyl)aniline. ^{1}H-NMR (CD_3OD) δ 8.07 (s, 1H), 7.83 (s, 1H), 7.64 (br s, 1H), 7.56 (d, J = 8.4 Hz, 2H), 7.39 to 7.28 (m, 5H), 4.10 (q, J = 7.1 Hz, 2H), 1.57 (t, J = 7.1 Hz, 3H); MS $[M+H]^+$ = 501; LCMS RT = 3.08 min.

Example 10: Preparation of ethyl 4-amino-5-{4-[({[4-bromo-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate



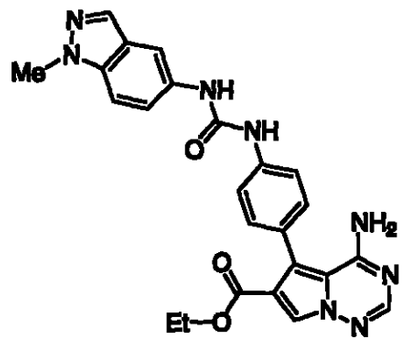
The procedure used for the preparation of Example 3 was used to prepare the title compound by substituting 4-bromo-3-(trifluoromethyl)aniline for 4-fluoro-3-(trifluoromethyl)aniline. ^{1}H-NMR (CD_3OD) δ 8.07 (s, 1H), 8.01 (d, J = 2.5 Hz, 1H), 7.83 (s, 1H), 7.68 (d, J = 8.8 Hz, 1H), 7.60 to 7.54 (m, 3H), 7.36 (d, J = 8.5 Hz, 2H), 4.08 (q, J = 7.2 Hz, 2H), 1.16 (t, J = 7.2 Hz, 3H); MS $[M+H]^+$ = 563; LCMS RT = 3.19 min.

Example 11: Preparation of ethyl 4-amino-5-{4-[({[4-(trifluoromethoxy)phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate



The procedure used for the preparation of Example 3 was used to prepare the title compound by substituting 4-(trifluoromethoxy)aniline for 4-fluoro-3-(trifluoromethyl)aniline. ^{1}H-NMR (CD_3OD) δ 8.07 (s, 1H), 7.83 (s, 1H), 7.57 (d, J = 7.3 Hz, 2H), 7.54 (d, J = 6.8 Hz, 2H), 7.35 (d, J = 8.5 Hz, 2H), 7.20 (d, J = 8.8 Hz, 2H), 4.10 (q, J = 7.2 Hz, 2H), 1.14 (t, J = 7.2 Hz, 3H); MS $[M+H]^+$ = 501; LCMS RT = 3.11 min.

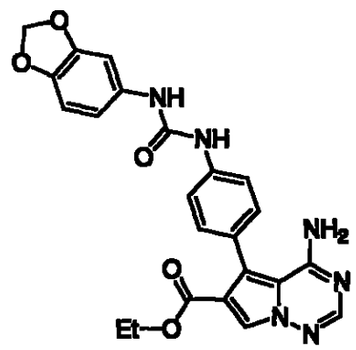
Example 12: Preparation of ethyl 4-amino-5-[4-({[(1-methyl-1*H*-indazol-5-yl)amino]carbonyl}amino)phenyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate



The procedure used for the preparation of Example 3 was used to prepare the title compound by substituting 1-methyl-1*H*-indazol-5-amine for 4-fluoro-3-(trifluoromethyl)aniline. ^{1}H-NMR (CD_3OD) δ 8.12 (s, 1H), 7.93 (d, J = 5.6 Hz, 2H), 7.91 (s, 1H), 7.59 to 7.51 (m, 3H), 7.36 (d, J = 8.6 Hz, 1H), 7.29 (d, J = 8.6 Hz, 2H),

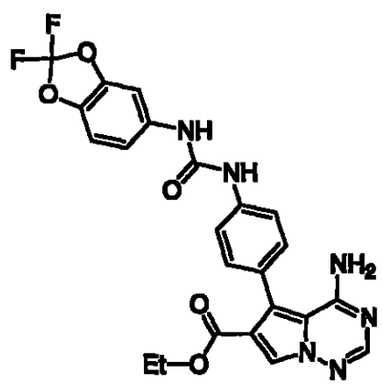
4.07 (q, J = 7.2 Hz, 2H), 4.00 (s, 3H), 1.09 (t, J = 7.2 Hz, 3H); MS $[M+H]^+$ = 471; LCMS RT = 2.90 min.

Example 13: Preparation of ethyl 4-amino-5-(4-{[(1,3-benzodioxol-5-ylamino)carbonyl]amino}phenyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate



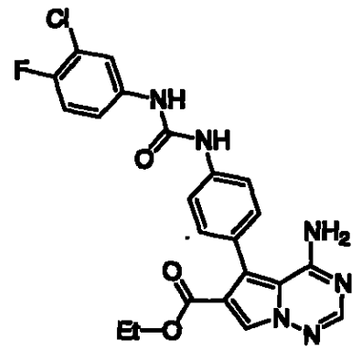
The procedure used for the preparation of Example 3 was used to prepare the title compound by substituting 1,3-benzodioxol-5-amine for 4-fluoro-3-(trifluoromethyl)aniline. ^{1}H-NMR (CD_3OD) δ 8.08 (s, 1H), 7.84 (s, 1H), 7.55 (d, J = 9.0 Hz, 2H), 7.35 (d, J = 9.0 Hz, 2H), 7.13 (t, J = 1.4Hz, 1H), 6.92 (br s, 1H), 6.76 (d, J = 1.2 Hz, 2H), 5.92 (s, 2H), 4.08 (q, J = 7.1 Hz, 2H), 1.16 (t, J = 7.1 Hz, 3H); MS $[M+H]^+$ = 461; LCMS RT = 3.04 min.

Example 14: Preparation of ethyl 4-amino-5-[4-({[(2,2-difluoro-1,3-benzodioxol-5-yl)amino]carbonyl}amino)phenyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate



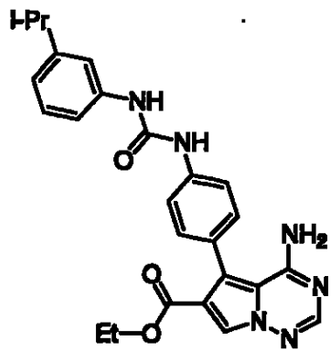
The procedure used for the preparation of Example 3 was used to prepare the title compound by substituting 2,2-difluoro-1,3-benzodioxol-5-amine for 4-fluoro-3-(trifluoromethyl)aniline. ^{1}H-NMR (CD_3OD) δ 8.08 (s, 1H), 7.84 (s, 1H), 7.59 (d, J = 2.1 Hz, 1H), 7.56 (d, J = 8.9 Hz, 2H), 7.36 (d, J = 8.9 Hz, 2H), 7.12 (d, J = 8.7 Hz, 1H), 7.03 (dd, J = 8.7, 2.1 Hz, 1H), 6.92 (br s, 1H), 4.09 (q, J = 7.2 Hz, 2H), 1.15 (t, J = 7.2 Hz, 3H); MS $[M+H]^+$ = 497; LCMS RT = 3.44 min.

Example 15: Preparation of ethyl 4-amino-5-[4-({[(3-chloro-4-fluorophenyl)amino]carbonyl}amino)phenyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate



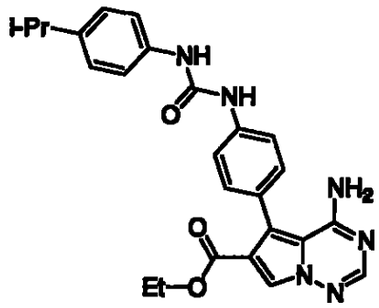
The procedure used for the preparation of Example 3 was used to prepare the title compound by substituting 3-chloro-4-fluoroaniline for 4-fluoro-3-(trifluoromethyl)aniline. ^{1}H-NMR (CD_3OD) δ 8.08 (s, 1H), 7.84 (s, 1H), 7.73 (dd, J = 6.3, 2.4 Hz, 1H), 7.56 (d, J = 8.8 Hz, 2H), 7.36 (d, J = 8.4 Hz, 2H), 7.33 to 7.27 (m, 1H), 7.17 (t, J = 9.2 Hz, 1H), 4.09 (q, J = 7.1 Hz, 2H), 1.16 (t, J = 7.1 Hz, 3H); MS $[M+H]^+$ = 469; LCMS RT = 3.37 min.

Example 16: Preparation of ethyl 4-amino-5-[4-({[(3-isopropylphenyl)amino]carbonyl}amino)phenyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate



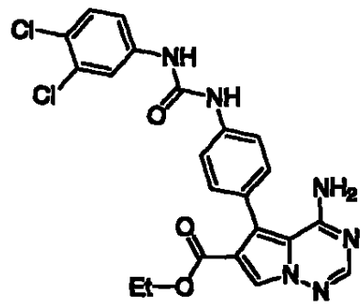
The procedure used for the preparation of Example 3 was used to prepare the title compound by substituting 3-isopropylaniline for 4-fluoro-3-(trifluoromethyl)aniline. ^{1}H-NMR (CD_3OD) δ 8.08 (s, 1H), 7.84 (s, 1H), 7.56 (d, J = 8.6 Hz, 2H), 7.39 to 7.32 (m, 3H), 7.26 to 7.19 (m, 2H), 6.92 (d, J = 7.2 Hz, 1H), 4.15 (q, J = 7.1 Hz, 2H), 1.16 (t, J = 7.1 Hz, 3H); MS $[M+H]^+$ = 459; LCMS RT = 3.07 min.

Example 17: Preparation of ethyl 4-amino-5-[4-({[(4-isopropylphenyl)amino]carbonyl}amino)phenyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate



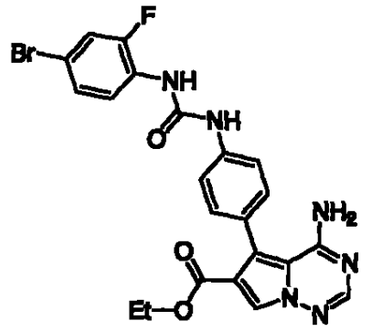
The procedure used for the preparation of Example 3 was used to prepare the title compound by substituting 4-isopropylaniline for 4-fluoro-3-(trifluoromethyl)aniline. ^{1}H-NMR (CD_3OD) δ 8.08 (s, 1H), 7.84 (s, 1H), 7.56 (d, J = 8.3 Hz, 2H), 7.37 to 7.32 (m, 4H), 7.18 (d, J = 8.4 Hz, 2H), 4.15 (q, J = 7.1 Hz, 2H), 1.16 (t, J = 7.1 Hz, 3H); MS $[M+H]^+$ = 459; LCMS RT = 3.09 min.

Example 18: Preparation of ethyl 4-amino-5-[4-({[(3,4-dichlorophenyl)amino]carbonyl}amino)phenyl]pyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate



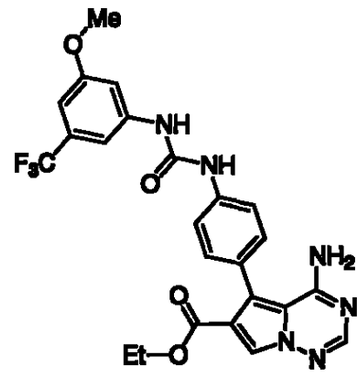
The procedure used for the preparation of Example 3 was used to prepare the title compound by substituting 3,4-dichloroaniline for 4-fluoro-3-(trifluoromethyl)aniline. ^{1}H-NMR (CD_3OD) δ 8.09 (s, 1H), 7.84 (s, 1H), 7.82 (d, J = 2.1 Hz, 1H), 7.57 (d, J = 8.3 Hz, 2H), 7.44 to 7.29 (m, 4H), 6.92 (s, 2H), 4.15 (q, J = 7.2 Hz, 2H), 1.16 (t, J = 7.2 Hz, 3H); MS $[M+H]^+$ = 485; LCMS RT = 3.14 min.

Example 19: Preparation of ethyl 4-amino-5-[4-({[(4-bromo-2-fluorophenyl)amino]carbonyl}amino)phenyl]pyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate



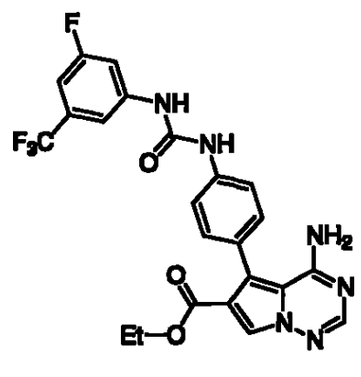
The procedure used for the preparation of Example 3 was used to prepare the title compound by substituting 4-bromo-2-fluoroaniline for 4-fluoro-3-(trifluoromethyl)aniline. ^{1}H-NMR (CD_3OD) δ 8.14 (s, 1H), 8.12 to 8.07 (m, 1H), 7.88 (s, 1H), 7.59 (d, J = 8.7 Hz, 2H), 7.42 to 7.27 (m, 3H), 6.92 (s, 1H), 4.15 (q, J = 7.1 Hz, 2H), 1.16 (t, J = 7.1 Hz, 3H); MS $[M+H]^+$ = 513; LCMS RT = 3.42 min.

Example 20: Preparation of ethyl 4-amino-5-{4-[({[3-methoxy-5-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate



The procedure used for the preparation of Example 3 was used to prepare the title compound by substituting 3-methoxy-5-(trifluoromethyl)aniline for 4-fluoro-3-(trifluoromethyl)aniline. ^{1}H-NMR (CD_3OD) δ 8.08 (s, 1H), 7.84 (s, 1H), 7.57 (d, J = 8.9 Hz, 2H), 7.40 to 7.35 (m, 4H), 6.83 (s, 1H), 4.10 (q, J = 7.1 Hz, 2H), 1.16 (t, J = 7.1 Hz, 3H); MS $[M+H]^+$ = 515; LCMS RT = 3.11 min.

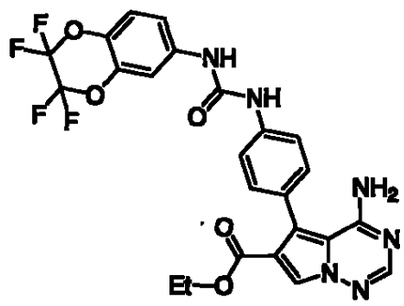
Example 21: Preparation of ethyl 4-amino-5-{4-[({[3-fluoro-5-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate



The procedure used for the preparation of Example 3 was used to prepare the title compound by substituting 3-fluoro-5-(trifluoromethyl)aniline for 4-fluoro-3-

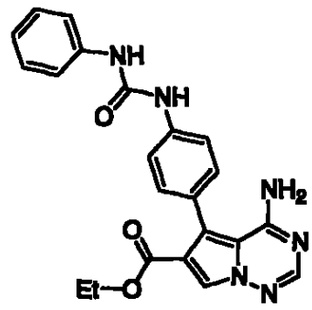
(trifluoromethyl)aniline. ^{1}H-NMR (CD_3OD) δ 8.08 (s, 1H), 7.84 (s, 1H), 7.65 (d, J = 10.9 Hz, 1H), 7.59(s, 1H), 7.58 (d, J = 8.3 Hz, 2H), 7.38 (d, J = 8.5 Hz, 2H), 7.05 (d, J = 9.1 Hz, 1H), 4.15 (q, J = 7.2 Hz, 2H), 1.16 (t, J = 7.2 Hz, 3H); MS $[M+H]^+$ = 503; LCMS RT = 3.56 min.

Example 22: Preparation of ethyl 4-amino-5-[4-({[(2,2,3,3-tetrafluoro-2,3-dihydro-1,4-benzodioxin-6-yl)amino]carbonyl}amino)phenyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate



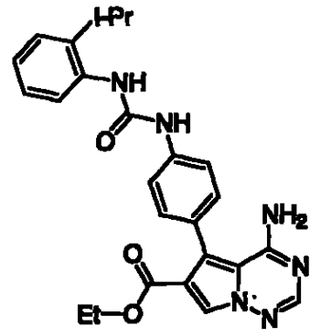
The procedure used for the preparation of Example 3 was used to prepare the title compound by substituting 2,2,3,3-tetrafluoro-2,3-dihydro-1,4-benzodioxin-6-amine for 4-fluoro-3-(trifluoromethyl)aniline. ^{1}H-NMR (CD_3OD) δ 8.07 (s, 1H), 7.83 (s, 1H), 7.63 (t, J = 1.3 Hz, 1H), 7.56 (d, J = 8.7 Hz, 2H), 7.35 (d, J = 8.6 Hz, 2H), 7.20 (d, J = 1.3 Hz, 2H), 4.12 (q, J = 7.2 Hz, 2H), 1.15 (t, J = 7.2 Hz, 3H); MS $[M+H]^+$ = 547; LCMS RT = 3.66 min.

Example 23: Preparation of ethyl 4-amino-5-{4-[(anilinocarbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate

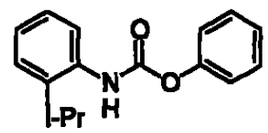


The procedure used for the preparation of Example 3 was used to prepare the title compound by substituting aniline for 4-fluoro-3-(trifluoromethyl)aniline. ^{1}H-NMR (CD_3OD) δ 8.09 (s, 1H), 7.84 (s, 1H), 7.56 (d, J = 8.8 Hz, 2H), 7.44 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 8.8 Hz, 2H), 7.33 to 7.27 (m, 2H), 7.03 (t, J = 7.4 Hz, 1H), 4.15 (q, J = 7.1 Hz, 2H), 1.15 (t, J = 7.1 Hz, 3H); MS $[M+H]^+$ = 417; LCMS RT = 2.53 min.

Example 24: Preparation of ethyl 4-amino-5-[4-({[(2-isopropylphenyl)amino]carbonyl}amino)phenyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate



Step 1: Preparation of phenyl (2-isopropylphenyl)carbamate



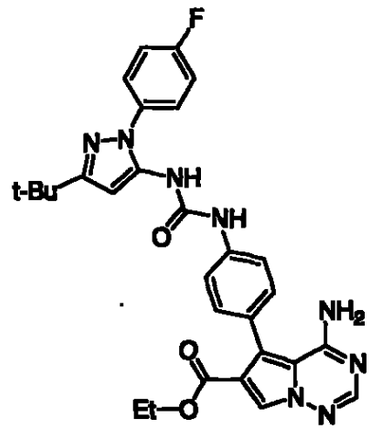
To a stirred solution of 2-isopropylaniline (200 mg, 1.5 mmol) in THF (9 mL) was added pyridine (0.24 mL, 3.0 mmol), then phenyl chloroformate (0.28 mL, 2.2 mmol) at rt. Some solid precipitated out. The mixture was stirred at rt for 4.5 h.

Water was added to the reaction and it was extracted with EtOAc. The organic solution was washed with water (5 mL) and dried over $MgSO_4$ and then filtered. The filtrate was concentrated in vacuo and crystallized from EtOAc-hexanes (1:9 v/v) to afford the title compound (130 mg, 34%). ^{1}H-NMR (DMSO-d_6) δ 9.45 (s, 1H), 7.44 to 7.36 (m, 2H), 7.35 to 7.28 (m, 2H), 7.25 to 7.14 (m, 5H), 3.27 (m, 1H), 1.17 (d, J = 6.9 Hz, 2H); TLC R_f = 0.33 (9:1 v/v hexanes-EtOAc).

Step 2: Preparation of the title compound

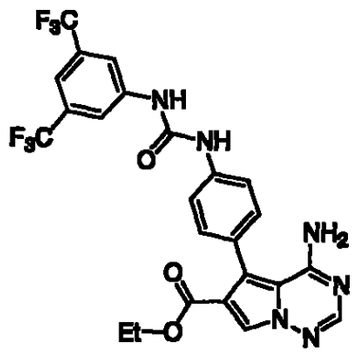
To a solution of THF (1.5 mL) was added phenyl (2-isopropylphenyl)carbamate (43 mg, 0.17 mmol) followed by Intermediate B (50 mg, 0.17 mmol) and triethylamine (23 µL, 0.17 mmol). The reaction was stirred at 50 °C for 36 h. The solution was concentrated in vacuo to dryness and then purified by preparative HPLC (10-100% ACN/H_2O with 0.1% TFA). The resulting fractions were combined and concentrated in vacuo. EtOAc (5 mL) was added and washed with aqueous saturated Na_2CO_3 (5 mL). The aqueous layer was back extracted with EtOAc (5 mL). The organic layer was combined, dried (Na_2SO_4), filtered, and concentrated to dryness to afford 19 mg of the above compound (0.042 mmol, yield 25%). ^{1}H-NMR (CD_3OD) δ 8.08 (s, 1H), 7.84 (s, 1H), 7.57 (d, J = 8.6 Hz, 2H), 7.53 to 7.49 (m, 1H), 7.38 to 7.32 (m, 3H), 7.21 to 7.16 (m, 2H), 6.92 (s, 1H), 4.09 (q, J = 7.1 Hz, 2H), 3.28 to 3.18 (m, 1H), 1.16 (t, J = 7.1 Hz, 3H); MS $[M+H]^+$ = 459; LCMS RT = 3.31 min.

Example 25: Preparation of ethyl 4-amino-5-[4-[({[3-*tert*-butyl-1-(4-fluorophenyl)-1*H*-pyrazol-5-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate



The procedure used for the preparation of Example 24 was used to prepare the title compound by substituting 3-*tert*-butyl-1-(4-fluorophenyl)-1*H*-pyrazol-5-amine for 2-isopropylaniline. ^{1}H-NMR (DMSO-d_6) δ 9.15 (s, 1H), 8.44 (s, 1H), 8.12 (s, 1H), 8.05 (br s, 1H), 7.93 (s, 1H), 7.57 (dd, J = 9.1, 5.0 Hz, 2H), 7.49 (d, J = 8.6 Hz, 2H), 7.37 (t, J = 8.8 Hz, 2H), 7.28 (d, J = 9.1 Hz, 2H), 6.38 (s, 1H), 5.05 (br s, 1H), 4.02 (q, J = 7.1 Hz, 2H), 1.27 (s, 9H), 1.08 (t, J = 7.1 Hz, 3H); MS $[M+H]^+$ = 557; LCMS RT = 3.12 min.

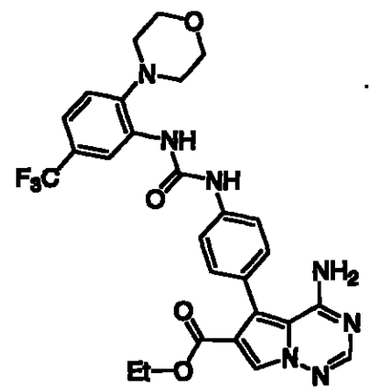
Example 26: Preparation of ethyl 4-amino-5-{4-[({[3,5-bis(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate



The procedure used for the preparation of Example 24 was used to prepare the title compound by substituting 3,5-bis(trifluoromethyl)aniline for 2-isopropylaniline. ^{1}H-NMR (CD_3OD) δ 8.11 (s, 2H), 8.09 (s, 1H), 7.86 (s, 1H), 7.60

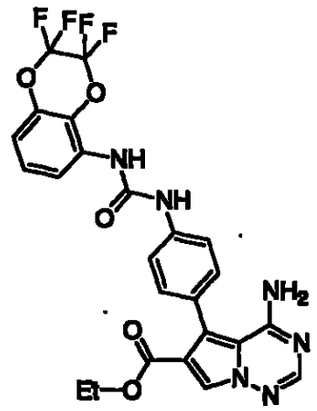
(d, J = 8.8 Hz, 2H), 7.52 (s, 1H), 7.35 (d, J = 8.5 Hz, 2H), 4.07 (q, J = 7.1 Hz, 2H), 1.14 (t, J = 7.1 Hz, 3H); MS $[M+H]^+$ = 553; LCMS RT = 3.40 min.

Example 27: Preparation of ethyl 4-amino-5-{4-[({[2-morpholin-4-yl-5-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate



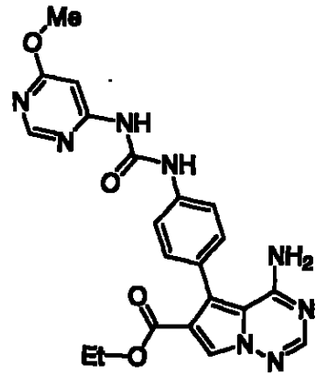
The procedure used for the preparation of Example 24 was used to prepare the title compound by substituting 2-morpholin-4-yl-5-(trifluoromethyl)aniline for 2-isopropylaniline. ^{1}H-NMR (CD_3OD) δ 8.50 (s, 1H)8.09 (s, 1H), 7.85 (s, 1H), 7.62 (d, J = 8.9 Hz, 2H), 7.42 to 7.29 (d, J = 8.7 Hz, 4H), 4.08 (q, J = 7.1 Hz, 2H), 3.98 to 3.93 (m, 4H), 2.98 to 2.89 (m, 4H), 1.16 (t, J = 7.1 Hz, 3H); MS $[M+H]^+$ = 570; LCMS RT = 3.18 min.

Example 28: Preparation of ethyl 4-amino-5-[4-({[(2,2,3,3-tetrafluoro-2,3-dihydro-1,4-benzodioxin-5-yl)amino]carbonyl}amino)phenyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate



The procedure used for the preparation of Example 24 was used to prepare the title compound by substituting 2,2,3,3-tetrafluoro-2,3-dihydro-1,4-benzodioxin-5-amine for 2-isopropylaniline. ^{1}H-NMR (CD_3OD) δ 8.10 (d, J = 8.0 Hz, 1H), 8.08 (s, 1H), 7.84 (s, 1H), 7.59 (d, J = 8.2 Hz, 2H), 7.38 (d, J = 8.2 Hz, 2H), 7.23 (t, J = 8.2 Hz, 1H), 6.93 (d, J = 8.2 Hz, 1H), 4.10 (q, J = 7.1 Hz, 2H), 1.16 (t, J = 7.1 Hz, 3H); MS $[M+H]^+$ = 547; LCMS RT = 3.27 min.

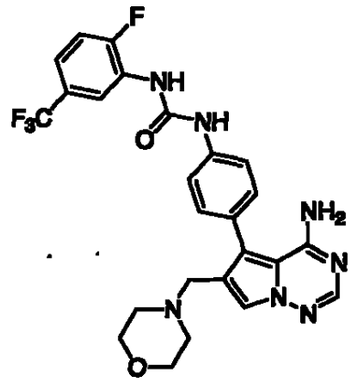
Example 29: Preparation of ethyl 4-amino-5-[4-({[(6-methoxypyrimidin-4-yl)amino]carbonyl}amino)phenyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate



The procedure used for the preparation of Example 24 was used to prepare the title compound by substituting 6-methoxypyrimidin-4-amine for 2-isopropylaniline. ^{1}H-NMR (DMSO-d_6) δ 9.82 (s, 1H), 9.60 (s, 1H), 8.50 (s, 1H), 8.13 (s, 1H), 7.93 (s, 1H), 7.56 (d, J = 8.5 Hz, 2H), 7.33 (d, J = 8.5 Hz, 2H), 7.09 (d,

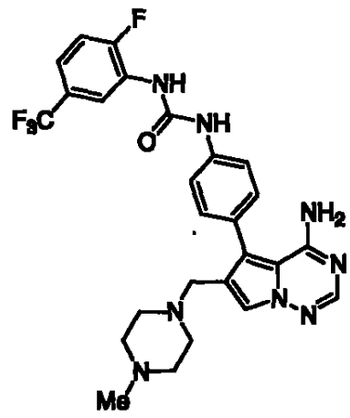
J = 1.1 Hz, 1H), 4.07 (q, J = 7.1 Hz, 2H), 3.89 (s, 3H), 1.09 (t, J = 7.1 Hz, 3H); MS $[M+H]^+$ = 449; LCMS RT = 2.94 min.

Example 30: Preparation of *N*-[4-[4-amino-6-(morpholin-4-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl]-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea



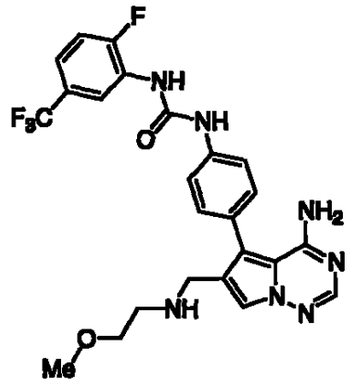
To a solution of Intermediate F (40.0 mg, 0.08 mmol) in CH_2Cl_2 (3.0 mL) was added AcOH (0.03 mL, 0.46 mmol) and morpholine (0.01 mL, 0.11 mmol). The reaction was stirred at rt for 1 h after which sodium triacetoxyborohydride (49.0 mg, 0.23 mmol) was added. The reaction was stirred at rt until completion. Reaction was diluted with CH_2Cl_2, transferred to a separatory funnel and washed with saturated aq $NaHCO_3$ (2x). Aqueous phase was back extracted with CH_2Cl_2 (2x). The organic was dried (Na_2SO_4) and evaporated to give a crude oil that was purified via HPLC (10-90% ACN/H_2O) to give the title compound (30 mg, 70%). ^{1}H-NMR (CD_3OD) δ 8.61 (d, J = 8.0 Hz, 1H), 7.76 (s, 1H), 7.66 (s, 1H), 7.62 (s, 1H), 7.60 (s, 1H), 7.40 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 3.65-3.62 (m, 4H), 3.48 (s, 2H), 2.40-2.36 (m, 4H); MS $[M+H]^+$ = 530; LCMS RT = 2.22 min; TLC R_f = 0.27 (1:3 v/v Acetone: CH_2Cl_2).

Example 31: Preparation of *N*-(4-{4-amino-6-[(4-methylpiperazin-1-yl)methyl]pyrrolo[2,1-f][1,2,4]triazin-5-yl}phenyl)-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea



The procedure used for the preparation of Example 30 was used to prepare the title compound by substituting 1-methylpiperazine for morpholine and purifying by preparative TLC (20:180:1 v/v/v MeOH-CH_2Cl_2-NH_4OH). ^{1}H-NMR (CD_3OD) δ 8.61 (d, J = 8.0 Hz, 1H), 7.77 (s, 1H), 7.67 (s, 1H), 7.61 (d, J = 8.0 Hz, 2H), 7.41-7.33 (m, 4H), 3.53 (s, 2H), 3.35 (s, 3H), 2.50 (br s, 4H), 2.32 (m, 4H); MS $[M+H]^+$ = 543; LCMS RT = 2.15 min; TLC R_f = 0.23 (20:180:1 v/v/v MeOH-CH_2Cl_2-NH_4OH).

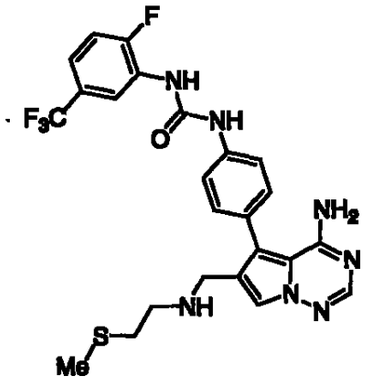
Example 32: Preparation of *N*-[4-(4-amino-6-{[(2-methoxyethyl)amino]methyl}pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)phenyl]-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea



The procedure used for the preparation of Example 30 was used to prepare the title compound by substituting 2-methoxyethanamine for morpholine and

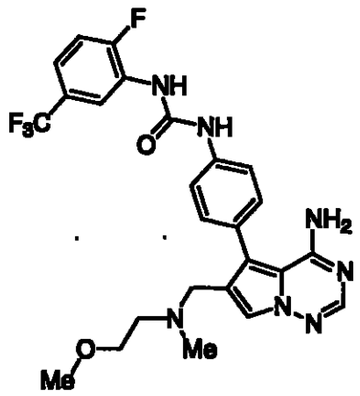
purifying by MPLC (Analogix) using 0-15% MeOH-CH_2Cl_2. ^{1}H-NMR (CD_3OD) δ 8.61 to 8.59 (d, J = 7.8 Hz, 1H), 7.80 (s, 1H), 7.79 (s, 1H), 7.67 to 7.65 (d, J = 8.6 Hz, 2H), 7.41 to 7.39 (d, J = 8.6 Hz, 2H), 7.35 to 7.33 (d, J = 8.9 Hz, 2H), 3.99 (s, 2H), 3.48 to 3.46 (t, J = 5.1 Hz, 2H), 3.31 (s, 3H), 2.91 to 2.89 (t, J = 5.2 Hz, 2H); MS $[M+H]^+$ = 518; LCMS RT = 2.26 min; TLC R_f = 0.30 (15:85 v/v MeOH-CH_2Cl_2).

Example 33: Preparation of *N*-[4-[4-amino-6-({[2-(methylthio)ethyl]amino}methyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea



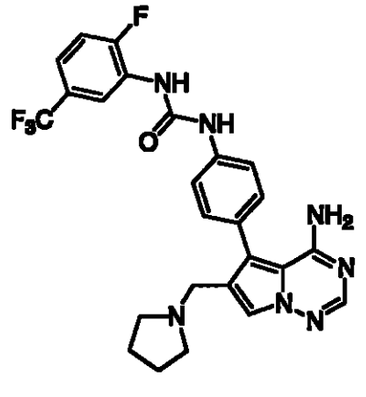
The procedure used for the preparation of Example 30 was used to prepare the title compound by substituting 2-(methylthio)ethanamine for morpholine and purifying by MPLC (Analogix) using 0-15% MeOH-CH_2Cl_2. ^{1}H-NMR (CD_3OD) δ 8.62 to 8.60 (d, J = 7.7 Hz, 1H), 7.78 (s, 1H), 7.71 (s, 1H), 7.65 to 7.63 (d, J = 8.6 Hz, 2H), 7.42 to 7.40 (d, J = 8.5 Hz, 2H), 7.35 to 7.33 (d, J = 8.8 Hz, 2H), 3.80 (s, 2H), 2.75 to 2.72 (t, J = 6.5 Hz, 2H), 2.58 to 2.55 (t, J = 6.6 Hz, 2H), 1.99 (s, 3H); MS $[M+H]^+$ = 534; LCMS RT = 2.36 min; TLC R_f = 0.50 (15:85 v/v MeOH-CH_2Cl_2).

Example 34: Preparation of *N*-[4-(4-amino-6-[[(2-methoxyethyl)(methyl)amino]methyl}pyrrolo[2,1-f][1,2,4]triazin-5-yl)phenyl]-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea



The procedure used for the preparation of Example 30 was used to prepare the title compound by substituting 2-methoxy-*N*-methylethanamine for morpholine and purifying by MPLC (Analogix) using 0-15% MeOH-CH_2Cl_2. ^{1}H-NMR (CD_3OD) δ 8.61 to 8.59 (d, *J* = 7.9 Hz, 1H), 7.80 (s, 1H), 7.78 (s, 1H), 7.66 to 7.64 (d, *J* = 8.6 Hz, 2H), 7.40 to 7.38 (d, *J* = 8.5 Hz, 2H), 7.35 to 7.32 (d, *J* = 8.9 Hz, 2H), 3.90 (s, 2H), 3.47 to 3.44 (t, *J* = 5.4 Hz, 2H), 3.29 (s, 3H), 2.79 to 2.77 (t, *J* = 5.4 Hz, 2H), 2.39 (s, 3H); MS $[M+H]^+$ = 532; LCMS RT = 2.69 min; TLC R_f = 0.16 (15:85 v/v MeOH- CH_2Cl_2).

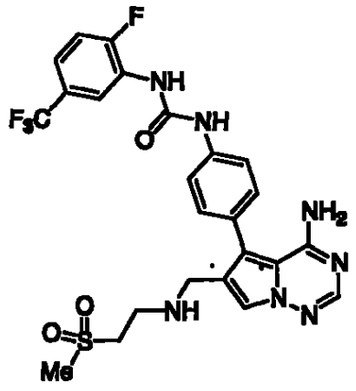
Example 35: Preparation of *N*-[4-[4-amino-6-(pyrrolidin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl]-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea



The procedure used for the preparation of Example 30 was used to prepare the title compound by substituting pyrrolidine for morpholine and purifying by

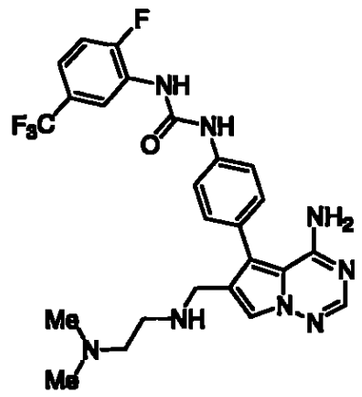
MPLC (Analogix) using 0-15% MeOH-CH_2Cl_2. ^{1}H-NMR (CD_3OD) δ 8.62 to 8.60 (d, J = 7.8 Hz, 1H), 7.78 (s, 1H), 7.74 (s, 1H), 7.64 to 7.62 (d, J = 8.4 Hz, 2H), 7.39 to 7.37 (d, J = 8.6 Hz, 2H), 7.35 to 7.33 (d, J = 8.8 Hz, 2H), 3.77 (s, 2H), 2.63 to 2.60 (m, 4H), 1.82 to 1.78 (m, 4H); MS $[M+H]^+$ = 514; LCMS RT = 2.69 min; TLC R_f = <0.10 (15:85 v/v MeOH- CH_2Cl_2).

Example 36: Preparation of *N*-{4-[4-amino-6-({[2-(methylsulfonyl)ethyl]amino}methyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea



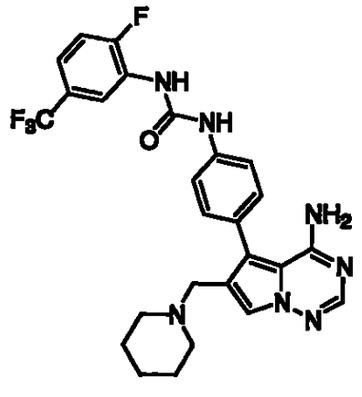
The procedure used for the preparation of Example 30 was used to prepare the title compound by substituting 2-(methylsulfonyl)ethanamine hydrochloride for morpholine and purifying by MPLC (Analogix) using 0-15% MeOH-CH_2Cl_2. ^{1}H-NMR (CD_3OD) δ 8.62 to 8.60 (d, J = 7.5 Hz, 1H), 7.77 (s, 1H), 7.69 (s, 1H), 7.64 to 7.62 (d, J = 8.7 Hz, 2H), 7.42 to 7.40 (d, J = 8.9 Hz, 2H), 7.35 to 7.33 (d, J = 8.9 Hz, 2H), 3.77 (s, 2H), 3.22 to 3.19 (t, J = 6.5 Hz, 2H), 3.03 to 2.99 (t, J = 6.7 Hz, 2H), 2.96 (s, 3H); MS $[M+H]^+$ = 566; LCMS RT = 2.25 min; TLC R_f = 0.21 (15:85 v/v MeOH- CH_2Cl_2).

Example 37: Preparation of *N*-{4-[4-amino-6-({[2-(dimethylamino)ethyl]amino}methyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea



The procedure used for the preparation of Example 30 was used to prepare the title compound by substituting *N,N*-dimethylethane-1,2-diamine for morpholine and purifying by via HPLC (10-90% ACN/H_2O). ^{1}H-NMR (CD_3OD) δ 8.62 (d, *J* = 7.4 Hz, 1H), 7.77 (s, 1H), 7.71 (s, 1H), 7.64 (d, *J* = 8.5 Hz, 2H), 7.40 (d, *J* = 8.5 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 3.73 (s, 2H), 2.61 (t, *J* = 6.5 Hz, 2H), 2.37 (t, *J* = 6.9 Hz, 2H), 2.17 (s, 6H); MS $[M+H]^+$ = 531; LCMS RT = 1.96 min.

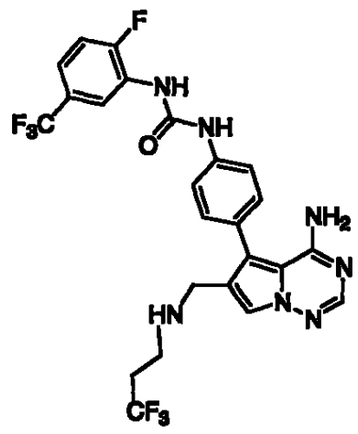
Example 38: Preparation of *N*-[4-[4-amino-6-(piperidin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl]-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea



The procedure used for the preparation of Example 30 was used to prepare the title compound by substituting piperidine for morpholine and purifying by via HPLC (10-90% ACN/H_2O). ^{1}H-NMR (CD_3OD) δ 8.63 (d, *J* = 8.2 Hz, 1H), 7.77 (s, 1H), 7.73 (s, 1H), 7.62 (d, *J* = 8.6 Hz, 2H), 7.37 (d, *J* = 8.8 Hz, 2H), 7.34 (d, *J* = 8.8

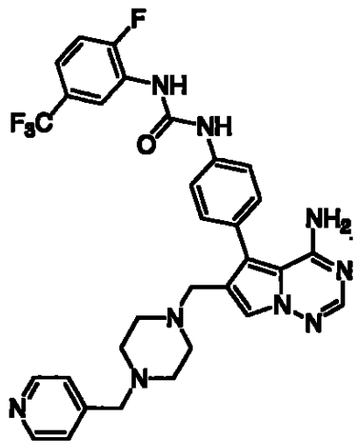
Hz, 2H), 3.50 (s, 2H), 2.36 to 2.27 (m, 4H), 1.60 to 1.50 (m, 4H), 1.40 to 1.35 (m, 2H); MS $[M+H]^+ = 528$; LCMS RT = 2.34 min.

Example 39: Preparation of *N*-[4-(4-amino-6-{[(3,3,3-trifluoropropyl)amino]methyl}pyrrolo[2,1-f][1,2,4]triazin-5-yl)phenyl]-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea



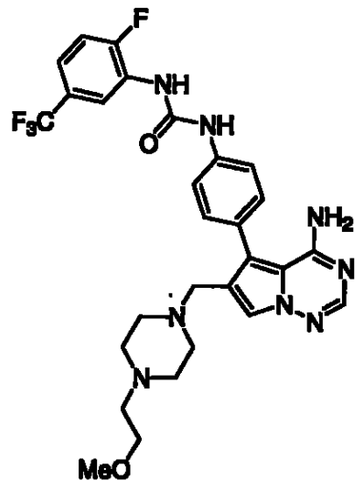
The procedure used for the preparation of Example 30 was used to prepare the title compound by substituting 3,3,3-trifluoropropan-1-amine for morpholine and purifying by via HPLC (10-90% ACN/H_2O). ^{1}H-NMR (CD_3OD) δ 8.62 (d, J = 7.3 Hz, 1H), 7.77 (s, 1H), 7.70 (s, 1H), 7.63 (d, J = 8.3 Hz, 2H), 7.39 (d, J = 7.9 Hz, 2H), 7.34 (d, J = 7.4 Hz, 2H), 3.73 (s, 2H), 2.74 (t, J = 7.3 Hz, 2H), 2.37 to 2.22 (m, 2H); MS $[M+H]^+ = 556$; LCMS RT = 2.41 min.

Example 40: Preparation of *N*-[4-(4-amino-6-{[4-(pyridin-4-ylmethyl)piperazin-1-yl]methyl}pyrrolo[2,1-f][1,2,4]triazin-5-yl)phenyl]-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea



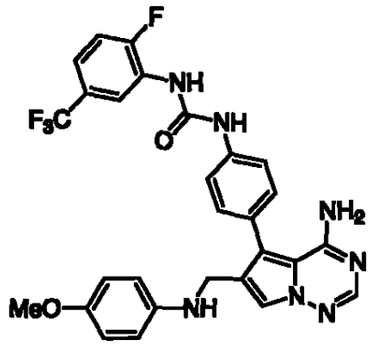
The procedure used for the preparation of Example 30 was used to prepare the title compound by substituting 1-(pyridin-4-ylmethyl)piperazine for morpholine and purifying by via HPLC (10-90% ACN/H_2O). ^{1}H-NMR (CD_3OD) δ 8.62 (d, J = 7.3 Hz, 1H), 8.43 (dd, J = 4.6, 1.6 Hz, 2H), 7.97 (s, 1H), 7.77 (s, 1H), 7.67 (s, 1H), 7.62 (d, J = 8.5 Hz, 2H), 7.41 to 7.31 (m, 6H), 3.54 (s, 2H), 3.51 (s, 2H), 3.32 to 3.29 (m, 4H); MS $[M+H]^+$ = 620; LCMS RT = 2.32 min.

Example 41: Preparation of *N*-[4-(4-amino-6-{[4-(2-methoxyethyl)piperazin-1-yl]methyl}pyrrolo[2,1-f][1,2,4]triazin-5-yl)phenyl]-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea



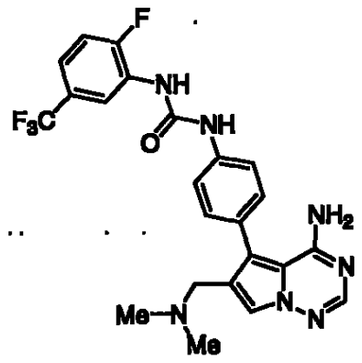
The procedure used for the preparation of Example 30 was used to prepare the title compound by substituting 1-(2-methoxyethyl)piperazine for morpholine and purifying by via HPLC (10-90% ACN/H_2O). ^{1}H-NMR (CD_3OD) δ 8.61 (d, J = 7.1 Hz, 1H), 7.77 (s, 1H), 7.67 (s, 1H), 7.62 (d, J = 8.9 Hz, 2H), 7.39 (d, J = 8.9 Hz, 2H), 7.34 (d, J = 8.3 Hz, 2H), 3.50(s, 3H), 3.48 (t, J = 5.3 Hz, 2H), 3.29 (s, 2H), 2.58 to 2.38 (m, 10H); MS $[M+H]^+$ = 587; LCMS RT = 2.55 min.

Example 42: Preparation of *N*-[4-(4-amino-6-[[(4-methoxyphenyl)amino]methyl}pyrrolo[2,1-f][1,2,4]triazin-5-yl)phenyl]-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea



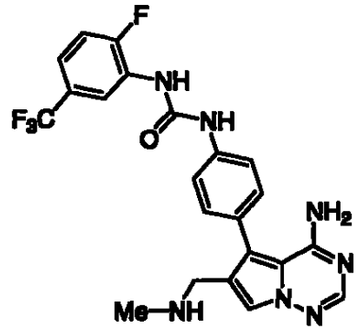
The procedure used for the preparation of Example 30 was used to prepare the title compound by substituting 4-methoxyaniline for morpholine and purifying by via HPLC (10-90% ACN/H_2O). ^{1}H-NMR (CD_3OD) δ 8.62 (d, J = 7.4 Hz, 1H), 7.75 (s, 1H), 7.65 to 7.58 (m, 3H), 7.41 (d, J = 8.1 Hz, 2H), 7.34 (d, J = 8.1 Hz, 2H), 6.70 (d, J = 8.8 Hz, 2H), 6.56 (d, J = 8.9 Hz, 2H), 4.16 (s, 2H), 3.68 (s, 3H); MS $[M+H]^+$ = 566; LCMS RT = 2.93 min.

Example 43: Preparation of *N*-(4-{4-amino-6-[(dimethylamino)methyl]pyrrolo[2,1-f][1,2,4]triazin-5-yl}phenyl)-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea



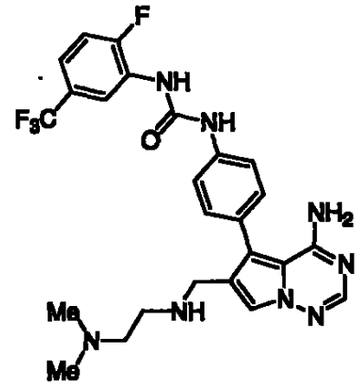
The procedure used for the preparation of Example 30 was used to prepare the title compound by substituting *N*-methylmethanamine for morpholine and purifying by via HPLC (10-90% ACN/H_2O). ^{1}H-NMR (CD_3OD) δ 8.62 (d, *J* = 8.0 Hz, 1H), 7.78 (s, 1H), 7.70 (s, 1H), 7.63 (d, *J* = 8.6 Hz, 2H), 7.37 (d, *J* = 8.6 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 3.52 (s, 2H), 2.18 (s, 6H); MS $[M+H]^+$ = 488; LCMS RT = 2.55 min.

Example 44: Preparation of *N*-(4-{4-amino-6-[(methylamino)methyl]pyrrolo[2,1-f][1,2,4]triazin-5-yl}phenyl)-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea



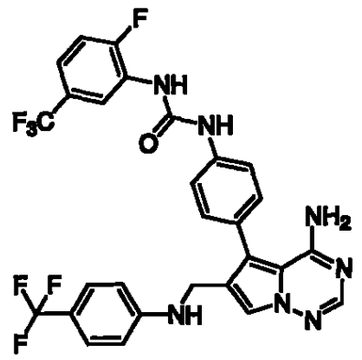
The procedure used for the preparation of Example 30 was used to prepare the title compound by substituting methanamine for morpholine and purifying by via HPLC (10-90% ACN/H_2O). ^{1}H-NMR (CD_3OD) δ 8.62 (d, *J* = 7.4 Hz, 1H), 7.77 (s, 1H), 7.70 (s, 1H), 7.64 (d, *J* = 8.6 Hz, 2H), 7.39 (d, *J* = 8.6 Hz, 2H), 7.34 (d, *J* = 8.5 Hz, 2H), 3.70 (s, 2H), 2.33 (s, 3H); MS $[M+H]^+$ = 474; LCMS RT = 2.55 min.

Example 45: Preparation of *N*-{4-[4-amino-6-({[3-(dimethylamino)propyl]amino}methyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea



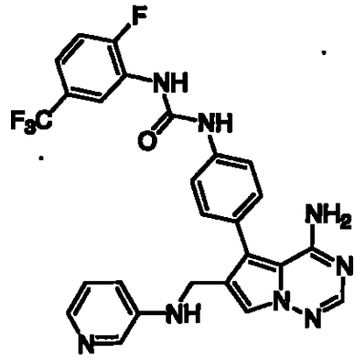
The procedure used for the preparation of Example 30 was used to prepare the title compound by substituting *N,N*-dimethylethane-1,2-diamine for morpholine and purifying by via HPLC (10-90% ACN/H_2O). ^{1}H-NMR (CD_3OD) δ 8.60 (d, J = 8.0 Hz, 1H), 7.97 (s, 1H), 7.84 (s, 1H), 7.69 (d, J = 8.0 Hz, 2H), 7.43 (d, J = 8.0 Hz, 2H), 7.35 (d, J = 8.6 Hz, 2H), 4.20 (s, 2H), 3.04 (t, J = 7.3 Hz, 2H), 2.94 (t, J = 7.3 Hz, 2H), 2.79 (s, 6H), 2.00 to 1.89 (m, 2H); MS $[M+H]^+$ = 545; LCMS RT = 2.28 min.

Example 46: Preparation of *N*-{4-[4-amino-6-({[4-(trifluoromethyl)phenyl]amino}methyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea



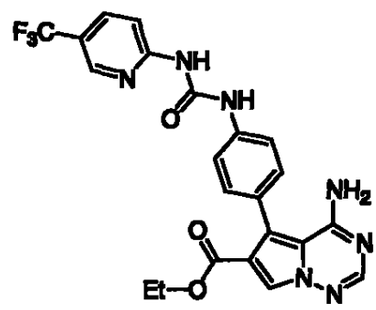
The procedure used for the preparation of Example 30 was used to prepare the title compound by substituting 4-(trifluoromethyl)aniline for morpholine and purifying via HPLC (10-90% ACN/H_2O). ^{1}H-NMR (CD_3OD) δ 8.68 (d, J = 8.0 Hz, 1H), 7.76 (s, 1H), 7.67 to 7.62 (m, 3H), 7.43 (d, J = 8.8 Hz, 2H), 7.36 to 7.27 (m, 4H), 6.61 (d, J = 8.7 Hz, 2H), 4.67 (s, 2H); MS $[M+H]^+$ = 604; LCMS RT = 3.31 min.

Example 47: Preparation of *N*-(4-{4-amino-6-[(pyridin-3-ylamino)methyl]pyrrolo[2,1-f][1,2,4]triazin-5-yl}phenyl)-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea

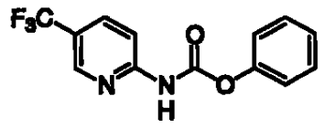


The procedure used for the preparation of Example 30 was used to prepare the title compound by substituting pyridin-3-amine for morpholine and purifying by via HPLC (10-90% ACN/H_2O). ^{1}H-NMR (CD_3OD) δ 8.61 (d, J = 8.2 Hz, 1H), 7.82 (d, J = 2.9 Hz, 1H), 7.75 (s, 1H), 7.72 (dd, J = 5.5, 1.6 Hz, 1H), 7.64 to 7.59 (m, 3H), 7.41 (d, J = 7.8 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 7.09 (dd, J = 8.3, 4.8 Hz, 1H), 6.94 to 6.88 (m, 1H), 4.24 (s, 2H); MS $[M+H]^+$ = 537; LCMS RT = 2.08 min.

Example 48: Preparation of ethyl 4-amino-5-{4-[({[5-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate



Step 1: Preparation of phenyl [5-(trifluoromethyl)pyridin-2-yl]carbamate



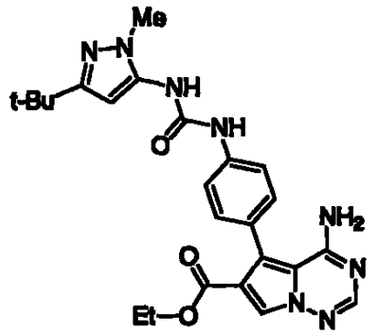
A solution of 5-(trifluoromethyl)pyridin-2-amine (100 mg, 0.617 mmol) and *N,N*-diisopropylethylamine (159.5 mg, 215 µL, 1.234 mmol) in 5 mL CH_2Cl_2 was treated with phenyl chloroformate (106 mg, 85 µL, 0.68 mmol) and left to stir for 3 h at rt. Solution was diluted with EtOAc and washed twice with 1 N HCl and 1 time with brine. The organic layer was dried (Na_2SO_4) and concentrated to provide a white solid. Tituration with 10% EtOAc in hexanes gave 120 mg (69%, 0.42 mmol) of the above compound as a white solid. ^{1}H-NMR (DMSO-d_6) δ 11.26 (s, 1H), 8.70 (s, 1H), 8.22 to 8.16 (m, 1H), 7.99 (d, J = 8 Hz, 1H), 7.45 to 7.40 (m, 2H), 7.30 to 7.20 (m, 3 H)

Step 2: Preparation of the title compound

A mixture of Intermediate B (57.9 mg, 0.195 mmol) and triethylamine in 2 mL THF was heated to 55 °C, providing a cloudy solution. Phenyl [5-(trifluoromethyl)pyridin-2-yl]carbamate (50 mg, 0.177 mmol) was added as a solid, and the mixture left to stir overnight. After 16 h, the solid precipitate was filtered, washed with ethyl acetate and dried to provide 66 mg (77 %, 0.14 mmol) of the above compound as a yellow solid. ^{1}H-NMR (DMSO-d_6) δ 9.33 (s, 1H), 8.95 (d, *J* = 2.3 Hz, 1H), 8.63 to 8.61 (m, 1H), 8.13 (s, 1H), 8.07 (br s, 1H), 7.93 (s, 1H), 7.56 to 7.53 (m, 2H), 7.51 to 7.48 (m, 1H), 7.40 (br s, 1H), 7.34 to 7.32 (m, 2H), 5.09 (br s,

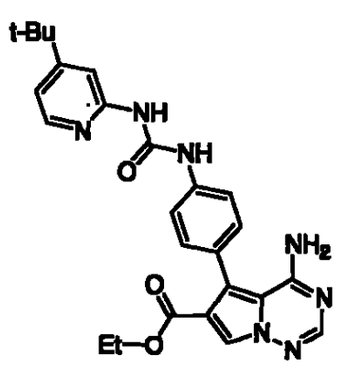
1H), 4.11 to 4.06 (q, J = 6.9 Hz, 2H), 1.13 to 1.10 (t, J = 7.1 Hz, 3H); MS $[M+H]^+$ = 486.0; LCMS RT = 3.36 min; TLC R_f = 0.46 (100% EtOAc).

Example 49: Preparation of ethyl 4-amino-5-[4-({[(3-*tert*-butyl-1-methyl-1*H*-pyrazol-5-yl)amino]carbonyl}amino)phenyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate



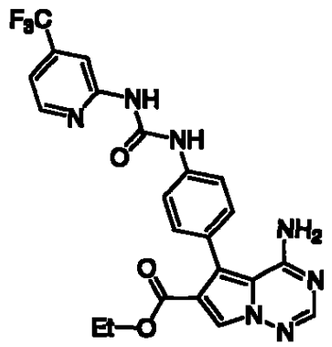
The procedure used for the preparation of Example 48 was used to prepare the title compound by substituting 3-*tert*-butyl-1-methyl-1*H*-pyrazol-5-amine for 5-(trifluoromethyl)pyridin-2-amine and purifying by recrystallization (EtOAc/EtOH). ^{1}H-NMR (DMSO-d_6) δ 9.08 (s, 1H), 8.56 (s, 1H), 8.12 (s, 1H), 8.11-8.04 (bs, 1H), 7.92 (s, 1H), 7.53 (d, J = 8.7 Hz, 2H), 7.30 (d, J = 8.7 Hz, 2H), 6.05 (s, 1H), 5.14-5.01 (bs, 1H) 4.03 (q, J = 7.2 Hz, 2H), 1.09 (t, J = 7.2 Hz, 3H); MS $[M+H]^+$ = 477.2; LCMS RT = 2.60 min.

Example 50: Preparation of ethyl 4-amino-5-[4-({[(4-*tert*-butylpyridin-2-yl)amino]carbonyl}amino)phenyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate



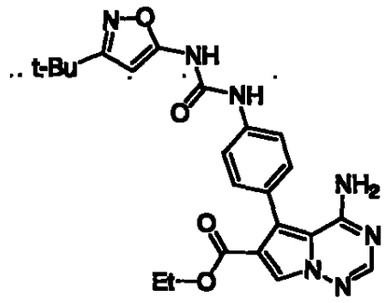
The procedure used for the preparation of Example 48 was used to prepare the title compound by substituting 4-*tert*-butylpyridin-2-amine for 5-(trifluoromethyl)pyridin-2-amine and purifying by HPLC (10-90% ACN/H_2O). ^{1}H-NMR (DMSO-d_6) δ 10.88 (s, 1H), 9.44 (s, 1H), 8.19 (d, J = 5.7 Hz), 8.12 (s, 1H), 8.11-8.10 (bs, 1H), 7.92 (s, 1H), 7.61 (d, J = 8.4 Hz, 2H), 7.49 (s, 1H), 7.32 (d, J = 8.4 Hz, 2H) 7.09-7.03 (m, 1H), 5.01-5,18 (bs, 1H), 4.07 (q, J = 7.2 Hz, 2H), 1.25 (s, 9H), 1.08 (t, J=7.2 Hz, 3H); MS $[M+H]^+$ = 474.2; LCMS RT = 2.63 min; TLC R_f = 0.27 (3:7 v/v THF-CH_2Cl_2).

Example 51: Preparation of ethyl 4-amino-5-[4-[({[4-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate



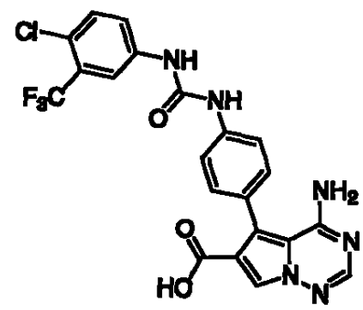
The procedure used for the preparation of Example 48 was used to prepare the title compound by substituting 4-(trifluoromethyl)pyridin-2-amine for 5-(trifluoromethyl)pyridin-2-amine and purifying by flash chromatography (1:3 v/v THF-CH_2Cl_2). ^{1}H-NMR (DMSO-d_6) δ 10.19 (s, 1H), 9.89 (s, 1H), 8.52 (d, J = 5.4 Hz, 1H), 8.12 (s, 1H), 8.12 to 8.10 (m, 2H), 7.93 (s, 1H), 7.59 (d, J = 6.9 Hz, 2H), 7.48 to 7.30 (m, 3H), 5.15 to 5.10 (m, 1H), 4.06 (q, J = 7.2 Hz, 2 H), 1.11 (t, J = 7.2 Hz, 3H); MS $[M+H]^+$ = 486.1; LCMS RT = 3.33 min; TLC R_f = 0.27 (3:7 v/v THF-CH_2Cl_2).

Example 52: Preparation of ethyl 4-amino-5-[4-({[(3-*tert*-butylisoxazol-5-yl)amino]carbonyl}amino)phenyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate



The procedure used for the preparation of Example 48 was used to prepare the title compound by substituting 3-*tert*-butylisoxazol-5-amine for 5-(trifluoromethyl)pyridin-2-amine and purifying by washing the precipitate formed during the reaction (1:1 v/v EtOAC-hexanes). ^{1}H-NMR (DMSO-d_6) δ 10.17 (s, 1H), 9.02 (s, 1H), 8.13 (s, 1H), 8.0-8.1 (bs, 1H), 7.93 (s, 1H), 7.54 (d, J = 8.7 Hz, 2H), 7.32 (J = 8.7 Hz, 2H), 6.07 (s, 1H), 5.2-5.0 (bs, 1H), 4.07 (q, J = 6.9 Hz, 2H), 1.25 (ms, 9H), 1.09 (t, J = 6.9 Hz, 3H); MS $[M+H]^+$ = 464.2; LCMS RT = 3.25 min; TLC R_f = 0.33 (3:7 v/v THF-CH_2Cl_2).

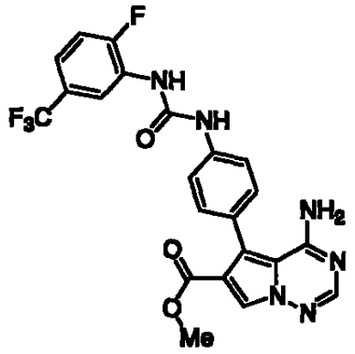
Example 53: Preparation of 4-amino-5-{4-[({[4-chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid



To a solution of MeOH (1.5 mL) was added ethyl 4-amino-5-{4-[({[4-chloro-3-(trifluromethyl)phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-

f][1,2,4]triazine-6-carboxylate, Example 2, (22 mg, 0.042 mmol), THF (3.0 mL), and 1N NaOH (0.42 mL, 0.42 mmol). The reaction was heated to 65 °C for 17 h. Upon cooling to rt the reaction was filtered through a plug of Celite®/Silica gel eluting with 85:15 v/v CH_2Cl_2-MeOH. The filtrate was concentrated in vacuo to dryness, diluted with CH_2Cl_2, dried (MgSO4), filtered, and concentrated in vacuo to dryness producing 3.8 mg of the above compound (0.0077 mmol, yield 18%). ^{1}H-NMR (DMSO-d_6) δ 8.18 (br s, 1H), 7.98 (br s, 1H), 7.88 (s, 1H), 7.67 (br s, 1H), 7.59 to 7.57 (d, J = 8.6 Hz, 1H), 7.53 to 7.51 (d, J = 7.7 Hz, 2H), 7.34 to 7.32 (d, J = 8.0 Hz, 2H), 6.56 (s, 1H), 5.06 (br s, 1H); MS $[M+H]^+$ = 491; LCMS RT = 3.18 min; TLC R_f = 0.20 (85:15 v/v CH_2Cl_2-MeOH).

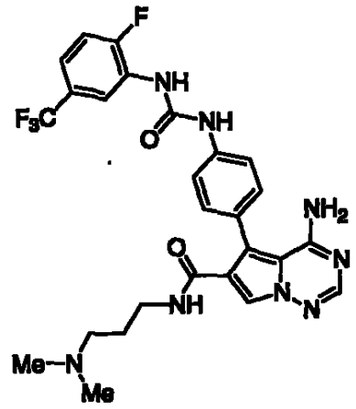
Example 54: Preparation of methyl 4-amino-5-{4-[({[2-fluoro-5-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate



To a solution of MeOH (4.0 mL) was added Intermediate E (30 mg, 0.060 mmol), THF (2.0 mL), and 1N NaOH (0.24 mL, 0.24 mmol). The reaction was stirred at rt for 2d. The solution was transferred to a Biotage Samplet and dried in a vacuum oven. The material was purified by flash chromatography (Biotage) eluting with 5:4:1 v/v/v CH_2Cl_2-EtOAc-MeOH. The clean fractions were combined, concentrated in vacuo to dryness producing 14mg of the above compound (0.029mmol, yield 48%). ^{1}H-NMR (DMSO-d_6) δ 9.33 (s, 1H), 8.96 (d, 1H, J = 2.4 Hz), 8.63 to 8.61 (dd, 7.3 Hz, 2.4 Hz, 1H), 8.15 (s, 1H), 8.09 (br s, 1H), 7.93 (s, 1H), 7.56 to 7.54 (m, 2H), 7.50 to 7.47 (m, 1H), 7.40 (m, 1H), 7.34 to 7.32 (m, 2H), 5.09

(br s, 1H), 3.63 (s, 3H); MS $[M+H]^+$ = 489; LCMS RT = 2.85 min; TLC R_f = 0.55 (5:4:1 v/v/v CH_2Cl_2-EtOAc-MeOH).

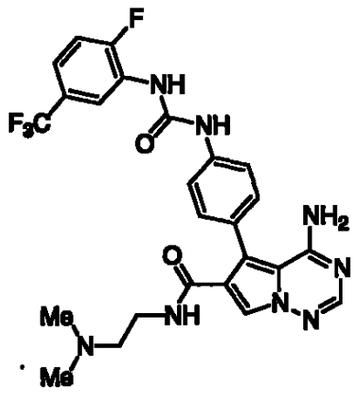
Example 55: Preparation of 4-amino-*N*-[3-(dimethylamino)propyl]-5-{4-[({[2-fluoro-5-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



To a solution of Intermediate G (41 mg, 0.09 mmol) in 0.5 mL DMF was added py-BOP (32.0 mg, 0.13 mmol *N,N*-dimethylpropane-1,3-diamine (13.25 mg, 0.13 mmol) as a solution in THF, diisopropylethylamine (24.9 mg, 0.19 mmol) and 4-dimethylaminopyridine (4 mg, 0.04 mmol). After 12 h the reaction was diluted with 150 mL CH_2Cl_2, washed with water and brine, then dried with sodium sulfate. This solution was concentrated and the residue purified by flash column (20% THF in CH_2Cl_2) to yield 25.4 mg of impure material. Tituration with ethyl acetate gave 10.3 mg of the desired product (0.018 mmol, 21 mg). ^{1}H-NMR (MeOD-d_4) δ 8.60 (d, J = 8 Hz, 1H), 7.97 (3, 1H), 7.84 (s, 1H), 7.65 (d, J = 9 Hz, 1H), 7.43 (d, J = 9 Hz, 2 H), 7.33 (d, J = 9 Hz, 2H), 3.25 (t, J = 7 Hz, 2H), 2.23 (t, J = 7 Hz, 2H), 2.21 (s, 6H), 1.61 (ap quintet, J = 7 Hz, 2H); MS $[M+H]^+$ = 559.3; LCMS RT = 2.63 min; TLC R_f = 0.14 (1:2 v/v THF:CH_2Cl_2).

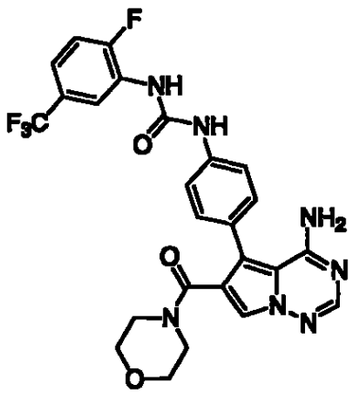
Example 56: Preparation of 4-amino-*N*-[2-(dimethylamino)ethyl]-5-{4-[({[2-fluoro-5-

(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



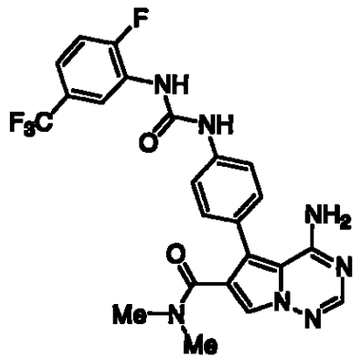
Preparation of this compound is described in Example 55, substituting *N,N*-dimethylethane-1,2-diamine for *N,N*-dimethylpropane-1,3-diamine providing 23.7 mg of product as a white solid (0.044 mmol, 34 % yield). ^{1}H-NMR (CD_3OD) δ 8.62 (d, J = 8 Hz, 1H), 8.01 (s, 1H), 7.84 (s, 1H), 7.66 (d, J = 8 Hz, 1H), 7.42 (d, J = 8 Hz, 2 H), 7.35 (d, J = 8 Hz, 2H), 3.90 (t, J = 7 Hz, 2H), 2.40 (t, J = 7 Hz, 2H), 2.20 (s, 6H); MS $[M+H]^+$ = 545.2; LCMS RT = 2.13 min; TLC R_f = 0.31 (1:3:9 v/v/v 2 M NH_3 in MeOH:THF:CH_2Cl_2).

Example 57: Preparation of *N*-{4-[4-amino-6-(morpholin-4-ylcarbonyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea



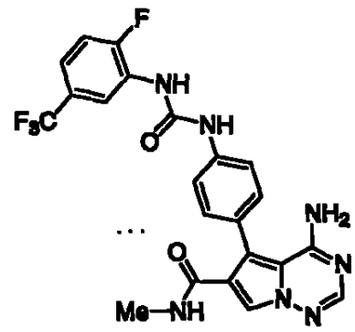
This compound was prepared via the same procedure as Example 55, substituting morpholine for *N,N*-dimethylpropane-1,3-diamine providing 7.2 mg of product as a white solid (0.013 mmol, 16 %). ^{1}H-NMR (CD_3OD) δ 8.62 (d, J = 8 Hz, 1H), 7.91 (s, 1H), 7.80 (s, 1H), 7.66 (d, J = 9 Hz, 1H), 7.43-7.39 (m, 2 H), 7.34 (d, J = 9 Hz, 2H), 3.26-3.45 (m, 4H), 3.2-3.0 (m, 4H), MS $[M+H]^+$ = 544.6; LCMS RT = 2.49 min; TLC R_f = 0.34 (1:2 v/v THF:CH_2Cl_2).

Example 58: Preparation of 4-amino-5-{4-[({[2-fluoro-5-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}-*N,N*-dimethylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxamide



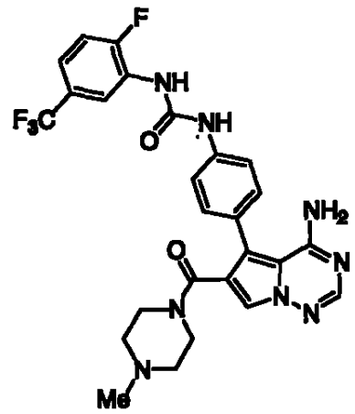
This compound was prepared via the same procedure as Example 55, substituting *N*-methylmethanamine for *N,N*-dimethylpropane-1,3-diamine providing 7.0 mg of product as a white solid (0.014 mmol, 17 %). ^{1}H-NMR (CD_3OD) δ 8.61 (d, J = 8 Hz, 1H), 7.85 (s, 1H), 7.79 (s, 1H), 7.60 (d, J = 9 Hz, 1H), 7.38 (d, J = 9 Hz, 2 H), 7.34 (d, J = 9 Hz, 2H), 2.93 (s, 3H), 2.72 (s, 3H), MS $[M+H]^+$ = 502.2; LCMS RT = 2.54 min; TLC R_f = 0.29 (1:2 v/v THF:CH_2Cl_2).

Example 59: Preparation of 4-amino-5-{4-[({[2-fluoro-5-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}-*N*-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxamide



This compound was prepared via the same procedure as Example 55, substituting methanamine for *N,N*-dimethylpropane-1,3-diamine providing mg of product as a white solid (mmol, yield). ^{1}H-NMR (CD_3OD) δ 8.61 (d, J = 8 Hz, 1H), 7.85 (s, 1H), 7.97 (s, 1H), 7.83 (d, J = 9 Hz, 1H), 7.61 (d, J = 9 Hz, 2 H), 7.43-7.39 (m, 2H) 7.34 (d, J = 9 Hz, 2H), 2.93 (s, 3H); MS $[M+H]^+$ = 488.5; LCMS RT = 2.50 min; TLC R_f = 0.26 (1:2 v/v THF:CH_2Cl_2).

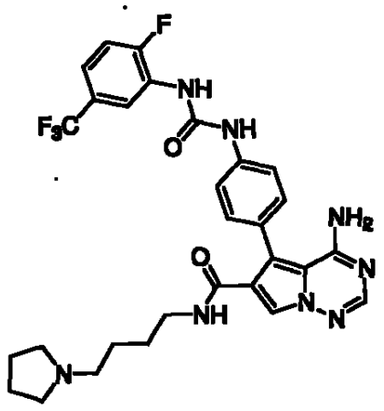
Example 60: Preparation of *N*-(4-{4-amino-6-[(4-methylpiperazin-1-yl)carbonyl]pyrrolo[2,1-f][1,2,4]triazin-5-yl}phenyl)-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea



This compound was prepared via the same procedure as Example 55, substituting 1-methylpiperazine for *N,N*-dimethylpropane-1,3-diamine providing 6.2 mg of product as a white solid (0.011 mmol, 9 % yield). ^{1}H-NMR (CD_3OD) δ 8.62-8.59 (m, 1H), 7.86 (s, 1H), 7.80 (d, J = 9 Hz, 1H), 7.64 (d, J = 9 Hz, 2 H), 7.42-7.39 (m, 2H) 7.34 (d, J = 9 Hz, 2H), 3.65-3.57 (m, 2H), 3.56-3.50 (m, 2H), 3.20-3.11 (m,

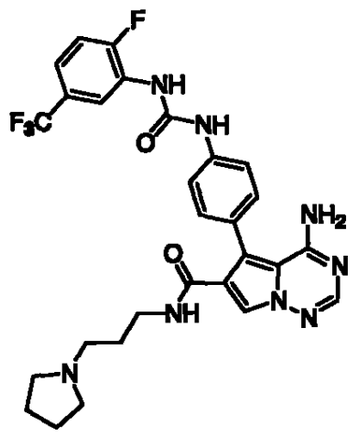
2H), 2.13 (s, 3H); MS $[M+H]^+$ = 557.0; LCMS RT = 2.13 min; TLC R_f = 0.21 (1:1 v/v THF:CH_2Cl_2).

Example 61: Preparation of 4-amino-5-{4-[({[2-fluoro-5-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}-*N*-(4-pyrrolidin-1-ylbutyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



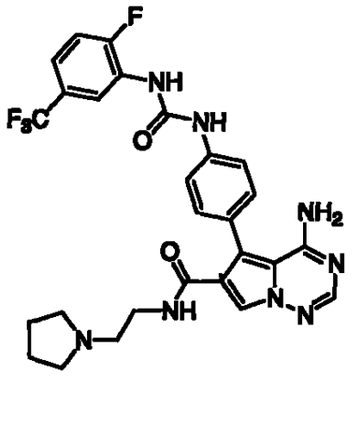
The procedure used for the preparation of Example 55 was used to prepare the title compound by substituting 4-pyrrolidin-1-ylbutan-1-amine for *N,N*-dimethylpropane-1,3-diamine and purifying via HPLC (10-90% ACN/H_2O). ^{1}H-NMR (CD_3OD) δ 8.61 (d, *J* = 7.4 Hz, 1H), 7.98 (s, 1H), 7.83 (s, 1H), 7.66 (d, *J* = 7.3 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.3 Hz, 2H), 3.24 (t, *J* = 5.8 Hz, 2H), 2.73 to 2.63 (m, 4H), 2.57 (t, *J* = 5.8 Hz, 2H), 1.86 to 1.78 (m, 4H), 1.48 to 1.39 (m, 4H); MS $[M+H]^+$ = 599; LCMS RT = 2.66 min.

Example 62: Preparation of 4-amino-5-{4-[({[2-fluoro-5-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}-*N*-(3-pyrrolidin-1-ylpropyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



The procedure used for the preparation of Example 55 was used to prepare the title compound by substituting 3-pyrrolidin-1-ylpropan-1-amine for *N,N*-dimethylpropane-1,3-diamine and purifying by via HPLC (10-90% ACN/H_2O). ^{1}H-NMR (CD_3OD) δ 8.62 (d, J = 7.7 Hz, 1H), 8.03 (s, 1H), 7.84 (s, 1H), 7.66 (d, J = 8.0 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.2 Hz, 2H), 3.28 to 3.21 (m, 2H), 2.64 to 2.55 (m, 4H), 2.44 to 2.36 (m, 2H), 1.84 to 1.76 (m, 4H), 1.71 to 1.60 (m, 2H); MS $[M+H]^+$ = 585; LCMS RT = 2.63 min.

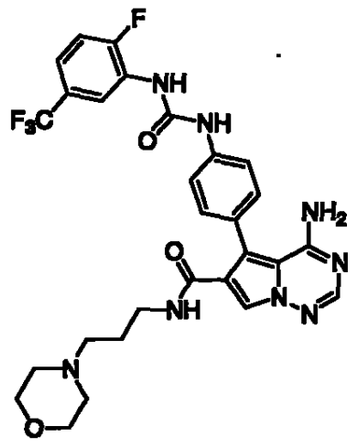
Example 63: Preparation of 4-amino-5-{4-[({[2-fluoro-5-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}-*N*-(2-pyrrolidin-1-ylethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



The procedure used for the preparation of Example 55 was used to prepare the title compound by substituting 2-pyrrolidin-1-ylethanamine for *N,N*-

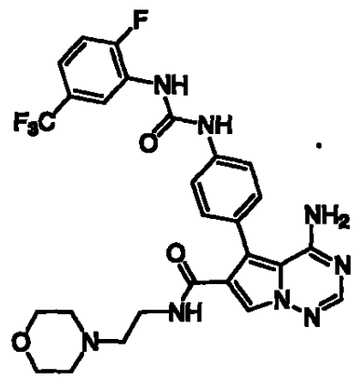
dimethylpropane-1,3-diamine and purifying via HPLC (10-90% ACN/H_2O). ^{1}H-NMR (CD_3OD) δ 8.62 (d, J = 7.6 Hz, 1H), 7.97 (s, 1H), 7.84 (s, 1H), 7.66 (d, J = 7.8 Hz, 2H), 7.43 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 8.5 Hz, 2H), 3.25 to 3.20 (m, 2H), 2.64 to 2.50 (m, 6H), 1.82 to 1.74 (m, 4H); MS $[M+H]^+$ = 571; LCMS RT = 2.23 min.

Example 64: Preparation of 4-amino-5-{4-[({[2-fluoro-5-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}-*N*-(3-morpholin-4-ylpropyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



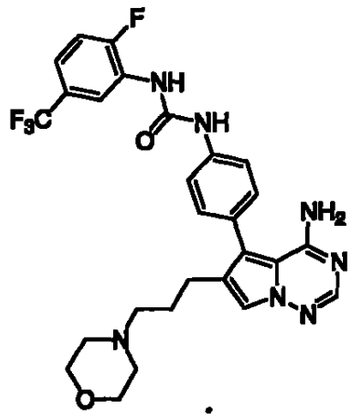
The procedure used for the preparation of Example 55 was used to prepare the title compound by substituting 3-morpholin-4-ylpropan-1-amine for *N,N*-dimethylpropane-1,3-diamine and purifying by via HPLC (10-90% ACN/H_2O). ^{1}H-NMR (CD_3OD) δ 8.62 (d, J = 7.2 Hz, 1H), 7.97 (s, 1H), 7.84 (s, 1H), 7.66 (d, J = 8.3 Hz, 2H), 7.44 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.7 Hz, 2H), 3.64 (t, J = 3.6 Hz, 4H), 3.26 (t, J = 6.1 Hz, 2H), 2.43 to 2.37 (m, 4H), 2.21 (t, J = 7.7 Hz, 2H), 1.68 to 1.54 (m, 2H); MS $[M+H]^+$ = 601; LCMS RT = 2.21 min.

Example 65: Preparation of 4-amino-5-{4-[({[2-fluoro-5-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}-*N*-(2-morpholin-4-ylethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



The procedure used for the preparation of Example 55 was used to prepare the title compound by substituting 2-morpholin-4-ylethanamine for *N,N*-dimethylpropane-1,3-diamine and purifying via HPLC (10-90% ACN/H_2O). ^{1}H-NMR (CD_3OD) δ 8.61 (d, *J* = 7.8 Hz, 1H), 8.03 (s, 1H), 7.84 (s, 1H), 7.69 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 8.5Hz, 2H), 7.35 (d, *J* = 8.2 Hz, 2H), 3.60 (t, *J* = 5.0 Hz, 4H), 3.39 to 3.33 (m, 2H), 2.37 to 2.30 (m, 6H); MS $[M+H]^+$ = 587; LCMS RT = 2.21min.

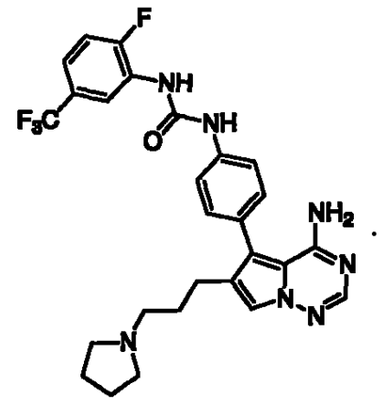
Example 66: Preparation of *N*-[4-[4-amino-6-(3-morpholin-4-ylpropyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl]-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea



To a solution of Intermediate I (53 mg, 0.11 mmol) in CH_2Cl_2 (3.0 mL) was added AcOH (0.036 mL, 0.63 mmol) and morpholine (0.019 mL, 0.22 mmol). The reaction was stirred at rt for 1 h after which sodium triacetoxyborohydride (66 mg,

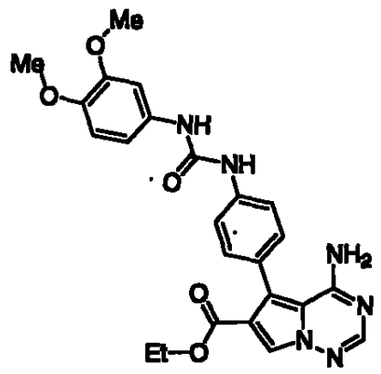
0.31 mmol) was added. The reaction was stirred at rt until completion. Reaction was diluted with CH_2Cl_2, transferred to a separatory funnel and washed with saturated aq $NaHCO_3$ (2x). Aqueous phase was back extracted with CH_2Cl_2 (2x). The organic was dried (Na_2SO_4) and evaporated to give a crude oil that was purified via HPLC (10-90% ACN/H_2O) to give the title compound (15mg, 24%). ^{1}H-NMR (CD_3OD) δ 8.62 (d, J = 7.8 Hz, 1H), 7.74 (s, 1H), 7.62 (d, *J* = 8.2 Hz, 2H), 7.53 (s, 1H), 7.38 to 7.31 (m, 4H), 3.62 (t, *J* = 5.2 Hz, 4H), 2.59 (t, *J* = 7.3 Hz, 2H), 2.38 to 2.23 (m, 6H), 1.74 to 1.62 (m, 2H); MS $[M+H]^+$ = 558; LCMS RT = 2.18 min.

Example 67: Preparation of *N*-{4-[4-amino-6-(3-pyrrolidin-1-ylpropyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea



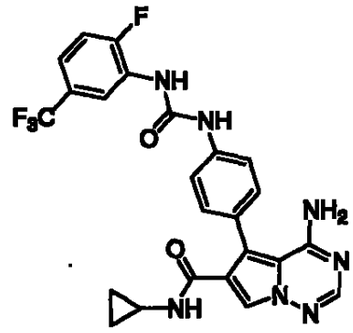
The procedure used for the preparation of Example 66 was used to prepare the title compound by substituting pyrrolidine for morpholine and purifying via HPLC (10-90% ACN/H_2O). ^{1}H-NMR (CD_3OD) δ 8.61 (d, J = 7.8 Hz, 1H), 7.74 (s, 1H), 7.63 (d, *J* = 8.3 Hz, 2H), 7.55 (s, 1H), 7.39 to 7.31 (m, 4H), 2.72 to 2.55 (m, 8H), 1.86 to 1.70 (m, 6H); MS $[M+H]^+$ = 542; LCMS RT = 2.15 min.

Example 68: Preparation of ethyl 4-amino-5-[4-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)phenyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate



The procedure used for the preparation of Example 3 was used to prepare the title compound by substituting 3,4-dimethoxyaniline for 4-fluoro-3-(trifluoromethyl)aniline. ^{1}H-NMR (CD_3OD) δ 8.27 (s, 1H), 8.15 (s, 1H), 8.06 (s, 1H), 7.98 (s, 1H), 7.67 (d, J = 8 Hz, 2H), 7.39 (d, J = 8 Hz, 2H), 7.34 (s, 1H), 6.95 (d, J = 9 Hz, 1H), 6.86 (d, J = 9 Hz, 3H), 4.15 (q, j = 7, 2H), 3.81 (s, 3H), 3.78 (s, 3H), 1.18 (t, j = 7Hz, 3H); MS $[M+H]^+$ = 477.1 LCMS RT = 2.50 min.

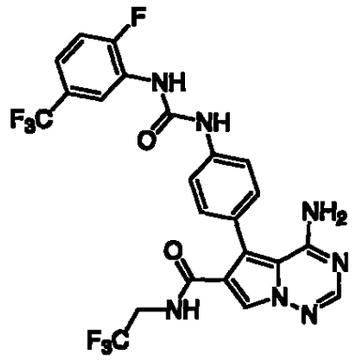
Example 69: Preparation of 4-amino-*N*-cyclopropyl-5-{4-[({[2-fluoro-5-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



A solution of Intermediate G (50 mg, 0.105 mmol), cyclopropylamine (11 μL, 0.106 mmol), py-BOP (82 mg, 0.158 mmol) and triethylamine (22 μL, 0.158 mmol) was allowed to stir at rt for 15 min and then concentrated in vacuo. The residue was purified by silica chromatography using 20 % THF in CH_2Cl_2 and the product then triturated with 30% aqueous methanol, affording 31.5 mg of the above compound

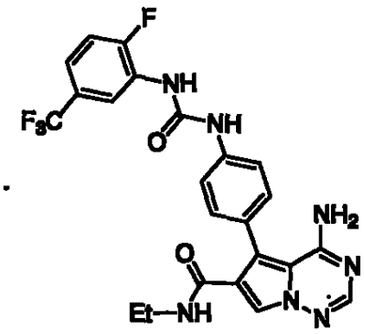
(0.061 mmol, yield 71%). ^{1}H-NMR (DMSO-d_6) δ 9.32 (s, 1H), 8.96 (s, 1H), 8.64 (bd, J = 6 Hz, 1H), 8.06 (s, 1H), 7.90 (s, 1H), 7.85 to 7.82 (m, 1H), 7.54 (d, J = 8 Hz, 2H), 7.53 to 7.50 (m, 2H), 7.45 to 7.35 (m, 1H), 7.31 (d, J = 8 Hz, 1H), 5.03 (bs, 1H), 2.63-2.59 (m 1H), 0.62 to 0.58 (m, 2H), 0.41 to 0.39 (m, 2H). MS $[M+H]^+$ = 514.2; LCMS RT = 3.11 min; TLC R_f = 0.33 (2:1 v/v CH_2Cl_2-THF).

Example 70: Preparation of 4-amino-5-{4-[({[2-fluoro-5-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}-*N*-(2,2,2-trifluoroethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carboxamide



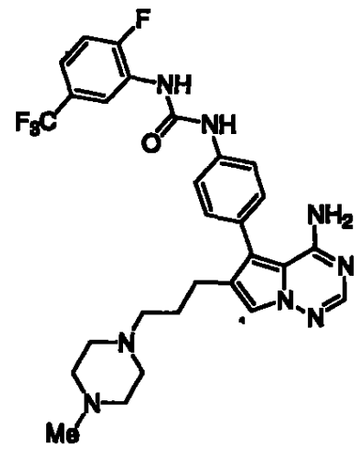
The procedure used for the preparation of Example 69 was used to prepare the title compound by substituting 2,2,2-trifluoroethanamine hydrochloride for cyclopropanamine. ^{1}H-NMR (DMSO-d_6) δ 9.29 (s, 1H), 8.93 (s, 1H), 8.64-8.58 (m, 1H), 8.51 (t, J = 6 Hz, 1H), 8.18 (s, 1H), 8.00 (bs, 1H), 7.91 (s, 1H), 7.52 (d, J = 8 Hz, 2H), 7.51 to 7.46 (m, 1H), 7.40 to 7.30 (m, 1H), 7.28 (d, J = 8 Hz, 2H), 5.05 (bs, 1H), 4.00 to 3.85 (m, 2H). MS $[M+H]^+$ = 556.2; LCMS RT = 3.32 min; TLC R_f = 0.33 (2:1 v/v CH_2Cl_2-THF).

Example 71: Preparation of 4-amino-*N*-ethyl-5-{4-[({[2-fluoro-5-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-*f*][1,2,4]triazine-6-carboxamide



The procedure used for the preparation of Example 69 was used to prepare the title compound by substituting ethanamine for cyclopropanamine. ^{1}H-NMR (CD_3OD) δ 8.62 to 8.60 (m, 1H), 7.98 (s, 1H), 7.84 (s, 1H), 7.63 (d, J = 9 Hz, 2H), 7.42 to 7.41 (m, 1H), 7.34 (d, J = 7 Hz, 2H), 1.04 (t, J = 7Hz, 3H); MS $[M+H]^+$ = 502.1; LCMS RT = 2.68 min; TLC R_f = 0.44 (3:2 v/v CH_2Cl_2-THF).

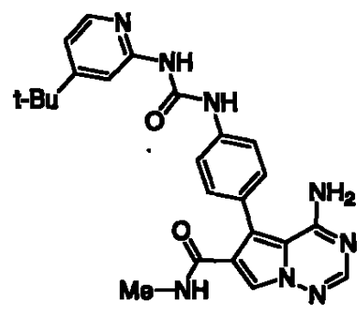
Example 72: Preparation of *N*-(4-{4-amino-6-[3-(4-methylpiperazin-1-yl)propyl]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}phenyl)-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea



The procedure used for the preparation of Example 66 was used to prepare the title compound by substituting 1-methylpiperazine for morpholine and purifying via HPLC (10-90% ACN/H_2O). ^{1}H-NMR (CD_3OD) δ 8.61 (d, J = 8.0 Hz, 1H), 7.74 (s, 1H), 7.63 (d, J = 8.7 Hz, 2H), 7.54 (s, 1H), 7.37 (d, J = 8.0 Hz, 2H), 7.34 (d, J =

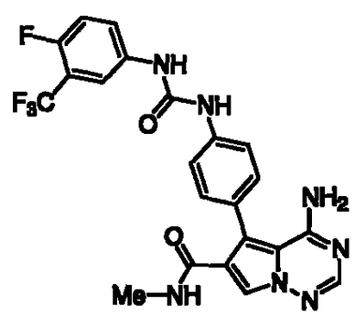
8.1 Hz, 2H), 2.79 to 2.37 (m, 12 H), 2.47 (s, 3H), 1.75 to 1.62 (m, 2H); MS $[M+H]^+$ = 571.4; LCMS RT = 2.48.

Example 73: Preparation of 4-amino-5-[4-({[(4-*tert*-butylpyridin-2-yl)amino]carbonyl}amino)phenyl]-*N*-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxamide



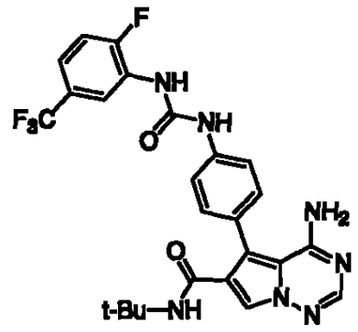
To a solution of DMF (1 mL) was added Intermediate X (50 mg, 0.18 mmol) followed by phenyl (4-*tert*-butylpyridin-2-yl)carbamate (48 mg, 0.18 mmol) and triethylamine (25 µL, 0.18 mmol). The reaction was stirred at rt overnight, concentrated to dryness, and purified by HPLC to afford 22 mg of the above compound (0.04 mmol, yield 26%). ^{1}H-NMR (DMSO-d_6) δ 10.9 (s, 1H), 9.48 (s, 1H), 8.17 (d, J = 5.4 Hz, 1H), 8.06 (s, 1H), 7.88 (s, 1H), 7.02 (d, J = 5.0 Hz, 1H), 7.61 to 7.54 (m, 3H), 7.29 (d, J = 8.3 Hz, 2H), 7.04 (dd, J = 5.5, 1.6 Hz, 1H), 2.61 (d, J = 4.7 Hz, 3H), 1.25 (s, 9H); MS $[M+H]^+$ = 459.2; LCMS RT = 2.49.

Example 74: Preparation of 4-amino-5-{4-[({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}-*N*-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxamide



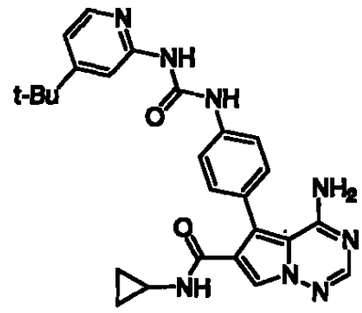
The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting phenyl [4-fluoro-3-(trifluoromethyl)phenyl]carbamate for phenyl (4-*tert*-butylpyridin-2-yl)carbamate. ^{1}H-NMR (CD_3OD) δ 7.97 (s, 1H), 7.91 (dd, J = 6.4, 3.0 Hz, 1H), 7.83 (s, 1H), 7.68 to 7.62 (m, 1H), 7.59 (d, J = 8.3 Hz, 2H), 7.40 (d, J = 8.3 Hz, 2H), 7.27 (t, J = 9.9 Hz, 1H), 2.76 (s, 3H); MS $[M+H]^+$ = 488.3; LCMS RT = 2.31.

Example 75: Preparation of 4-amino-*N*-(*tert*-butyl)-5-{4-[({[2-fluoro-5-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



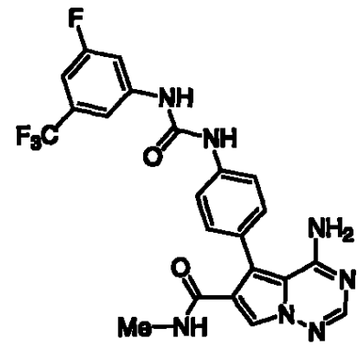
The procedure used for the preparation of Example 69 was used to prepare the title compound by substituting 2-methylpropan-2-amine for cyclopropanamine. ^{1}H-NMR (DMSO-d_6) δ 9.35 (s, 1H), 8.95 (s, 1H), 8.61 (d, J = 5Hz, 1H), 8.02 (s, 1H), 7.88 (s, 1H), 7.98 to 7.92 (m, 1H), 7.57 (d, J = 8 Hz, 2H), 7.45 to 7.44 (m, 1H), 7.41 to 7.36 (m, 1H), 7.34 (d, J = 8Hz, 2H), 6.62 (s, 1H), 1.15 (s, 9H); MS $[M+H]^+$ = 530.3; LCMS RT = 2.94 min; TLC R_f = 0.68 (3:2 v/v CH_2Cl_2-THF).

Example 76: Preparation of 4-amino-5-[4-({[(4-*tert*-butylpyridin-2-yl)amino]carbonyl}amino)phenyl]-*N*-cyclopropylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



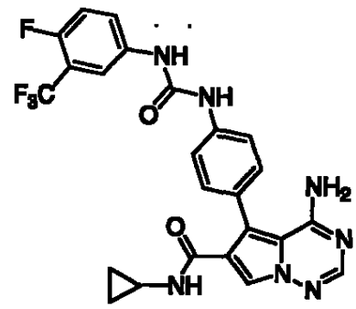
The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting Intermediate W for Intermediate X. ^{1}H-NMR (CD_3OD) δ 8.22 (d, J = 6.3 Hz, 1H), 7.98 (s, 1H), 7.83 (s, 1H), 7.71 (d, J = 8.6 Hz, 2H), 7.42 (d, J = 8.6 Hz, 2H), 7.21 (s, 1H), 7.10 (dd, J = 5.6, 1.7 Hz, 1H), 2.72 to 2.59 (m, 1H), 1.31 (s, 9H), 0.72 to 0.62 (m, 2H), 0.42 to 0.33 (m, 2H); MS $[M+H]^+$ = 485.3; LCMS RT = 2.70.

Example 77: Preparation of 4-amino-5-[4-[({[3-fluoro-5-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl]-*N*-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxamide



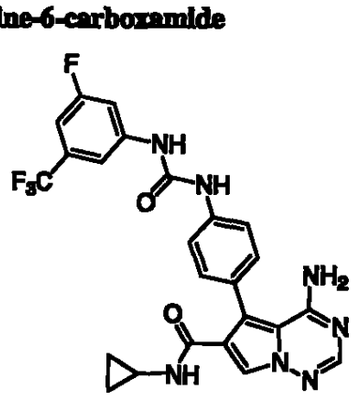
The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting phenyl [3-fluoro-5-(trifluoromethyl)phenyl]carbamate for phenyl (4-*tert*-butylpyridin-2-yl)carbamate. ^{1}H-NMR (DMSO-d_6) δ 8.04 (s, 1H), 7.88 (s, 1H), 7.70 (s, 1H), 7.61 (d, J = 11.0 Hz, 1H), 7.52 (d, J = 8.6 Hz, 2H), 7.29 (d, J = 8.6 Hz, 2H), 7.21 (d, J = 8.1 Hz, 1H), 3.11 to 3.08 (m, 1H), 2.62 (d, J = 3.4 Hz, 3H); MS $[M+H]^+$ = 488.2; LCMS RT = 3.05.

Example 78: Preparation of 4-amino-*N*-cyclopropyl-5-{4-[({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



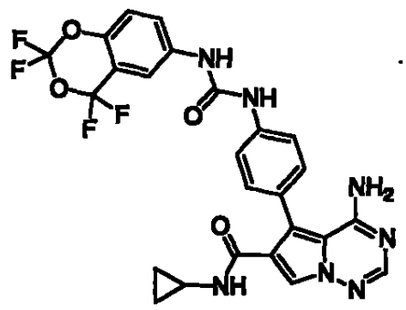
The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting Intermediate W for Intermediate X and by substituting phenyl [4-fluoro-3-(trifluoromethyl)phenyl]carbamate for phenyl (4-*tert*-butylpyridin-2-yl)carbamate. ^{1}H-NMR (CD_3OD) δ 7.62 (s, 1H), 7.55 (dd, J = 7.8, 2.8 Hz, 1H), 7.47 (s, 1H), 7.34 to 7.27 (m, 1H), 7.24 (d, J = 8.4 Hz, 2H), 7.03 (d, J = 8.4 Hz, 2H), 6.91 (t, J = 9.8 Hz, 1H), 2.36 to 2.24 (m, 1H), 0.39 to 0.28 (m, 2H), 0.058 to -0.027 (m, 2H); **MS** $[M+H]^+$ = 514.2; **LCMS RT** = 3.11.

Example 79: Preparation of 4-amino-*N*-cyclopropyl-5-{4-[({[3-fluoro-5-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



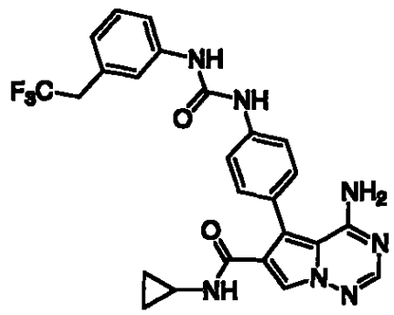
The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting Intermediate W for Intermediate X and by substituting phenyl [3-fluoro-5-(trifluoromethyl)phenyl]carbamate for phenyl (4-*tert*-butylpyridin-2-yl)carbamate. ^{1}H-NMR (Acetone-d_6) δ 7.67 (s, 1H), 7.51 (s, 1H), 7.33 (s, 1H), 7.24 (d, J = 1.5 Hz, 1H), 7.15 (d, J = 9.0 Hz, 2H), 6.92 (d, J = 9.0 Hz, 2H), 6.84 (d, J = 8.6 Hz, 1H), 2.74 to 2.69 (m, 1H), 2.29 to 2.21 (m, 1H), 0.24 to 0.15 (m, 2H), 0.045 to -0.021 (m, 2H); MS $[M+H]^+$ = 514.3; LCMS RT = 3.19.

Example 80: Preparation of 4-amino-*N*-cyclopropyl-5-[4-({[(2,2,4,4-tetrafluoro-4*H*-1,3-benzodioxin-6-yl)amino]carbonyl}amino)phenyl]pyrrolo[2,1-*f*][1,2,4]triazine-6-carboxamide



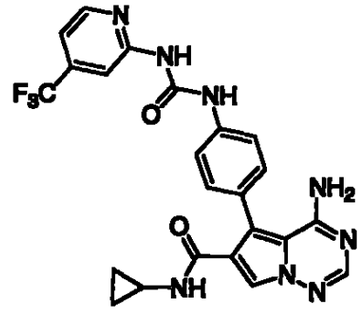
The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting Intermediate W for Intermediate X and by substituting phenyl (2,2,4,4-tetrafluoro-4*H*-1,3-benzodioxin-6-yl)carbamate for phenyl (4-*tert*-butylpyridin-2-yl)carbamate. ^{1}H-NMR (CD_3OD) δ 8.02 (d, J = 2.5 Hz, 1H), 7.98 (s, 1H), 7.84 (s, 1H), 7.67 (dd, J = 9.1, 2.8 Hz, 1H), 7.61 (d, J = 8.8 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 9.1 Hz, 1H), 2.72 to 2.63 (m, 1H), 0.73 to 0.65 (m, 2H), 0.42 to 0.35 (m, 2H); MS $[M+H]^+$ = 558.2; LCMS RT = 3.29.

Example 81: Preparation of 4-amino-*N*-cyclopropyl-5-{4-[({[3-(2,2,2-trifluoroethyl)phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-*f*][1,2,4]triazine-6-carboxamide



The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting Intermediate W for Intermediate X and by substituting phenyl [3-(2,2,2-trifluoroethyl)phenyl]carbamate for phenyl (4-*tert*-butylpyridin-2-yl)carbamate. ^{1}H-NMR (Acetone-d_6) δ 7.64 (s, 1H), 7.47 (s, 1H), 7.38 (d, J = 4.0 Hz, 1H), 7.11 (d, J = 8.7 Hz, 2H), 7.06 (d, J = 8.7 Hz, 2H), 6.89 to 6.83 (m, 4H), 3.22 to 3.09 (m, 2H), 2.74 to 2.68 (m, 1H), 2.30 to 2.20 (m, 1H), 0.25 to 0.17 (m 2H), 0.040 to -0.027 (m, 2H); MS $[M+H]^+$ = 510.2; LCMS RT = 3.01.

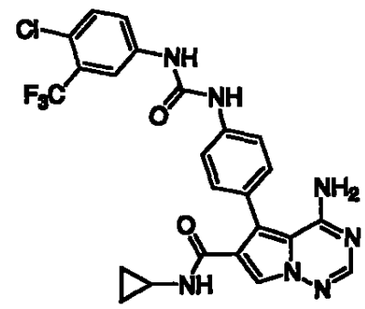
Example 82: Preparation of 4-amino-*N*-cyclopropyl-5-{4-[({[4-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting Intermediate W for Intermediate X and by substituting phenyl [4-(trifluoromethyl)pyridin-2-yl]carbamate for phenyl (4-*tert*-butylpyridin-2-yl)carbamate. ^{1}H-NMR (DMSO-d_6) δ 8.52 (d, J = 5.8 Hz, 1H), 8.06 (s, 1H), 8.04 (s, 1H), 7.87 (s, 1H), 7.56 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 5.0 Hz, 1H),

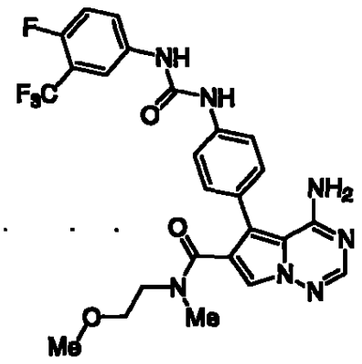
7.30 (d, J = 8.4 Hz, 2H), 3.12 to 3.09 (m, 1H), 2.68 to 2.60 (m, 1H), 0.62 to 0.55 (m 2H), 0.44 to 0.36 (m, 2H); MS $[M+H]^+$ = 497.2; LCMS RT = 2.94.

Example 83: Preparation of 4-amino-5-{4-[({[4-chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}-*N*-cyclopropylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



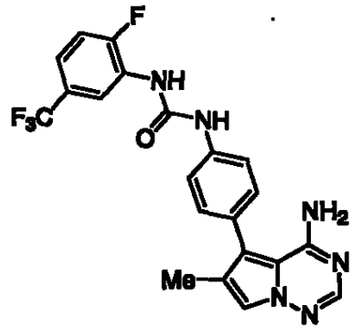
The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting Intermediate W for Intermediate X and by substituting phenyl [4-chloro-3-(trifluoromethyl)phenyl]carbamate for phenyl (4-*tert*-butylpyridin-2-yl)carbamate. ^{1}H-NMR (DMSO-d_6) δ 8.11 (d, J = 2.4 Hz, 1H), 8.04 (s, 1H), 7.87 (s, 1H), 7.66 to 7.58 (m, 2H), 7.52 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 3.13 to 3.09 (m, 1H), 2.69 to 2.60 (m, 1H), 0.64 to 0.56 (m 2H), 0.43 to 0.37 (m, 2H); MS $[M+H]^+$ = 530.2; LCMS RT = 3.25.

Example 84: Preparation of 4-amino-5-{4-[({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}-*N*-(2-methoxyethyl)-*N*-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



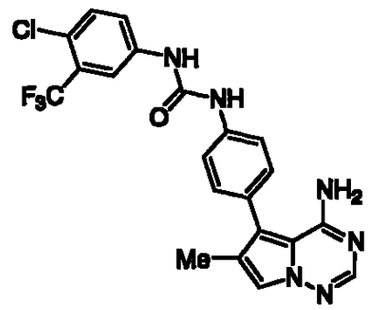
The procedure used for the preparation of Example 69 was used to prepare the title compound by substituting 2-methoxy-*N*-methylethanamine for cyclopropanamine. ^{1}H-NMR (DMSO-d_6) δ 9.07 (s, 1H), 8.98 to 8.91 (m, 1H), 8.01 to 7.97 (m, 1H), 7.90 (s, 1H), 7.87 to 7.81 (m, 1H), 7.68 to 7.60 (m, 1H), 7.59 to 7.50 (m, 2H), 7.48 to 7.40 (m, 1H), 7.17 to 7.10 (m, 1H), 3.44 to 3.40 (m, 2H), 3.25 to 3.10 (m, 5H), 2.83 (s, 3H – rotamer A), 2.65 (s, 3H – rotamer b) ; MS $[M+H]^+$ = 546.2; LCMS RT = 3.04 min; TLC R_f = 0.47 (55:40:5 v/v CH_2Cl_2-THF-EtOH).

Example 85: Preparation of *N*-[4-(4-amino-6-methylpyrrolo[2,1-*f*][1,2,4]triazin-5-yl)phenyl]-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea



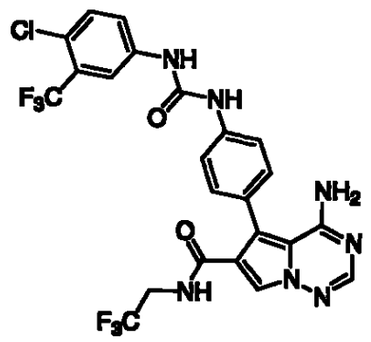
The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting Intermediate T for Intermediate X and by substituting phenyl [2-fluoro-5-(trifluoromethyl)phenyl]carbamate for phenyl (4-*tert*-butylpyridin-2-yl)carbamate. ^{1}H-NMR (CD_3OD) δ 8.61 (d, J = 2.6 Hz, 1H), 7.73 (s, 1H), 7.62 (d, J = 8.7 Hz, 2H), 7.49 (s, 1H), 7.37 to 7.31 (m, 4H), 2.14 (s, 3H); MS $[M+H]^+$ = 445.1; LCMS RT = 2.80.

Example 86: Preparation of *N*-[4-(4-amino-6-methylpyrrolo[2,1-f][1,2,4]triazin-5-yl)phenyl]-N'-[4-chloro-3-(trifluoromethyl)phenyl]urea



The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting Intermediate T for Intermediate X and by substituting phenyl [4-chloro-3-(trifluoromethyl)phenyl]carbamate for phenyl (4-*tert*-butylpyridin-2-yl)carbamate. ^{1}H-NMR (CD_3OD) δ 8.05 (d, J = 2.4 Hz, 1H), 7.73 (s, 1H), 7.67 to 7.58 (m, 3H), 7.50 (s, 1H), 7.48 (d, J = 8.1 Hz, 1H), 7.33 (d, J = 8.7 Hz, 2H), 2.18 (s, 3H); MS $[M+H]^+$ = 461.1; LCMS RT = 2.89.

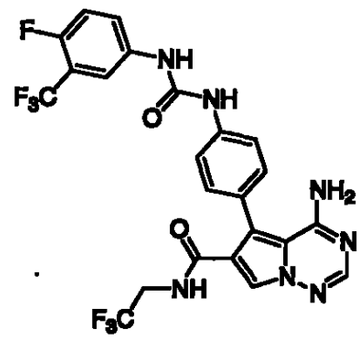
Example 87: Preparation of 4-amino-5-[4-[({[4-chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl]-*N*-(2,2,2-trifluoroethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting Intermediate M for Intermediate X and by substituting phenyl [4-chloro-3-(trifluoromethyl)phenyl]carbamate for phenyl (4-*tert*-butylpyridin-2-yl)carbamate. ^{1}H-NMR (CD_3OD) δ 8.04 (s, 1H), 8.00 (d, J = 2.4 Hz,

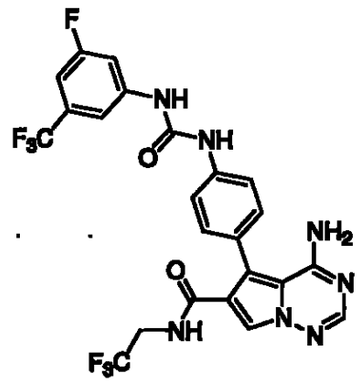
1H), 7.84 (s, 1H), 7.64 (dd, J = 8.4, 2.8 Hz, 1H), 7.59 (d, J = 8.4 Hz, 2H), 7.49 (d, J = 8.6 Hz, 1H), 7.38 (d, J = 8.4 Hz, 2H), 3.94 (q, J = 9.2 Hz, 2H); MS $[M+H]^+$ = 572.1; LCMS RT = 3.07.

Example 88: Preparation of 4-amino-5-{4-[({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}-*N*-(2,2,2-trifluoroethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



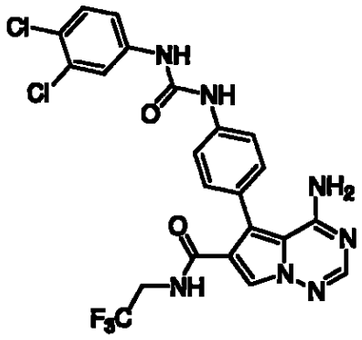
The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting Intermediate M for Intermediate X and by substituting phenyl [4-fluoro-3-(trifluoromethyl)phenyl]carbamate for phenyl (4-*tert*-butylpyridin-2-yl)carbamate. ^{1}H-NMR (CD_3OD) δ 8.04 (s, 1H), 7.90 (dd, J = 6.3, 2.7 Hz, 1H), 7.85 (s, 1H), 7.68 to 7.63 (m, 1H), 7.59 (d, J = 8.6 Hz, 2H), 7.39 (d, J = 8.7 Hz, 2H), 7.26 (t, J = 9.8 Hz, 1H), 3.94 (q, J = 9.2 Hz, 2H); MS $[M+H]^+$ = 556.1; LCMS RT = 2.94.

Example 89: Preparation of 4-amino-5-{4-[({[3-fluoro-5-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}-*N*-(2,2,2-trifluoroethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting Intermediate M for Intermediate X and by substituting phenyl [3-fluoro-5-(trifluoromethyl)phenyl]carbamate for phenyl (4-*tert*-butylpyridin-2-yl)carbamate. ^{1}H-NMR (CD_3OD) δ 8.04 (s, 1H), 7.84 (s, 1H), 7.66 to 7.53 (m, 4H), 7.38 (d, J = 8.7 Hz, 2H), 7.03 (d, J = 8.2 Hz, 1H), 3.94 (q, J = 9.2 Hz, 2H); MS $[M+H]^+$ = 556.1; LCMS RT = 3.02.

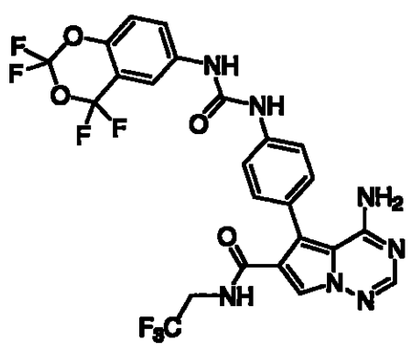
Example 90: Preparation of 4-amino-5-[4-({[(3,4-dichlorophenyl)amino]carbonyl}amino)phenyl]-*N*-(2,2,2-trifluoroethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting Intermediate M for Intermediate X and by substituting phenyl (3,4-dichlorophenyl)carbamate for phenyl (4-*tert*-butylpyridin-2-yl)carbamate. ^{1}H-NMR (CD_3OD) δ 8.04 (s, 1H), 7.85 (s, 1H), 7.81 (d, J = 2.4 Hz,

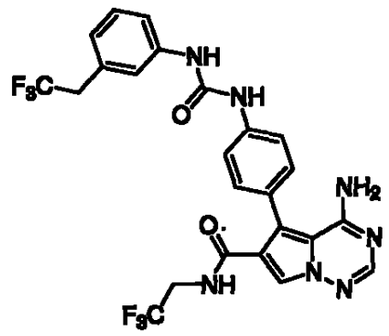
1H), 7.58 (d, J = 8.8 Hz, 2H), 7.43 to 7.37 (m, 3H), 7.31 (dd, J = 8.9, 2.5 Hz, 1H), 3.94 (q, J = 9.2 Hz, 2H); MS $[M+H]^+$ = 538.1; LCMS RT = 2.97.

Example 91: Preparation of 4-amino-5-[4-({[(2,2,4,4-tetrafluoro-4*H*-1,3-benzodioxin-6-yl)amino]carbonyl}amino)phenyl]-*N*-(2,2,2-trifluoroethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



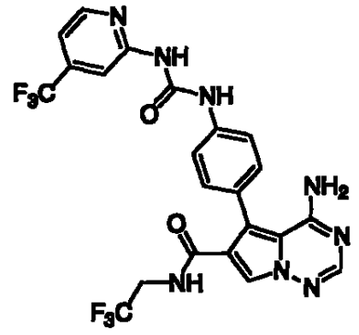
The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting Intermediate M for Intermediate X and by substituting phenyl (2,2,4,4-tetrafluoro-4*H*-1,3-benzodioxin-6-yl)carbamate for phenyl (4-*tert*-butylpyridin-2-yl)carbamate. ^{1}H-NMR (CD_3OD) δ 8.04 (s, 1H), 8.01 (d, J = 2.3 Hz, 1H), 7.84 (s, 1H), 7.66 (dd, J = 9.2, 2.8 Hz, 1H), 7.60 (d, J = 8.3 Hz, 2H), 7.39 (d, J = 8.3 Hz, 2H), 7.23 (d, J = 9.3 Hz, 1H), 3.94 (q, J = 9.2 Hz, 2H); MS $[M+H]^+$ = 600.0; LCMS RT = 3.11.

Example 92: Preparation of 4-amino-*N*-(2,2,2-trifluoroethyl)-5-{4-[({[3-(2,2,2-trifluoroethyl)phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting Intermediate M for Intermediate X and by substituting phenyl [3-(2,2,2-trifluoroethyl)phenyl]carbamate for phenyl (4-*tert*-butylpyridin-2-yl)carbamate. ^{1}H-NMR (CD_3OD) δ 8.04 (s, 1H), 7.85 (s, 1H), 7.59 (d, J = 8.6 Hz, 2H), 7.46 (d, J = 8.6 Hz, 2H), 7.38 (d, J = 8.5 Hz, 2H), 7.26 (d, J = 8.5 Hz, 2H), 3.94 (q, J = 9.2 Hz, 2H), 3.42 (q, J = 10.2 Hz, 2H); MS $[M+H]^+$ = 552.1; LCMS RT = 2.84.

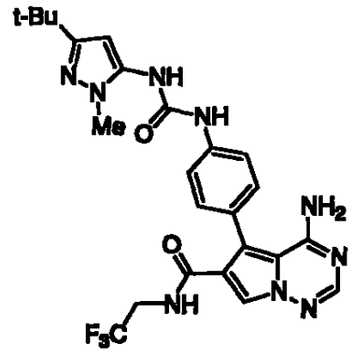
Example 93: Preparation of 4-amino-*N*-(2,2,2-trifluoroethyl)-5-[4-[({[4-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting Intermediate M for Intermediate X and by substituting phenyl [4-(trifluoromethyl)pyridin-2-yl]carbamate for phenyl (4-*tert*-butylpyridin-2-yl)carbamate. ^{1}H-NMR (CD_3OD) δ 8.54 (d, J = 5.1 Hz, 1H), 8.19 (s,

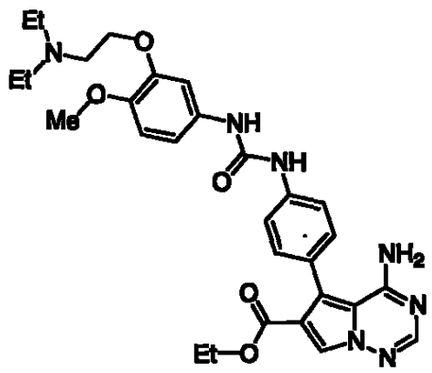
1H), 8.06 (br s, 1H), 7.91 (s, 1H), 7.60 (d, J = 8.7 Hz, 2H), 7.35 (d, J = 5.6 Hz, 2H), 7.31 (d, J = 8.9 Hz, 2H), 3.94 (q, J = 9.2 Hz, 2H); MS $[M+H]^+$ = 539.0; LCMS RT = 2.77.

Example 94: Preparation of 4-amino-5-[4-({[(3-*tert*-butyl-1-methyl-1*H*-pyrazol-5-yl)amino]carbonyl}amino)phenyl]-*N*-(2,2,2-trifluoroethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



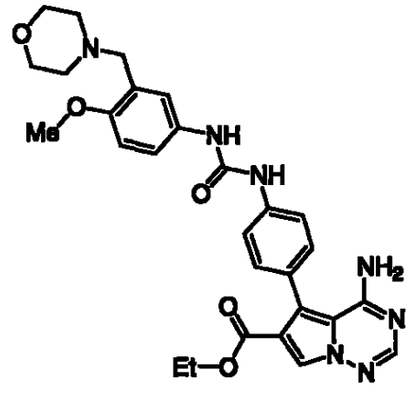
The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting Intermediate M for Intermediate X and by substituting phenyl (3-*tert*-butyl-1-methyl-1*H*-pyrazol-5-yl)carbamate for phenyl (4-*tert*-butylpyridin-2-yl)carbamate. ^{1}H-NMR (CD_3OD) δ 8.04 (s, 1H), 7.85 (s, 1H), 7.59 (d, J = 8.5 Hz, 2H), 7.39 (d, J = 8.7 Hz, 2H), 6.13 (s, 1H), 3.94 (q, J = 9.2 Hz, 2H), 3.70 (s, 3H), 1.28 (s, 9H); MS $[M+H]^+$ = 530.1; LCMS RT = 2.45.

Example 95: Preparation of ethyl 4-amino-5-(4-{[({3-[2-(diethylamino)ethoxy]-4-methoxyphenyl}amino)carbonyl]amino}phenyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate



The procedure used for the preparation of Example 3 was used to prepare the title compound by substituting 3-[2-(diethylamino)ethoxy]-4-methoxyaniline for 4-fluoro-3-(trifluoromethyl)aniline. ^{1}H-NMR (CD_3OD) δ 8.07 (s, 1H), 7.83 (s, 1H), 7.56 (d, J = 8.8 Hz, 2H), 7.33 (d, J = 8.9 Hz, 2H), 7.26 (s, 1H), 6.91 (d, J = 1.1 Hz, 2H), 4.20 to 4.10 (m, 4H), 3.81 (s, 3H), 3.18 to 2.99 (m, 2H), 2.86 to 2.74 (m, 4H), 1.18 to 1.10 (m, 9H); MS $[M+H]^+$ = 562.4; LCMS RT = 2.57.

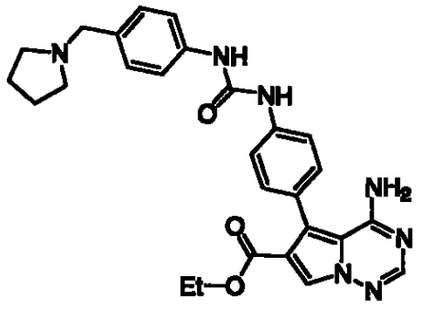
Example 96: **Preparation of ethyl 4-amino-5-{4-[({[4-methoxy-3-(morpholin-4-ylmethyl)phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate**



The procedure used for the preparation of Example 3 was used to prepare the title compound by substituting 4-methoxy-3-(morpholin-4-ylmethyl)aniline for 4-fluoro-3-(trifluoromethyl)aniline. ^{1}H-NMR (CD_3OD) δ 8.11 (s, 1H), 7.91 (s, 1H),

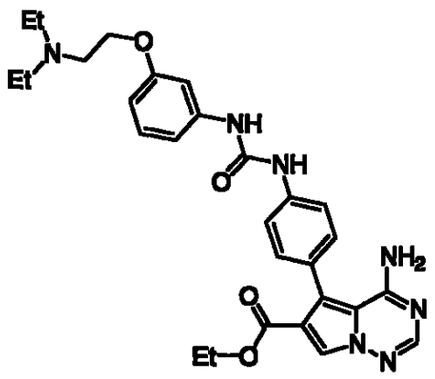
7.50 (d, J = 8.5 Hz, 2H), 7.36 to 7.32 (m, 2H), 7.27 (d, J = 8.5 Hz, 2H), 6.89 (d, J = 9.6, 1H), 4.08 (q, J = 7.3 Hz, 2H), 3.71 (s, 2H), 3.59 to 3.53 (m, 4H), 3.28 (s, 3H), 2.39 to 2.33 (m, 4H), 1.08 (t, J = 7.2 Hz, 3H); MS $[M+H]^+$ = 546.2; LCMS RT = 2.47.

Example 97: **Preparation of ethyl 4-amino-5-{4-[({[4-(pyrrolidin-1-ylmethyl)phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate**



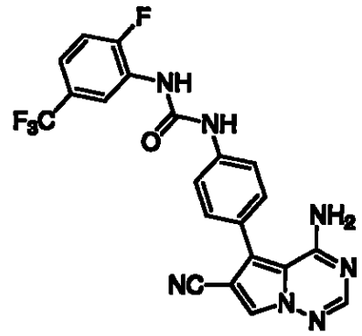
The procedure used for the preparation of Example 3 was used to prepare the title compound by substituting 4-(pyrrolidin-1-ylmethyl)aniline for 4-fluoro-3-(trifluoromethyl)aniline. ^{1}H-NMR (CD_3OD) δ 8.07 (s, 1H), 7.83 (s, 1H), 7.56 (d, J = 8.5 Hz, 2H), 7.47 (d, J = 8.5 Hz, 2H), 7.33 (t, J = 8.9 Hz, 4H), 4.13 (q, J = 7.3 Hz, 2H), 3.78 (s, 2H), 2.79 to 2.70 (m, 4H), 1.91 to 1.84 (m, 4H), 1.15 (t, J = 7.2 Hz, 3H); MS $[M+H]^+$ = 500.2; LCMS RT = 2.46.

Example 98: **Preparation of ethyl 4-amino-5-(4-{[({3-[2-(diethylamino)ethoxy]phenyl}amino)carbonyl]amino}phenyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate**



The procedure used for the preparation of Example 3 was used to prepare the title compound by substituting 3-[2-(diethylamino)ethoxy]aniline for 4-fluoro-3-(trifluoromethyl)aniline and purifying via HPLC (10-90% ACN/H_2O). ^{1}H-NMR (CD_3OD) δ 8.05 (s, 1H), 7.82 (s, 1H), 7.57 (d, J = 8.4 Hz, 2H), 7.35 to 7.30 (m, 3H), 7.20 (t, J = 8.0 Hz, 1H), 6.94 (dd, J = 7.9, 2.0 Hz, 1H), 6.63 (dd, J = 8.4, 1.9 Hz, 1H), 4.17 to 4.03 (m, 4H), 3.29 to 3.25 (m, 2H), 3.10 to 2.97 (m, 4H), 1.28 to 1.19 (m, 9H); MS $[M+H]^+$ = 532.4; LCMS RT = 2.57.

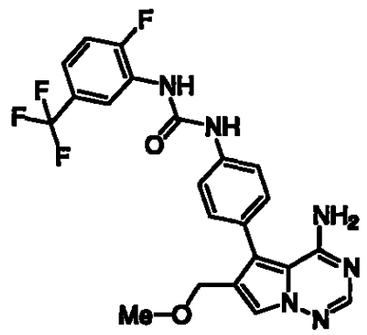
Example 99: **Preparation of *N*-[4-(4-amino-6-cyanopyrrolo[2,1-f][1,2,4]triazin-5-yl)phenyl]-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea**



The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting Intermediate P for Intermediate X and by substituting phenyl [2-fluoro-5-(trifluoromethyl)phenyl]carbamate for phenyl (4-*tert*-butylpyridin-2-yl)carbamate. ^{1}H-NMR (CD_3OD) δ 8.62 (d, J = 7.0 Hz, 1H), 8.19 (s,

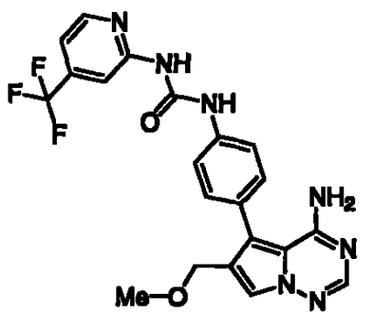
1H), 7.91 (s, 1H), 7.69 (d, J = 8.6 Hz, 2H), 7.50 (d, J = 8.6 Hz, 2H), 7.34 (d, J = 8.7 Hz, 2H); MS $[M+H]^+$ = 456.1; LCMS RT = 3.10.

Example 100: **Preparation of *N*-{4-[4-amino-6-(methoxymethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea**



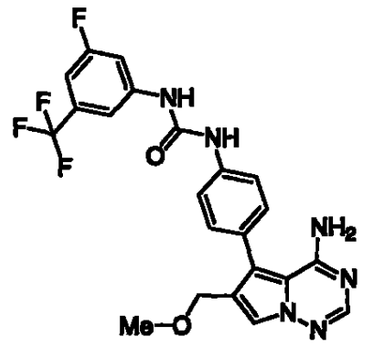
The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting Intermediate U for Intermediate X and by substituting phenyl [2-fluoro-5-(trifluoromethyl)phenyl]carbamate for phenyl (4-*tert*-butylpyridin-2-yl)carbamate. ^{1}H-NMR (CD_3OD) δ 8.61 (d, J = 7.6 Hz, 1H), 7.78 (s, 1H), 7.68 (s, 1H), 7.62 (d, J = 8.7 Hz, 2H), 7.40 (d, J = 8.6 Hz, 2H), 7.33 (d, J = 8.7 Hz, 2H), 4.35 (s, 2H), 3.30 (s, 3H); MS $[M+H]^+$ = 475.2; LCMS RT = 2.81.

Example 101: **Preparation of *N*-{4-[4-amino-6-(methoxymethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-[4-(trifluoromethyl)pyridin-2-yl]urea**



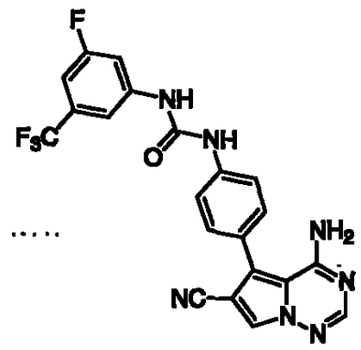
The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting Intermediate U for Intermediate X and by substituting phenyl [4-(trifluoromethyl)pyridin-2-yl]carbamate for phenyl (4-*tert*-butylpyridin-2-yl)carbamate. ^{1}H-NMR (CD_3OD) δ 8.52 (d, J = 5.4 Hz, 1H), 7.79 (s, 1H), 7.76 (s, 1H), 7.71 to 7.67 (m, 3H), 7.43 (d, J = 8.6 Hz, 2H), 7.28 (d, J = 5.3 Hz, 1H), 4.36 (s, 2H), 3.29 (s, 3H); MS $[M+H]^+$ = 458.1; LCMS RT = 2.66.

Example 102: Preparation of *N*-[4-[4-amino-6-(methoxymethyl)pyrrolo[2,1-*f*][1,2,4]triazin-5-yl]phenyl]-N'-[3-fluoro-5-(trifluoromethyl)phenyl]urea



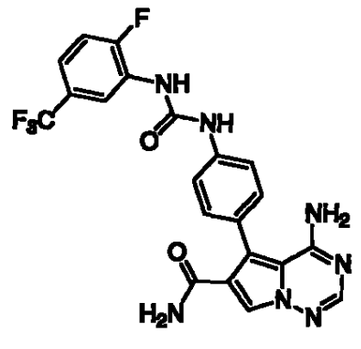
The procedure used for the preparation of Example 76 was used to prepare the title compound by substituting Intermediate U for Intermediate X and by substituting phenyl [3-fluoro-5-(trifluoromethyl)phenyl]carbamate for phenyl (4-*tert*-butylpyridin-2-yl)carbamate. ^{1}H-NMR (CD_3OD) δ 7.77 (s, 1H), 7.67 (s, 1H), 7.66 to 7.60 (m, 4H), 7.39 (d, J = 8.5 Hz, 2H), 7.03 (d, J = 8.9 Hz, 1H), 4.34 (s, 2H), 3.20 (s, 3H); MS $[M+H]^+$ = 475.2; LCMS RT = 2.88.

Example 103: Preparation of *N*-[4-(4-amino-6-cyanopyrrolo[2,1-*f*][1,2,4]triazin-5-yl)phenyl]-N'-[3-fluoro-5-(trifluoromethyl)phenyl]urea



The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting Intermediate P for Intermediate X and by substituting phenyl [3-fluoro-5-(trifluoromethyl)phenyl]carbamate for phenyl (4-*tert*-butylpyridin-2-yl)carbamate. ^{1}H-NMR (CD_3OD) δ 8.18 (s, 1H), 7.90 (s, 1H), 7.70 to 7.62 (m, 3H), 7.59 (s, 1H), 7.49 (d, J = 8.9 Hz, 2H), 7.06 (d, J = 8.9 Hz, 1H); MS $[M+H]^+$ = 456.4; LCMS RT = 3.26.

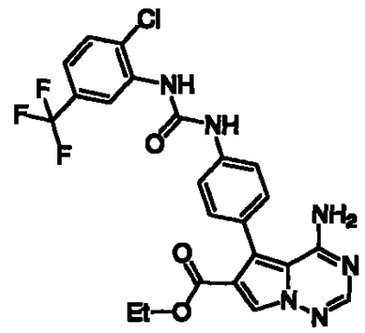
Example 104: Preparation of 4-amino-5-{4-[({[2-fluoro-5-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting Intermediate Q for Intermediate X and by substituting phenyl [2-fluoro-5-(trifluoromethyl)phenyl]carbamate for phenyl (4-*tert*-butylpyridin-2-yl)carbamate. ^{1}H-NMR (CD_3OD) δ 8.61 (d, J = 7.9 Hz, 1H), 8.23 (s,

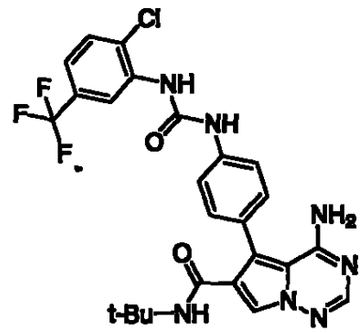
1H), 7.99 (s, 1H), 7.66 (d, J = 8.7 Hz, 2H), 7.46 (d, J = 8.7 Hz, 2H), 7.35 (d, J = 8.7 Hz, 2H); MS $[M+H]^+$ = 474.3; LCMS RT = 2.89.

Example 105: Preparation of ethyl 4-amino-5-[4-[({[2-chloro-5-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate



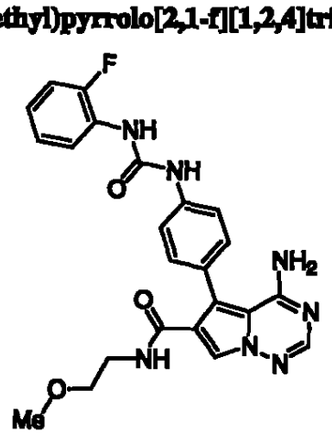
To a solution of DCE (5 mL) was added Intermediate B (300 mg, 1.01 mmol) followed by 2-chloro-1-isocyanato-4-(trifluoromethyl)benzene (0.32 mL, 2.12 mmol). The reaction was stirred under N_2 at rt for 1 h, and then aq 2N HCl (0.50 mL, 1.01 mmol) was added to the reaction followed by DMF (5 mL). The solution was heated for an additional 1 h. Upon cooling to rt the solution was diluted with EtOAc, transferred to a separatory funnel, and washed with aq saturated $NaHCO_3$. The aq layer was back extracted with EtOAc. The combined organic layers were collected, dried, concentrated, and purified by column chromatography (95:5 v/v CH_2Cl_2-MeOH). The resulting fractions containing product were concentrated and triturated using CH_2Cl_2 and hexanes. The product was filtered and dried in vacuo to afford 408 mg of the above compound as a white solid (0.79 mmol, yield 78%). ^{1}H-NMR (DMSO-d_6) δ 9.72 (s, 1H), 8.67 (s, 1H), 8.64 (s, 1H), 8.13 (s, 1H), 8.08 (br s, 1H), 7.93 (s, 1H), 7.72 (d, J = 8.5 Hz, 1H), 7.56 (d, J = 8.8 Hz, 2H), 7.39 to 7.36 (m, 1H), 7.34 (d, J = 8.6 Hz, 2H), 5.10 (br s, 1H), 4.09 (q, J = 7.0 Hz, 2H), 1.12 (t, J = 7.1 Hz, 3H); MS $[M+H]^+$ = 519; LCMS RT = 3.58 min; TLC R_f = 0.26 (95:5 v/v CH_2Cl_2-MeOH).

Example 106: **Preparation of 4-amino-*N*-(*tert*-butyl)-5-[4-[({[2-chloro-5-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide**



The procedure used for the preparation of Example 105 was used to prepare the title compound by substituting Intermediate L for Intermediate B. ^{1}H-NMR (DMSO-d_6) δ 9.74 (s, 1H), 8.67 (s, 1H), 8.64 (d, J = 2.4 Hz, 1H), 8.03 (s, 1H), 7.89 (s, 1H), 7.72 (d, J = 7.5 Hz, 1H), 7.59 (d, J = 8.6 Hz, 2H), 7.39 (s, 1H), 7.36 (d, J = 8.7 Hz, 2H), 6.64 (s, 1H), 1.19 (s, 9H); MS $[M+H]^+$ = 546; LCMS RT = 3.09 min; TLC R_f = 0.47 (9:1 v/v CH_2Cl_2-MeOH).

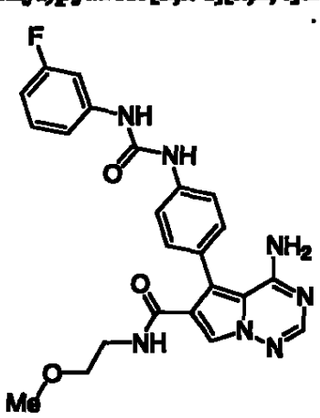
Example 107: **Preparation of 4-amino-5-[4-({[(2-fluorophenyl)amino]carbonyl}amino)phenyl]-*N*-(2-methoxyethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide**



To an EPA vial charged with Intermediate N (50 mg, 0.11 mmol) was added CH_2Cl_2 (2 mL). 1-fluoro-2-isocyanatobenzene (15 mg, 0.11 mmol) was added and

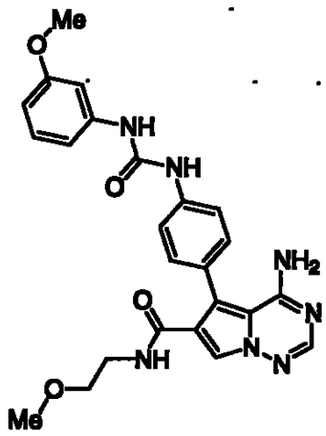
stirred at room temperature for 20 min. Then the reaction was heated to 42 °C and shaken at this temperature overnight. A TLC was run 3:7 v/v EtOAc-hexanes and showed that the reaction had consumed nearly all the SM. To the vial was added TFA (100 µL). It was stirred overnight at room temperature. LCMS showed desired product had formed. The sample was concentrated down by GeneVac and DMSO (2 mL) was added. The sample was purified by Prep LCMS to afford 27.3 mg of the above compound (0.059 mmol, yield 58%). ^{1}H-NMR (DMSO-d_6) δ 3.2 (s, 3H) 7.0 (m, 1H) 7.2 (t, J = 7.3 Hz, 1H) 7.2 (s, 1H) 7.3 (d, J = 7.3 Hz, 2H) 7.6 (d, J = 7.8 Hz, 3H) 7.6 (s, 2H) 7.9 (s, 1H) 8.2 (m, 3H) 8.6 (s, 1H) 9.2 (s, 1H). MS $[M+H]^+$ = 464; LCMS RT = 2.86 min.

Example 108: **Preparation of 4-amino-5-[4-({[(3-fluorophenyl)amino]carbonyl}amino)phenyl]-*N*-(2-methoxyethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carboxamide**



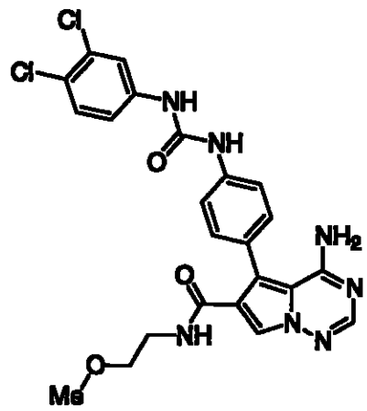
The procedure used for the preparation of Example 107 was used to prepare the title compound by substituting 1-fluoro-3-isocyanatobenzene for 1-fluoro-2-isocyanatobenzene. ^{1}H-NMR (DMSO-d_6) δ 3.2 (d, J = 11.2 Hz, 2H) 3.3 (d, J = 11.7 Hz, 2H) 3.3 (s, 1H) 6.8 (m, 1H) 7.1 (d, J = 7.8 Hz, 1H) 7.3 (d, J = 8.8 Hz, 1H) 7.5 (m, 4H) 7.6 (s, 2H) 7.9 (s, 1H) 8.1 (s, 2H) 9.0 (d, J = 19.6 Hz, 3H); MS $[M+H]^+$ = 464; LCMS RT = 2.90 min.

Example 109: **Preparation of 4-amino-*N*-(2-methoxyethyl)-5-[4-({[(3-methoxyphenyl)amino]carbonyl}amino)phenyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide**



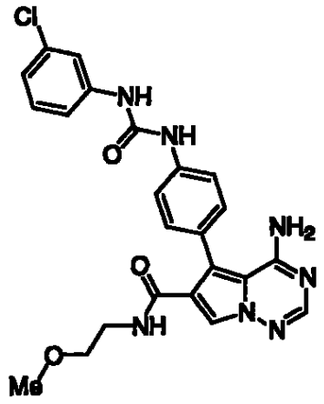
The procedure used for the preparation of Example 107 was used to prepare the title compound by substituting 1-isocyanato-3-methoxybenzene for 1-fluoro-2-isocyanatobenzene. ^{1}H-NMR (DMSO-d_6) δ 3.2 (s, 3H) 3.3 (m, 5H) 6.6 (d, J = 7.8 Hz, 1H) 7.0 (d, J = 8.3 Hz, 1H) 7.2 (m, 3H) 7.3 (d, J = 7.8 Hz, 2H) 7.6 (d, J = 7.8 Hz, 3H) 7.6 (s, 1H) 7.9 (s, 1H) 8.1 (s, 2H) 8.8 (s, 1H) 8.9 (s, 1H); MS $[M+H]^+$ = 476; LCMS RT = 2.84 min.

Example 110: **Preparation of 4-amino-5-[4-({[(3,4-dichlorophenyl)amino]carbonyl}amino)phenyl]-*N*-(2-methoxyethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide**



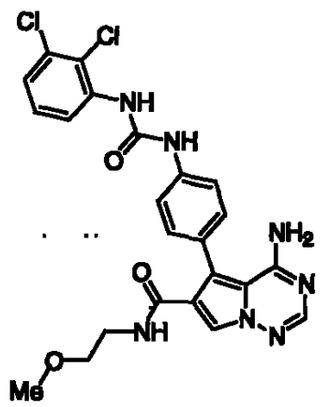
The procedure used for the preparation of Example 107 was used to prepare the title compound by substituting 1,2-dichloro-4-isocyanatobenzene for 1-fluoro-2-isocyanatobenzene. ^{1}H-NMR (DMSO-d_6) δ 3.2 (s, 2H) 3.3 (d, J = 11.7 Hz, 2H) 3.3 (s, 1H) 7.3 (m, 4H) 7.5 (t, J = 8.3 Hz, 4H) 7.6 (s, 2H) 7.9 (d, J = 13.7 Hz, 1H) 8.1 (s, 2H) 9.0 (s, 1H) 9.1 (s, 1H); MS $[M+H]^+$ = 514; LCMS RT = 3.17 min.

Example 111: **Preparation of 4-amino-5-[4-({[(3-chlorophenyl)amino]carbonyl}amino)phenyl]-*N*-(2-methoxyethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide**



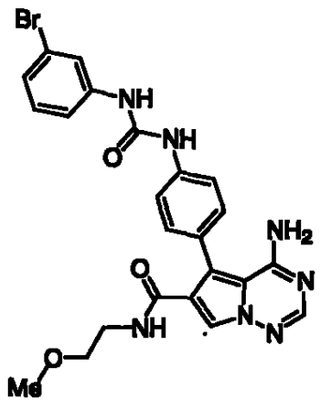
The procedure used for the preparation of Example 107 was used to prepare the title compound by substituting 1-chloro-3-isocyanatobenzene for 1-fluoro-2-isocyanatobenzene. ^{1}H-NMR (DMSO-d_6) δ 3.2 (s, 2H) 3.3 (d, J = 11.2 Hz, 3H) 3.3 (s, 2H) 7.0 (d, J = 6.4 Hz, 1H) 7.3 (m, 2H) 7.6 (d, J = 7.8 Hz, 3H) 7.6 (s, 2H) 7.7 (s, 1H) 7.9 (s, 1H) 8.1 (s, 2H) 9.0 (d, J = 4.9 Hz, 3H); MS $[M+H]^+$ = 480; LCMS RT = 3.02 min.

Example 112: **Preparation of 4-amino-5-[4-({[(2,3-dichlorophenyl)amino]carbonyl}amino)phenyl]-*N*-(2-methoxyethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide**



The procedure used for the preparation of Example 107 was used to prepare the title compound by substituting 1,2-dichloro-3-isocyanatobenzene for 1-fluoro-2-isocyanatobenzene. ^{1}H-NMR (DMSO-d_6) δ 3.2 (s, 1H) 3.3 (d, J = 5.9 Hz, 2H) 7.3 (s, 2H) 7.3 (d, J = 7.8 Hz, 4H) 7.6 (d, J = 8.3 Hz, 3H) 7.6 (s, 2H) 7.9 (s, 1H) 8.1 (s, 1H) 8.2 (d, J = 8.3 Hz, 1H) 8.5 (s, 1H) 9.7 (s, 1H); MS $[M+H]^+$ = 514; LCMS RT = 3.12 min.

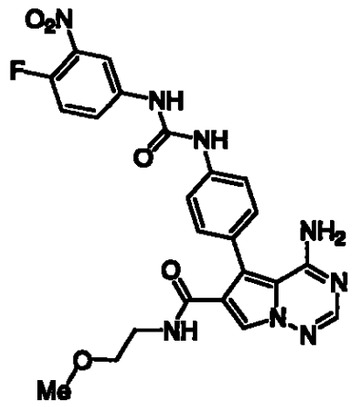
Example 113: **Preparation of 4-amino-5-[4-({[(3-bromophenyl)amino]carbonyl}amino)phenyl]-*N*-(2-methoxyethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide**



The procedure used for the preparation of Example 107 was used to prepare the title compound by substituting 1-bromo-3-isocyanatobenzene for 1-fluoro-2-isocyanatobenzene. ^{1}H-NMR (DMSO-d_6) δ 3.2 (s, 3H) 3.3 (m, 2H) 7.2 (d, J = 7.3

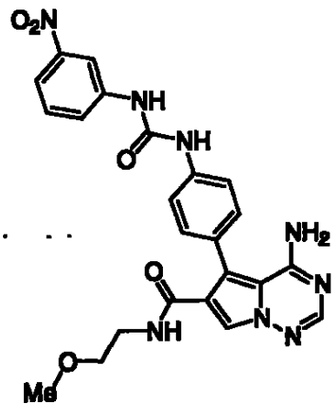
Hz, 1H) 7.3 (t, J = 7.8 Hz, 2H) 7.3 (d, J = 7.3 Hz, 4H) 7.6 (d, J = 8.3 Hz, 3H) 7.6 (s, 1H) 7.9 (s, 1H) 7.9 (s, 1H) 8.1 (s, 1H) 9.0 (s, 3H); MS $[M+H]^+$ = 524; LCMS RT = 3.04 min.

Example 114: **Preparation of 4-amino-5-[4-({[(4-fluoro-3-nitrophenyl)amino]carbonyl}amino)phenyl]-*N*-(2-methoxyethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide**



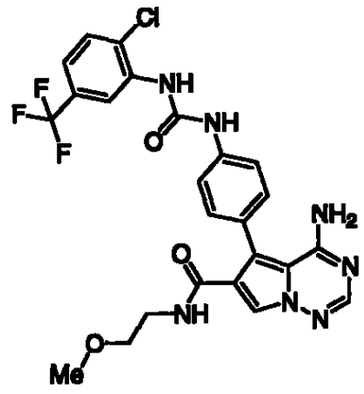
The procedure used for the preparation of Example 107 was used to prepare the title compound by substituting 1-fluoro-4-isocyanato-2-nitrobenzene for 1-fluoro-2-isocyanatobenzene. ^{1}H-NMR (DMSO-d_6) δ 3.2 (s, 3H) 3.3 (m, 2H) 7.3 (d, J = 8.3 Hz, 3H) 7.5 (m, 4H) 7.7 (s, 1H) 7.7 (s, 1H) 7.9 (s, 1H) 8.1 (s, 1H) 8.5 (s, 1H) 9.1 (s, 1H) 9.3 (s, 1H); MS $[M+H]^+$ = 509; LCMS RT = 2.93 min.

Example 115: **Preparation of 4-amino-*N*-(2-methoxyethyl)-5-[4-({[(3-nitrophenyl)amino]carbonyl}amino)phenyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide**



The procedure used for the preparation of Example 107 was used to prepare the title compound by substituting 1-isocyanato-3-nitrobenzene for 1-fluoro-2-isocyanatobenzene. ^{1}H-NMR (DMSO-d_6) δ 3.2 (s, 1H) 3.3 (d, J = 4.4 Hz, 1H) 3.3 (s, 1H) 7.3 (d, J = 7.8 Hz, 3H) 7.6 (d, J = 7.3 Hz, 5H) 7.7 (s, 2H) 7.7 (d, J = 7.8 Hz, 2H) 7.8 (d, J = 8.3 Hz, 2H) 8.0 (s, 1H) 8.1 (s, 1H) 8.6 (m, 1H) 9.1 (s, 1H) 9.3 (s, 1H); MS $[M+H]^+$ = 491; LCMS RT = 2.92 min.

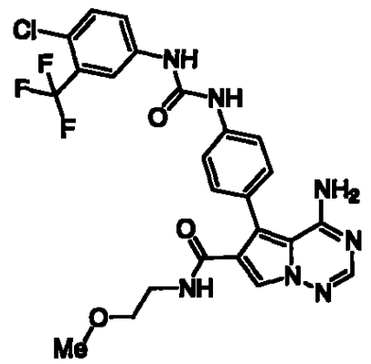
Example 116: **Preparation of 4-amino-5-{4-[({[2-chloro-5-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}-*N*-(2-methoxyethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide**



The procedure used for the preparation of Example 107 was used to prepare the title compound by substituting 1-chloro-2-isocyanato-4-(trifluoromethyl)benzene for 1-fluoro-2-isocyanatobenzene. ^{1}H-NMR (DMSO-d_6) δ 3.2 (s, 2H) 3.3 (d, J =

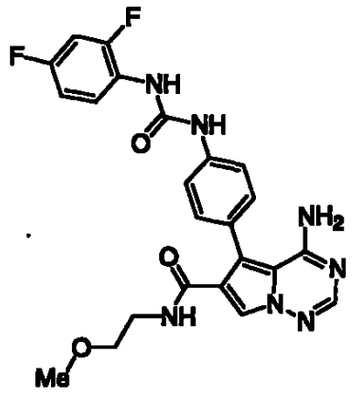
11.7 Hz, 2H) 3.3 (s, 1H) 7.4 (dd, J = 16.9, 8.6 Hz, 3H) 7.6 (d, J = 7.8 Hz, 3H) 7.7 (s, 2H) 7.7 (d, J = 8.3 Hz, 2H) 8.0 (s, 1H) 8.1 (s, 2H) 8.7 (d, J = 12.2 Hz, 3H) 9.7 (s, 1H); MS $[M+H]^+$ = 548; LCMS RT = 3.24 min.

Example 117: **Preparation of 4-amino-5-{4-[({[4-chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}-*N*-(2-methoxyethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide**



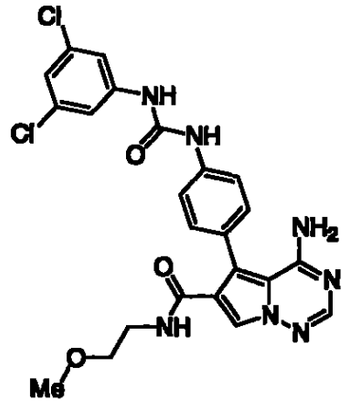
The procedure used for the preparation of Example 107 was used to prepare the title compound by substituting 1-chloro-4-isocyanato-2-(trifluoromethyl)benzene for 1-fluoro-2-isocyanatobenzene. ^{1}H-NMR (DMSO-d_6) δ 3.2 (s, 1H) 3.3 (m, 2H) 7.3 (d, J = 7.3 Hz, 3H) 7.6 (d, J = 7.3 Hz, 3H) 7.6 (m, 4H) 7.9 (s, 1H) 8.1 (s, 3H) 9.1 (s, 1H) 9.3 (s, 2H); MS $[M+H]^+$ = 548; LCMS RT = 3.26 min.

Example 118: **Preparation of 4-amino-5-[4-({[(2,5-difluorophenyl)amino]carbonyl}amino)phenyl]-*N*-(2-methoxyethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide**



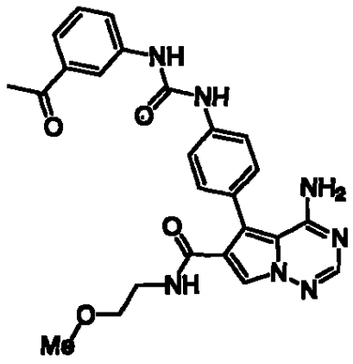
The procedure used for the preparation of Example 107 was used to prepare the title compound by substituting 2,4-difluoro-1-isocyanatobenzene for 1-fluoro-2-isocyanatobenzene. ^{1}H-NMR (DMSO-d_6) δ H) 6.8 (s, 1H) 7.3 (d, J = 7.8 Hz, 3H) 7.6 (d, J = 7.8 Hz, 2H) 7.6 (s, 1H) 7.9 (s, 1H) 8.1 (s, 2H) 8.8 (s, 1H) 9.3 (s, 1H); MS $[M+H]^+$ = 482; LCMS RT = 2.97 min.

Example 119: **Preparation of 4-amino-5-[4-({[(3,5-dichlorophenyl)amino]carbonyl}amino)phenyl]-*N*-(2-methoxyethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carboxamide**



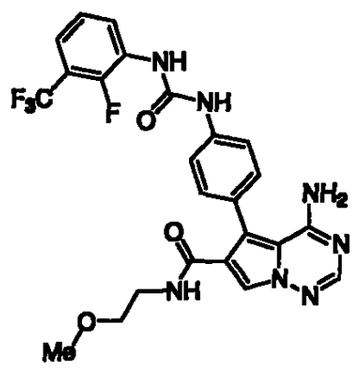
The procedure used for the preparation of Example 107 was used to prepare the title compound by substituting 1,3-dichloro-5-isocyanatobenzene for 1-fluoro-2-isocyanatobenzene. ^{1}H-NMR (DMSO-d_6) δ 3.2 (s, 3H) 3.3 (d, J = 17.1 Hz, 3H) 7.2 (s, 1H) 7.3 (d, J = 7.8 Hz, 3H) 7.6 (s, 6H) 7.6 (s, 2H) 8.1 (s, 2H) 9.1 (s, 1H) 9.1 (s, 1H); MS $[M+H]^+$ = 514; LCMS RT = 3.23 min.

Example 120: **Preparation of 5-[4-({[(3-acetylphenyl)amino]carbonyl}amino)phenyl]-4-amino-*N*-(2-methoxyethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide**



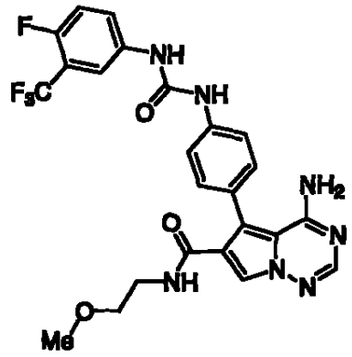
The procedure used for the preparation of Example 107 was used to prepare the title compound by substituting 1-(3-isocyanatophenyl)ethanone for 1-fluoro-2-isocyanatobenzene. ^{1}H-NMR (DMSO-d_6) δ 3.2 (s, 1H) 3.3 (s, 1H) 3.3 (s, 1H) 7.3 (d, J = 7.8 Hz, 3H) 7.5 (t, J = 7.6 Hz, 2H) 7.6 (m, 7H) 7.7 (d, J = 7.3 Hz, 2H) 8.0 (s, 1H) 8.1 (d, J = 15.7 Hz, 3H) 8.9 (s, 2H) 9.0 (s, 1H); MS $[M+H]^+$ = 488; LCMS RT = 2.78 min.

Example 121: **Preparation of 4-amino-5-{4-[({[2-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}-*N*-(2-methoxyethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide**



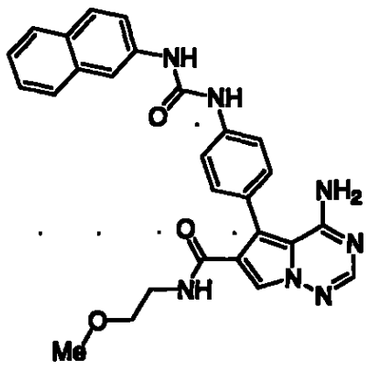
The procedure used for the preparation of Example 107 was used to prepare the title compound by substituting 2-fluoro-1-isocyanato-3-(trifluoromethyl)benzene for 1-fluoro-2-isocyanatobenzene. ^{1}H-NMR (DMSO-d_6) δ 3.2 (s, 3H) 3.3 (d, J = 16.6 Hz, 3H) 7.4 (m, 5H) 7.4 (s, 2H) 7.6 (d, J = 7.3 Hz, 4H) 7.6 (s, 2H) 7.9 (s, 1H) 8.1 (s, 2H) 8.5 (s, 2H) 8.9 (s, 1H) 9.3 (s, 2H); MS $[M+H]^+$ = 532; LCMS RT = 3.14 min.

Example 122: Preparation of 4-amino-5-{4-[({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}-*N*-(2-methoxyethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



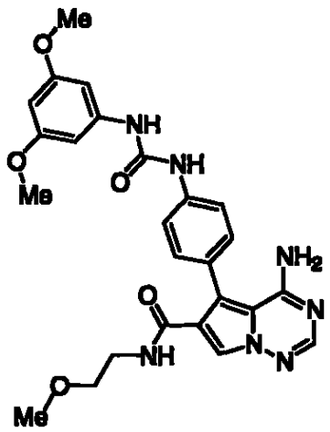
The procedure used for the preparation of Example 107 was used to prepare the title compound by substituting 1-fluoro-4-isocyanato-2-(trifluoromethyl)benzene for 1-fluoro-2-isocyanatobenzene. ^{1}H-NMR (DMSO-d_6) δ 2.5 (m, 5H) 3.4 (s, 2H) 7.3 (d, J = 7.8 Hz, 2H) 7.5 (t, J = 9.5 Hz, 1H) 7.6 (d, J = 7.8 Hz, 2H) 7.6 (d, J = 4.9 Hz, 3H) 7.9 (s, 1H) 8.0 (d, J = 4.9 Hz, 1H) 8.1 (s, 1H) 9.0 (s, 1H) 9.1 (s, 1H); MS $[M+H]^+$ = 532; LCMS RT = 3.16 min.

Example 123: Preparation of 4-amino-*N*-(2-methoxyethyl)-5-(4-{[(2-naphthylamino)carbonyl]amino}phenyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



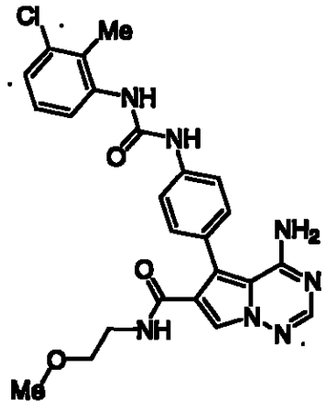
The procedure used for the preparation of Example 107 was used to prepare the title compound by substituting 2-isocyanatonaphthalene for 1-fluoro-2-isocyanatobenzene. ^{1}H-NMR (DMSO-d_6) δ 3.2 (s, 2H) 3.3 (d, J = 14.7 Hz, 2H) 7.4 (m, 4H) 7.5 (t, J = 7.3 Hz, 2H) 7.5 (d, J = 8.8 Hz, 2H) 7.6 (d, J = 8.3 Hz, 5H) 7.8 (m, 4H) 8.1 (s, 3H) 9.0 (s, 3H); MS $[M+H]^+$ = 496; LCMS RT = 3.07 min.

Example 124: **Preparation of 4-amino-5-[4-({[(3,5-dimethoxyphenyl)amino]carbonyl}amino)phenyl]-*N*-(2-methoxyethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide**



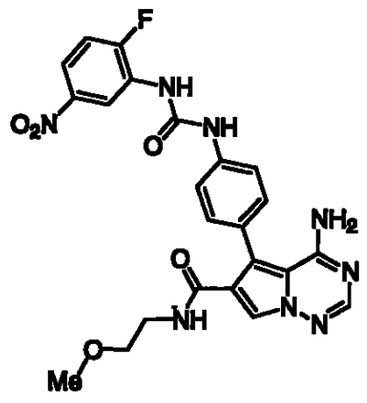
The procedure used for the preparation of Example 107 was used to prepare the title compound by substituting 1-isocyanato-3,5-dimethoxybenzene for 1-fluoro-2-isocyanatobenzene. ^{1}H-NMR (DMSO-d_6) δ 3.0 (s, 1H) 3.2 (s, 3H) 3.3 (m, 3H) 3.7 (s, 4H) 6.7 (s, 3H) 7.3 (d, J = 7.8 Hz, 3H) 7.5 (d, J = 7.8 Hz, 3H) 7.6 (s, 2H) 8.1 (s, 2H) 8.7 (s, 2H) 8.8 (s, 1H); MS $[M+H]^+$ = 506; LCMS RT = 2.88 min.

Example 125: **Preparation of 4-amino-5-[4-({[(3-chloro-2-methylphenyl)amino]carbonyl}amino)phenyl]-*N*-(2-methoxyethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide**



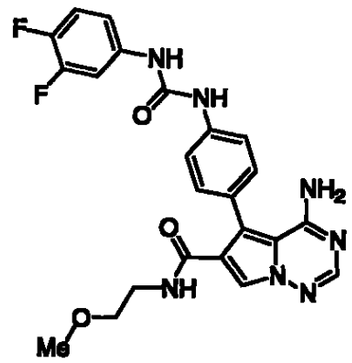
The procedure used for the preparation of Example 107 was used to prepare the title compound by substituting 1-chloro-3-isocyanato-2-methylbenzene for 1-fluoro-2-isocyanatobenzene. ^{1}H-NMR (DMSO-d_6) δ 2.3 (s, 3H) 2.5 (d, J = 16.6 Hz, 9H) 3.5 (s, 1H) 5.2 (s, 1H) 7.2 (m, 2H) 7.3 (d, J = 7.3 Hz, 2H) 7.6 (d, J = 7.8 Hz, 2H) 7.6 (s, 1H) 7.8 (d, J = 6.4 Hz, 1H) 7.9 (s, 1H) 8.1 (s, 1H) 8.2 (s, 1H) 9.2 (s, 1H); MS $[M+H]^+$ = 494; LCMS RT = 3.00 min.

Example 126: **Preparation of 4-amino-5-[4-({[(2-fluoro-5-nitrophenyl)amino]carbonyl}amino)phenyl]-*N*-(2-methoxyethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide**



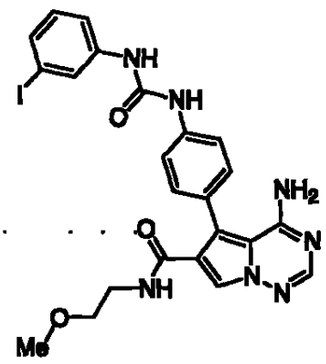
The procedure used for the preparation of Example 107 was used to prepare the title compound by substituting 1-fluoro-2-isocyanato-4-nitrobenzene for 1-fluoro-2-isocyanatobenzene. ^{1}H-NMR (DMSO-d_6) δ 3.2 (s, 2H) 3.3 (d, J = 5.4 Hz, 1H) 3.3 (s, 1H) 7.4 (d, J = 8.3 Hz, 3H) 7.6 (t, J = 9.0 Hz, 5H) 7.7 (s, 2H) 7.9 (d, J = 11.2 Hz, 2H) 8.1 (s, 2H) 9.1 (s, 1H) 9.2 (s, 1H) 9.4 (s, 1H); MS $[M+H]^+$ = 509; LCMS RT = 2.95 min.

Example 127: **Preparation of 4-amino-5-[4-({[(3,4-difluorophenyl)amino]carbonyl}amino)phenyl]-*N*-(2-methoxyethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide**



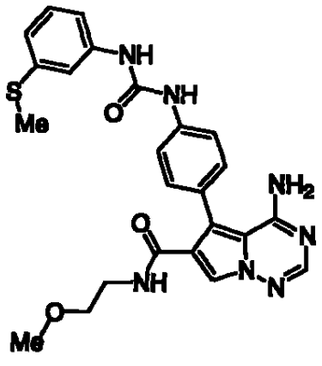
The procedure used for the preparation of Example 107 was used to prepare the title compound by substituting 1,2-difluoro-4-isocyanatobenzene for 1-fluoro-2-isocyanatobenzene. ^{1}H-NMR (DMSO-d_6) δ 3.2 (s, 3H) 3.3 (m, 3H) 7.1 (d, J = 7.8 Hz, 1H) 7.3 (m, 4H) 7.6 (d, J = 8.3 Hz, 3H) 7.6 (s, 3H) 7.9 (s, 1H) 8.1 (s, 1H) 9.0 (d, J = 11.2 Hz, 3H); MS $[M+H]^+$ = 482; LCMS RT = 2.95 min.

Example 128: **Preparation of 4-amino-5-[4-({[(3-iodophenyl)amino]carbonyl}amino)phenyl]-*N*-(2-methoxyethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide**



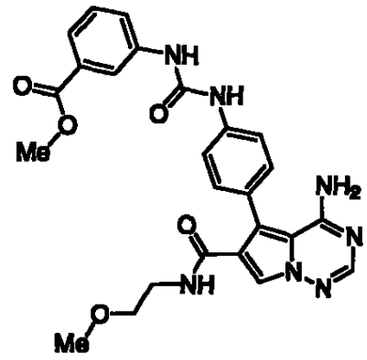
The procedure used for the preparation of Example 107 was used to prepare the title compound by substituting 1-iodo-3-isocyanatobenzene for 1-fluoro-2-isocyanatobenzene. ^{1}H-NMR (DMSO-d_6) δ 3.2 (s, 4H) 3.3 (m, 1H) 7.1 (t, J = 7.6 Hz, 1H) 7.3 (m, 5H) 7.5 (m, 3H) 7.6 (s, 1H) 7.9 (s, 1H) 8.0 (s, 1H) 8.1 (s, 2H) 8.9 (d, J = 18.6 Hz, 3H); MS $[M+H]^+$ = 572; LCMS RT = 3.09 min.

Example 129: Preparation of 4-amino-*N*-(2-methoxyethyl)-5-{4-[({[3-(methylthio)phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-*f*][1,2,4]triazine-6-carboxamide



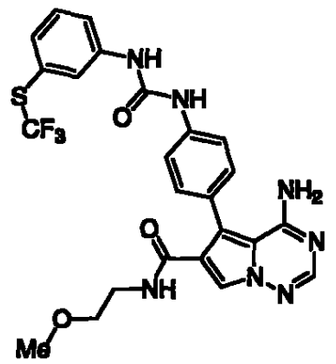
The procedure used for the preparation of Example 107 was used to prepare the title compound by substituting 1-isocyanato-3-(methylthio)benzene for 1-fluoro-2-isocyanatobenzene. ^{1}H-NMR (DMSO-d_6) δ 3.2 (s, 3H) 3.3 (m, 3H) 6.9 (d, J = 7.3 Hz, 1H) 7.2 (m, 3H) 7.3 (d, J = 7.3 Hz, 3H) 7.5 (s, 2H) 7.6 (d, J = 7.8 Hz, 3H) 7.6 (s, 2H) 7.9 (s, 1H) 8.1 (s, 2H) 8.8 (s, 1H) 8.9 (s, 2H); MS $[M+H]^+$ = 492; LCMS RT = 2.97 min.

Example 130: **Preparation of methyl 3-[({[4-(4-amino-6-{[(2-methoxyethyl)amino]carbonyl}pyrrolo[2,1-f][1,2,4]triazin-5-yl)phenyl]amino}carbonyl)amino]benzoate**



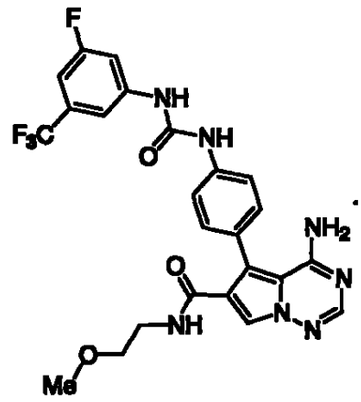
The procedure used for the preparation of Example 107 was used to prepare the title compound by substituting methyl 3-isocyanatobenzoate for 1-fluoro-2-isocyanatobenzene. ^{1}H-NMR (DMSO-d_6) δ 3.2 (s, 3H) 3.3 (m, 2H) 3.9 (s, 2H) 7.3 (d, J = 7.8 Hz, 3H) 7.4 (t, J = 7.6 Hz, 1H) 7.6 (d, J = 7.8 Hz, 4H) 7.6 (m, 3H) 7.9 (s, 1H) 8.1 (s, 2H) 8.2 (s, 1H) 8.9 (s, 1H) 9.0 (s, 1H); MS $[M+H]^+$ = 504; LCMS RT = 2.87 min.

Example 131: **Preparation of 4-amino-*N*-(2-methoxyethyl)-5-(4-{[({3-[(trifluoromethyl)thio]phenyl}amino)carbonyl]amino}phenyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide**



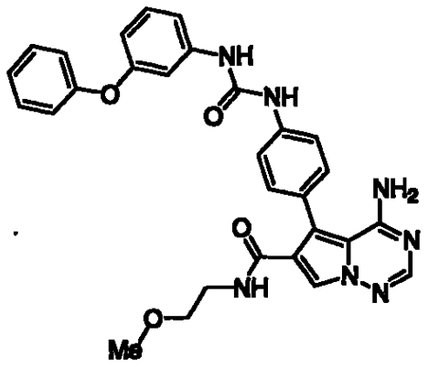
The procedure used for the preparation of Example 107 was used to prepare the title compound by substituting 1-isocyanato-3-[(trifluoromethyl)thio]benzene for 1-fluoro-2-isocyanatobenzene. ^{1}H-NMR (DMSO-d_6) δ 2.5 (d, J = 16.1 Hz, 9H) 5.2 (s, 1H) 7.3 (d, J = 7.3 Hz, 3H) 7.5 (t, J = 7.6 Hz, 1H) 7.6 (d, J = 6.4 Hz, 3H) 7.6 (s, 1H) 7.9 (s, 1H) 8.0 (s, 1H) 8.1 (s, 1H) 9.0 (s, 1H) 9.1 (s, 1H); MS $[M+H]^+$ = 546; LCMS RT = 3.26 min.

Example 132: **Preparation of 4-amino-5-{4-[({[3-fluoro-5-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}-*N*-(2-methoxyethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide**



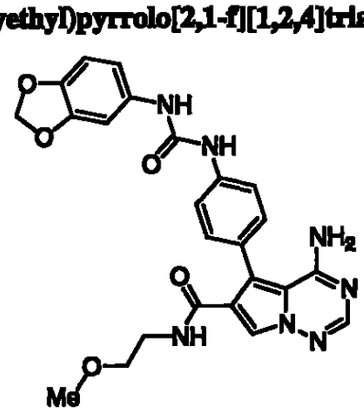
The procedure used for the preparation of Example 107 was used to prepare the title compound by substituting 1-fluoro-3-isocyanato-5-(trifluoromethyl)benzene for 1-fluoro-2-isocyanatobenzene. ^{1}H-NMR (DMSO-d_6) δ 3.5 (s, 3H) 7.2 (s, 2H) 7.3 (d, J = 8.3 Hz, 4H) 7.6 (s, 2H) 7.6 (s, 4H) 7.7 (s, 2H) 8.1 (s, 2H) 9.1 (s, 2H) 9.3 (s, 2H); MS $[M+H]^+$ = 532; LCMS RT = 3.22 min.

Example 133: **Preparation of 4-amino-*N*-(2-methoxyethyl)-5-[4-({[(3-phenoxyphenyl)amino]carbonyl}amino)phenyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide**



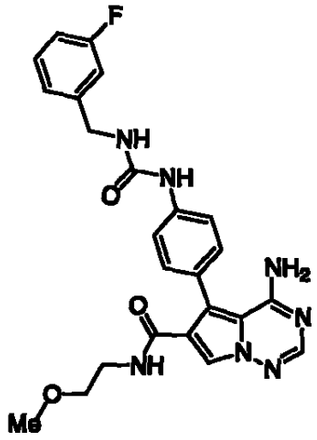
The procedure used for the preparation of Example 107 was used to prepare the title compound by substituting 1-isocyanato-3-phenoxybenzene for 1-fluoro-2-isocyanatobenzene. ^{1}H-NMR (DMSO-d_6) δ 3.2 (s, 2H) 3.5 (s 2 H) 6.6 (s, 1H) 7.0 (d, J = 7.8 Hz, 2H) 7.2 (s, 3H) 7.3 (s, 2H) 7.3 (d, J = 7.8 Hz, 5H) 7.4 (s, 3H) 7.5 (s, 1H) 7.6 (s, 1H) 7.9 (s, 1H) 8.1 (s, 1H) 8.8 (d, J = 15.7 Hz, 3H); MS $[M+H]^+$ = 538; LCMS RT = 3.22 min.

Example 134: Preparation of 4-amino-5-(4-{[(1,3-benzodioxol-5-ylamino)carbonyl]amino}phenyl)-*N*-(2-methoxyethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carboxamide



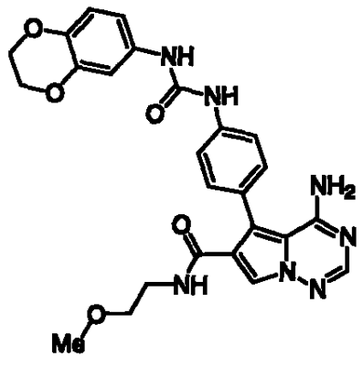
The procedure used for the preparation of Example 107 was used to prepare the title compound by substituting 5-isocyanato-1,3-benzodioxole for 1-fluoro-2-isocyanatobenzene. ^{1}H-NMR (DMSO-d_6) δ 3.2 (s, 2H) 6.0 (s, 5H) 6.8 (s, 2H) 7.2 (s, 2H) 7.3 (d, J = 7.3 Hz, 5H) 7.5 (s, 2H) 8.1 (s, 2H) 8.6 (s, 2H) 8.8 (s, 2H); MS $[M+H]^+$ = 490; LCMS RT = 2.78 min.

Example 135: **Preparation of 4-amino-5-[4-({[(3-fluorobenzyl)amino]carbonyl}amino)phenyl]-*N*-(2-methoxyethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide**



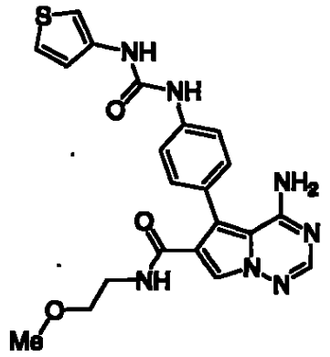
The procedure used for the preparation of Example 107 was used to prepare the title compound by substituting 1-fluoro-3-(isocyanatomethyl)benzene for 1-fluoro-2-isocyanatobenzene. ^{1}H-NMR (DMSO-d_6) δ 4.3 (s, 3H) 6.8 (s, 2H) 7.1 (s, 1H) 7.1 (s, 4H) 7.3 (s, 4H) 7.4 (s, 1H) 7.5 (s, 4H) 7.9 (s, 1H) 8.1 (s, 2H) 8.8 (s, 2H); MS $[M+H]^+ = 478$; LCMS RT = 2.82 min.

Example 136: **Preparation of 4-amino-5-(4-{[(2,3-dihydro-1,4-benzodioxin-6-ylamino)carbonyl]amino}phenyl)-*N*-(2-methoxyethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide**



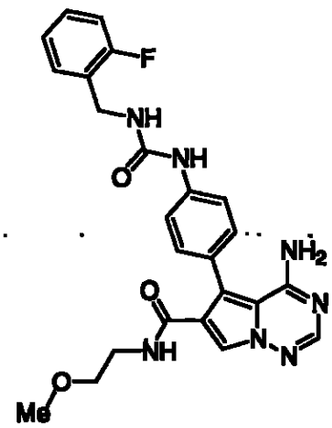
The procedure used for the preparation of Example 107 was used to prepare the title compound by substituting 6-isocyanato-2,3-dihydro-1,4-benzodioxine for 1-fluoro-2-isocyanatobenzene. ^{1}H-NMR (DMSO-d_6) δ 3.0 (s, 3H) 3.2 (s, 2H) 3.5 (s, 2H) 6.8 (s, 2H) 7.1 (s, 1H) 7.3 (d, J = 7.3 Hz, 4H) 7.5 (s, 4H) 7.9 (s, 1H) 8.1 (s, 2H) 8.5 (s, 2H) 8.8 (s, 2H); MS $[M+H]^+$ = 504; LCMS RT = 2.78 min.

Example 137: Preparation of 4-amino-*N*-(2-methoxyethyl)-5-(4-{[(3-thienylamino)carbonyl]amino}phenyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



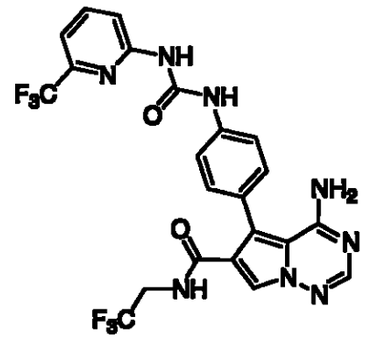
The procedure used for the preparation of Example 107 was used to prepare the title compound by substituting 3-isocyanatothiophene for 1-fluoro-2-isocyanatobenzene. ^{1}H-NMR (DMSO-d_6) δ 3.0 (s, 4H) 7.3 (s, 5H) 7.6 (s, 3H) 7.9 (s, 2H) 8.1 (s, 3H) 8.8 (s, 2H) 9.0 (s, 2H); MS $[M+H]^+$ = 452; LCMS RT = 2.77 min.

Example 138: Preparation of 4-amino-5-[4-({[(2-fluorobenzyl)amino]carbonyl}amino)phenyl]-*N*-(2-methoxyethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



The procedure used for the preparation of Example 107 was used to prepare the title compound by substituting 1-fluoro-2-(isocyanatomethyl)benzene for 1-fluoro-2-isocyanatobenzene. ^{1}H-NMR (DMSO-d_6) δ 3.5 (s, 4H) 4.4 (s, 3H) 7.3 (d, J = 7.8 Hz, 9 H) 7.4 (s, 2H) 7.5 (s, H) 8.1 (s, 1H) 8.8 (s, 2H); MS $[M+H]^+$ = 478; LCMS RT = 2.82 min.

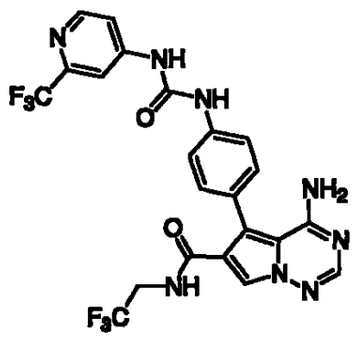
Example 139: **Preparation of 4-amino-*N*-(2,2,2-trifluoroethyl)-5-{4-[({[6-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide**



The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting Intermediate M for Intermediate X and by substituting phenyl [6-(trifluoromethyl)pyridin-2-yl]carbamate for phenyl (4-*tert*-butylpyridin-2-yl)carbamate. ^{1}H-NMR (CD_3OD) δ 8.05 (s, 1H), 7.97 (s, 1H), 7.85

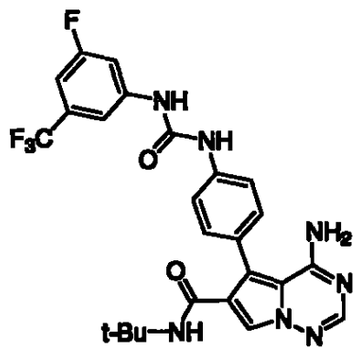
(s, 1H), 7.67 (d, J = 8.7 Hz, 2H), 7.56 (d, J = 8.7 Hz, 1H), 7.46 to 7.41 (m, 3H), 3.94 (q, J = 8.9 Hz, 2H); MS $[M+H]^+$ = 539.0; LCMS RT = 2.71.

Example 140: **Preparation of 4-amino-*N*-(2,2,2-trifluoroethyl)-5-{4-[({[2-(trifluoromethyl)pyridin-4-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide**



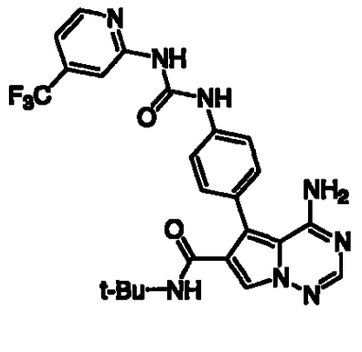
The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting Intermediate M for Intermediate X and by substituting phenyl [2-(trifluoromethyl)pyridin-4-yl]carbamate for phenyl (4-*tert*-butylpyridin-2-yl)carbamate. ^{1}H-NMR (CD_3OD) δ 8.47 (d, J = 5.9 Hz, 1H), 8.04 (s, 1H), 8.03 (d, J = 2.9 Hz,1H), 7.85 (s, 1H), 7.66 (dd, J = 5.4, 1.9 Hz, 1H), 7.62 (d, J = 8.9 Hz, 2H), 7.41 (d, J = 8.8 Hz, 2H), 3.94 (q, J = 9.2 Hz, 2H); MS $[M+H]^+$ = 539.0; LCMS RT = 2.56.

Example 141: **Preparation of 4-amino-*N*-(*tert*-butyl)-5-{4-[({[3-fluoro-5-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide**



The procedure used for the preparation of Example 105 was used to prepare the title compound by substituting Intermediate L for Intermediate B and by substituting 1-fluoro-3-isocyanato-5-(trifluoromethyl)benzene for 1-chloro-2-isocyanato-4-(trifluoromethyl)benzene. ^{1}H-NMR (DMSO-d_6) δ 9.34 (s, 1H), 9.14 (s, 1H), 8.03 (s, 1H), 7.88 (s, 1H), 7.72 to 7.70 (m, 1H), 7.65 to 7.62 (m, 1H), 7.61 to 7.57 (m, 2H), 7.35 to 7.34 (m, 2H), 7.24 to 7.22 (m, 1H), 6.61 (m, 1H), 1.18 (s, 9H); MS $[M+H]^+$ = 530; LCMS RT = 3.09 min; TLC R_f = 0.54 (5:4:1 v/v/v CH_2Cl_2-EtOAc-MeOH).

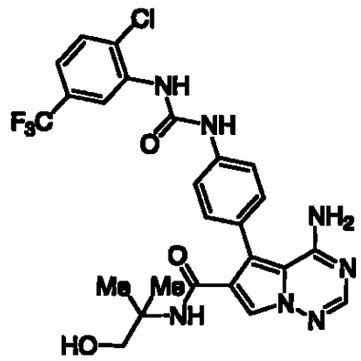
Example 142: Preparation of 4-amino-*N*-(*tert*-butyl)-5-{4-[({[4-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting Intermediate L for Intermediate X and by substituting phenyl [4-(trifluoromethyl)pyridin-2-yl]carbamate for phenyl (4-*tert*-

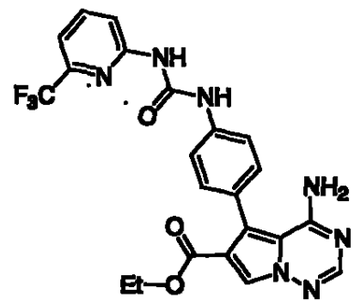
butylpyridin-2-yl)carbamate. ^{1}H-NMR (DMSO-d_6) δ 9.91 (s, 1H), 9.76 (s, 1H), 8.54 to 8.53 (d, J = 5.1 Hz, 1H), 8.06 (s, 1H), 8.03 (s, 1H), 7.89 (s, 1H), 7.64 to 7.62 (d, J = 8.6 Hz, 2H), 7.37 to 7.35 (d, J = 8.6 Hz, 2H), 6.67 (s, 1H), 1.19 (s, 9H); MS $[M+H]^+$ = 513; LCMS RT = 2.84 min; TLC R_f = 0.37 (5:4:1 v/v/v CH_2Cl_2-EtOAc-MeOH).

Example 143: Preparation of 4-amino-5-{4-[({[2-chloro-5-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}-*N*-(2-hydroxy-1,1-dimethylethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



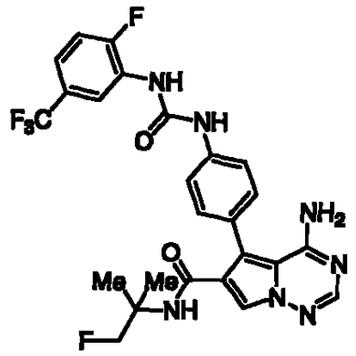
To a solution of DMF (2 mL) was added Intermediate J (50 mg, 0.10 mmol) followed by benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (45 mg, 0.10 mmol), 4-methylmorpholine (0.01 mL, 0.10 mmol), and 2-amino-2-methylpropan-1-ol (0.01 mL, 0.10 mmol). The solution was stirred under N_2 at rt for 17 h. The reaction mixture was evaporated by rotary evaporation and then purified via column chromatography (5:4:1 v/v/v CH_2Cl_2-EtOAc-MeOH) to afford 38 mg of the above compound (0.068 mmol, yield 67%) ^{1}H-NMR (DMSO-d_6) δ 9.73 (s, 1H), 8.67 (s, 1H), 8.64 (d, J = 2.2 Hz, 1H), 8.03 (s, 1H), 7.89 (s, 1H), 7.72 (d, J = 8.5 Hz, 1H), 7.59 (d, J = 8.6 Hz, 2H), 7.39 to 7.38 (m, 1H), 7.36 (d, J = 8.5 Hz, 2H), 6.52 (s, 1H), 4.77 (t, J = 5.8 Hz, 1H), 3.29 (d, J = 5.9 Hz, 2H), 1.12 (s, 6H); MS $[M+H]^+$ = 562; LCMS RT = 3.16 min; TLC R_f = 0.32 (5:4:1 v/v/v CH_2Cl_2-EtOAc-MeOH).

Example 144: **Preparation of ethyl 4-amino-5-{4-[({[6-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate**



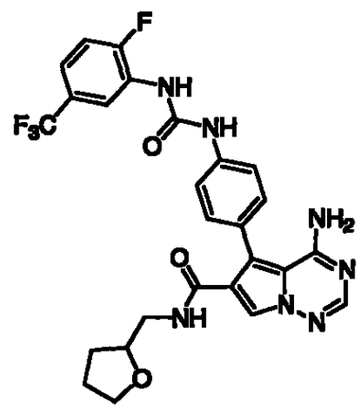
The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting Intermediate B for Intermediate X and by substituting phenyl [6-(trifluoromethyl)pyridin-2-yl]carbamate for phenyl (4-*tert*-butylpyridin-2-yl)carbamate. ^{1}H-NMR (DMSO-d_6) δ 9.89 (s, 1H), 9.74 (s, 1H), 8.13 (s, 1H), 8.02 to 7.97 (m, 2H), 7.92 (s, 1H), 7.55 (d, J = 9 Hz, 2H), 7.53 to 7.50 (m, 1H), 7.35 (d, J = 9 Hz, 2H), 5.12 (bs, 1H), 4.07 (q, J = 7 Hz, 2H), 1.09 (t, J = 7 Hz, 3H); MS $[M+H]^+$ = 486.0; LCMS RT = 2.92 min; TLC R_f = 0.38 (3:1 v/v CH_2Cl_2-THF).

Example 145: **Preparation of 4-amino-*N*-(2-fluoro-1,1-dimethylethyl)-5-{4-[({[2-fluoro-5-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide**



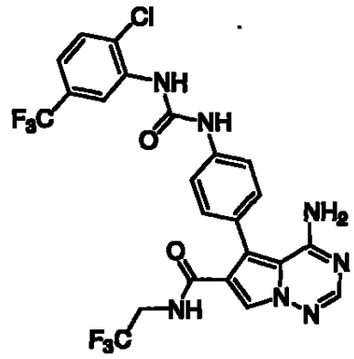
The procedure used for the preparation of Example 69 was used to prepare the title compound by substituting 1-fluoro-2-methylpropan-2-amine for cyclopropanamine. ^{1}H-NMR (DMSO-d_6) σ 9.20 (bs, 1H), 8.60 (d, J = 7 Hz, 1H), 8.07 (s, 1H), 7.89 (s, 1H), 7.57 (d, J = 8Hz, 2H), 7.45 to 7.41 (m, 1H), 7.40 to 7.30 (m, 1H), 7.35 (d, J = 8 Hz, 2H), 6.86 (s, 1H), 5.02 (bs, 1H) 4.39 (d, J = 24 Hz, 2H), 1.15 (s, 9H); MS $[M+H]^+$ = 548.4; LCMS RT = 3.35 min; TLC R_f = 0.58 (3:2 v/v CH_2Cl_2-THF).

Example 146: Preparation of 4-amino-5-{4-[({[2-fluoro-5-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}-*N*-(tetrahydrofuran-2-ylmethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



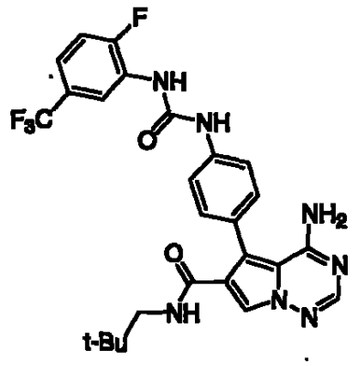
The procedure used for the preparation of Example 69 was used to prepare the title compound by substituting 1-(tetrahydrofuran-2-yl)methanamine for cyclopropanamine. ^{1}H-NMR (DMSO-d_6) δ 9.32 (s, 1H), 8.94 (d, J = 3 Hz, 1H), 8.63 to 8.59 (m. 1H), 8.08 (s, 1H), 7.89 (s, 1H), 7.60 to 7.55 (m, 1H), 7.54 (d, J = 8 Hz, 2H), 7.50 to 7.45 (m, 1H), 7.41 to 7.34 (m, 1H), 7.32 (d, J = 8 Hz, 2H), 5.01 (bs, 1H), 3.80 to 3.72 (m, 1H) 3.76 to 3.60 (m, 1H), 3.58 to 3.50 (m, 1H), 3.20 to 3.12 (m, 1H), 1.80 to 1.69 (m, 1H) ; MS $[M+H]^+$ = 558.3; LCMS RT = 3.13 min; TLC R_f = 0.29 (3:2 v/v CH_2Cl_2-THF).

Example 147: **Preparation of 4-amino-5-{4-[({[2-chloro-5-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}-*N*-(2,2,2-trifluoroethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide**



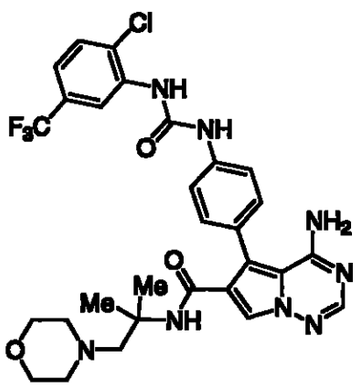
The procedure used for the preparation of Example 143 was used to prepare the title compound by substituting 2,2,2-trifluoroethanamine for 2-amino-2-methylpropan-1-ol. ^{1}H-NMR (DMSO-d_6) δ 9.70 (s, 1H), 8.67 (s, 1H), 8.64 (s, 1H), 8.52 (t, J = 6.2 Hz, 1H), 8.19 (s, 1H), 7.92 (s, 1H), 7.72 (d, J = 8.3 Hz, 1H), 7.54 (d, J = 8.7 Hz, 2H), 7.39 to 7.36 (m, 1H), 7.30 (d, J = 8.5 Hz, 2H), 3.98 to 3.91 (m, 2H); MS $[M+H]^+$ = 573; LCMS RT = 3.11 min; TLC R_f = 0.43 (5:4:1 v/v/v CH_2Cl_2-EtOAc-MeOH).

Example 148: **Preparation of 4-amino-*N*-(2,2-dimethylpropyl)-5-{4-[({[2-fluoro-5-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide**



The procedure used for the preparation of Example 69 was used to prepare the title compound by substituting 2,2-dimethylpropan-1-amine for cyclopropanamine. ^{1}H-NMR (DMSO-d_6) δ 9.33 (s, 1H), 8.94 (d, J = 3 Hz, 1H), 8.61 (dd, J = 7, 2 Hz, 1H), 8.06 (s, 1H), 7.89 (s, 1H), 7.57 (d, J = 9 Hz, 2H), 7.50 to 7.45 (m, 1H), 7.41 to 7.36 (m, 1H), 7.35 (d, J = 9 Hz, 2H) 7.26 (t, J = 6 Hz, 1H), 5.00 (bs, 1H), 2.91 (d, J = 6 Hz, 1H), 0.72 (s, 9H) ; MS $[M+H]^+$ = 544.5; LCMS RT = 3.13 min; TLC R_f = 0.51 (3:2 v/v CH_2Cl_2-THF).

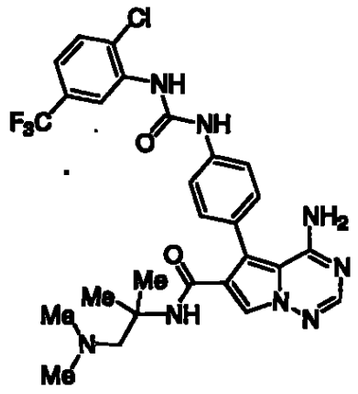
Example 149: **Preparation of 4-amino-5-{4-[({[2-chloro-5-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}-*N*-(1,1-dimethyl-2-morpholin-4-ylethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide**



The procedure used for the preparation of Example 66 was used to prepare the title compound by substituting Intermediate AC for Intermediate L ^{1}H-NMR (CD_3OD) δ 8.66 (d, J = 1.7 Hz, 1H), 7.95 (s, 1H), 7.83 (s, 1H), 7.72 (d, J = 8.8 Hz, 2H), 7.62 (d, J = 8.7 Hz, 1H), 7.47 (d, J = 8.8 Hz, 2H), 7.31 (dd, J = 8.5, 2.1 Hz, 1H), 3.62 to 3.53 (m, 4H), 2.44 (s, 2H), 2.42 to 2.34 (m, 4H), 1.18 (s, 6H); MS $[M+H]^+$ = 631.2; LCMS RT = 2.84.

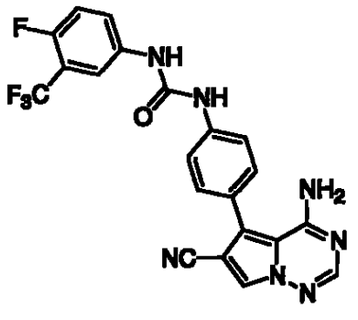
Example 150: **Preparation of 4-amino-5-{4-[({[2-chloro-5-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}-*N*-**

[2-(dimethylamino)-1,1-dimethylethyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



The procedure used for the preparation of Example 66 was used to prepare the title compound by substituting Intermediate AC for Intermediate I and by substituting *N*-methylmethanamine for morpholine. ^{1}H-NMR (CD_3OD) δ 8.66 (s, 1H), 8.00 (s, 1H), 7.84 (s, 1H), 7.71 (d, J = 8.4 Hz, 2H), 7.63 (d, J = 8.7 Hz, 1H), 7.46 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.9 Hz, 1H), 2.27 (s, 2H), 2.04 (s, 6H), 1.13 (s, 6H); MS $[M+H]^+$ = 456.1; MS $[M+H]^+$ = 589.4; LCMS RT = 2.50.

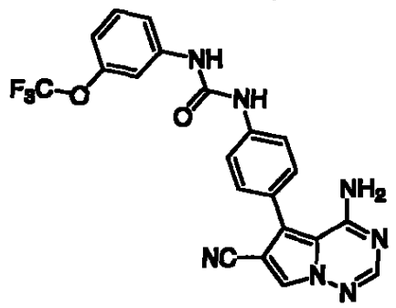
Example 151: Preparation of *N*-[4-(4-amino-6-cyanopyrrolo[2,1-f][1,2,4]triazin-5-yl)phenyl]-N'-[4-fluoro-3-(trifluoromethyl)phenyl]urea



The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting Intermediate P for Intermediate X and by substituting phenyl [4-fluoro-3-(trifluoromethyl)phenyl]carbamate for phenyl (4-*tert*-butylpyridin-2-yl)carbamate. ^{1}H-NMR (CD_3OD) δ 8.18 (s, 1H), 7.94 to 7.89 (m,

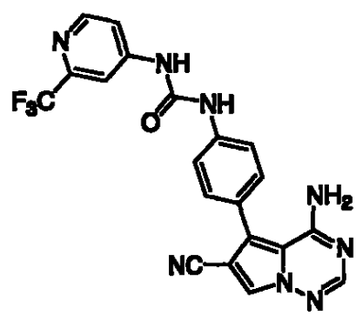
2H), 7.69 to 7.64 (m, 3H), 7.48 (d, J = 8.1 Hz, 2H), 7.26 (t, J = 9.9 Hz, 1H); MS $[M+H]^+$ = 456.1; LCMS RT = 3.09.

Example 152: **Preparation of *N*-[4-(4-amino-6-cyanopyrrolo[2,1-f][1,2,4]triazin-5-yl)phenyl]-N'-[3-(trifluoromethoxy)phenyl]urea**



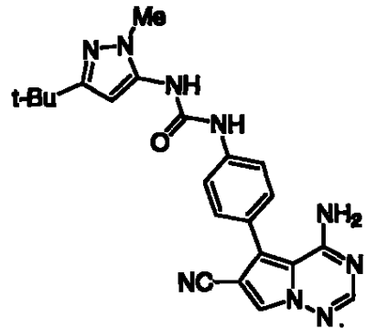
The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting Intermediate P for Intermediate X and by substituting phenyl [3-(trifluoromethoxy)phenyl]carbamate for phenyl (4-*tert*-butylpyridin-2-yl)carbamate. ^{1}H-NMR (CD_3OD) δ 8.17 (s, 1H), 7.90 (s, 1H), 7.68 to 7.61 (m, 3H), 7.48 (d, J = 8.1 Hz, 2H), 7.40 to 7.29 (m, 2H), 6.91 (d, J = 8.0 Hz, 1H); MS $[M+H]^+$ = 454.1; LCMS RT = 3.11.

Example 153: **Preparation of *N*-[4-(4-amino-6-cyanopyrrolo[2,1-f][1,2,4]triazin-5-yl)phenyl]-N'-[2-(trifluoromethyl)pyridin-4-yl]urea**



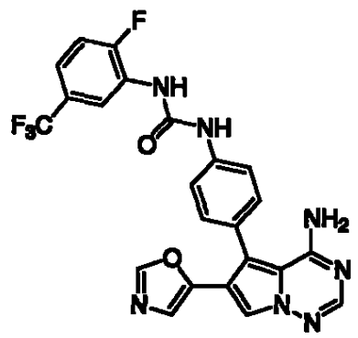
The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting Intermediate P for Intermediate X and by substituting phenyl [2-(trifluoromethyl)pyridin-4-yl]carbamate for phenyl (4-*tert*-butylpyridin-2-yl)carbamate. ^{1}H-NMR (CD_3OD) δ 8.47 (d, J = 6.1 Hz, 1H), 8.18 (s, 1H), 8.05 (d, J = 2.2 Hz, 1H), 7.09 (s, 1H), 7.71 to 7.64 (m, 3H), 7.50 (d, J = 8.1 Hz, 2H); MS $[M+H]^+$ = 439.0; LCMS RT = 2.72.

Example 154: **Preparation of *N*-[4-(4-amino-6-cyanopyrrolo[2,1-f][1,2,4]triazin-5-yl)phenyl]-N'-(3-*tert*-butyl-1-methyl-1*H*-pyrazol-5-yl)urea**



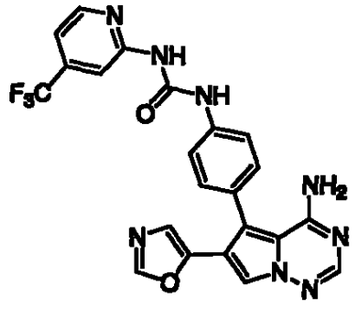
The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting Intermediate P for Intermediate X and by substituting phenyl (3-*tert*-butyl-1-methyl-1*H*-pyrazol-5-yl)carbamate for phenyl (4-*tert*-butylpyridin-2-yl)carbamate. ^{1}H-NMR (CD_3OD) δ 8.18 (s, 1H), 7.90 (s, 1H), 7.65 (d, J = 8.0 Hz, 2H), 7.47 (d, J = 8.0 Hz, 2H), 7.17 (m 1H), 7.11 (m, 1H), 6.13 (s, 1H), 3.71 (s, 3H), 1.28 (s, 9H); MS $[M+H]^+$ = 430.1; LCMS RT = 2.56.

Example 155: **Preparation of *N*-{4-[4-amino-6-(1,3-oxazol-5-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea**



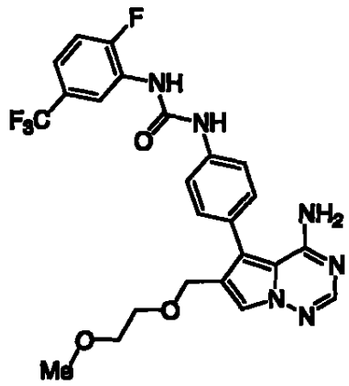
The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting Intermediate AB for Intermediate X and by substituting phenyl [2-fluoro-5-(trifluoromethyl)phenyl]carbamate for phenyl (4-*tert*-butylpyridin-2-yl)carbamate. ^{1}H-NMR (CD_3OD) δ 8.63 (d, J = 6.8 Hz, 1H), 8.13 (s, 1H), 7.98 (s, 1H), 7.83 (s, 1H), 7.69 (d, J = 8.5 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.3 Hz, 2H), 6.49 (s, 1H); MS $[M+H]^+$ = 498.1; LCMS RT = 2.82.

Example 156: Preparation of *N*-{4-[4-amino-6-(1,3-oxazol-5-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-[4-(trifluoromethyl)pyridin-2-yl]urea



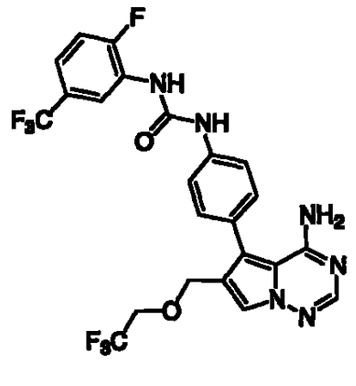
The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting Intermediate AB for Intermediate X and by substituting phenyl [4-(trifluoromethyl)pyridin-2-yl]carbamate for phenyl (4-*tert*-butylpyridin-2-yl)carbamate. ^{1}H-NMR (CD_3OD) δ 8.50 (d, J = 5.3 Hz, 1H), 8.12 (s, 1H), 7.98 (s, 1H), 7.84 (s, 1H), 7.77 (s, 1H), 7.76 (d, J = 8.1 Hz, 2H), 7.45 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 6.3 Hz, 1H), 6.51 (s, 1H); MS $[M+H]^+$ = 481.0; LCMS RT = 2.70.

Example 157: **Preparation of *N*-(4-{4-amino-6-[(2-methoxyethoxy)methyl]pyrrolo[2,1-f][1,2,4]triazin-5-yl}phenyl)-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea**



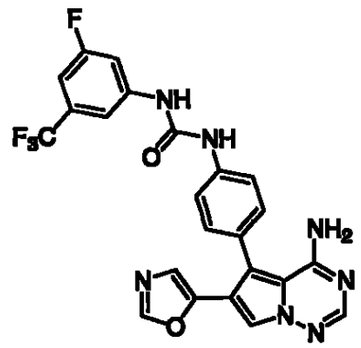
The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting Intermediate Z for Intermediate X and by substituting phenyl [2-fluoro-5-(trifluoromethyl)phenyl]carbamate for phenyl (4-*tert*-butylpyridin-2-yl)carbamate. ^{1}H-NMR (CD_3OD) δ 8.62 (d, J = 8.0 Hz, 1H), 7.79 (s, 1H), 7.71 (s, 1H), 7.62 (d, J = 8.1, 2H), 7.44 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 9.0 Hz, 2H), 4.45 (s, 2H), 3.59 to 3.48(m, 4H), 3.33 (s, 3H); MS $[M+H]^+$ = 519.2; LCMS RT = 3.13.

Example 158: **Preparation of *N*-(4-{4-amino-6-[(2,2,2-trifluoroethoxy)methyl]pyrrolo[2,1-f][1,2,4]triazin-5-yl}phenyl)-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea**



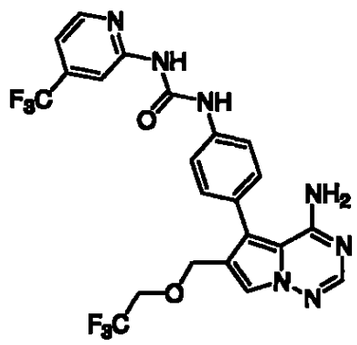
The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting Intermediate AA for Intermediate X and by substituting phenyl [2-fluoro-5-(trifluoromethyl)phenyl]carbamate for phenyl (4-*tert*-butylpyridin-2-yl)carbamate. ^{1}H-NMR (CD_3OD) δ 8.53 (d, J = 6.7 Hz, 1H), 7.70 (s, 1H), 7.63 (s, 1H), 7.52 (d, J = 8.3, 2H), 7.33 (d, J = 8.3 Hz, 2H), 7.24 (d, J = 8.3 Hz, 2H), 4.47 (s, 2H), 4.00 (q, J = 7.9 Hz, 2H); MS $[M+H]^+$ = 543.3; LCMS RT = 3.10.

Example 159: Preparation of *N*-{4-[4-amino-6-(1,3-oxazol-5-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-[3-fluoro-5-(trifluoromethyl)phenyl]urea



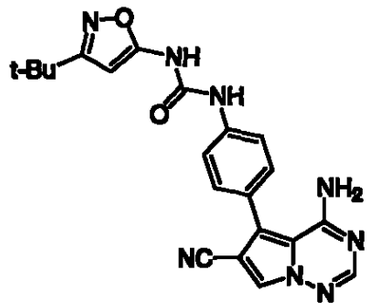
The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting Intermediate AB for Intermediate X and by substituting phenyl [3-fluoro-5-(trifluoromethyl)phenyl]carbamate for phenyl (4-*tert*-butylpyridin-2-yl)carbamate. ^{1}H-NMR (CD_3OD) δ 8.12 (s, 1H), 7.97 (s, 1H), 7.83 (s, 1H), 7.71 to 7.60 (m, 4H), 7.42 (d, J = 8.2 Hz, 2H), 7.05 (d, J = 8.1 Hz, 1H), 6.49 (s, 1H); MS $[M+H]^+$ = 498.2; LCMS RT = 2.90.

Example 160: Preparation of *N*-(4-{4-amino-6-[(2,2,2-trifluoroethoxy)methyl]pyrrolo[2,1-f][1,2,4]triazin-5-yl}phenyl)-N'-[4-(trifluoromethyl)pyridin-2-yl]urea



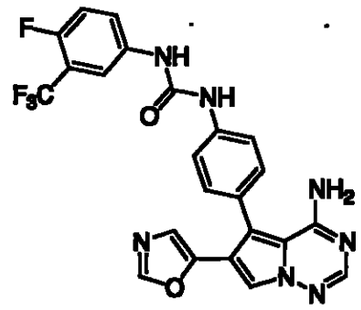
The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting Intermediate AA for Intermediate X and by substituting phenyl [4-(trifluoromethyl)pyridin-2-yl]carbamate for phenyl (4-*tert*-butylpyridin-2-yl)carbamate. ^{1}H-NMR (DMSO-d_6) δ 9.90 (s, 1H), 9.75 (s, 1H), 8.53 (d, J = 4.7 Hz, 1H), 8.05 (s, 1H), 7.85 (s, 1H), 7.82 (s, 1H), 7.62 (d, J = 8.6 Hz, 2H), 7.39 to 7.32 (m, J = 8.0 Hz, 3H), 4.49 (s, 2H), 3.97 (q, J = 9.1 Hz, 2H); MS $[M+H]^+$ = 526.0; LCMS RT = 2.90.

Example 161: **Preparation of *N*-[4-(4-amino-6-cyanopyrrolo[2,1-f][1,2,4]triazin-5-yl)phenyl]-N'-(3-*tert*-butylisoxazol-5-yl)urea**



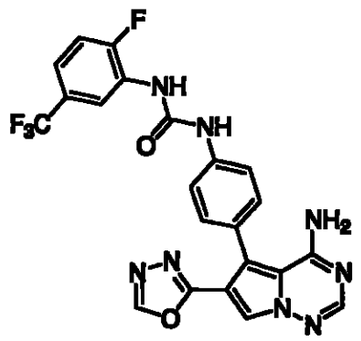
The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting Intermediate P for Intermediate X and by substituting phenyl (3-*tert*-butylisoxazol-5-yl)carbamate for phenyl (4-*tert*-butylpyridin-2-yl)carbamate. ^{1}H-NMR (CD_3OD) δ 8.17 (s, 1H), 7.90 (s, 1H), 7.68 (d, J = 7.8 Hz, 2H), 7.48 (d, J = 7.8 Hz, 2H), 6.13 (s, 1H), 1.31 (s, 9H); MS $[M+H]^+$ = 417.1; LCMS RT = 2.87.

Example 162: **Preparation of *N*-{4-[4-amino-6-(1,3-oxazol-5-yl)pyrrolo[2,1-*f*][1,2,4]triazin-5-yl]phenyl}-N'-[4-fluoro-3-(trifluoromethyl)phenyl]urea**



The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting Intermediate AB for Intermediate X and by substituting phenyl [4-fluoro-3-(trifluoromethyl)phenyl]carbamate for phenyl (4-*tert*-butylpyridin-2-yl)carbamate. ^{1}H-NMR (CD_3OD) δ 8.12 (s, 1H), 7.97 (s, 1H), 7.92 (dd, J = 2.7, 6.2 Hz, 1H), 7.83 (s, 1H), 7.70 to 7.62 (m, 3H), 7.41 (d, J = 8.0 Hz, 2H), 7.28 (t, J = 9.5 Hz, 1H), 6.49 (s, 1H); MS $[M+H]^+$ = 498.2; LCMS RT = 3.14.

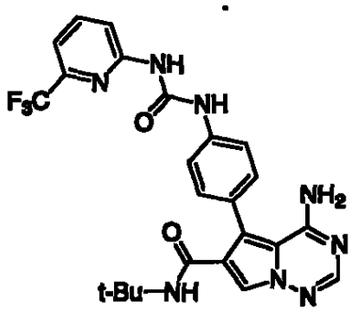
Example 163: **Preparation of *N*-{4-[4-amino-6-(1,3,4-oxadiazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-5-yl]phenyl}-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea**



The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting Intermediate AD for Intermediate X and by substituting phenyl [2-fluoro-5-(trifluoromethyl)phenyl]carbamate for phenyl (4-*tert*-

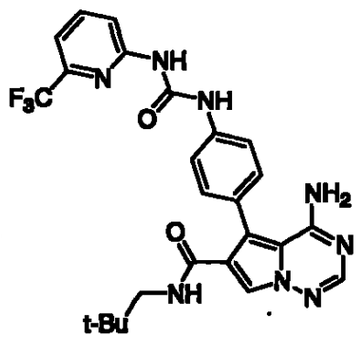
butylpyridin-2-yl)carbamate. ^{1}H-NMR (CD_3OD) δ 8.80 (s, 1H), 8.62 (d, J = 6.7 Hz, 1H), 8.28 (s, 1H), 7.89 (s, 1H), 7.64 (d, J = 8.2 Hz, 2H), 7.45 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 8.9 Hz, 2H); MS $[M+H]^+$ = 499.2; LCMS RT = 2.82.

Example 164: **Preparation of 4-amino-*N*-(*tert*-butyl)-5-{4-[({[6-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide**



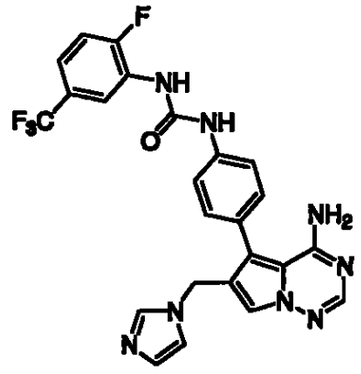
The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting Intermediate L for Intermediate X and by substituting phenyl [6-(trifluoromethyl)pyridin-2-yl]carbamate for phenyl (4-*tert*-butylpyridin-2-yl)carbamate. ^{1}H-NMR (DMSO-d_6) δ 9.88 (s, 1H), 9.73 (s, 1H), 8.05 to 7.99 (m, 1H), 8.04 (d, J = 8 Hz, h H), 7.88 (s, 1H), 7.55 (d, J = 8 Hz, 2H), 7.50 to 7.46 (m, 1H), 7.36 (d, J = 8 Hz, 2H), 6.66 (s, 1H), 5.00 (bs, 1H), 1.16 (s, 9H); MS $[M+H]^+$ = 513.1; LCMS RT = 2.84 min; TLC R_f = 0.64 (3:2 v/v CH_2Cl_2-THF).

Example 165: **Preparation of 4-amino-*N*-(2,2-dimethylpropyl)-5-{4-[({[6-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide**



The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting Intermediate AE for Intermediate X and by substituting phenyl [6-(trifluoromethyl)pyridin-2-yl]carbamate for phenyl (4-*tert*-butylpyridin-2-yl)carbamate. ^{1}H-NMR (DMSO-d_6) δ 9.87 (s, 1H), 9.77 (s, 1H), 8.07 (s, 1H), 8.06 to 7.81 (m, 3 H), 7.89 (s, 1H), 7.54 (d, J = 8 Hz, 2H), 7.55 to 7.50 (m, 1H), 7.36 (d, J = 8 Hz, 2H), 7.28 to 7.20 (m, 1H), 4.95 (bs, 1H), 2.91 (d, J = 6 Hz, 2H), 0.72 (s, 9H); MS $[M+H]^+$ = 527.1; LCMS RT = 2.89 min; TLC R_f = 0.64 (3:2 v/v CH_2Cl_2-THF).

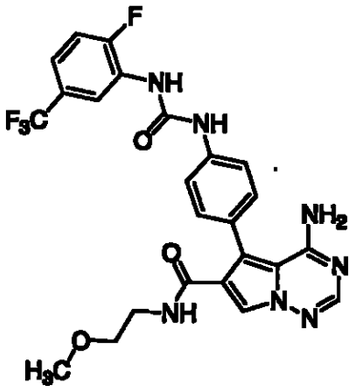
Example 166: **Preparation of 1-[4-(4-Amino-6-imidazol-1-ylmethyl-pyrrolo[2,1-f][1,2,4]triazin-5-yl)-phenyl]-3-(2-fluoro-5-trifluoromethyl-phenyl)-urea**



The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting Intermediate AE for Intermediate X and by substituting phenyl [2-fluoro-5-(trifluoromethyl)phenyl]carbamate for phenyl (4-*tert*-

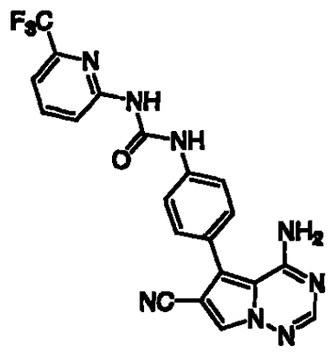
butylpyridin-2-yl)carbamate ^{1}H-NMR (CD_3OD) δ 8.61 (d, J = 7.5 Hz, 1H), 7.80 (s, 1H), 7.72 (s, 1H), 7.61 (d, J = 8.6 Hz, 2H), 7.46 (s, 1H), 7.34 (d, J = 8.6 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 6.93 (d, J = 5.1 Hz, 2H), 5.17 (s, 2H); MS $[M+H]^+$ = 511.3; LCMS RT = 2.63 min.

Example 167: **Preparation of 4-amino-5-{4-[({[2-fluoro-5-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}-*N*-(2-methoxyethyl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carboxamide**



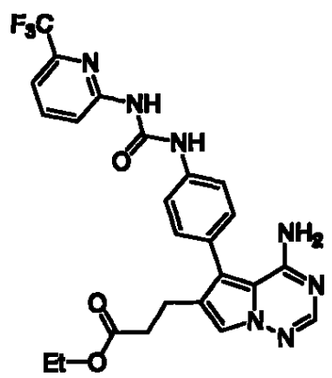
The procedure used for the preparation of Example 69 was used to prepare the title compound by substituting 2-methoxyethanamine for cyclopropanamine. ^{1}H-NMR (CD_3OD) δ 8.62 (d, J = 7.5 Hz, 1H), 8.03 (s, 1H), 7.84 (s, 1H), 7.69 (d, J = 9.0 Hz, 2H), 7.45 (d, J = 9.0, 2H), 7.35 (d, J = 8.8 Hz, 2H), 3.39 to 3.34 (m, 4H), 3.24 (s, 3H); MS $[M+H]^+$ = 532.1; LCMS RT = 3.05 min.

Example 168: Preparation of N-[4-(4-amino-6-cyanopyrrolo[2,1-f][1,2,4]triazin-5-yl)phenyl]-N'-[6-(trifluoromethyl)pyridin-2-yl]urea



The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting Intermediate P for Intermediate X and by substituting phenyl [6-(trifluoromethyl)pyridin-2-yl]carbamate for phenyl (4-tert-butylpyridin-2-yl)carbamate. ^{1}H-NMR (DMSO-d_6) δ 9.89 (s, 1H), 9.75 (s, 1H), 8.51 (s, 1H), 8.03 to 7.99 (m, 3H), 7.63 (d, J = 8.4, 2H), 7.51 to 7.44 (m, 3H); MS $[M+H]^+$ = 439; LCMS RT = 2.62 min.

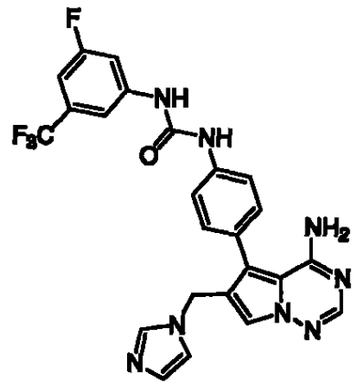
Example 169: Preparation of ethyl 3-(4-amino-5-[4-[({[6-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazin-6-yl)propanoate



The procedure used for the preparation of Intermediate I was used to prepare the title compound by substituting phenyl [6-(trifluoromethyl)pyridin-2-yl]carbamate for phenyl [2-fluoro-5-(trifluoromethyl)phenyl]carbamate. ^{1}H-NMR (DMSO-d_6) δ 9.88 (s1H), 9.73 (s, 1H), 8.05 to 7.98 (m, 3H), 7.79 (s, 1H), 7.61 to 7.57 (m, 3H),

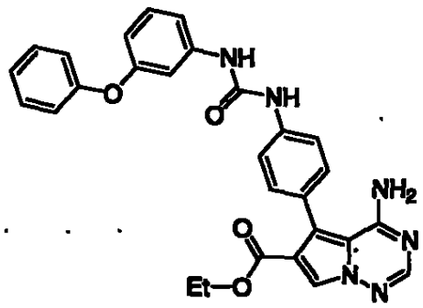
7.51 to 7.49 (m, 1H), 7.33 (d, J = 8.7, 2H), 4.03 to 3.97 (m, 2H), 2.74 to 2.70 (m, 2H), 2.55 to 2.51 (m, 2H), 1.15 to 1.11 (m, 3H); MS $[M+H]^+$ = 514; LCMS RT = 2.65 min.

Example 170: Preparation of N-{4-[4-amino-6-(1H-imidazol-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-[3-fluoro-5-(trifluoromethyl)phenyl]urea



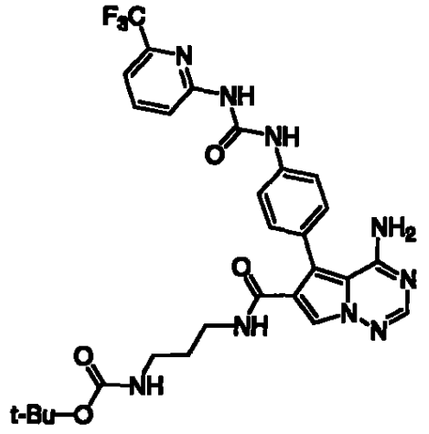
The procedure used for the preparation of Example 166 was used to prepare the title compound by substituting phenyl [3-fluoro-5-(trifluoromethyl)phenyl]carbamate for phenyl [2-fluoro-5-(trifluoromethyl)phenyl]carbamate. ^{1}H-NMR (CD_3OD) δ 8.55 to 8.58 (m, 1H), 7.98 (s, 1H), 7.97 (s, 1H), 7.65 to 7.80 (m, 2H), 7.63 (d, J = 9 Hz, 2H), 7.41 to 7.43 (m, 1H), 7.2 to 7.4 (m, 1H), 7.25 (d, J = 9 Hz, 2H), 7.00 tp 7.1 (m, 1H), 5.46 (s, 2H), 4.89 (bs, 4H); MS $[M+H]^+$ = 511.0; LCMS RT = 2.29 min.

Example 171: Preparation of ethyl 4-amino-5-[4-({[(3-phenoxyphenyl)amino]carbonyl}amino)phenyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate



The procedure used for the preparation of Example 1 was used to prepare the title compound by substituting 3-phenoxyphenyl isocyanate for 1-fluoro-2-isocyanato-4-(trifluoromethyl)benzene. ^{1}H-NMR (DMSO-d_6) δ 8.60 (s, 1H), 8.82 (s, 1H), 8.11 (s, 1H), 7.91 (s, 1H), 7.50 to 7.48 (m, 2H), 7.41 to 7.37 (m, 2H), 7.29 to 7.25 (m, 4H), 7.15 to 7.11 (m, 2H), 7.04 to 7.01 (m, 2H), 4.10 to 4.04 (m, 2H), 1.12 to 1.08 (m, 3H); MS $[M+H]^+$ = 509.1; LCMS RT = 3.48 min.

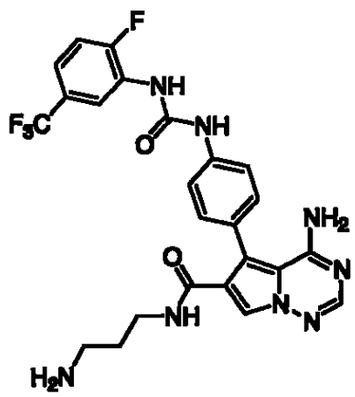
Example 172: Preparation of tert-butyl (3-{[(4-amino-5-{4-[({[6-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazin-6-yl)carbonyl]amino}propyl)carbamate



The procedure used for the preparation of Example 55 was used to prepare the title compound by substituting tert-butyl (3-aminopropyl)carbamate for N,N-dimethylpropane-1,3-diamine and phenyl [6-(trifluoromethyl)pyridin-2-yl]carbamate for phenyl [2-fluoro-5-(trifluoromethyl)phenyl]carbamate. ^{1}H-NMR (DMSO-d_6)

δ 9.88 (s, 1H), 9.72 (s, 1H), 8.06 to 7.97 (m, 3H), 7.89 (s, 1H), 7.78 to 7.75 (m, 1H), 7.53 to 7.48 (m, 3H), 7.33 to 7.31 (m, 2H), 6.75 to 6.72 (m, 1H), 3.11 to 3.06 (m, 2H), 2.91 to 2.86 (m, 2H), 1.52 to 1.48 (m, 2H), 1.35 (s, 9H); MS $[M+H]^+$ = 614.2; LCMS RT = 2.55 min.

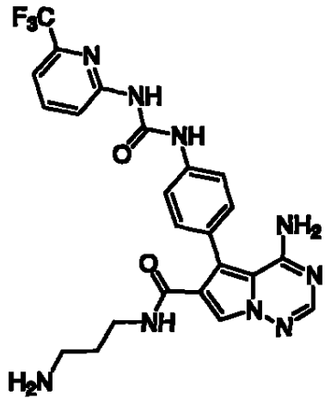
Example 173: Preparation of 4-amino-N-(3-aminopropyl)-5-{4-[({[2-fluoro-5-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



To a solution of DMF (5 mL) was added Intermediate G (100 mg, 0.21 mmol) and BOP (93 mg, 0.21 mmol) followed by NMM (23 μL, 0.21 mmol), and tert-butyl (3-aminopropyl)carbamate (37 mg, 0.21 mmol). The reaction was allowed to stir under N_2 at rt for 2h. The solution was then diluted with EtOAc (20 mL) and aq $NaHCO_3$ (20 mL), transferred to separatory funnel, and separated. The aqueous layer was back extracted with EtOAc (2 x 20 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude material was purified by flash chromatography (9:1 v/v CH_2Cl_2/MeOH). The isolated product, tert-butyl (3-{[(4-amino-5-{4-[({[2-fluoro-5-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazin-6-yl)carbonyl]amino}propyl)carbamate, was treated with CH_2Cl_2 (5 mL) and TFA (5 mL) and was left stirring under N_2 at rt for 17h. The reaction mixture was then concentrated in vacuo and purified by preparative HPLC (10-90% ACN/H_2O with 0.1% TFA). The resulting purified fractions were diluted in EtOAc (20 mL) and aq $NaHCO_3$ (20 mL) and separated. The organic layer was washed with H_2O, isolated,

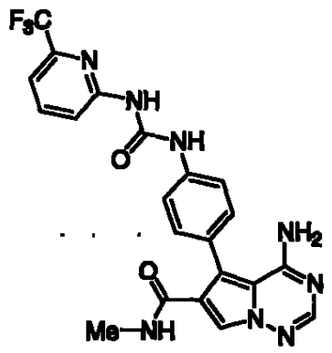
dried (MgSO4), filtered, and concentrated to dryness producing 29 mg of the above compound as a white solid (0.055 mmol, yield 26%). ^{1}H-NMR (DMSO-d_6) δ 9.59 to 9.55 (br s, 1H), 8.58 to 8.56 (d, J = 9.7 Hz, 1H), 8.05 (s, 1H), 7.89 (s, 1H), 7.76 to 7.74 (m, 1H), 7.57 to 7.55 (d, J = 8.5 Hz, 2H), 7.50 to 7.45 (m, 1H), 7.39 to 7.35 (m, 1H), 7.32 to 7.29 (d, J = 8.6 Hz, 2H), 3.19 to 3.14 (m, 2H), 2.57 to 2.54 (m, 2H), 1.57 to 1.50 (m, 2H); MS $[M+H]^+$ = 531.3; LCMS RT = 2.52 min.

Example 174: Preparation of 4-amino-N-(3-aminopropyl)-5-{4-[({[6-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



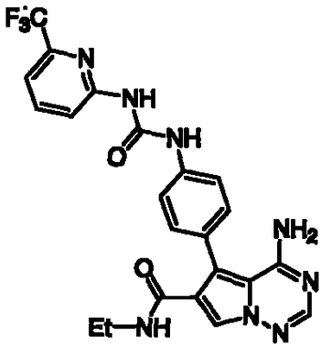
The procedure used for the preparation of Example 173 was used to prepare the title compound by substituting Example 250 for Intermediate G. ^{1}H-NMR (CD_3OD) δ 7.99 (s, 1H), 7.98 to 7.94 (m, 1H), 7.84 (s, 1H), 7.68 to 7.65 (m, 2H), 7.52 (d, J = 8.5, 1H), 7.47 to 7.43 (m, 3H), 3.35 (m, 2H), 2.83 to 2.80 (m, 2H), 1.82 to 1.75 (m, 2H); MS $[M+H]^+$ = 514.1; LCMS RT = 1.85 min.

Example 175: Preparation of 4-amino-N-methyl-5-{4-[({[6-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



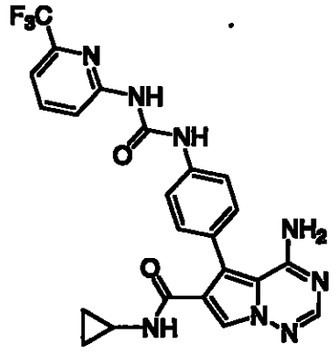
A solution of Intermediate AH (40mg, 1eq) and HATU (50mg, 1.5eq) in 1ml anhydrous DMF were stirred at RT for 0.5 h. Then the above mixture was added into a 0.2ml anhydrous DMF solution of the amine (1.5eq). Triethylamine (26.5mg, 3eq) was added into the reaction and the reaction was stirred at the RT for overnight. The reaction mixture was purified without work-up on Prep LC-MS using gradient Water and Acetonitrile with 0.1% TFA as modifier. MS $[M+H]^+$ = 471.14; LCMS RT = 2.97 min.

Example 176: Preparation of 4-amino-N-ethyl-5-{4-[({[6-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



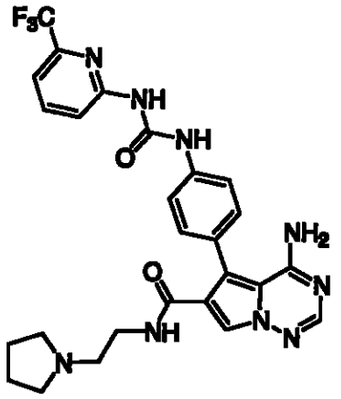
The procedure used for the preparation of Example 175 was used to prepare the title compound by substituting ethylamine for methylamine. MS $[M+H]^+$ = 485.16; LCMS RT = 2.91 min.

Example 177: Preparation of 4-amino-N-cyclopropyl-5-{4-[({[6-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



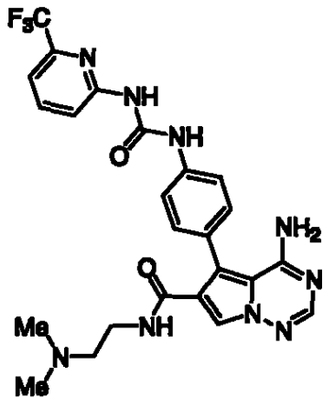
The procedure used for the preparation of Example 175 was used to prepare the title compound by substituting cyclopropylamine for methylamine. MS $[M+H]^+$ = 497.16; LCMS RT = 2.94 min.

Example 178: Preparation of 4-amino-N-(2-pyrrolidin-1-ylethyl)-5-{4-[({[6-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



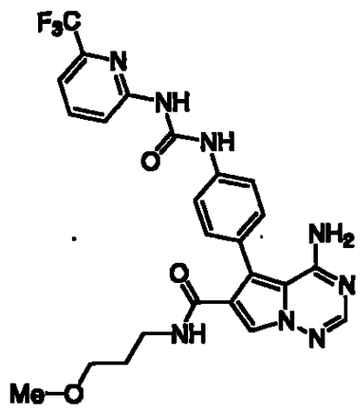
The procedure used for the preparation of Example 175 was used to prepare the title compound by substituting N-(2-aminoethyl)- pyrrolidine for methylamine. MS $[M+H]^+ = 554.22$; LCMS RT = 2.6 min.

Example 179: Preparation of 4-amino-N-[2-(dimethylamino)ethyl]-5-{4-[({[6-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



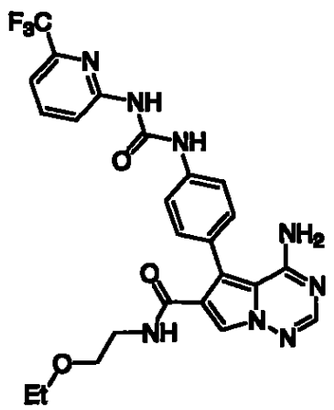
The procedure used for the preparation of Example 175 was used to prepare the title compound by substituting N,N-dimethylethylenediamine for methylamine. MS $[M+H]^+ = 528.2$; LCMS RT = 2.6 min.

Example 180: Preparation of 4-amino-N-(3-methoxypropyl)-5-{4-[({[6-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



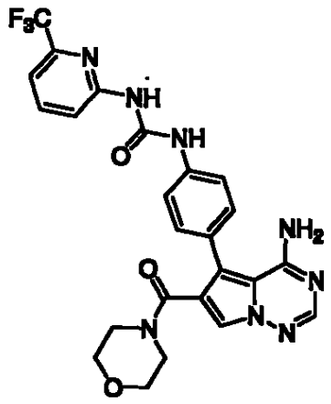
The procedure used for the preparation of Example 175 was used to prepare the title compound by substituting 3-methoxypropylamine for methylamine. MS $[M+H]^+ = 528.18$; LCMS RT = 2.9 min.

Example 181: Preparation of 4-amino-N-(2-ethoxyethyl)-5-{4-[({[6-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



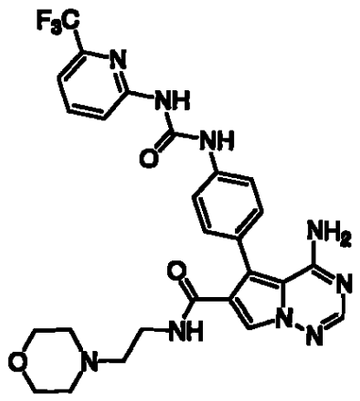
The procedure used for the preparation of Example 175 was used to prepare the title compound by substituting 2-ethoxyethylamine for methylamine. MS $[M+H]^+ = 529.18$; LCMS RT = 2.96 min.

Example 182: Preparation of N-[4-[4-amino-6-(morpholin-4-ylcarbonyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-[6-(trifluoromethyl)pyridin-2-yl]urea



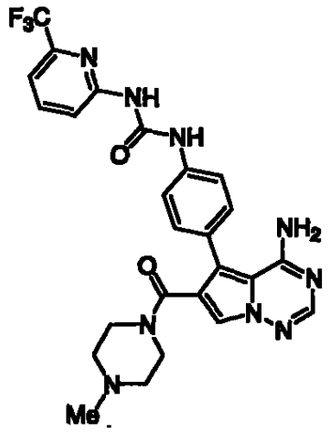
The procedure used for the preparation of Example 175 was used to prepare the title compound by substituting morpholine for methylamine. MS $[M+H]^+$ = 527.17; LCMS RT = 2.84 min.

Example 183: Preparation of 4-amino-N-(2-morpholin-4-ylethyl)-5-{4-[({[6-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



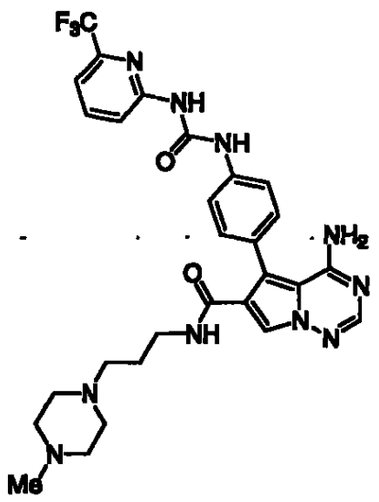
The procedure used for the preparation of Example 175 was used to prepare the title compound by substituting 4-(2-aminoethyl)morpholine for methylamine. MS $[M+H]^+$ = 570.21; LCMS RT = 2.58 min.

Example 184: Preparation of N-(4-{4-amino-6-[(4-methylpiperazin-1-yl)carbonyl]pyrrolo[2,1-f][1,2,4]triazin-5-yl}phenyl)-N'-[6-(trifluoromethyl)pyridin-2-yl]urea



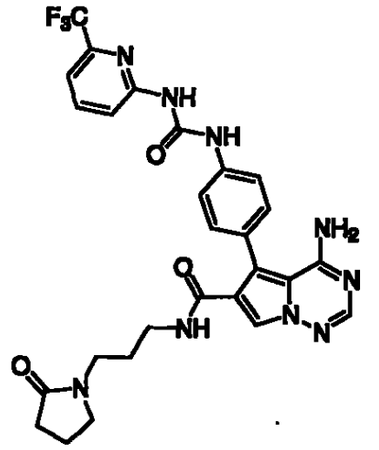
The procedure used for the preparation of Example 175 was used to prepare the title compound by substituting 1-methylpiperazine for methylamine. MS $[M+H]^+$ = 540.2; LCMS RT = 2.55 min.

Example 185: Preparation of 4-amino-N-[3-(4-methylpiperazin-1-yl)propyl]-5-{4-[({[6-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



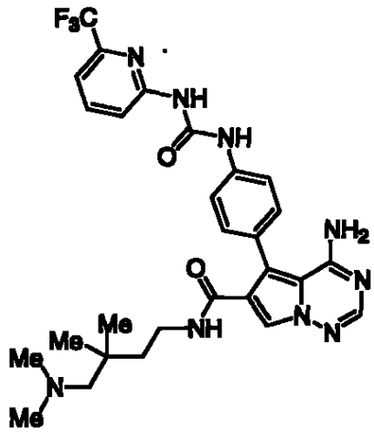
The procedure used for the preparation of Example 175 was used to prepare the title compound by substituting 1-(3-aminopropyl)-4- methylpiperazine for methylamine. MS $[M+H]^+$ = 597.26; LCMS RT = 2.5 min.

Example 186: Preparation of 4-amino-N-[3-(2-oxopyrrolidin-1-yl)propyl]-5-{4-[({[6-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



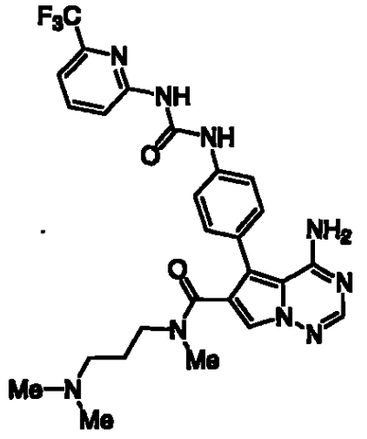
The procedure used for the preparation of Example 175 was used to prepare the title compound by substituting 1-(3-aminopropyl)-2- pyrrolidinone for methylamine. MS $[M+H]^+$ = 582.21; LCMS RT = 2.81 min.

Example 187: Preparation of 4-amino-N-[4-(dimethylamino)-3,3-dimethylbutyl]-5-{4-[({[6-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



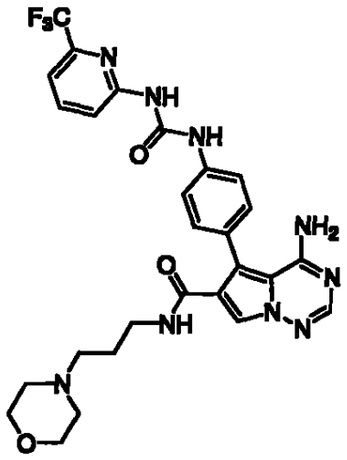
The procedure used for the preparation of Example 175 was used to prepare the title compound by substituting 2,2,N*1*,N*1*-tetramethyl-butane-1,4-diamine for methylamine. MS $[M+H]^+ = 570.25$; LCMS RT = 2.65 min.

Example 188: Preparation of 4-amino-N-[3-(dimethylamino)propyl]-N-methyl-5-{4-[({[6-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



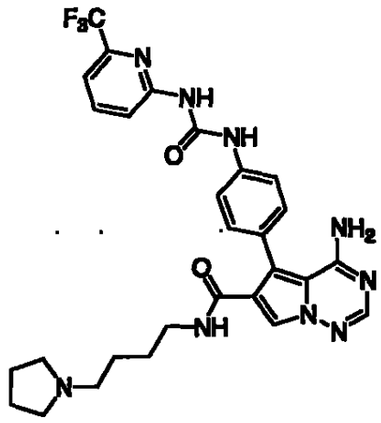
The procedure used for the preparation of Example 175 was used to prepare the title compound by substituting N,N,N'-trimethyl-1,3- propanediamine for methylamine. MS $[M+H]^+ \approx 556.23$; LCMS RT = 2.57 min.

Example 189: Preparation of 4-amino-N-(3-morpholin-4-ylpropyl)-5-{4-[({[6-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



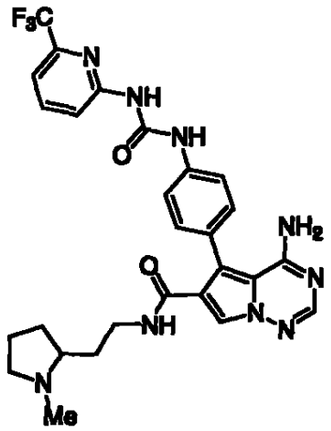
The procedure used for the preparation of Example 175 was used to prepare the title compound by substituting 4-(3- aminopropyl) morpholine for methylamine. MS $[M+H]^+ \approx 584.23$; LCMS RT = 2.6 min.

Example 190: Preparation of 4-amino-N-(4-pyrrolidin-1-ylbutyl)-5-{4-[({[6-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



The procedure used for the preparation of Example 175 was used to prepare the title compound by substituting 4-(1- pyrrolidino) butylamine for methylamine. MS $[M+H]^+ = 582.25$; LCMS RT = 2.6 min.

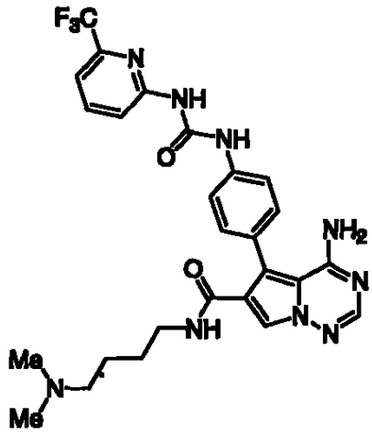
Example 191: Preparation of 4-amino-N-[2-(1-methylpyrrolidin-2-yl)ethyl]-5-{4-[({[6-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



The procedure used for the preparation of Example 175 was used to prepare the title compound by substituting 2-(2-aminoethyl)-1- methylpyrrolidine for methylamine. MS $[M+H]^+ = 568.23$; LCMS RT = 2.6 min.

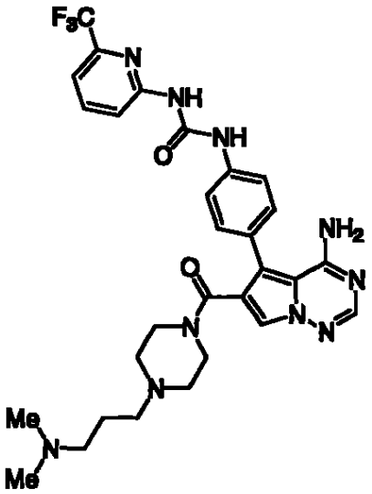
Example 192: Preparation of 4-amino-N-[4-(dimethylamino)butyl]-5-{4-[({[6-(trifluoromethyl)pyridin-2-

yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



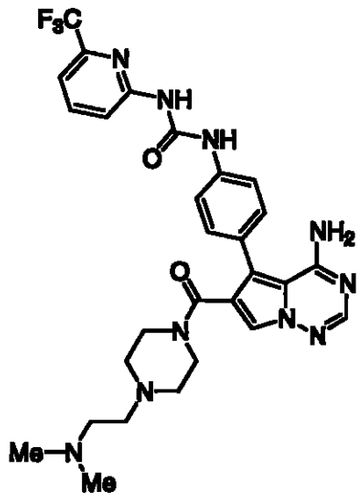
The procedure used for the preparation of Example 175 was used to prepare the title compound by substituting 4-dimethylaminobutylamine for methylamine. MS $[M+H]^+ = 556.23$; LCMS RT = 2.6 min.

Example 193: Preparation of N-{4-[4-amino-6-({4-[3-(dimethylamino)propyl]piperazin-1-yl}carbonyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-[6-(trifluoromethyl)pyridin-2-yl]urea



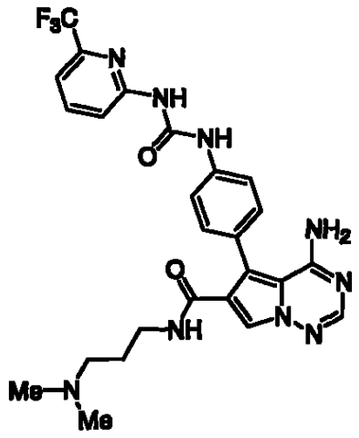
The procedure used for the preparation of Example 175 was used to prepare the title compound by substituting 1-(3-dimethylaminopropyl)- piperazine for methylamine. MS $[M+H]^+ = 611.27$; LCMS RT = 2.45 min.

Example 194: Preparation of N-{4-[4-amino-6-({4-[2-(dimethylamino)ethyl]piperazin-1-yl}carbonyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-[6-(trifluoromethyl)pyridin-2-yl]urea



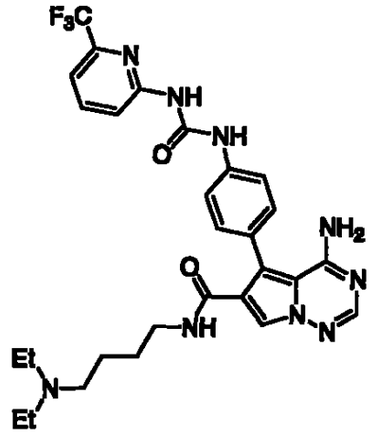
The procedure used for the preparation of Example 175 was used to prepare the title compound by substituting 1-(2-dimethylaminoethyl)- piperazine for methylamine. MS $[M+H]^+ = 597.26$; LCMS RT = 2.52 min.

Example 195: Preparation of 4-amino-N-[3-(dimethylamino)propyl]-5-{4-[({[6-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



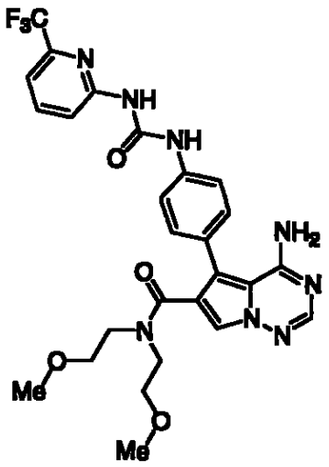
The procedure used for the preparation of Example 175 was used to prepare the title compound by substituting 3- (dimethylamino)propylamine for methylamine. MS $[M+H]^+ = 542.22$; LCMS RT = 2.6 min.

Example 196: Preparation of 4-amino-N-[4-(diethylamino)butyl]-5-{4-[({[6-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



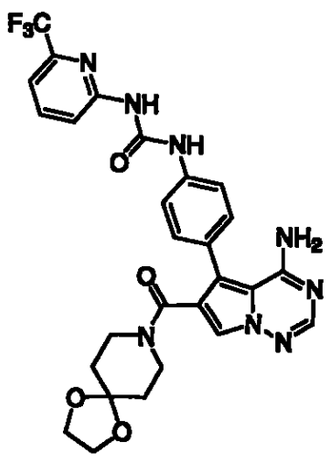
The procedure used for the preparation of Example 175 was used to prepare the title compound by substituting 4-diethylaminobutylamine for methylamine. MS $[M+H]^+ = 598.28$; LCMS RT = 2.67 min.

Example 197: Preparation of 4-amino-N,N-bis(2-methoxyethyl)-5-{4-[({[6-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



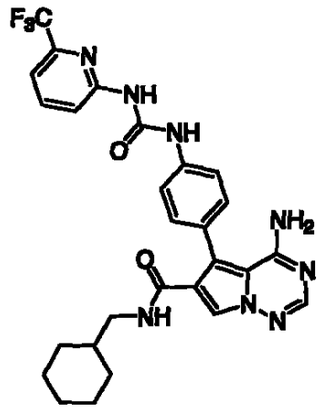
The procedure used for the preparation of Example 175 was used to prepare the title compound by substituting bis(2-methoxyethyl)amine for methylamine. MS $[M+H]^+ = 573.21$; LCMS RT = 2.93 min.

Example 198: Preparation of N-{4-[4-amino-6-(1,4-dioxa-8-azaspiro[4.5]dec-8-ylcarbonyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-[6-(trifluoromethyl)pyridin-2-yl]urea



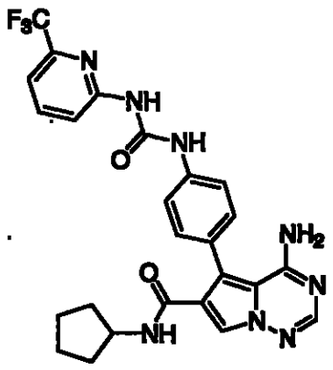
The procedure used for the preparation of Example 175 was used to prepare the title compound by substituting 1,4-dioxa-8- azaspiro[4.5]decane for methylamine. MS $[M+H]^+ = 583.2$; LCMS RT = 2.93 min.

Example 199: Preparation of 4-amino-N-(cyclohexylmethyl)-5-{4-[({[6-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



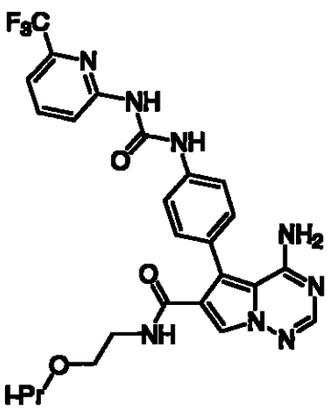
The procedure used for the preparation of Example 175 was used to prepare the title compound by substituting cyclohexanemethylamine for methylamine. MS $[M+H]^+ = 553.22$; LCMS RT = 3.31 min.

Example 200: Preparation of 4-amino-N-cyclopentyl-5-{4-[({[6-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



The procedure used for the preparation of Example 175 was used to prepare the title compound by substituting cyclopentylamine for methylamine. MS $[M+H]^+$ = 525.19; LCMS RT = 3.1 min.

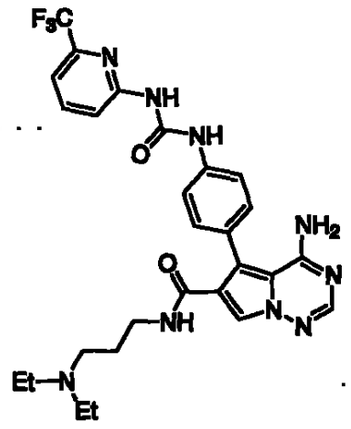
Example 201: Preparation of 4-amino-N-(2-isopropoxyethyl)-5-{4-[({[6-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



The procedure used for the preparation of Example 175 was used to prepare the title compound by substituting 2-aminoethyl isopropyl ether for methylamine. MS $[M+H]^+$ = 543.2; LCMS RT = 3.05 min.

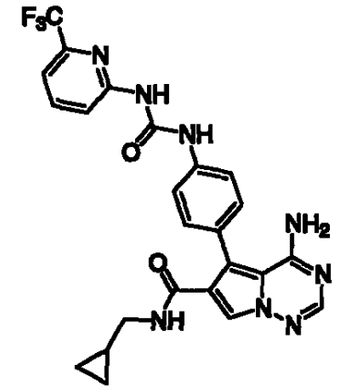
Example 202: Preparation of 4-amino-N-[3-(diethylamino)propyl]-5-{4-[({[6-(trifluoromethyl)pyridin-2-

yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



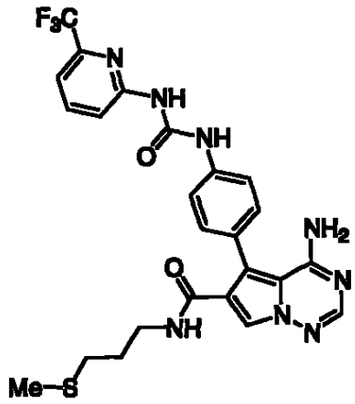
The procedure used for the preparation of Example 175 was used to prepare the title compound by substituting N,N-diethyl-1,3- propanediamine for methylamine. MS $[M+H]^+ = 570.25$; LCMS RT = 2.62 min.

Example 203: Preparation of 4-amino-N-(cyclopropylmethyl)-5-{4-[({[6-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



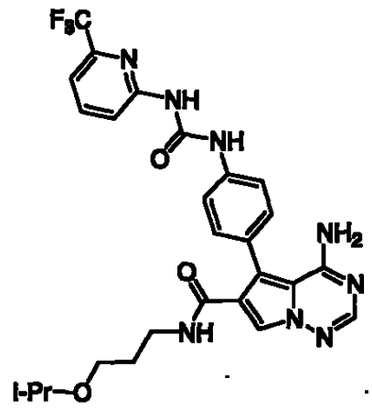
The procedure used for the preparation of Example 175 was used to prepare the title compound by substituting cyclopropanemethylamine for methylamine. MS $[M+H]^+ = 511.17$; LCMS RT = 3.04 min.

Example 204: Preparation of 4-amino-N-[3-(methylthio)propyl]-5-{4-[({[6-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



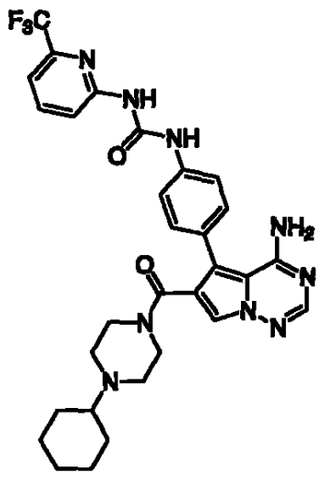
The procedure used for the preparation of Example 175 was used to prepare the title compound by substituting 3-(methylthio)propylamine for methylamine. MS $[M+H]^+ = 545.16$; LCMS RT = 3.06 min.

Example 205: Preparation of 4-amino-N-(3-isopropoxypropyl)-5-{4-[({[6-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



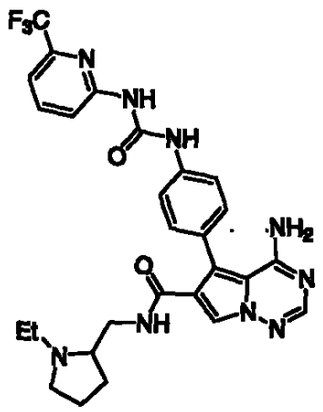
The procedure used for the preparation of Example 175 was used to prepare the title compound by substituting 3-isopropoxypropylamine for methylamine. MS $[M+H]^+ = 557.22$; LCMS RT = 3.05 min.

Example 206: Preparation of N-(4-{4-amino-6-[(4-cyclohexylpiperazin-1-yl)carbonyl]pyrrolo[2,1-f][1,2,4]triazin-5-yl}phenyl)-N'-[6-(trifluoromethyl)pyridin-2-yl]urea



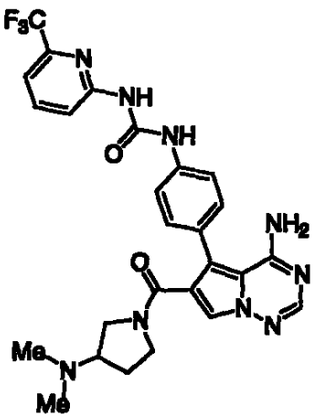
The procedure used for the preparation of Example 175 was used to prepare the title compound by substituting 1-cyclohexylpiperazine for methylamine. MS $[M+H]^+ = 608.26$; LCMS RT = 2.63 min.

Example 207: Preparation of 4-amino-N-[(1-ethylpyrrolidin-2-yl)methyl]-5-{4-[({[6-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



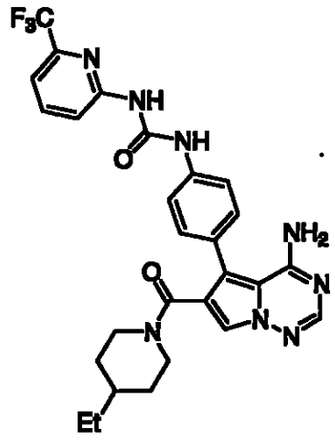
The procedure used for the preparation of Example 175 was used to prepare the title compound by substituting 2-(aminomethyl)-1- ethylpyrrolidine for methylamine. MS $[M+H]^+ = 568.23$; LCMS RT = 2.64 min.

Example 208: Preparation of N-[4-(4-amino-6-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}pyrrolo[2,1-f][1,2,4]triazin-5-yl)phenyl]-N'-[6-(trifluoromethyl)pyridin-2-yl]urea



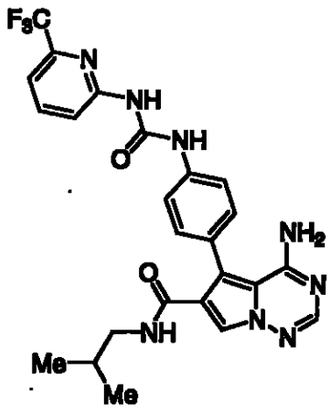
The procedure used for the preparation of Example 175 was used to prepare the title compound by substituting 3- (dimethylamino)pyrrolidine for methylamine. MS $[M+H]^+ = 554.22$; LCMS RT = 2.54 min.

Example 209: Preparation of N-(4-{4-amino-6-[(4-ethylpiperidin-1-yl)carbonyl]pyrrolo[2,1-f][1,2,4]triazin-5-yl}phenyl)-N'-[6-(trifluoromethyl)pyridin-2-yl]urea



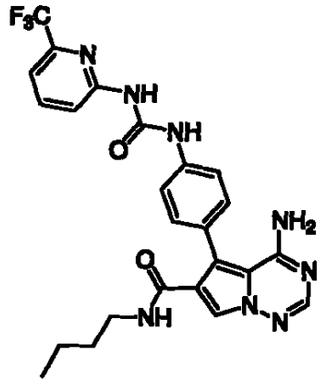
The procedure used for the preparation of Example 175 was used to prepare the title compound by substituting 4-ethylpiperidine for methylamine. MS $[M+H]^+$ = 553.22; LCMS RT = 3.25 min.

Example 210: Preparation of 4-amino-N-isobutyl-5-{4-[({[6-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



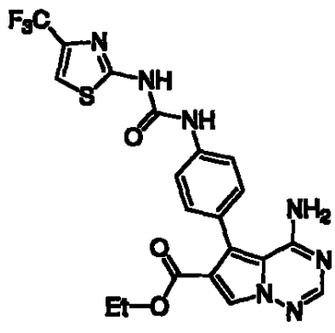
The procedure used for the preparation of Example 175 was used to prepare the title compound by substituting isobutylamine for methylamine. MS $[M+H]^+$ = 513.19; LCMS RT = 3.11 min.

Example 211: Preparation of 4-amino-N-butyl-5-{4-[({[6-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



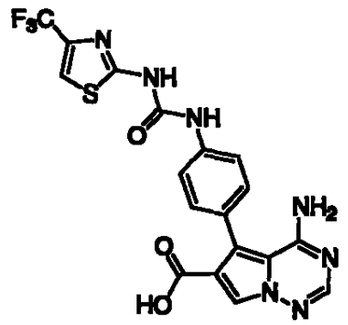
The procedure used for the preparation of Example 175 was used to prepare the title compound by substituting N-butylamine for methylamine. MS $[M+H]^+$ = 513.19; LCMS RT = 3.14 min.

Example 212: Preparation of ethyl 4-amino-5-{4-[({[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate



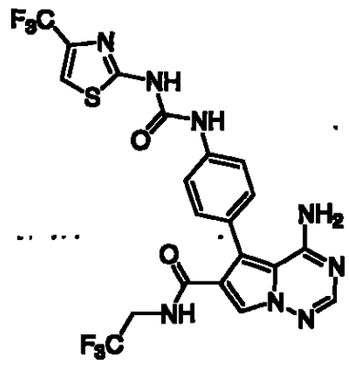
The procedure used for the preparation of Example 24 was used to prepare the title compound by substituting 4-(trifluoromethyl)-1,3-thiazol-2-amine for 2-isopropylaniline. ^{1}H-NMR (DMSO-d_6) δ 11.0 (s, 1H), 9.15 (s, 1H), 8.13 (s, 1H), 7.93 (s, 1H), 7.87 (s, 1H), 7.57 to 7.55 (m, 2H), 7.35 to 3.33 (m, 2H), 1.12 to 1.09 (m, 3H); MS $[M+H]^+$ = 492; LCMS RT = 2.73 min.

Example 213: Preparation of ethyl 4-amino-5-{4-[({[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid



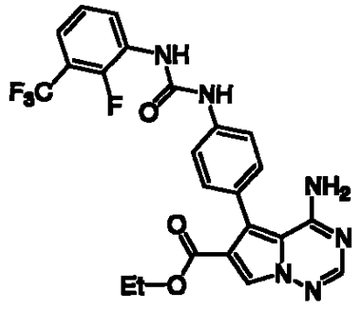
The procedure used for Step 2 in the preparation of Intermediate J was used to prepare the title compound by substituting phenyl [4-(trifluoromethyl)-1,3-thiazol-2-yl]carbamate for phenyl [2-chloro-5-(trifluoromethyl)phenyl]carbamate. ^{1}H-NMR (DMSO-d_6) δ 12.3 to 12.2 (br s,1H), 11.2 to 11.1 (br s, 1H), 9.41 to 9.18 (br s, 1H), 8.30 (s, 1H), 8.29 to 8.1 (br s, 1H), 7.90 (s,1H), 7.82 (s, 1H), 7.65 to 7.58 (m, 2H), 7.55 to 7.30 (m, 2H), 5.27 to 4.71 (br s, 1H); MS $[M+H]^+$ = 464; LCMS RT = 2.28 min.

Example 214: Preparation of 4-amino-N-(2,2,2-trifluoroethyl)-5-{4-[({[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



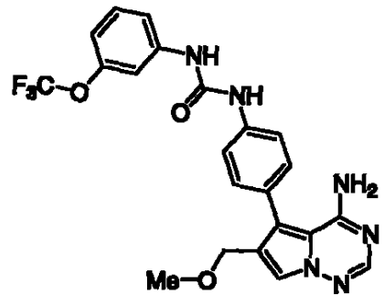
The procedure used for the preparation of Example 69 was used to prepare the title compound by substituting Example 213 for Intermediate G and substituting 2,2,2-trifluoroethanamine for cyclopropanamine. ^{1}H-NMR (DMSO-d_6) δ 11.0 (s, 1H), 9.13 (s, 1H), 8.55 to 8.52 (m, 1H), 8.19 (s, 1H), 7.91 (s, 1H), 7.85 (s, 1H), 7.55 to 7.52 (m, 2H), 7.32 to 7.30 (m, 2H), 3.97 to 3.93 (m, 2H); MS $[M+H]^+$ = 544.9; LCMS RT = 2.52 min.

Example 215: Preparation of ethyl 4-amino-5-{4-[({[2-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate



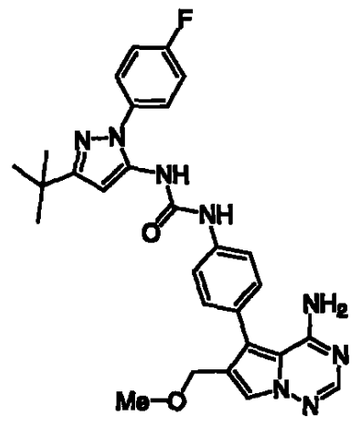
The procedure used for the preparation of Example 24 was used to prepare the title compound by substituting 2-fluoro-3-(trifluoromethyl)phenylamine for 2-isopropylaniline. ^{1}H-NMR (DMSO-d_6) δ 9.33 (s, 1H), 8.92 (s, 1H), 8.52 to 8.45 (m, 1H), 8.16 (s, 1H), 8.10 (bs, 1H), 7.96 (s, 1H), 7.57 (d, J = 9.0 Hz, 2H), 7.40 to 7.34 (m, 4H), 5.14 (bs, 1H), 4.10(q, J = 8.0 Hz, 2H), 1.12 (q, J = 7.8 Hz, 3H); MS $[M+H]^+$ = 503.2; LCMS RT = 3.14 min.

Example 216: Preparation of ethyl N-{4-[4-amino-6-(methoxymethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-[3-(trifluoromethoxy)phenyl]urea



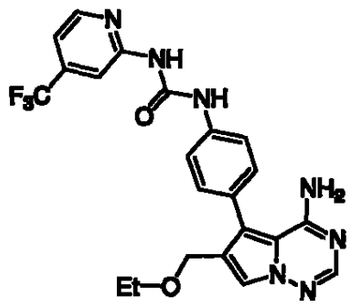
The procedure used for the preparation of Example 24 was used to prepare the title compound by substituting 3-methoxyaniline for 2-isopropylaniline and Intermediate U for intermediate B. ^{1}H-NMR (DMSO-d_6) δ 7.81 (s, 1H), 7.73 (s, 1H), 7.65 to 7.71 (m, 2H), 7.61 (d, J = 9 Hz, 2H), 7.40 ((d, J = 9Hz, 2H), 7.37 (m, 1H), 7.33 to 7.36 (m, 2H), 6.90 to 6.95 (m, 1H), 4.36 (s, 2H), 3.30 (s, 3H); MS $[M+H]^+$ = 473.1; LCMS RT = 2.69 min.

Example 217: Preparation of N-{4-[4-amino-6-(methoxymethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-[3-tert-butyl-1-(4-fluorophenyl)-1H-pyrazol-5-yl]urea



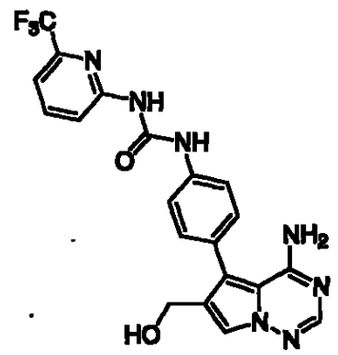
The procedure used for the preparation of Example 24 was used to prepare the title compound by substituting 3-tert-butyl-1-(4-fluorophenyl)-1H-pyrazol-5-amine for 2-isopropylaniline. ^{1}H-NMR (CD_3OD) δ 7.78 (s, 1H), 7.68 (s, 1H), 7.52 to 7.58 (m, 2H), 7.52 (d, J = 9 Hz, 2H) 7.37 (d, J = 9Hz, 2H), 7.28 to 7.31 (m, 2H), 6.44 (s, 1H), 4.34 (s, 2H), 3.30 (s, 3H), 1.26 (s, 9H); MS $[M+H]^+$ = 529.2; LCMS RT = 3.04 min.

Example 218: Preparation of N-{4-[4-amino-6-(ethoxymethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-[4-(trifluoromethyl)pyridin-2-yl]urea



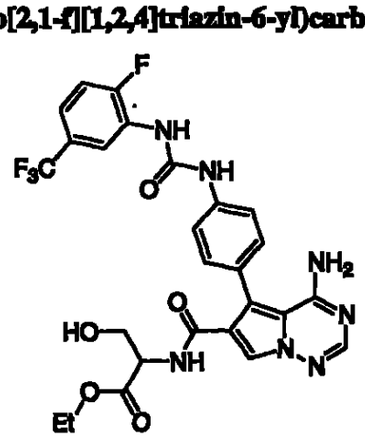
The procedure used for the preparation of Example 246 was used to prepare the title compound by substituting phenyl [4-(trifluoromethyl)pyridin-2-yl]carbamate for 1-fluoro-2-isocyanato-4-(trifluoromethyl)benzene. ^{1}H-NMR (DMSO-d_6) δ 9.99 (s, 1H), 9.82 (s, 1H), 8.56 (d, J = 5 Hz, 1H), 8.10 (s, 1H), 7.87 (s, 1H), 7.77 (s, 1H), 7.65 (d, J = 9 Hz, 2H), 7.62 to 7.65 (m, 1H), 7.30 to 7.42 (m, 4 H), 4.32 (s, 2H), 3.40 (q, J = 7 Hz, 2H), 1.09 (t, J = 7 Hz, 3H); MS $[M+H]^+$ = 472.1; LCMS RT = 2.73 min.

Example 219: Preparation of N-{4-[4-amino-6-(hydroxymethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-[6-(trifluoromethyl)pyridin-2-yl]urea



The procedure used in Step 1 of the preparation of Intermediate F was used to prepare the title compound by substituting Example 144 for Intermediate E. ^{1}H-NMR (DMSO-d_6) δ 9.87 (s, 1H), 9.71 (s, 1H), 8.03 to 7.99 (m, 3H), 7.82 (s, 1H), 7.65 (s, 1H), 7.57 to 7.55 (m, 3H), 7.50 to 7.47 (m, 1H), 7.37 (d, J = 8.5 Hz, 2H), 4.97 to 4.94 (m, 1H), 4.36 (d, J = 5.2 Hz, 2H); MS $[M+H]^+$ = 444.0; LCMS RT = 2.24 min.

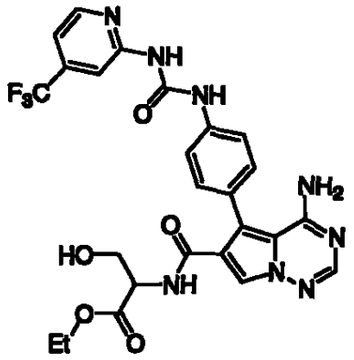
Example 220: Preparation of ethyl N-[(4-amino-5-{4-[({[2-fluoro-5-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazin-6-yl)carbonyl]serinate



The procedure used for the preparation of Example 143 was used to prepare the title compound by substituting methyl serinate hydrochloride for 2-amino-2-methylpropan-1-ol and Intermediate G for Intermediate J. ^{1}H-NMR (DMSO-d_6) δ 9.33 (s, 1H), 8.95 (d, J = 2.5 Hz, 1H), 8.62 to 8.60 (d, J = 8.8 Hz, 1H), 8.20 (s, 1H), 7.91 (s, 1H), 7.78 to 7.76 (d, J = 7.8 Hz, 1H), 7.55 to 7.53 (d, J = 8.7 Hz, 2H), 7.50 to

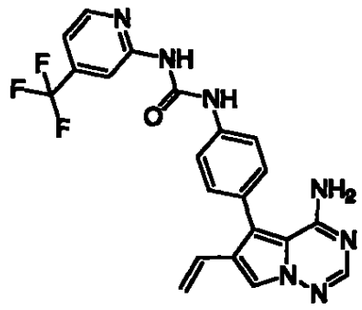
7.47 (m, 1H), 7.40 to 7.37 (m, 1H), 7.34 to 7.32 (d, J = 8.4 Hz, 2H), 4.98 to 4.95 (t, J = 5.9 Hz, 1H), 4.38 to 4.34 (m, 1H), 4.08 to 4.03 (q, J = 7.2 Hz, 2H), 3.70 to 3.61 (m, 2H), 1.18 to 1.15 (t, J = 7.1 Hz, 3H); MS $[M+H]^+$ = 590.0; LCMS RT = 2.69 min.

Example 221: Preparation of ethyl N-[(4-amino-5-{4-[({[4-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazin-6-yl)carbonyl]serinate



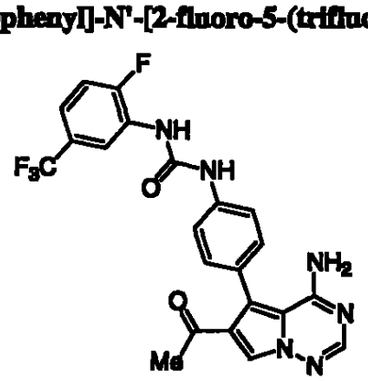
The procedure used for the preparation of Example 143 was used to prepare the title compound by substituting methyl serinate hydrochloride for 2-amino-2-methylpropan-1-ol and Example 250 for Intermediate J. ^{1}H-NMR (DMSO-d_6) δ 9.87 (s, 1H), 9.74 (s, 1H), 8.54 to 8.53 (d, J = 5.4 Hz, 1H), 8.20 (s, 1H), 8.06 (s, 1H), 7.91 (s, 1H), 7.79 to 7.77 (d, J = 7.6 Hz, 1H), 7.59 to 7.57 (d, J = 8.7 Hz, 2H), 7.37 to 7.33 (m, 3H), 4.98 to 4.95 (t, J = 5.8 Hz, 1H), 4.39 to 4.34 (m, 1H), 4.08 to 4.03 (q, J = 7.0 Hz, 2H), 3.72 to 3.61 (m, 2H), 1.18 to 1.14 (t, J = 7.1 Hz, 3H); MS $[M+H]^+$ = 573.0; LCMS RT = 2.55 min.

Example 222: Preparation of N-[4-(4-amino-6 vinylpyrrolo[2,1-f][1,2,4]triazin-5-yl)phenyl]-N'-[4-(trifluoromethyl)pyridin-2-yl]urea



Potassium tert-butoxide (0.51g, 4.53 mmol) was suspended in 1,4-dioxane (40 mL) and treated with methyl(triphenyl)phosphonium bromide (1.6 g, 4.53 mmol). The resulting yellow suspension was stirred at room temperature for 30 min. The mixture was then treated with Intermediate AG (1.0 g, 2.27 mmol). The mixture was stirred for 3 hours at room temperature. The mixture was then poured into water and stirred for 1 hour. The mixture was then filtered and rinsed with water and methanol. The remaining solid was dried under reduced pressure providing 0.62 g of product as an light brown solid (1.41 mmol, 62 % yield). ^{1}H-NMR (DMSO-d_6) δ 10.0(bs, 1H), 9.86 (bs, 1H), 8.53 (d, J = 5.1 Hz, 1H), 8.07 (s, 1H), 8.04 (s, 1H), 7.84 (s, 1H), 7.64 (d, J = 8.5 Hz, 2H), 7.35 (d, J = 5.2 Hz, H), 7.30 (d, J = 8.4 Hz, 2H), 6.39 (q, J = 11.0 Hz, 1H), 5.63 (dd, J = 1.6 Hz, 1H), 5.11 (dd, J = 1.6 Hz, 1H); MS $[M+H]^+$ = 440.0; LCMS RT = 2.89 min.

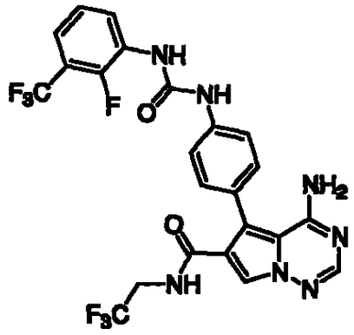
Example 223: Preparation of N-[4-(6-acetyl-4-aminopyrrolo[2,1-f][1,2,4]triazin-5-yl)phenyl]-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea



The procedure used for the preparation of Example 233 was used to prepare the title compound by substituting Example XXX for Example 269. ^{1}H-NMR

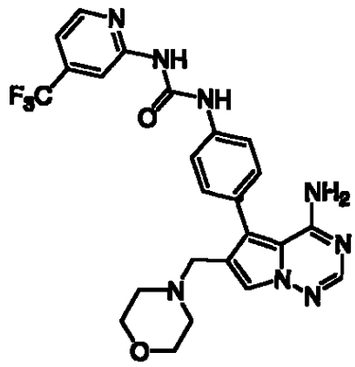
(DMSO-d_6) δ 9.32 (s, 1H), 8.95 (d, J = 2Hz, 1H), 8.61 (dd, J = 2, 5 Hz, 1H), 8.37 (s, 1H), 8.05 (bs, 1H), 7.92 (s, 1H), 7.54 (d, J = 9 Hz, 2H), 7.46 to 7.52 (m, 1H), 7.36 to 7.40 (m, 1H), 7.31, d, J = 9 Hz, 2H), 5.02 (bs, 1H), 2.30 (s, 3H); MS $[M+H]^+$ = 473.3; LCMS RT = 2.95 min.

Example 224: Preparation of 4-amino-5-[4-[({[2-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl]-N-(2,2,2-trifluoroethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



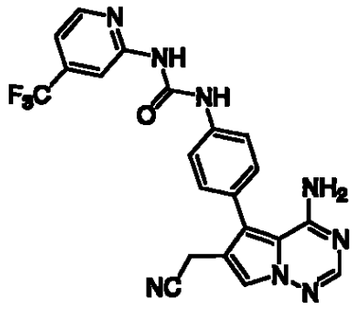
The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting Intermediate M for intermediate X and by (2-Fluoro-3-trifluoromethyl-phenyl)-carbamic acid phenyl ester for phenyl (4-*tert*butylpyridin-2-yl)carbamate. ^{1}H-NMR (DMSO-d_6) δ 9.34 (s, 1H), 8.94 (s, 1H), 8.58 to 8.48 (m, 2H), 8.23 (s, 1H), 7.98 (bs, 1H), 7.96 (s, 1H), 7.56 (d, *J* = 7.5 Hz, 2H), 7.41 to 7.33 (m, 4H), 5.11 (bs, 1H), 4.10(m, 2H); MS $[M+H]^+$ = 556.1; LCMS RT = 3.00 min.

Example 225: Preparation of N-[4-[4-amino-6-(morpholin-4-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl]-N'-[4-(trifluoromethyl)pyridin-2-yl]urea



The procedure used for the preparation of Example 30 was used to prepare the title compound by substituting Intermediate AG for Intermediate F. ^{1}H-NMR (CD_3OD) δ 8.54 (s, 1H), 8.06 (s, 1H), 8.05 (s, 1H), 7.64 to 7.41 (m, 2H), 7.39 to 7.38 (m, 2H), 3.57 to 3.50 (m, 2H), 3.42 to 3.41 (m, 2H), 2.67 to 2.66 (m, 2H), 2.47 to 2.32 (m, 4H); MS $[M+H]^+$ = 513.0; LCMS RT = 1.92 min.

Example 226: Preparation of N-[4-[4-amino-6-(cyanomethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl]-N'-[4-(trifluoromethyl)pyridin-2-yl]urea

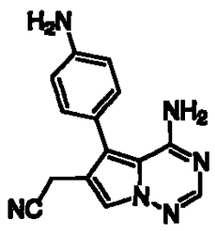


Step 1: Preparation of [4-amino-5-(4-nitrophenyl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]acetonitrile



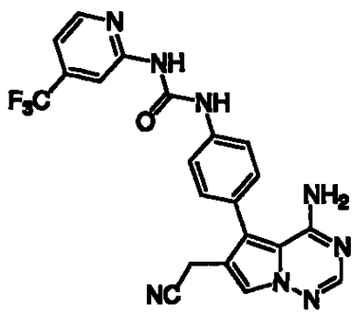
The procedure used for the preparation of Intermediate U Step 1was used to prepare the title compound by substituting DMF for methanol and sodium cyanide for sodium hydride. MS $[M+H]^+ = 295.4$; LCMS RT = 2.11 min.

Step 2: Preparation of 4-amino-5-(4-aminophenyl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]acetonitrile



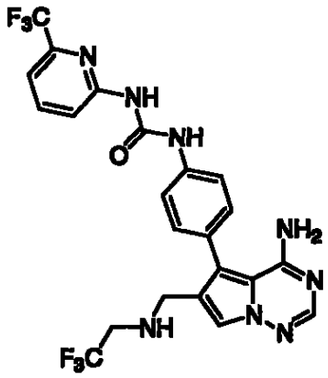
A solution of 4-amino-5-(4-aminophenyl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]acetonitrile (250 mg, 0.85 mmol) and tin (II) chloride (1.61 g, 8.5 mmol) in 75 mL EtOH was heated at 80 C for 1h. The reaction was then diluted with EtOAc and diluted with sat. $NaHCO_3$. After 15 min vigorous stirring the mixture was filterered thru a pad of celite, washing well with EtOAc. The organic layer was then separated, dried (Na_2SO_4) and evaporated to dryness. Trituration with Et_2O provided 210 mg of the title compound (93% yield). MS $[M+H]^+ = 265$; LCMS RT = 2.63 min.

Step 3: Preparation of [Preparation of N-{4-[4-amino-6-(cyanomethyl) pyrrolo [2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-[4-(trifluoromethyl)pyridin-2-yl]urea



The procedure used for the preparation of Example 101 was used to prepare the title compound by substituting 4-amino-5-(4-aminophenyl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]acetonitrile for intermediate U. ^{1}H-NMR (DMSO-d_6) δ 8.54 (d, J = 5 Hz, 1H), 8.07 (s, 1H), 7.87 (s, 1H), 7.77 (s, 1H), 7.66 (d, J = 9 Hz, 2H), 7.36 (d, J = 9 Hz, 2H), 7.34 to 7.36 (m, 1H), 3.81 (s, 2H); MS $[M+H]^+$ = 453.1; LCMS RT = 2.67 min.

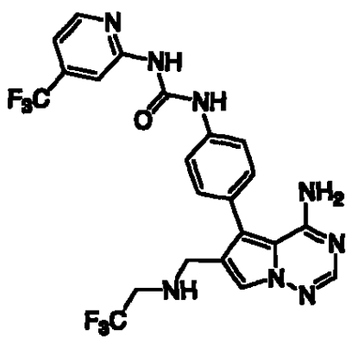
Example 227: Preparation of N-[4-(4-amino-6-{[(2,2,2-trifluoroethyl)amino]methyl}pyrrolo[2,1-f][1,2,4]triazin-5-yl)phenyl]-N'-[6-(trifluoromethyl)pyridin-2-yl]urea



The procedure used for the preparation of Example 30 was used to prepare the title compound by substituting 2,2,2-trifluoroethanamine for morpholine and N-[4-(4-amino-6-formylpyrrolo[2,1-f][1,2,4]triazin-5-yl)phenyl]-N'-[6-(trifluoromethyl)pyridin-2-yl]urea for Intermediate F. ^{1}H-NMR (DMSO-d_6) δ 9.88 (s, 1H), 9.75 (s, 1H), 8.02 to 7.99 (m, 2H), 7.82 (s, 1H), 7.69 (s, 1H), 7.57 to 7.48 (m,

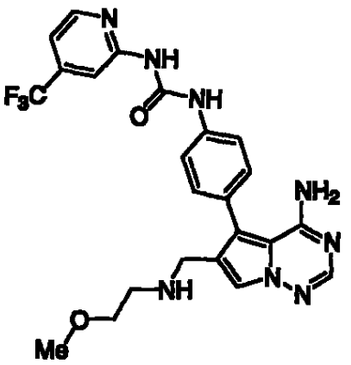
4H), 7.38 to 3.36 (m, 2H), 3.67 to 3.66 (s, 2H), 3.28 to 3.14 (m, 2H), 2.66 to 2.56 (m, 2H); MS $[M+H]^+$ = 525.0; LCMS RT = 2.10 min.

Example 228: Preparation of N-[4-(4-amino-6-{[(2,2,2-trifluoroethyl)amino]methyl}pyrrolo[2,1-f][1,2,4]triazin-5-yl)phenyl]-N'-[4-(trifluoromethyl)pyridin-2-yl]urea



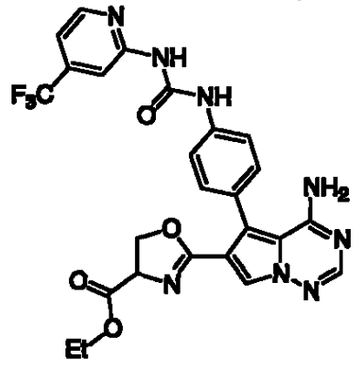
The procedure used for the preparation of Example 30 was used to prepare the title compound by substituting 2,2,2-trifluoroethanamine for morpholine and Intermediate AG for Intermediate F. ^{1}H-NMR (CD_3OD) δ 8.51 (d, J = 5.3 Hz, 1H), 7.77 (s, 1H), 7.48 (br s, 1H), 7.70 to 7.68 (m, 3H), 7.44 to 7.42 (m, 2H), 7.29 to 7.27 (m, 2H), 3.81 (s, 2H), 3.18 to 3.11 (m, 2H); MS $[M+H]^+$ = 525.1; LCMS RT = 2.19 min.

Example 229: Preparation of N-[4-(4-amino-6-{[(2-methoxyethyl)amino]methyl}pyrrolo[2,1-f][1,2,4]triazin-5-yl)phenyl]-N'-[4-(trifluoromethyl)pyridin-2-yl]urea



The procedure used for the preparation of Example 30 was used to prepare the title compound by substituting 2-methoxyethanamine for morpholine and Intermediate AG for Intermediate F. ^{1}H-NMR (CD_3OD) δ 8.51 (d, J = 5.3 Hz, 1H), 7.80 (s, 1H), 7.78 (s, 1H), 7.75 to 7.72 (m, 3H), 7.43 to 7.41 (m, 2H), 7.28 (d, J = 5.6 Hz, 1H), 3.97 (s, 2H), 3.48 to 3.45 (m, 2H), 2.89 to 2.86 (m, 2H); MS $[M+H]^+$ = 501.0; LCMS RT = 1.99 min.

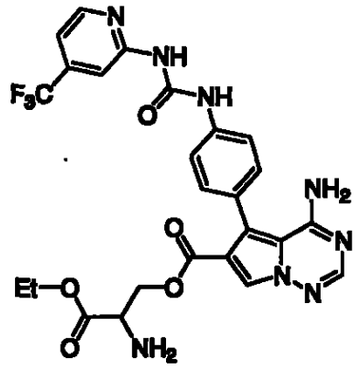
Example 230: Preparation of ethyl 2-(4-amino-5-{4-[({[4-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazin-6-yl)-4,5-dihydro-1,3-oxazole-4-carboxylate



To a solution of THF (2 mL) was added ethyl N-[(4-amino-5-{4-[({[4-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazin-6-yl)carbonyl]serinate (Example 221) (50 mg, 0.09 mmol) which was cooled to -78 °C. DAST (13 μL, 0.10 mmol) was added and the reaction proceeded for 1h while stirring under N_2. Anhydrous K_2CO_3 was then added and the solution was allowed to warm to rt over the following 30min. The reaction mixture was transferred to a separatory funnel, diluted with EtOAc (20 mL), washed with aq saturated $NaHCO_3$ (20 mL) and H_2O (20 mL). The organic was collected, dried (MgSO4), and evaporated in vacuo. The crude material was purified by preparative HPLC (10-90% ACN/H_2O with 0.1% TFA). The fractions were left overnight resulting in the partial formation of a new product. The two products were separated

by column chromatography 5:4:1 v/v/v DCM/EtOAc/MeOH resulting in the isolation of 9 mg of the title compound (0.016 mmol, 18%). ^{1}H-NMR (DMSO-d_6) δ 9.91 (s, 1H), 9.78 (s, 1H), 8.54 to 8.53 (d, J = 5.0 Hz, 1H), 8.08 (s, 1H), 8.05 (s, 1H), 7.91 (s, 1H), 7.58 to 7.56 (d, J = 8.6 Hz, 2H), 7.37 to 7.36 (d, J = 5.1 Hz, 1H), 7.34 to 7.32 (d, J = 8.6 Hz, 2H), 4.75 to 4.71 (m, 1H), 4.38 to 4.29 (m, 2H), 4.13 to 4.08 (q, J = 7.1 Hz, 2H), 1.21 to 1.18 (t, J = 7.0 Hz, 3H); MS $[M+H]^+$ = 555.1; LCMS RT = 2.84 min.

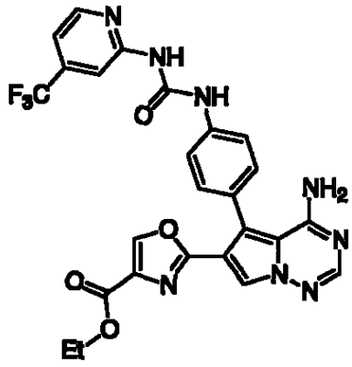
Example 231: Preparation of 2-amino-3-ethoxy-3-oxopropyl 4-amino-5-{4-[({[4-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate



To a solution of THF (2 mL) was added ethyl N-[(4-amino-5-{4-[({[4-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazin-6-yl)carbonyl]serinate (Example 221) (50 mg, 0.09 mmol) which was cooled to -78 °C. DAST (13 μL, 0.10 mmol) was added and the reaction proceeded for 1h while stirring under N_2. Anhydrous K_2CO_3 was then added and the solution was allowed to warm to rt over the following 30min. The reaction mixture was transferred to a separatory funnel, diluted with EtOAc (20 mL), washed with aq saturated $NaHCO_3$ (20 mL) and H_2O (20 mL). The organic was collected, dried (MgSO4), and evaporated in vacuo. The crude material was purified by preparative HPLC (10-90% ACN/H_2O with 0.1% TFA). The fractions were left overnight resulting in the partial formation of a new product. The two products were separated

by column chromatography 5:4:1 v/v/v DCM/EtOAc/MeOH resulting in the isolation of 4 mg of the title compound (0.0075 mmol, 9%). ^{1}H-NMR (DMSO-d_6) δ 9.92 (s, 1H), 9.78 (s, 1H), 8.54 to 8.53 (d, J = 5.4 Hz, 1H), 8.15 (s, 1H), 8.07 (s, 1H), 7.93 (s, 1H), 7.60 to 7.58 (d, J = 8.8 Hz, 2H), 7.37 to 7.35 (d, J = 6.4 Hz, 1H), 7.33 to 7.31 (d, J = 8.6 Hz, 2H), 4.25 to 4.21(m, 1H), 4.12 to 4.08 (m, 1H), 4.07 to 4.02 (q, J = 7.0 Hz, 2H), 3.55 to 3.52 (t, J = 4.9 Hz, 1H), 1.15 to 1.11 (t, J = 7.2 Hz, 3H); MS $[M+H]^+$ = 573.1; LCMS RT = 2.38 min.

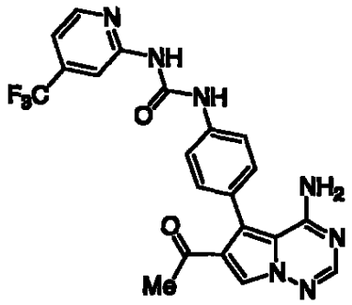
Example 232: Preparation of ethyl 2-(4-amino-5-[4-[({[4-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazin-6-yl)-1,3-oxazole-4-carboxylate



To a solution of THF (16 mL) was added ethyl N-[(4-amino-5-{4-[({[4-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazin-6-yl)carbonyl]serinate (Example 221) (437 mg, 0.76 mmol) which was cooled to -78 °C. DAST (0.14 mL, 1.07 mmol) was added and the reaction proceeded for 1h while stirring under N_2. Additional DAST (0.14 mL, 1.07 mmol) was added and the solution was stirred for 30min. The acetone/dry ice cooling bath was replaced with an ice/water bath and DBU (0.41 mL, 2.75 mmol) and $BrCCl_3$ (0.27 mL, 2.75 mmol) were added and the solution was allowed to warm to rt over 17h. Additional DBU (0.41 mL, 2.75 mmol) and $BrCCl_3$ (0.27 mL, 2.75 mmol) were added and the solution was allowed to stir for 6h. The reaction mixture was transferred to a separatory funnel, diluted with EtOAc (50 mL), washed with aq

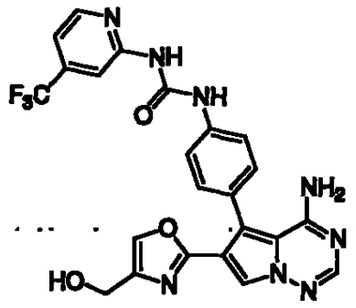
saturated $NaHCO_3$ (50 mL) and H_2O (50 mL). The aqueous fraction was back extracted with DCM (3 x 30 mL). The combined organic layers were dried (MgSO4), evaporated in vacuo and flashed 5:4:1 v/v/v DCM/EtOAc/MeOH resulting in the isolation of 33 mg of the title compound (0.060 mmol, yield 8%). ^{1}H-NMR (DMSO-d_6) δ 9.93 (s, 1H), 9.77 (s, 1H), 8.70 (s, 1H), 8.55 to 8.54 (d, J = 5.0 Hz, 1H), 8.30 (s, 1H), 8.06 (s, 1H), 7.95 (s, 1H), 7.64 to 7.61 (d, J = 8.8 Hz, 2H), 7.42 to 7.40 (d, J = 8.8 Hz, 2H), 7.38 to 7.36 (d, J = 6.2 Hz, 1H), 4.28 to 4.23 (q, J = 7.6 Hz, 2H), 1.28 to 1.25 (t, J = 7.1 Hz, 3H); MS $[M+H]^+$ = 553.1; LCMS RT = 3.04 min.

Example 233: Preparation of N-[4-(6-acetyl-4-aminopyrrolo[2,1-f][1,2,4]triazin-5-yl)phenyl]-N'-[4-(trifluoromethyl)pyridin-2-yl]urea



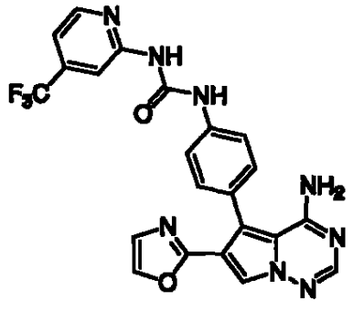
The procedure used for the preparation of Intermediate F step 2 was used to prepare the title compound by substituting Example 269 for *N*-{4-[4-amino-6-(hydroxymethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea. ^{1}H-NMR (CD_3OD) δ 8.51 (d, J = 5 Hz, 1H), 8.15 (s, 1H), 7.97 (s, 1H), 7.89 (s, 1H), 7.77 (d, J = 9 Hz, 2H), 7.38 (d, J = 9 Hz, 2H), 7.26 (d, J = 5Hz, 1H), 2.29 (s, 3H); MS $[M+H]^+$ = 456.0; LCMS RT = 2.71 min.

Example 234: Preparation of N-(4-{4-amino-6-[4-(hydroxymethyl)-1,3-oxazol-2-yl]pyrrolo[2,1-f][1,2,4]triazin-5-yl}phenyl)-N'-[4-(trifluoromethyl)pyridin-2-yl]urea

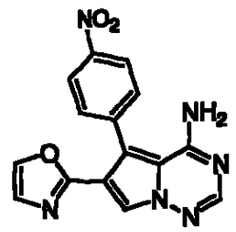


The procedure used for the preparation of Example 241 was used to prepare the title compound by substituting Example 232 for Example 237. ^{1}H-NMR (DMSO-d_6) δ 9.91 (s, 1H), 9.76 (s, 1H), 8.53 (d, J = 5.4 Hz, 1H), 8.17 (s, 1H), 8.05 (s, 1H), 7.92 (s, 1H), 7.75 (s, 1H), 7.62 (s, 1H), 7.61 (d, J = 8.6 Hz, 2H), 7.40 to 7.36 (m, 3H), 5.14 to 5.11 (m, 1H), 4.31 (d, J = 5.7 Hz, 2H); MS $[M+H]^+$ = 511.0; LCMS RT = 2.33 min.

Example 235: Preparation of N-[4-[4-amino-6-(1,3-oxazol-2-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl]-N'-[4-(trifluoromethyl)pyridin-2-yl]urea

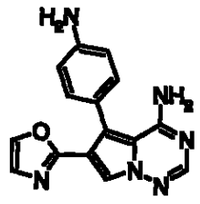


Step 1: Preparation of 5-(4-Nitro-phenyl)-6-oxazol-2-yl-pyrrolo[2,1-f][1,2,4]triazin-4-ylamine



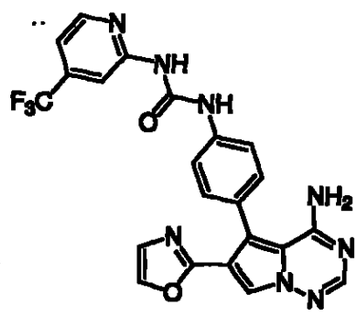
The procedure used for the preparation of the first step of intermediate M was used to prepare 4-Amino-5-(4-nitro-phenyl)-pyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid (2,2-dimethoxy-ethyl)-amideby substituting 2,2-Dimethoxy-ethylamine for 2,2,2-trifluoro-ethylamine hydrochloride salt. To a solution of methanesulfonic acid (1.5ml) was added P_2O_5 (225.0 mg, 1.58 mmol) followed by the addition of 4-amino-5-(4-nitro-phenyl)-pyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid (2,2-dimethoxy-ethyl)-amide (150 mg, 0.388 mmol). The dark brown mixture was heated to 100 °C and allowed to stir for 18 hrs. The mixture was then poured over ice (15 g), stirred for fifteen minutes and enough saturated sodium carbonate solution was added to neutralize the reaction. A white precipitate was filtered and collected (35 mg, 27%). ^{1}H-NMR (DMSO-d_6) δ 8.33 (s, 1H), 8.31 (m, 2H), 8.03 (d, J = 10 Hz, 2H), 7.73 (d, J = 10 Hz, 2H), 7.28 (s, 1H). MS $[M+H]^+$ = 323.2; LCMS RT = 2.51 min.

Step 2: Preparation of 5-(4-Amino-phenyl)-6-oxazol-2-yl-pyrrolo[2,1-f][1,2,4]triazin-4-ylamine.



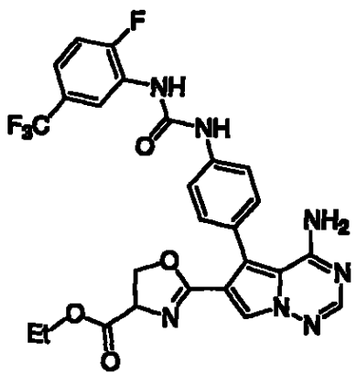
The procedure used for the preparation of intermediate B was used to prepare the title compound substituting 5-(4-Nitro-phenyl)-6-oxazol-2-yl-pyrrolo[2,1-f][1,2,4]triazin-4-ylamine for 4-amino-5-(4-aminophenyl)pyrrole[2,1-f][1,2,4]triazine-6carboxylate. MS $[M+H]^+$ = 293.3; LCMS RT = 0.38 min.

Step 3: Preparation of N-{4-[4-amino-6-(1,3-oxazol-2-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-[4-(trifluoromethyl)pyridin-2-yl]urea



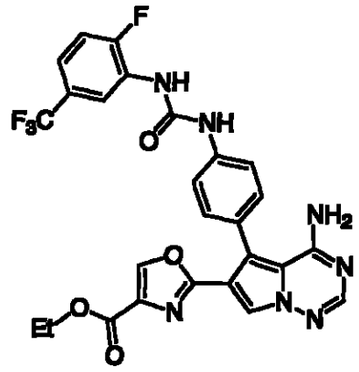
The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting 5-(4-amino-phenyl)-6-oxazol-2-yl-pyrrolo[2,1-f][1,2,4]triazin-4-ylamine for intermediate X and phenyl [4-(trifluoromethyl)pyridin-2-yl]carbamate for phenyl (4-*tert*butylpyridin-2-yl)carbamate. ^{1}H-NMR (DMSO-d_6) δ 9.94 (s, 1H), 9.79 (s, 1H), 8.55 (d, J = 6.2 Hz, 1H), 8.23 (s, 1H), 8.07 (s, 1H), 8.00 (s, 1H), 7.94 (s, 1H), 7.61 (d, J = 7.9 Hz, 2H), 7.40 (d, J = 7.9 Hz, 2H), 7.36(s, 1H), 7.18 (s,1H); MS $[M+H]^+$ = 481.1; LCMS RT = 3.11 min.

Example 236: Preparation of ethyl 2-(4-amino-5-{4-[({[2-fluoro-5-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazin-6-yl)-4,5-dihydro-1,3-oxazole-4-carboxylate



The procedure used for the preparation of Example 230 was used to prepare the title compound by substituting ethyl N-[(4-amino-5-{4-[({[2-fluoro-5-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazin-6-yl)carbonyl]serinate (Example 220) for ethyl 2-(4-amino-5-{4-[({[4-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazin-6-yl)-4,5-dihydro-1,3-oxazole-4-carboxylate (Example 221). ^{1}H-NMR (DMSO-d_6) δ 9.31 (s, 1H), 8.96 to 8.95 (d, J = 2.9 Hz, 1H), 8.63 to 8.61 (d, J = 7.2 Hz, 1H), 8.08 (s, 1H), 7.91 (s, 1H), 7.54 to 7.52 (d, J = 8.6 Hz, 2H), 7.50 to 7.48 (d, J = 10.9 Hz, 1H), 7.41 to 7.38 (m, 1H), 7.33 to 7.31 (d, J = 8.6 Hz, 2H), 4.76 to 4.71(m, 1H), 4.38 to 4.29 (m, 2H), 4.13 to 4.08 (q, J = 6.5 Hz, 2H), 1.21 to 1.18 (t, J = 7.2 Hz, 3H); MS $[M+H]^+$ = 572.2; LCMS RT = 2.94 min.

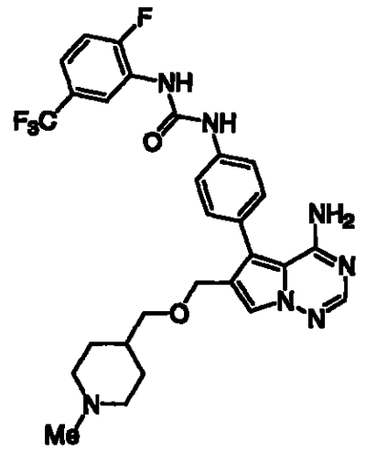
Example 237: Preparation of ethyl 2-(4-amino-5-{4-[({[2-fluoro-5-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazin-6-yl)-1,3-oxazole-4-carboxylate



To a solution of THF (2 mL) and DCM (2 mL) cooled in an ice/water bath was added ethyl 2-(4-amino-5-{4-[({[2-fluoro-5-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazin-6-yl)-4,5-dihydro-1,3-oxazole-4-carboxylate (Example 236) followed by DBU (24 µL, 0.16 mmol) and $BrCCl_3$ (16 µL, 0.16 mmol). The solution was allowed to stir under N_2 for 1h and then the solution was left to warm to rt while stirring for 17h. The reaction mixture was evaporated in vacuo and then purified by flash chromatography 50:45:5 v/v/v DCM/EtOAc/MeOH resulting in the isolation of 16

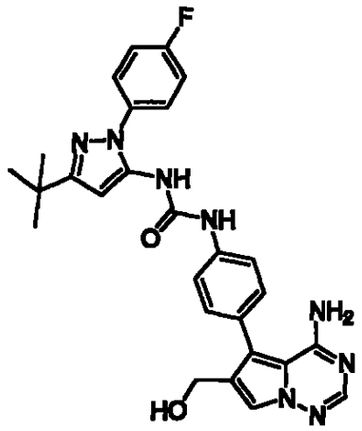
mg of the title compound as a white solid (0.028 mmol, yield 65%). ^{1}H-NMR (DMSO-d_6) δ 9.35 (s, 1H), 8.96 (d, J = 2.8 Hz, 1H), 8.69 (s, 1H), 8.62 to 8.60 (d, J = 9.3 Hz, 1H), 8.29 (s, 1H), 7.94 (s, 1H), 7.58 to 7.56 (d, J = 8.4 Hz, 2H), 7.52 to 7.47 (m, 1H), 7.40 to 7.37 (m, 3H), 4.27 to 4.23 (q, J = 6.3 Hz, 2H), 1.28 to 1.24 (t, J = 7.1 Hz, 3H); MS $[M+H]^+$ = 570.1; LCMS RT = 3.16 min.

Example 238: Preparation of N-[4-(4-amino-6-[[(1-methylpiperidin-4-yl)methoxy]methyl}pyrrolo[2,1-f][1,2,4]triazin-5-yl)phenyl]-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea



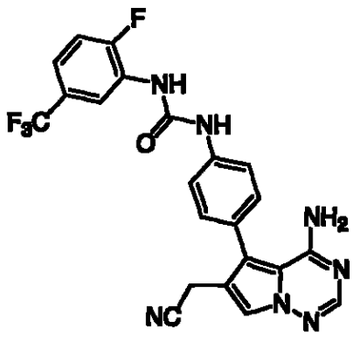
The procedure used for the preparation of Example 271 was used to prepare the title compound by substituting (1-methylpiperidin-4-yl)methanol for methanol and the product from Intermediate F (Step 1) for Example 262. ^{1}H-NMR (DMSO-d_6) δ 8.58 to 8.57 (m, 1H), 8.05 to 7.93 (m, 2H), 1.68 to 7.64 (m, 2H), 7.51 to 7.46 (m, 1H), 7.38 to 7.36 (m, 2H), 4.46 (s, 2H), 4.02 to 4.00 (m, 1H), 3.27 to 3.09 (m, 4H), 2.66 (s, 3H), 1.62 to 1.55 (m, 2H), 1.25 to 1.15 (m, 2H); MS $[M+H]^+$ = 572.1; LCMS RT = 2.06 min.

Example 239: Preparation of N-{4-[4-amino-6-(hydroxymethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-[3-tert-butyl-1-(4-fluorophenyl)-1H-pyrazol-5-yl]urea



The procedure used for the preparation of Intermediate F step 1 was used to prepare the title compound by substituting Example 25 for Intermediate E. ^{1}H-NMR (DMSO-d_6) δ 9.11 (s, 1H), 8.42 (s, 1H), 7.81 (s, 1H), 7.64 (s, 1H), 7.48 to 7.58 (m, 5 H), 7.28 to 7.48 (m, 5H), 6.36 (s, 1H), 4.94 (t, J = 5 Hz, 1H), 4.34 (d, J = 5 Hz, 2H), 1.26 (s, 9H); MS $[M+H]^+$ = 515.2; LCMS RT = 2.48 min.

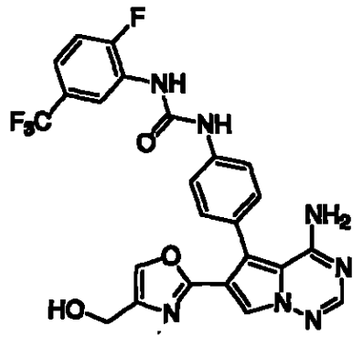
Example 240: Preparation of N-{4-[4-amino-6-(cyanomethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea



The procedure used for the preparation of Example 226 was used to prepare the title compound by substituting phenyl [2-fluoro-5-(trifluoromethyl)phenyl]carbamate for phenyl [2-fluoro-5-(trifluoromethyl)phenyl]carbamate. ^{1}H-NMR (DMSO-d_6) δ 9.41 (s, 1H), 9.01 (d, J = 3 Hz, 1H), 8.62 (d, J = 3, 8 Hz, 1H), 7.81 (s, 1H), 7.77 (s, 1H), 7.61 (d, J = 9 Hz,

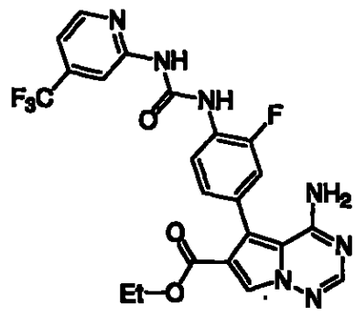
2H), 7.47 to 7.54 (m, 1H), 7.38 to 7.42 (m, 1H), 7.35 (d, J = 9 Hz, 2H), 5.35 (dd, J = 2, 6 Hz), 3.82 (s, 2H); MS $[M+H]^+$ = 470.1; LCMS RT = 2.80 min.

Example 241: Preparation of N-(4-{4-amino-6-[4-(hydroxymethyl)-1,3-oxazol-2-yl]pyrrolo[2,1-f][1,2,4]triazin-5-yl}phenyl)-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea



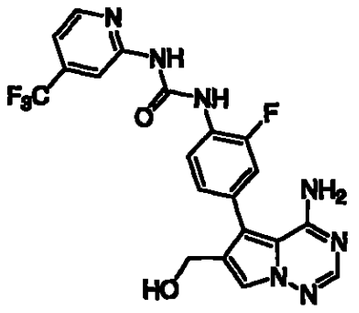
The procedure used for the preparation of Intermediate F Step 1 was used to prepare the title compound by substituting ethyl 2-(4-amino-5-{4-[({[2-fluoro-5-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazin-6-yl)-1,3-oxazole-4-carboxylate (Example 232) for Intermediate E. ^{1}H-NMR (DMSO-d_6) δ 9.35 (s, 1H), 8.97 to 8.96 (d, J = 3.4 Hz, 1H), 8.63 to 8.61 (d, J = 7.4 Hz, 1H), 8.17 (s, 1H), 7.93 (s, 1H), 7.75 (s, 1H), 7.58 to 7.56 (d, J = 8.7 Hz, 2H), 7.53 to 7.48 (m, 1H), 7.41 to 7.36 (m, 3H), 5.16 to 5.13 (t, J = 5.6 Hz, 1H), 4.32 to 4.31 (d, J = 5.5 Hz, 2H); MS $[M+H]^+$ = 528.1; LCMS RT = 2.68 min.

Example 242: Preparation of ethyl 4-amino-5-{3-fluoro-4-[({[4-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate



The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting Intermediate AJ for Intermediate X and by substituting phenyl [4-(trifluoromethyl)pyridin-2-yl]carbamate for phenyl (4-*tert*-butylpyridin-2-yl)carbamate. ^{1}H-NMR (DMSO-d_6) δ 10.14 (s, 1H), 10.11 to 10.04 (br s, 1H), 8.54 to 8.53 (d, J = 5.3 Hz, 1H), 8.28 to 8.23 (t, J = 8.4 Hz, 1H), 8.14 (s, 1H), 8.01 (s, 1H), 7.94 (s, 1H), 7.39 to 7.33 (m, 2H), 7.18 to 7.16 (d, J = 10.0 Hz, 1H), 4.12 to 4.06 (q, J = 8.3 Hz, 2H), 1.14 to 1.10 (t, J = 7.1 Hz, 3H); MS $[M+H]^+$ = 504.1; LCMS RT = 3.12 min.

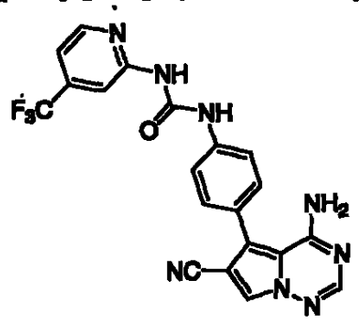
Example 243: Preparation of N-{4-[4-amino-6-(hydroxymethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]-2-fluorophenyl}-N'-[4-(trifluoromethyl)pyridin-2-yl]urea



The procedure used for the preparation of Intermediate F Step 1 was used to prepare the title compound by substituting ethyl 4-amino-5-{3-fluoro-4-[({[4-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate (Example 242) for Intermediate E. ^{1}H-NMR (DMSO-d_6) δ 10.13 (s, 1H), 10.07 to 10.02 (br s, 1H), 8.54 to 8.53 (d, J = 5.3 Hz,

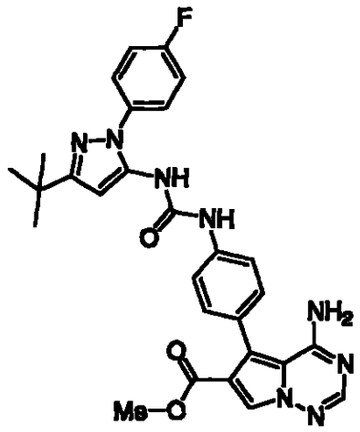
1H), 8.29 to 8.24 (t, J = 8.5 Hz, 1H), 8.03 (s, 1H), 7.84 (s, 1H), 7.67 (s, 1H), 7.39 (s, 1H), 7.38 to 7.35 (d, J = 8.7 Hz, 1H), 7.21 to 7.19 (d, J = 9.7 Hz, 1H), 5.02 to 5.00 (t, J = 5.1 Hz, 1H), 4.39 to 4.37 (d, J = 5.2 Hz, 2H); MS $[M+H]^+$ = 462.0; LCMS RT = 2.44 min.

Example 244: Preparation of N-[4-(4-amino-6-cyanopyrrolo[2,1-f][1,2,4]triazin-5-yl)phenyl]-N'-[4-(trifluoromethyl)pyridin-2-yl]urea



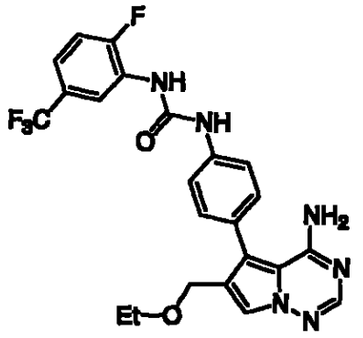
The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting Intermediate P for Intermediate X and by substituting phenyl [2-fluoro-5-(trifluoromethyl)phenyl]carbamate for for phenyl (4-*tert*-butylpyridin-2-yl)carbamate . ^{1}H-NMR (DMSO-d_6) δ 9.96 (s, 1H), 9.78 (s, 1H), 8.55 (d, J = 5 Hz, 1H), 8.52 (s, 1H), 8.07 (s, 1H), 7.99 (s, 1H), 7.69 (d, J = 9 Hz, 2H), 7.45 (d, J = 9 Hz, 2H), 7.36 (d, J = 5 Hz, 1H); MS $[M+H]^+$ = 439.1; LCMS RT = 3.01 min.

Example 245: Preparation of methyl 4-amino-5-{4-[({[3-tert-butyl-1-(4-fluorophenyl)-1H-pyrazol-5-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate

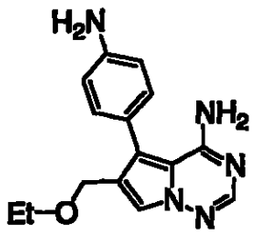


The procedure used for the preparation of Example 25 was used to prepare the title compound by substituting methyl 4-amino-5-(4-aminophenyl)pyrrolo[2,1f][1,2,4] triazine-6-carboxylate for Intermediate B. ^{1}H-NMR (DMSO-d_6) δ 9.14 (s, 1H), 8.43 (s, 1H), 8.13 (s, 1H), 7.92 (s, 1H), 7.25 to 7.60 (m, 8H), 6.36 (s, 1H), 7.32 to 7.40 (m, 4H), 7.17 to 7.25 (m, 1H), 7.14 (bs, 1H), 6.34 (s, 1H), 3.61 (s, 1H); MS $[M+Na]^+$ = 565.2; LCMS RT = 3.13 min.

Example 246: Preparation of N-[4-[4-amino-6-(ethoxymethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl]-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea

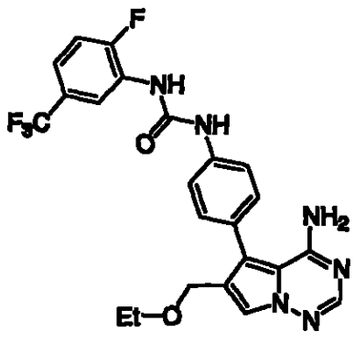


Step 1: Preparation of 6-(ethoxymethyl)-5-(4-nitrophenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine



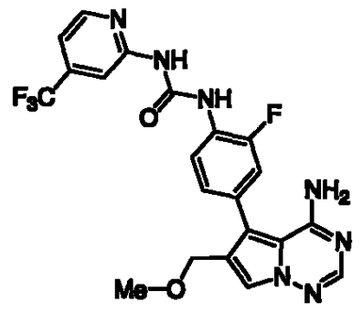
The method used in the preparation of Intermediate U was used to prepare the title compounds by substituting ethanol for methanol. MS $[M+H]^+$ = 284.1; LCMS RT = 0.35 min.

Step 2: Preparation of N-{4-[4-amino-6-(ethoxymethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea



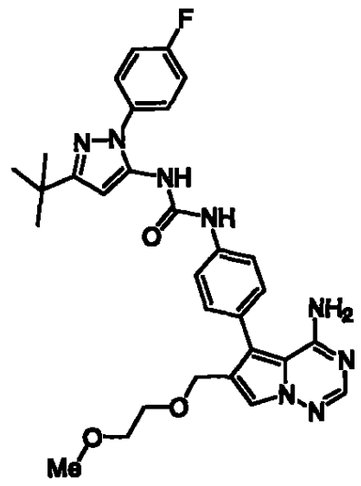
The procedure used for the preparation of Example 1 was used to prepare the title compound by substituting 6-(ethoxymethyl)-5-(4-aminophenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine in place of Intermediate B. ^{1}H-NMR (DCM-d_2) δ 12.19 (s, 1H), 8.51 (d, J = 7.5 Hz, 1H), 8.01 (s, 1H), 7.74 (s, 1H), 7.4-7.3 (bs, 1H), 7.29-7.14 (m, 5H), 6.8 (s, 1H), 4.34 (s, 2H), 3.40 (q, J = 7.0 Hz, 2H), 0.80 (m, 3H); MS $[M+H]^+$ = 489.2; LCMS RT = 3.92 min.

Example 247: Preparation of N-{4-[4-amino-6-(methoxymethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]-2-fluorophenyl}-N'-[4-(trifluoromethyl)pyridin-2-yl]urea



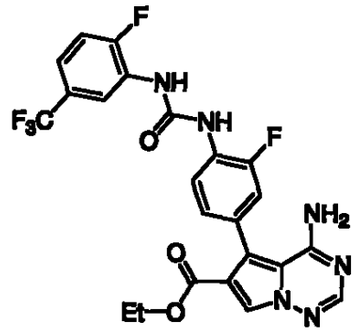
The procedure used for the preparation of Example 271 was used to prepare the title compound by substituting N-{4-[4-amino-6-(hydroxymethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]-2-fluorophenyl}-N'-[4-(trifluoromethyl)pyridin-2-yl]urea (Example 243) for N-{4-[4-amino-6-(hydroxymethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-(4-methylpyridin-2-yl)urea (Example 262). ^{1}H-NMR (DMSO-d_6) δ 10.14 (s, 1H), 10.09 to 10.04 (br s, 1H), 8.54 to 8.53 (d, J = 5.5 Hz, 1H), 8.30 to 8.26 (t, J = 8.5 Hz, 1H), 8.00 (s, 1H), 7.86 (s, 1H), 7.76 (s, 1H), 7.39 to 7.38 (d, J = 5.2 Hz, 1H), 7.35 to 7.32 (d, J = 12.0 Hz, 1H), 7.21 to 7.18 (d, J = 10.2 Hz, 1H), 4.28 (s, 2H), 3.22 (s, 3H); MS $[M+H]^+$ = 476.1; LCMS RT = 2.77 min.

Example 248: Preparation of N-(4-{4-amino-6-[(2-methoxyethoxy)methyl]pyrrolo[2,1-f][1,2,4]triazin-5-yl}phenyl)-N'-[3-tert-butyl-1-(4-fluorophenyl)-1H-pyrazol-5-yl]urea



The procedure used for preparation of Example 73 was used to prepare the title compound by substituting Intermediate Z for Intermediate X and substituting phenyl (3-*tert*-butyl-1-(4-fluorophenyl)-1*H*-pyrazol-5-)-carbamate for phenyl (4-*tert*-butylpyridin-2-yl)carbamate. ^{1}H-NMR (DMSO-d_6) δ 9.13 (s, 1H), 8.43 (s, 1H), 7.83 (s, 1H), 7.73 (s, 1H), 7.58-7.49 (m, 4H), 7.38 (d, J = 9.4 Hz 2H), 7.31 (d, J = 9.4 Hz, 2H), 6.37 (s, 1H), 4.30(s, 2H), 3.46-3.43 (m, 2H), 3.40-3.37 (m, 2H), 3.20 (s, 3H), 1.26 (s, 9H); MS $[M+H]^+$ = 573.1; LCMS RT = 2.71 min.

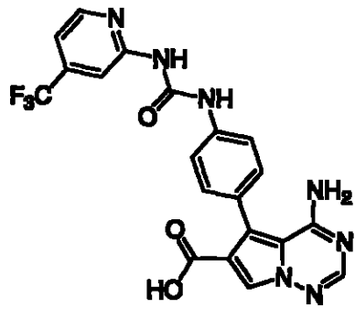
Example 249: Preparation of ethyl 4-amino-5-{3-fluoro-4-[({[2-fluoro-5-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate



The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting Intermediate AJ for Intermediate X and phenyl [2-

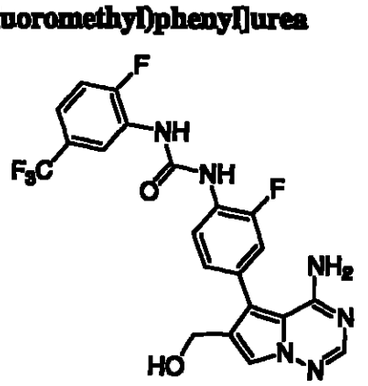
fluoro-5-(trifluoromethyl)phenyl]carbamate for phenyl (4-tert-butylpyridin-2-yl)carbamate. ^{1}H-NMR (DMSO-d_6) δ 9.42 (s, 1H), 9.28 (s, 1H), 8.65 to 8.63 (m, 1H), 8.27 to 8.22 (m, 1H), 8.13 (s, 1H), 7.93 (s, 1H), 4.11 to 4.06 (m, 2H), 1.14 to 1.10 (m, 3H); MS $[M+H]^+$ = 521.3; LCMS RT = 2.98 min.

Example 250: Preparation of 4-amino-5-{4-[({[4-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid



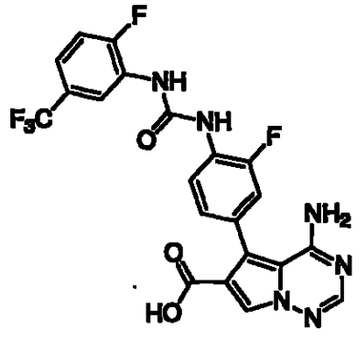
The procedure used for the preparation of Intermediate G was used to prepare the title compound by substituting Example 51 for Intermediate E. ^{1}H-NMR (DMSO-d_6) δ 12.3 (s, 1H), 9.87 (s, 1H), 9.75 (s, 1H), 8.53 (d, J = 5.3 Hz, 2H), 8.07 to 8.06 (m, 3H), 7.86 (s, 1H), 7.58 to 7.56 (m, 2H), 7.36 to 7.33 (m, 3H); MS $[M+H]^+$ = 458.0; LCMS RT = 2.28 min.

Example 251: Preparation of N-{4-[4-amino-6-(hydroxymethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]-2-fluorophenyl}-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea



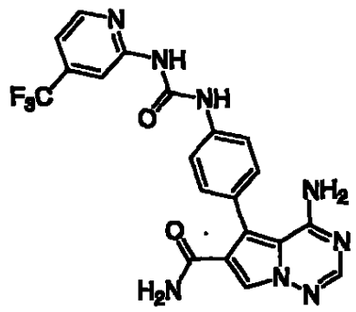
The procedure used for the preparation of Intermediate AF was used to prepare the title compound by substituting Example 249 for Example 51. ^{1}H-NMR (DMSO-d_6) δ 9.41 (s, 1H), 9.40 (s, 1H), 9.26 to 8.63 (m, 1H), 8.28 to 8.24 (m, 1H), 7.83 (s, 1H), 7.66 (s, 1H), 7.53 to 7.48 (m, 1H), 7.41 to 7.33 (m, 2H), 7.18 (d, J = 8.2 Hz, 1H), 5.01 to 4.98 (m, 1H), 4.37 (d, J = 5.0 Hz, 2H); MS $[M+H]^+$ = 479.1; LCMS RT = 2.49 min.

Example 252: Preparation of 4-amino-5-{3-fluoro-4-[({[2-fluoro-5-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid



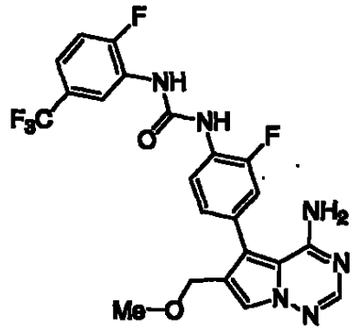
The procedure used for the preparation of Intermediate G was used to prepare the title compound by substituting Example 249 for Intermediate E. ^{1}H-NMR (DMSO-d_6) δ 12.3 (s, 1H), 9.43 (s, 1H), 9.27 (s, 1H), 8.65 to 8.63 (m, 1H), 8.25 to 8.20 (m, 1H), 8.07 (s, 1H), 8.02 (s, 1H); MS $[M+H]^+$ = 433.1; LCMS RT = 2.58 min.

Example 253: Preparation of 4-amino-5-{4-[({[4-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



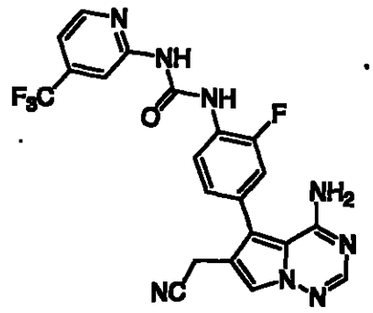
The procedure used for the preparation of Example 104 was used to prepare the title compound by substituting phenyl [4-(trifluoromethyl)pyridin-2-yl]carbamate for phenyl [3-fluoro-5-(trifluoromethyl)phenyl]carbamate. ^{1}H-NMR (CD_3OD) δ 8.52 (d, J = 5 Hz, 1H), 8.06 (s, 1H), 7.84 (s, 1H), 7.71 (s, 1H), 7.70 (d, J = 9 Hz, 2H), 7.46 (d, J = 9 Hz, 2H), 7.28 (d, J = 5 Hz, 1H); MS $[M+H]^+$ = 457.0; LCMS RT = 2.36 min.

Example 254: Preparation of N-{4-[4-amino-6-(methoxymethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]-2-fluorophenyl}-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea



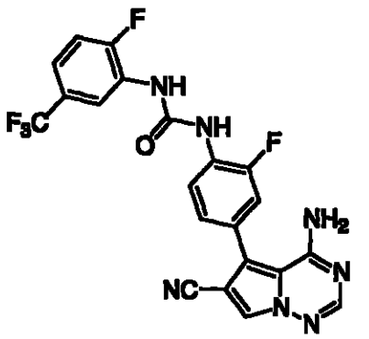
The procedure used for the preparation of Example 271 was used to prepare the title compound by Example 251 for Example 262. ^{1}H-NMR (CD_3OD) δ 8.65 (d, *J* = 8.0 Hz, 1H), 8.31 to 8.27 (m, 1H), 7.80 (s, 1H), 7.70 (s, 1H), 7.35 to 7.23 (m, 4H), 4.37 (s, 2H), 3.33 (s, 3H); MS $[M+H]^+$ = 493.1; LCMS RT = 2.84 min.

Example 255: Preparation of N-{4-[4-amino-6-(cyanomethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]-2-fluorophenyl}-N'-[4-(trifluoromethyl)pyridin-2-yl]urea



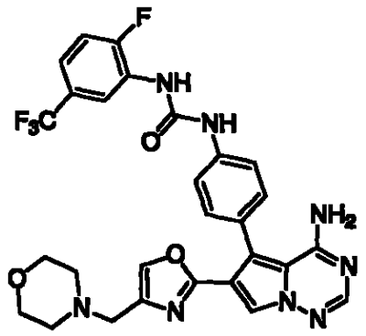
The procedure used for the preparation of Example 271 was used to prepare the title compound by substituting N-{4-[4-amino-6-(hydroxymethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]-2-fluorophenyl}-N'-[4-(trifluoromethyl)pyridin-2-yl]urea (Example 243) for N-{4-[4-amino-6-(hydroxymethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-(4-methylpyridin-2-yl)urea (Example 262) and sodium cyanide for MeOH. ^{1}H-NMR (Acetone-d_6) δ 10.99 (s, 1H), 9.39 (s, 1H), 8.59 to 8.58 (d, J = 5.1 Hz, 1H), 8.51 to 8.47 (t, J = 8.5 Hz, 1H), 7.84 (s, 1H), 7.82 to 7.81 (d, J = 6.4 Hz, 1H), 7.75 (s, 1H), 7.38 to 7.35 (m, 2H), 7.30 to 7.28 (d, J = 8.4 Hz, 1H), 3.86 (s, 2H); MS $[M+H]^+$ = 471.0; LCMS RT = 2.75 min.

Example 256: Preparation of N-[4-(4-amino-6-cyanopyrrolo[2,1-f][1,2,4]triazin-5-yl)-2-fluorophenyl]-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea



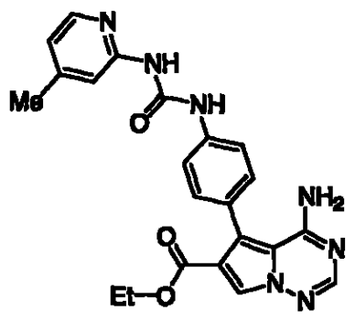
The procedure used for the preparation of Intermediate O was used to prepare the title compound by substituting Intermediate AN for Intermediate H. ^{1}H-NMR (CD_3OD) δ 8.66 to 8.64 (m, 1H), 8.41 to 8.37 (m, 1H), 8.20 (s, 1H), 7.92 (s, 1H), 7.40 to 7.31 (m, 4H); MS $[M+H]^+$ = 474.1; LCMS RT = 2.92 min.

Example 257: Preparation of N-(4-{4-amino-6-[4-(morpholin-4-ylmethyl)-1,3-oxazol-2-yl]pyrrolo[2,1-f][1,2,4]triazin-5-yl}phenyl)-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea



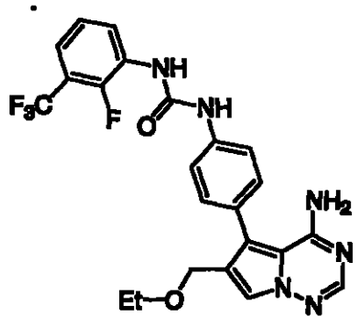
The procedure used for the preparation of Example 66 was used to prepare the title compound by substituting Intermediate AM for Intermediate I. ^{1}H-NMR (CD_3OD) δ 8.62 to 8.60 (d, J = 7.6 Hz, 1H), 8.15 (s, 1H), 7.85 (s, 1H), 7.65 (s, 1H), 7.61 to 7.59 (d, J = 8.7 Hz, 2H), 7.42 to 7.40 (d, J = 8.5 Hz, 2H), 7.35 to 7.33 (m, 2H), 3.69 to 3.66 (t, J = 4.7 Hz, 4H), 3.46 (s, 2H), 2.53 to 2.50 (t, J = 4.6 Hz, 4H); MS $[M+H]^+$ = 597.1; LCMS RT = 2.44 min.

Example 258: Preparation of ethyl 4-amino-5-[4-({[(4-methylpyridin-2-yl)amino]carbonyl}amino)phenyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate



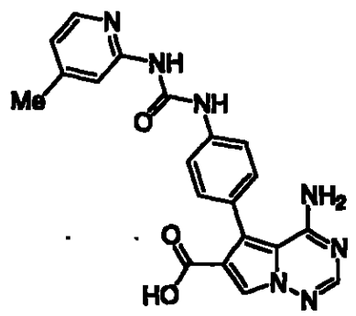
The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting Intermediate B for Intermediate X and by substituting diphenyl (4-methylpyridin-2-yl)imidodicarbonate for phenyl (4-*tert*-butylpyridin-2-yl)carbamate. ^{1}H-NMR (DMSO-d_6) δ 10.83 (s, 1H), 9.45 (s, 1H), 8.15 to 8.13 (d, J = 5.3 Hz, 1H), 8.13 (s, 1H), 7.93 (s, 1H), 7.62 to 7.60 (d, J = 8.3 Hz, 2H), 7.34 to 7.32 (d, J = 8.3 Hz, 2H), 7.28 (s, 1H), 6.87 to 6.86 (d, J = 5.3 Hz, 1H), 4.11 to 4.06 (q, J = 7.1 Hz, 2H), 2.30 (s, 3H) 1.13 to 1.10 (t, J = 7.1 Hz, 3H); MS $[M+H]^+$ = 432.1; LCMS RT = 2.30 min.

Example 259: Preparation of N-[4-[4-amino-6-(ethoxymethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl]-N'-[2-fluoro-3-(trifluoromethyl)phenyl]urea



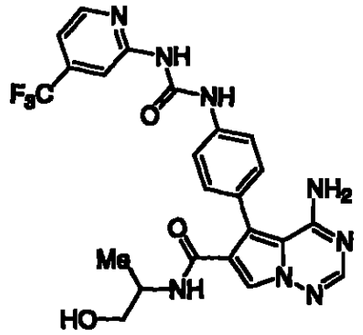
The procedure used for preparation of Example 1 was used to prepare the title compound by substituting 6-(ethoxymethyl)-5-(4-nitrophenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine for Intermediate B and substituting 2-fluoro-1-isocyanato-3-(trifluoromethyl)benzene for 1-fluoro-2-isocyanato-4-(trifluoromethyl)benzene. ^{1}H-NMR (DMSOD6) δ 9.28 (s, 1H), 8.89 (s, 1H), 8.48-8.42 (m, 1H), 7.83 (s, 1H), 7.73 (s, 1H), 7.59 (s, 1H), 7.56 (s, 1H), 7.36-7.32 (m, 4H), 4.28(s, 2H), 3.37 (q, J= 5.2 Hz, 2H), 1.06 (t, J= 7 Hz, 3H); MS $[M+H]^+$ = 489.1; LCMS RT = 2.87.

Example 260: Preparation of 4-amino-5-[4-({[(4-methylpyridin-2-yl)amino]carbonyl}amino)phenyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid



The procedure used for the preparation of Intermediate G was used to prepare the title compound by substituting ethyl 4-amino-5-[4-({[(4-methylpyridin-2-yl)amino]carbonyl}amino)phenyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate (Example 258) for Intermediate E. ^{1}H-NMR (DMSO-d_6) δ 12.28 (s, 1H) 10.82 (s, 1H), 9.46 (s, 1H), 8.14 to 8.13 (d, J = 5.4 Hz, 1H), 8.07 (s, 1H), 7.91 (s, 1H), 7.60 to 7.58 (d, J = 8.6 Hz, 2H), 7.34 to 7.31 (d, J = 8.6 Hz, 2H), 7.27 (s, 1H), 6.86 to 6.85 (d, J = 5.9 Hz, 1H), 2.30 (s, 3H); MS $[M+H]^+$ = 404.2; LCMS RT = 0.38 min.

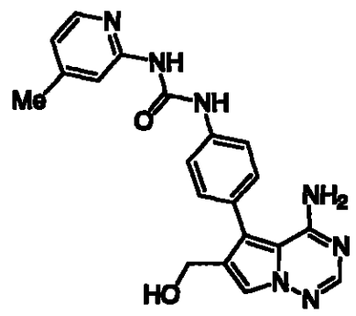
Example 261: Preparation of 4-amino-N-(2-hydroxy-1-methylethyl)-5-{4-[({[4-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



The procedure used for the preparation of Example 143 was used to prepare the title compound by substituting 1-aminopropan-2-ol for 2-amino-2-methylpropan-1-ol and Example 250 for Intermediate J. ^{1}H-NMR (DMSO-d_6) δ 9.87 (s, 1H), 9.74 (s, 1H), 8.54 to 8.53 (d, J = 5.0 Hz, 1H), 8.11 (s, 1H), 8.06 (s, 1H), 7.89 (s, 1H), 7.59 to 7.57 (d, J = 8.6 Hz, 2H), 7.37 to 7.31 (m, 4H), 4.65 to 4.62 (t, J = 5.8 Hz, 1H),

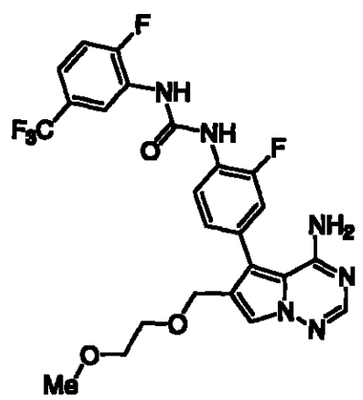
3.85 to 3.79 (m, 1H), 3.23 to 3.16 (m, 2H), 1.01 to 1.00 (d, J = 6.7 Hz, 3H); MS $[M+H]^+$ = 515.0; LCMS RT = 2.41 min.

Example 262: Preparation of N-{4-[4-amino-6-(hydroxymethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-(4-methylpyridin-2-yl)urea



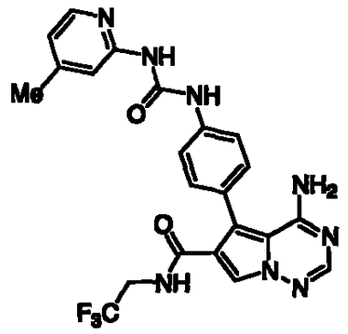
The procedure used for the preparation of Intermediate F Step 1 was used to prepare the title compound by substituting ethyl 4-amino-5-[4-({[(4-methylpyridin-2-yl)amino]carbonyl}amino)phenyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate (Example 258) for Intermediate E. ^{1}H-NMR (DMSO-d_6) δ 10.84 (s, 1H), 9.45 (s, 1H), 8.14 to 8.13 (d, J = 5.6 Hz, 1H), 7.82 (s, 1H), 7.65 (s, 1H), 7.64 to 7.62 (d, J = 8.5 Hz, 2H), 7.37 to 7.35 (d, J = 8.5 Hz, 2H), 7.27 (s, 1H), 6.86 to 6.85 (d, J = 5.1 Hz, 1H), 4.97 to 4.95 (t, J = 5.3 Hz, 1H), 4.38 to 4.37 (d, J = 5.4 Hz, 2H), 2.30 (s, 3H); MS $[M+H]^+$ = 390.0; LCMS RT = 1.51 min.

Example 263: Preparation of N-(4-{4-amino-6-[(2-methoxyethoxy)methyl]pyrrolo[2,1-f][1,2,4]triazin-5-yl}-2-fluorophenyl)-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea



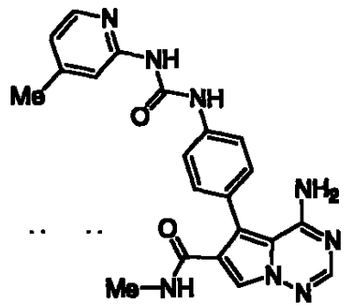
The procedure used for the preparation of Example 271 was used to prepare the title compound by substituting 3-methoxypropan-1-ol for methanol and Example 251 for Example 262. ^{1}H-NMR (CD_3OD) δ 8.64 (d, J = 6.9 Hz, 1H), 8.31 to 8.26 (m, 1H), 7.79 (s, 1H), 7.71 (s, 1H), 7.37 to 7.33 (m, 3H), 7.25 (d, J = 8.4 Hz, 1H), 4.49 (s, 2H), 3.54 to 3.52 (m, 2H), 3.33 (s, 3H); MS $[M+H]^+$ = 537.1; LCMS RT = 2.82 min.

Example 264: Preparation of 4-amino-5-[4-({[(4-methylpyridin-2-yl)amino]carbonyl}amino)phenyl]-N-(2,2,2-trifluoroethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



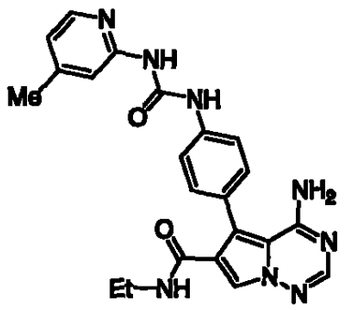
The procedure used for the preparation of Example 143 was used to prepare the title compound by substituting 2,2,2-trifluoroethanamine for 2-amino-2-methylpropan-1-ol and 4-amino-5-[4-({[(4-methylpyridin-2-yl)amino]carbonyl}amino)phenyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid (Example 260) for Intermediate J. ^{1}H-NMR (DMSO-d_6) δ 10.80 (s, 1H), 9.44 (s, 1H), 8.52 to 8.49 (t, J = 6.2 Hz, 1H), 8.18 (s, 1H), 8.14 to 8.13 (d, J = 5.3 Hz, 1H), 7.91 (s, 1H), 7.59 to 7.57 (d, J = 8.6 Hz, 2H), 7.31 to 7.28 (d, J = 8.6 Hz, 2H), 7.28 (s, 1H), 6.86 to 6.85 (d, J = 5.2 Hz, 1H), 3.97 to 3.93 (m, 2H), 2.30 (s, 3H); MS $[M+H]^+$ = 485.1; LCMS RT = 2.06 min.

Example 265: Preparation of 4-amino-N-methyl-5-[4-({[(4-methylpyridin-2-yl)amino]carbonyl}amino)phenyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



The procedure used for the preparation of Example 143 was used to prepare the title compound by substituting methanamine for 2-amino-2-methylpropan-1-ol and 4-amino-5-[4-({[(4-methylpyridin-2-yl)amino]carbonyl}amino)phenyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid (Example 260) for Intermediate J. ^{1}H-NMR (DMSO-d_6) δ 10.80 (s, 1H), 9.45 (s, 1H), 8.14 to 8.13 (d, J = 5.4 Hz, 1H), 8.05 (s, 1H), 7.89 (s, 1H), 7.82 to 7.80 (m, 1H), 7.59 to 7.57 (d, J = 8.6 Hz, 2H), 7.31 to 7.29 (d, J = 8.4 Hz, 2H), 7.28 (s, 1H), 6.86 to 6.85 (d, J = 5.1 Hz, 1H), 2.64 to 2.63 (d, J = 4.7 Hz, 3H), 2.30 (s, 3H); MS $[M+H]^+$ = 417.0; LCMS RT = 1.54 min.

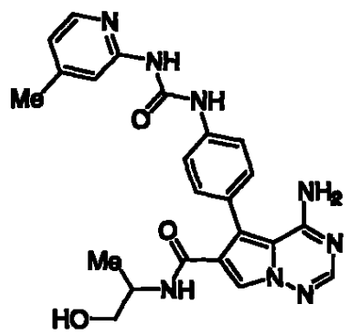
Example 266: Preparation of 4-amino-N-ethyl-5-[4-({[(4-methylpyridin-2-yl)amino]carbonyl}amino)phenyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



The procedure used for the preparation of Example 143 was used to prepare the title compound by substituting ethanamine for 2-amino-2-methylpropan-1-ol and 4-amino-5-[4-({[(4-methylpyridin-2-yl)amino]carbonyl}amino)phenyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid (Example 260) for Intermediate J. ^{1}H-NMR

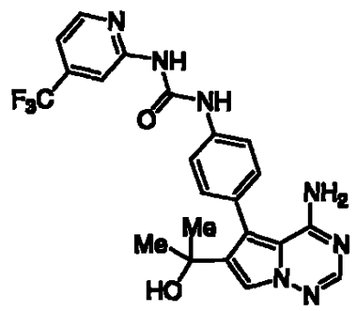
(DMSO-d_6) δ 10.80 (s, 1H), 9.45 (s, 1H), 8.14 to 8.13 (d, J = 5.1 Hz, 1H), 8.06 (s, 1H), 7.89 (s, 1H), 7.76 to 7.73 (t, J = 5.9 Hz, 1H), 7.59 to 7.57 (d, J = 8.6 Hz, 2H), 7.32 to 7.30 (d, J = 8.6 Hz, 2H), 7.28 (s, 1H), 6.86 to 6.85 (d, J = 6.9 Hz, 1H), 3.16 to 3.09 (m, 2H), 2.30 (s, 3H) 1.03 to 1.00 (t, J = 7.1 Hz, 3H); MS $[M+H]^+$ = 431.1; LCMS RT = 1.80 min.

Example 267: Preparation of 4-amino-N-(2-hydroxy-1-methylethyl)-5-[4-({[(4-methylpyridin-2-yl)amino]carbonyl}amino)phenyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



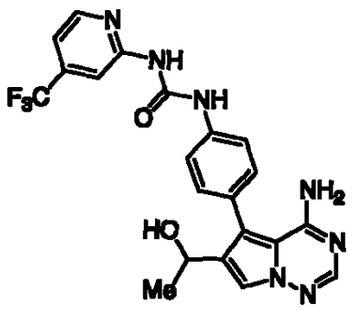
The procedure used for the preparation of Example 143 was used to prepare the title compound by substituting 2-aminopropan-1-ol for 2-amino-2-methylpropan-1-ol and 4-amino-5-[4-({[(4-methylpyridin-2-yl)amino]carbonyl}amino)phenyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid (Example 260) for Intermediate J. ^{1}H-NMR (DMSO-d_6) δ 10.82 (s, 1H), 9.45 (s, 1H), 8.14 to 8.13 (d, J = 5.2 Hz, 1H), 8.10 (s, 1H), 7.89 (s, 1H), 7.61 to 7.59 (d, J = 8.8 Hz, 2H), 7.33 to 7.31 (d, J = 8.6 Hz, 2H), 7.30 to 7.28 (m, 2H), 6.87 to 6.85 (d, J = 5.8 Hz, 1H), 4.65 to 4.62 (t, J = 5.7 Hz, 1H), 3.84 to 3.78 (m, 1H). 3.22 to 3.16 (m, 2H), 2.30 (s, 3H), 1.01 to 0.99 (d, J = 6.7 Hz, 3H)); MS $[M+H]^+$ = 461.1; LCMS RT = 1.62 min.

Example 268: Preparation of N-{4-[4-amino-6-(1-hydroxy-1-methylethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-[4-(trifluoromethyl)pyridin-2-yl]urea

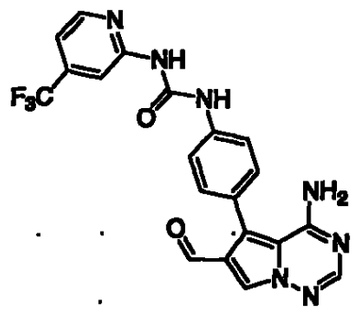


A solution of Example 51 (78 mg, 0.155 mmol) in 5 mL THF was treated with methylmagneaium bromide (0.78 mL, 2.3 mmol, 3N in Et_2O) and heated to 60 C for 4h. The reaction was quenched with MeOH and diluted with EtOAc and washed with sat. NH_4Cl. The organic layer was dried with sodium sulfate and evaporated to dryness. The residue was titurated with Et_2O to provide 64 mg of the title product (87% yield). ^{1}H-NMR (DMSO-d_6) δ 9.98 (s, 1H), 9.79 (s, 1H), 8.52 (d, J = 5 Hz, 1H), 8.70 (s, 1H), 7.77 (s, 1H), 7.58 (d, J = 9 Hz, 2H), 7.56 (s, 1H), 7.33 (d, J = 9 Hz, 2H), 7.30 to 7.35 (m, 1 H), 7.11 (bs, 2 H), 4.91 (s, 1 H), 1.24 (s, 6H); MS $[M+H]^+$ = 472.1; LCMS RT = 2.48 min.

Example 269: Preparation of N-{4-[4-amino-6-(1-hydroxyethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-[4-(trifluoromethyl)pyridin-2-yl]urea

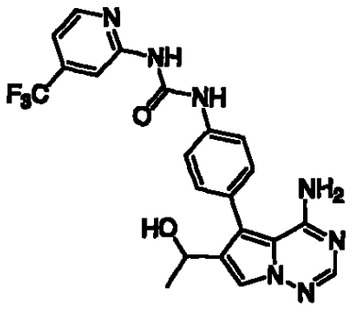


Step 1: Preparation of 4-amino-5-{4-[({[4-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid;



The procedure used for the preparation of Intermediate F was used to prepare the title compound by substituting Example 51 for Intermediate E. ^{1}H-NMR (DMSO-d_6) δ 9.97 (s, 1H), 9.78 (s, 1H), 9.75 (s, 1H), 8.54 (d, J = 5Hz, 1H), 8.27 (s, 1H), 8.07 (s, 1H), 7.96 (s, 1H), 7.67 (d, J = 9 Hz, 2H), 7.75 (d, J = 9 Hz, 2H), 7.36 (d, J = 5 Hz, 1H), 5.33 to 5.37 (m, 1H); MS $[M+H]^+$ = 422.0; LCMS RT = 2.77 min.

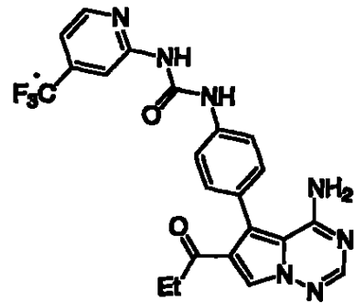
Step 2: Preparation of Preparation N-{4-[4-amino-6-(1-hydroxyethyl)pyrrolo[2,1f][1,2,4]triazin-5-yl]phenyl}-N'-[4-(trifluoromethyl)pyridin-2-yl]urea



A solution of 4-amino-5-{4-[({[4-(trifluoromethyl)pyridin-2-yl] amino} carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid (60 mg, 0.136 mmol) in 5 mL THF was treated with methylmagnesium bromide (0.68 mL, 2.1 mmol, 3 M in Et_2O) dropwise over 2 min. The reaction was allowed to stir for 15 min, then quenched with MeOH, diluted with EtOAc and washed with aq. NH_4Cl. The organic layer was dried with sodium sulfate and evaporated to dryness. The residue was triturated with Et_2O to provide 50.1 mg of the title compound (82% yield). ^{1}H-NMR

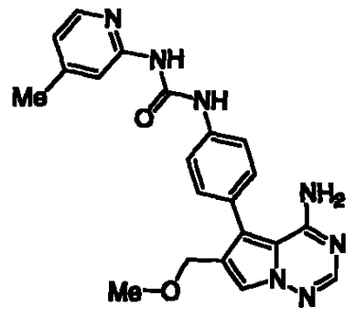
(DMSO-d_6) δ 10.05 (s, 1H), 9.82 (s, 1H), 8.52 (d, J = 5 Hz, 1H), 8.09 (s, 1H), 7.81 (s, 1H), 7.64 (s, 1H), 7.61 (d, J = 9 Hz, 2H), 7.34 (d, J = 9 Hz, 2H), 4.96 (d, J = 5 Hz, 1 H), 4.63 (dq, J = 5, 6 Hz, 1 H), 1.24 (d, J = 6 Hz, 3 H); MS $[M+H]^+$ = 458.0; LCMS RT = 2.41 min.

Example 270: Preparation of N-[4-(4-amino-6-propionylpyrrolo[2,1-f][1,2,4]triazin-5-yl)phenyl]-N'-[4-(trifluoromethyl)pyridin-2-yl]urea



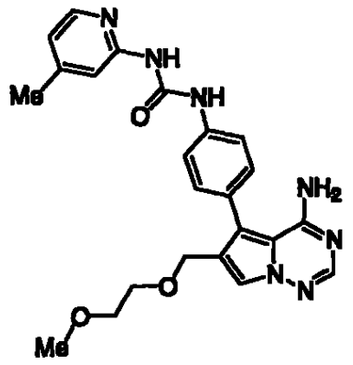
The procedure used for the preparation of Example 233 was used to prepare the title compound by substituting Example 274 for Example 269. ^{1}H-NMR (DMSO-d_6) δ 9.98 (s, 1H), 9.85 (s,1H), 8.53 (d, J = 5 Hz, 1H), 8.37 (s, 1H), 8.07 (s, 1H), 8.00 to 8.10 (bs, 1H), 7.59 (d, J = 9 Hz, 2H), 7.30 to 7.39 (m, 3H), 2.71 (d, J = 7 Hz, 2H), 0.92 (t, J = 7 Hz, 3H); MS $[M+Na]^+$ = 492.0; LCMS RT = 2.87 min.

Example 271: Preparation of N-{4-[4-amino-6-(methoxymethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-(4-methylpyridin-2-yl)urea



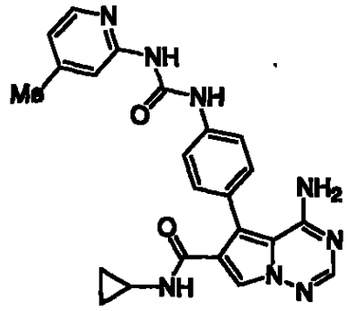
To a solution of DCM (5 mL) was added N-{4-[4-amino-6-(hydroxymethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-(4-methylpyridin-2-yl)urea (Example 262) (40 mg, 0.10 mmol) followed by 2M thionyl chloride in DCM (0.51 mL, 1.03 mmol). The solution was stirred at rt for 1h and was then evaporated in vacuo. THF (5 mL) and MeOH (5 mL) were added to the crude reaction followed by triethylamine (43 μL, 0.31 mmol). The solution was heated to 50 °C for 3d and then evaporated in vacuo and purified by MPLC (Isco) 0-5% MeOH/DCM. The resulting purified fractions were combined and evaporated producing 25 mg of the title compound (0.061 mmol, yield 60%). ^{1}H-NMR (DMSO-d_6) δ 10.86 (s, 1H), 9.46 (s, 1H), 8.14 to 8.13 (d, J = 6.3 Hz, 1H), 7.84 (s, 1H), 7.75 (s, 1H), 7.65 to 7.63 (d, J = 8.7 Hz, 2H), 7.36 to 7.34 (d, J = 8.6 Hz, 2H), 7.27 (s, 1H), 6.87 to 6.86 (d, J = 5.0 Hz, 1H), 4.27 (s, 2H), 3.20 (s, 3H), 2.30 (s, 3H); MS $[M+H]^+$ = 404.0; LCMS RT = 1.99 min.

Example 272: Preparation of N-(4-{4-amino-6-[(2-methoxyethoxy)methyl]pyrrolo[2,1-f][1,2,4]triazin-5-yl}phenyl)-N'-(4-methylpyridin-2-yl)urea



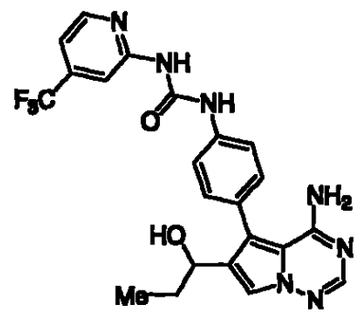
The procedure used for the preparation of Example 271 was used to prepare the title compound by substituting 2-methoxyethanol for MeOH. ^{1}H-NMR (DMSO-d_6) δ 10.85 (s, 1H), 9.46 (s, 1H), 8.14 to 8.13 (d, J = 5.4 Hz, 1H), 7.84 (s, 1H), 7.75 (s, 1H), 7.65 to 7.62 (d, J = 8.6 Hz, 2H), 7.38 to 7.36 (d, J = 8.1 Hz, 2H), 7.26 (s, 1H), 6.87 to 6.85 (d, J = 5.9 Hz, 1H), 4.33 (s, 2H), 3.49 to 3.46 (m, 2H), 3.43 to 3.40 (m, 2H), 3.22 (s, 2H), 2.30 (s, 3H); MS $[M+H]^+$ = 448.0; LCMS RT = 2.00 min.

Example 273: Preparation of 4-amino-N-cyclopropyl-5-[4-({[(4-methylpyridin-2-yl)amino]carbonyl}amino)phenyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



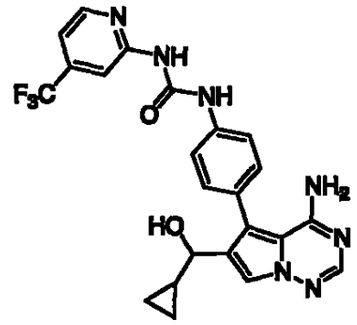
The procedure used for the preparation of Example 143 was used to prepare the title compound by substituting cyclopropanamine for 2-amino-2-methylpropan-1-ol and 4-amino-5-[4-({[(4-methylpyridin-2-yl)amino]carbonyl}amino)phenyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid (Example 260) for Intermediate J. ^{1}H-NMR (DMSO-d_6) δ 10.79 (s, 1H), 9.45 (s, 1H), 8.15 to 8.13 (d, J = 5.6 Hz, 1H), 8.05 (s, 1H), 7.89 (s, 1H), 7.83 to 7.82 (d, J = 3.6 Hz, 1H), 7.59 to 7.57 (d, J = 8.7 Hz, 2H), 7.31 to 7.29 (m, 3H), 6.86 to 6.85 (d, J = 5.1 Hz, 1H), 2.68 to 2.63 (m, 1H), 2.30 (s, 3H). 0.63 to 0.58 (m, 2H), 0.44 to 0.40 (m, 2H); MS $[M+H]^+$ = 465.1; LCMS RT = 1.86 min.

Example 274: Preparation of N-[4-[4-amino-6-(1-hydroxypropyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl]-N'-[4-(trifluoromethyl)pyridin-2-yl]urea



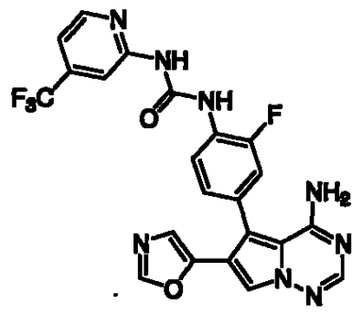
The procedure used for the preparation of Example 269 was used to prepare the title compound by substituting ethylmagnesium bromide for methylmagnesium bromide. ^{1}H-NMR (DMSO-d_6) δ 9.95 (s, 1H), 9.77 (s, 1H), 8.53 (d, J = 5 Hz, 1H), 8.04 (s, 1H), .1 to 8.2 (bs, 1H), 8.05 to 8.10 (m, 1H), 7.65 (d, J = 9 Hz, 2H), 7.39 (d, J = 9 Hz, 2H), 7.32 to 7.40 (m, 1H); MS $[M+H]^+$ = 472.0; LCMS RT = 2.59 min.

Example 275: Preparation of N-(4-{4-amino-6-[cyclopropyl(hydroxy)methyl]pyrrolo[2,1-f][1,2,4]triazin-5-yl}phenyl)-N'-[4-(trifluoromethyl)pyridin-2-yl]urea



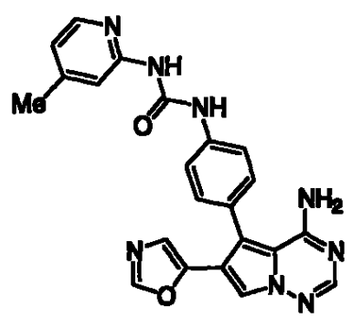
The procedure used for the preparation of Example 269 was used to prepare the title compound by substituting cyclopropylmagnesium bromide for methylmagnesium bromide. ^{1}H-NMR (DMSO-d_6) δ 9.95 (s, 1H), 9.83 (s, 1H), 8.61 (d, J = 5 Hz, 1H), 8.14 (s, 1H), 7.91 (s, 1H), 7.78 (s, 1H), 7.69 (d, J = 9 Hz, 2H), 7.40 to 46 (m, 3H), 5.00 (d, J = 5 Hz, 1H), 4.00-4.02 (m, 1H), 0.25 to 0.48 (m, 3H), 0.00 to 0.08 (m, 2H); MS $[M+H]^+$ = 484.0; LCMS RT = 2.60 min.

Example 276: Preparation of N-{4-[4-amino-6-(1,3-oxazol-5-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]-2-fluorophenyl}-N'-[4-(trifluoromethyl)pyridin-2-yl]urea



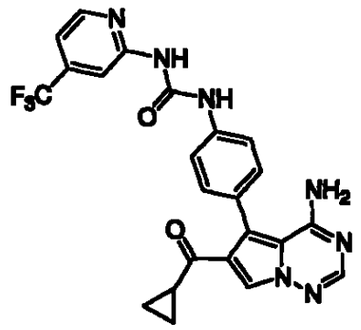
To a solution of THF (10 mL) and MeOH (10 mL) cooled in an ice/water bath was added 0.5 M sodium methoxide in MeOH (0.96 mL, 0.48 mmol) followed by TosMIC (93 mg, 0.48 mmol). The solution was allowed to stir for 5min and then Intermediate AL (73 mg, 0.16 mmol) was added. The solution was heated to 60 °C for 17h. The reaction mixture was allowed to cool and was transferred to a separatory funnel, diluted with EtOAc (20 mL), washed with aq saturated $NaHCO_3$ (20 mL) and H_2O (20 mL). The aqueous layer was back extracted with EtOAc (2 x 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, evaporated in vacuo and purified by flash chromatography 5:4:1 v/v/v DCM/EtOAc/MeOH the resulting purified fractions were combined and evaporated providing 26 mg of the title compound as a white solid (0.052 mmol, yield 33%). ^{1}H-NMR (DMSO-d_6) δ 10.18 (s, 1H), 10.16 to 10.12 (br s, 1H), 8.55 to 8.54 (d, J = 5.4 Hz, 1H), 8.35 to 8.31 (t, J = 8.3 Hz, 1H), 8.30 (s, 1H), 8.10 (s, 1H), 8.01 (s, 1H), 7.91 (s, 1H), 7.39 to 7.36 (m, 2H), 7.23 to 7.21 (d, J = 10.4 Hz, 1H), 6.63 (s, 1H); MS $[M+H]^+$ = 499.0; LCMS RT = 2.85 min.

Example 277: Preparation of N-{4-[4-amino-6-(1,3-oxazol-5-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-(4-methylpyridin-2-yl)urea



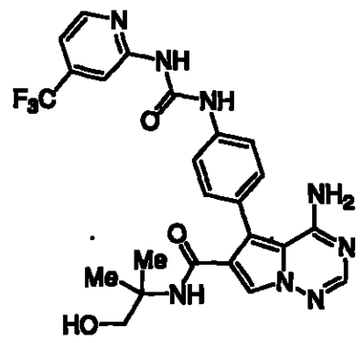
The procedure used for the preparation of Example 276 was used to prepare the title compound by Intermediate AK for Intermediate 5. ^{1}H-NMR (DMSO-d_6) δ 10.92 (s, 1H), 9.50 (s, 1H), 8.29 (s, 1H), 8.15 to 8.14 (d, J = 4.9 Hz, 1H), 8.09 (s, 1H), 7.90 (s, 1H), 7.69 to 7.67 (d, J = 8.4 Hz, 2H), 7.38 to 7.36 (d, J = 8.5 Hz, 2H), 7.27 (s, 1H), 6.87 to 6.86 (d, J = 5.8 Hz, 1H), 6.57 (s, 1H), 2.30 (s, 3H); MS $[M+H]^+$ = 427.1; LCMS RT = 2.09 min.

Example 278: Preparation of N-[4-[4-amino-6-(cyclopropylcarbonyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl]-N'-[4-(trifluoromethyl)pyridin-2-yl]urea

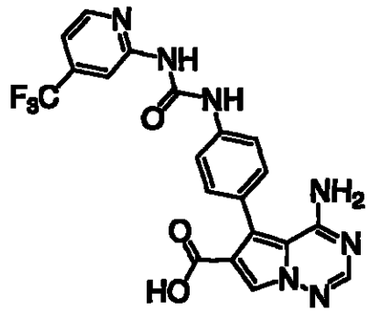


The procedure used for the preparation of Example 233 was used to prepare the title compound by substituting Example 275 for Example 269. ^{1}H-NMR (DMSO-d_6) δ 9.87 (s, 1H), 9.74 (s, 1H), 8.53 (d, J = 5 Hz, 1H), 8.51 (s, 1H), 8.05 (s, 1H), 8.00 to 8.05 (bs, 1H), 7.57 (d, J = 9 Hx, 2H), 7.30 to 7.40 (m, 3H), 2.40 (m, 1H), 0.76 to 0.9 (m, 4H); MS $[M+H]^+$ = 482.0; LCMS RT = 2.96 min.

Example 279: Preparation of 4-amino-N-(2-hydroxy-1,1-dimethylethyl)-5-{4-[({[4-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide

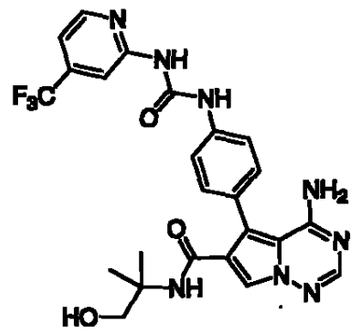


Step 1: Preparation of 4-amino-5-{4-[({[4-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid



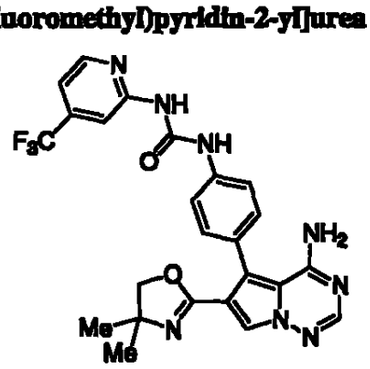
The procedure used for the preparation of Intermediate G was used to prepare the title compound by substituting Example 51 for Intermediate E. ^{1}H-NMR (DMSO-d_6) δ 12.28 (bs, 1H), 9.87 (s, 1H) 9.75 (s, 1H), 8.53 (d, J = 5 Hz, 1H), 8.07 (s, 1H), 8.06 (s, 1H), 7.91 (s, 1H), 7.57 (d, J = 9 Hz, 2H), 7.34 to 7.37 (m, 1H), 7.34 (d, J = 9 Hz, 2H); MS $[M+H]^+$ = 458.1; LCMS RT = 2.53 min.

Step 2: Preparation 4-amino-N-(2-hydroxy-1,1-dimethylethyl)-5-{4-[({[4-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



The procedure used for the preparation of Example 143 was used to prepare the title compound by substituting 4-amino-5-{4-[({[4-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid for Intermediate J. ^{1}H-NMR (DMSO-d_6) δ 9.92 (s, 1H), 9.77 (s, 1H), 8.54 (d, *J*= 5.0Hz, 1H), 8.06 (s, 1H), 8.03 (s, 1H), 7.89 (s, 1H), 7.62 (d, *J*= 8.8Hz, 2H), 7.36 (d, *J*= 8.8Hz, 4H), 6.53(s, 1H), 4.75 (t, *J*= 6.2 Hz, 2H), 3.27 (d, *J*= 5.9 Hz, 2H), 1.09(s, 6H); MS $[M+H]^+$ = 529.0; LCMS RT = 2.59 min.

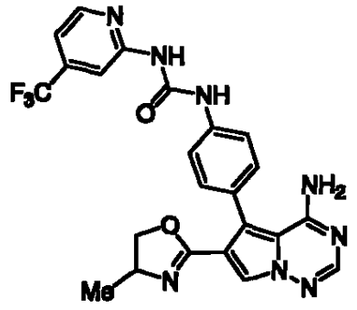
Example 280: Preparation of N-{4-[4-amino-6-(4,4-dimethyl-4,5-dihydro-1,3-oxazol-2-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-[4-(trifluoromethyl)pyridin-2-yl]urea



A solution of Example 279 (25 mg, 0.047 mmol) in 2 mL CH_2Cl_2 was treated with thionyl chloride (0.95 mmol, 11.2 mg) and allowed to stir for 15 min. The reaction was diluted with ethyl acetate and washed with sodium bicarbonate. The organic layer was dried (Na_2SO_4), filtered and concentrated to dryness. The residue was triturated with Et_2O/hexanes to give 19.4 mg of the above compound as a yellow

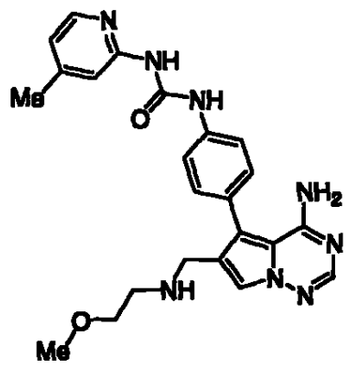
solid (yield 81%). ^{1}H-NMR (DMSO-d_6) δ 10.40 (s, 1H), 9.96 (s, 1H), 8.91 (s, 1H), 8.54 (d, *J*= 6.2Hz, 1H), 8.13 (s, 1H), 8.07 (s, 1H), 7.64 (d, *J*= 8.8Hz, 2H), 7.44 (d, *J*= 8.8Hz, 4H), 7.35 (d, *J*= 5.3Hz, 1H), 5.67 (bs, 1H), 4.54 (s, 2H), 1.47 (s, 6H); MS $[M+H]^+$ = 511.0; LCMS RT = 2.44 min.

Example 281: Preparation of N-{4-[4-amino-6-(4-methyl-4,5-dihydro-1,3-oxazol-2-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-[4-(trifluoromethyl)pyridin-2-yl]urea



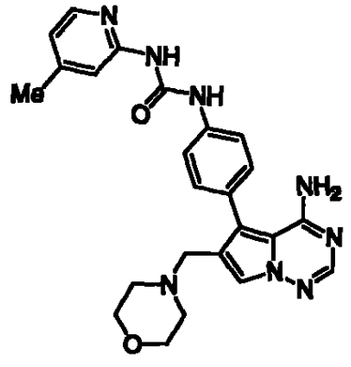
The procedure used for the preparation of Example 230 was used to prepare the title compound by substituting 4-amino-N-(2-hydroxy-1-methylethyl)-5-{4-[({[4-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide (Example 261) for ethyl 2-(4-amino-5-{4-[({[4-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazin-6-yl)-4,5-dihydro-1,3-oxazole-4-carboxylate (Example 221). ^{1}H-NMR (DMSO-d_6) δ 9.89 (s, 1H), 9.77 (s, 1H), 8.54 to 8.53 (d, *J* = 5.3 Hz, 1H), 8.05 (s, 1H), 8.01 (s, 1H), 7.90 (s, 1H), 7.58 to 7.56 (d, *J* = 8.7 Hz, 2H), 7.37 to 7.36 (m, 1H), 7.35 to 7.33 (d, *J* = 8.6 Hz, 2H), 4.28 to 4.24 (t, *J* = 8.6 Hz, 2H), 4.15 to 4.06 (m, 1H), 3.71 to 3.67 (t, *J* = 7.9 Hz, 2H, 1.13 to 1.11 (d, *J* = 6.6 Hz, 3H); MS $[M+H]^+$ = 497.0; LCMS RT = 2.43 min.

Example 282: Preparation of N-[4-(4-amino-6-{[(2-methoxyethyl)amino]methyl}pyrrolo[2,1-f][1,2,4]triazin-5-yl)phenyl]-N'-(4-methylpyridin-2-yl)urea



The procedure used for the preparation of Example 66 was used to prepare the title compound by substituting Intermediate AK for Intermediate I and 2-methoxyethanamine for morpholine. ^{1}H-NMR (CD_3OD) δ 8.15 to 8.14 (d, J = 5.3 Hz, 1H), 7.81 (s, 1H), 7.80 (s, 1H), 7.74 to 7.72 (d, J = 8.7 Hz, 2H), 7.42 to 7.40 (d, J = 8.6 Hz, 2H), 7.00 (s, 1H), 6.90 to 6.89 (d, J = 5.3 Hz, 1H), 4.04 (s, 2H), 3.49 to 3.46 (t, J = 5.1 Hz, 2H), 2.95 to 2.92 (t, J = 5.1 Hz, 2H), 2.37 (s, 3H), 1.93 (s, 3H); MS $[M+H]^+$ = 446.9; LCMS RT = 1.25 min.

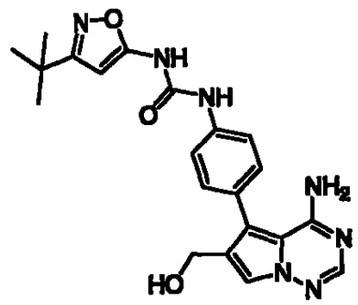
Example 283: Preparation of N-{4-[4-amino-6-(morpholin-4-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-(4-methylpyridin-2-yl)urea



The procedure used for the preparation of Example 66 was used to prepare the title compound by substituting Intermediate AK for Intermediate I. ^{1}H-NMR (DMSO-d_6) δ 10.90 to 10.87 (br s, 1H), 9.48 (s, 1H), 8.14 to 8.13 (d, J = 5.1 Hz, 1H), 7.82 (s, 1H), 7.64 (s, 1H), 7.64 to 7.62 (d, J = 8.5 Hz, 2H), 7.40 to 7.38 (d, J = 8.5

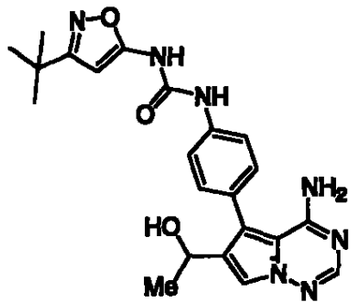
Hz, 2H), 7.26 (s, 1H), 6.87 to 6.85 (d, J = 5.6 Hz, 1H), 3.55 to 3.50 (m, 4H), 3.34 to 3.33 (br s, 2H), 2.32 to 2.28 (m, 4H), 2.30 (s, 3H); MS $[M+H]^+$ = 459.0; LCMS RT = 1.16 min.

Example 284: Preparation of N-[4-[4-amino-6-(hydroxymethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl]-N'-(3-tert-butylisoxazol-5-yl)urea



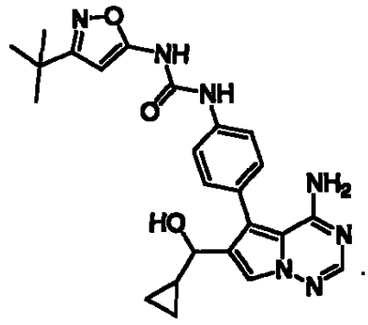
The procedure used for the preparation of Intermediate F was used to prepare the title compound by substituting Example 52 for Intermediate E. ^{1}H-NMR (DMSO-d_6) δ 10.13 (s, 1H), 8.96 (s, 1H), 7.82 (s, 1H), 7.65 (s, 1H), 7.56 (d, J = 9 Hz, 2H), 7.35 (d, J = 9 Hz, 2H), 6.05 (s, 1H), 4.94 (t, J = 5 Hz, 1 H), 4.35 (d, J = 5 Hz, 2H), 1.24 (s, 9H); MS $[M+H]^+$ = 422.1; LCMS RT = 2.26 min.

Example 285: Preparation of N-[4-[4-amino-6-(1-hydroxyethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl]-N'-(3-tert-butylisoxazol-5-yl)urea



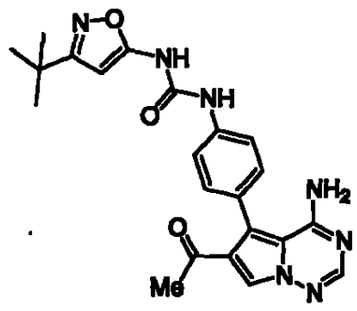
The procedure used for the preparation of Example 269 was used to prepare the title compound by substituting Example 52 for Example 51. ^{1}H-NMR (DMSO-d_6) δ 10.19 (s, 1H), 9.07 (s, 1H), 8.81 (s, 1H), 7.64 (s, 1H), 7.56 (d, J = 8 Hz, 2H), 7.30 to 7.40 (m, 2H), 6.05 (s, 1H), 4.95 (m, 1), 4.60 to 4.64 (m, 1H), 1.36 (m, 2H), 1.23 (s, 9H); MS $[M+H]^+$ = 436.1; LCMS RT =2.41 min.

Example 286: Preparation of N-(4-[4-amino-6-[cyclopropyl(hydroxy)methyl]pyrrolo[2,1-f][1,2,4]triazin-5-yl}phenyl)-N'-(3-tert-butylisoxazol-5-yl)urea



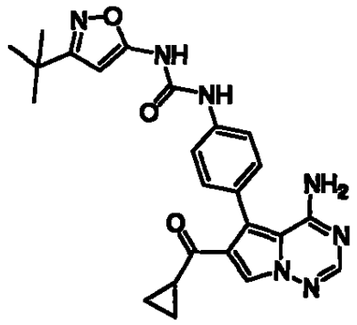
The procedure used for the preparation of Example 269 was used to prepare the title compound by substituting Example 52 for Example 51 and by substituting cyclopropylmagnesium bromide for methylmagnesium bromide. ^{1}H-NMR (DMSO-d_6) δ 10.24 (s, 1H), 9.07 (s, 1H), 8.81 (s, 1H), 7.64 (s, 1H), 7.56 (d, J = 8 Hz, 2H), 7.30 to 7.40 (m, 2H), 6.05 (s, 1H) 4.98 (d, J = 5Hz, 1H), 3.97 to 4.01 (m, 1H), 1.28 (s, 9H), 0.25 to 0.48 (m, 3H), 0.00 to 0.08 (m, 2H); MS $[M+H]^+$ = 434.1; LCMS RT =2.63 min.

Example 287: Preparation of N-[4-(6-acetyl-4-aminopyrrolo[2,1-f][1,2,4]triazin-5-yl)phenyl]-N'-(3-tert-butylisoxazol-5-yl)urea



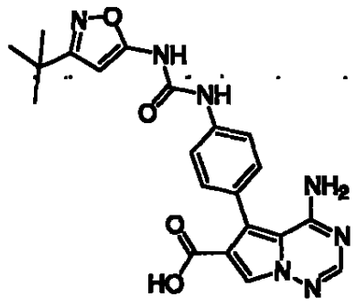
The procedure used for the preparation of Example 233 was used to prepare the title compound by substituting Example 285 for Example 269 . ^{1}H-NMR (DMSO-d_6) δ 10.15 (s, 1H), 8.98 (s, 1H), 8.37 (s, 1H), (8.01 (bs, 1H), 7.92 (s, 1H), 7.53 (d, J = 9 Hz, 2H), 7.30 (d, J = 9 Hz, 2H), 6.05 (s, 1H), 2.27 (s, 3H); MS $[M+H]^+$ = 434.1; LCMS RT = 2.63 min.

Example 288: Preparation of N-[4-[4-amino-6-(cyclopropylcarbonyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl]-N'-(3-tert-butylisoxazol-5-yl)urea



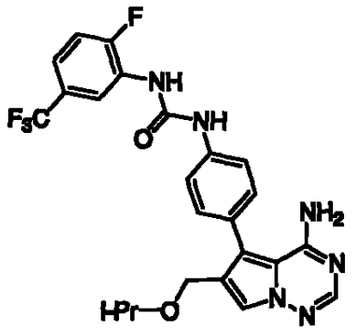
The procedure used for the preparation of Example 233 was used to prepare the title compound by substituting Example286 for Example 269. ^{1}H-NMR (DMSO-d_6) δ δ 10.15 (s, 1H), 8.98 (s, 1H), 8.37 (s, 1H), (8.01 (bs, 1H), 7.92 (s, 1H), 7.53 (d, J = 9 Hz, 2H), 7.30 (d, J = 9 Hz, 2H), 6.05 (s, 1H); MS $[M+H]^+$ = 460.1; LCMS RT = 2.81 min.

Example 289: Preparation of 4-amino-5-[4-({[(3-tert-butylisoxazol-5-yl)amino]carbonyl}amino)phenyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid



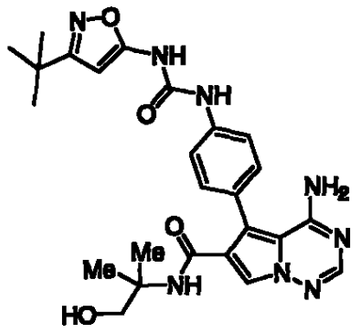
The procedure used for the preparation of Intermediate G was used to prepare the title compound by substituting Example 52 for Intermediate E. ^{1}H-NMR (DMSO-d_6) δ 10.18 (s, 1H), 9.04 (s, 1H), 8.07 (s, 1H), 7.19 (s, 1H), 7.52 (d, J= 8.2 Hz, 1H), 7.31 (d, J= 8.2Hz, 2H), 6.05 (s, 1H), 5.73 (s, 1H), 1.24 (s, 9H); MS $[M+H]^+$ = 436.1; LCMS RT = 2.43 min.

Example 290: Preparation of N-{4-[4-amino-6-(isopropoxymethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea



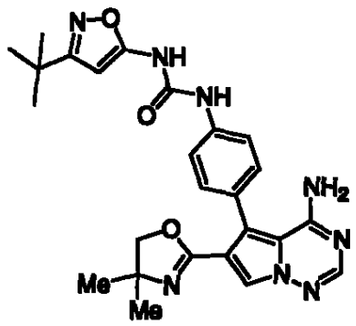
The procedure used for the preparation of Example 246 was used to prepare the title compound by substituting isopropyl alcohol for ethanol. ^{1}H-NMR (DMSO-d_6) δ 12.25 (s, 1H), 8.48 (d, J= 6.8Hz, 1H), 8.27 (s, 1H), 8.04 (s, 1H), 7.61-7.51 (m, 3H), 7.18 (d, J= 8.2Hz, 2H), 6.70 (d, J= 8.2Hz, 2H), 4.33 (s, 2H), 3.55 (m, 1H), 1.04 (d, J= 6.2Hz, 6H); MS $[M+H]^+$ = 503.1; LCMS RT = 3.70 min.

Example 291: Preparation of 4-amino-5-[4-({[(3-tert-butylisoxazol-5-yl)amino]carbonyl}amino)phenyl]-N-(2-hydroxy-1,1-dimethylethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



The procedure used for the preparation of Example 143 was used to prepare the title compound by substituting Example 289 for Intermediate J. ^{1}H-NMR (DMSO-d_6) δ 10.14 (s, 1H), 9.00 (s, 1H), 8.03 (s, 1H), 7.89 (s, 1H), 7.56 (d, *J*= 8.8Hz, 2H), 7.34 (d, *J*= 8.8Hz, 4H), 6.51(s, 1H), 6.06 (s, 1H), 5.74 (s, 1H), 4.75 (t, *J*= 3.8 Hz, 1H), 3.27 (bs, 2) 1.24(s, 9H), 1.09 (s, 6H) ; MS $[M+H]^+$ = 507.1; LCMS RT = 2.46 min.

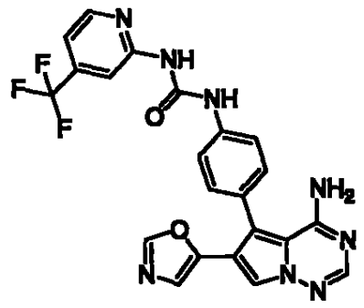
Example 292: Preparation of N-[4-[4-amino-6-(4,4-dimethyl-4,5-dihydro-1,3-oxazol-2-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl]-N'-(3-tert-butylisoxazol-5-yl)urea



The procedure used for the preparation of Example 280 was used to prepare the title compound by substituting Example 291 for Example 279. ^{1}H-NMR

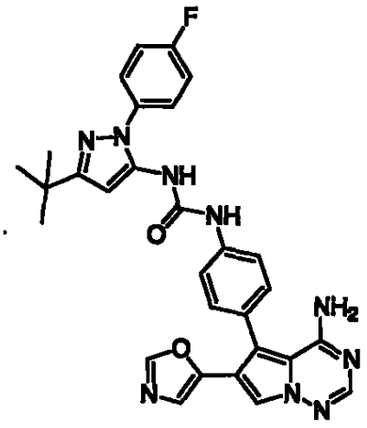
(DMSO-d_6) δ 10.19 (s, 1H), 9.43 (s, 1H), 8.61 (s, 1H), 8.41 (bs, 1H), 8.01 (s, 1H), 7.56 (d, J= 8.8Hz, 2H), 7.40 (d, J= 8.8Hz, 2H), 6.12(s, 1H), 5.41 (bs, 1H), 4.45 (s, 2H), 1.41 (s, 6H), 1.24(s, 9H); MS $[M+H]^+$ = 489.1; LCMS RT = 2.36 min.

Example 293: Preparation of N-{4-[4-amino-6-(1,3-oxazol-5-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-(4-tert-butylpyridin-2-yl)urea



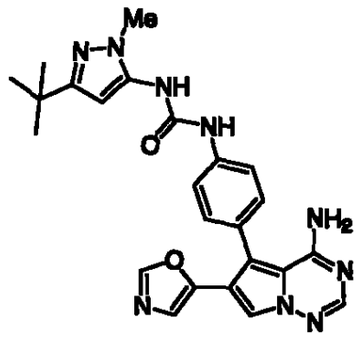
The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting Intermediate AB for Intermediate X. ^{1}H-NMR (DMSO-d_6) δ 10.96 to 10.93 (br s, 1H), 9.48 (s, 1H), 8.30 (s, 1H), 8.20 to 8.18 (d, J = 6.1 Hz, 1H), 8.09 (s, 1H), 7.90 (s, 1H), 7.70 to 7.68 (d, J = 8.6 Hz, 2H), 7.50 (s, 1H), 7.38 to 7.36 (d, J = 8.5 Hz, 2H), 7.08 to 7.06 (d, J = 5.4 Hz, 1H), 6.57 (s, 1H), 1.28 (s, 9H); MS $[M+H]^+$ = 469.1; LCMS RT = 2.44 min.

Example 294: Preparation of N-{4-[4-amino-6-(1,3-oxazol-5-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-[3-tert-butyl-1-(4-fluorophenyl)-1H-pyrazol-5-yl]urea



The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting Intermediate AB for Intermediate X and by substituting phenyl [3-tert-butyl-1-(4-fluorophenyl)-1H-pyrazol-5-yl]carbamate for phenyl (4-*tert*-butylpyridin-2-yl)carbamate. ^{1}H-NMR (DMSO-d_6) δ 9.19 (s, 1H), 8.45 (s, 1H), 8.28 (s, 1H), 8.07 (s, 1H), 7.89 (s, 1H), 7.58 to 7.54 (m, 4H), 7.39 to 7.31 (m, 4H), 6.53 (s, 1H), 6.36 (s, 1H), 1.28 (s, 9H); MS $[M+H]^+$ = 552.1; LCMS RT = 2.88 min.

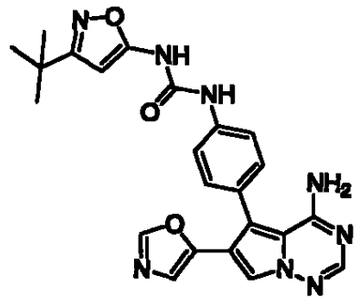
Example 295: Preparation of N-{4-[4-amino-6-(1,3-oxazol-5-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)urea



The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting Intermediate AB for Intermediate X and by substituting phenyl (3-tert-butyl-1-methyl-1H-pyrazol-5-yl)carbamate for phenyl (4-

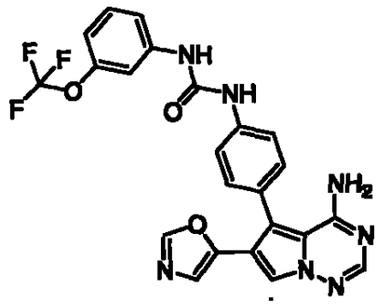
tert-butylpyridin-2-yl)carbamate. ^{1}H-NMR (DMSO-d_6) δ 9.10 (s, 1H), 8.54 (s, 1H), 8.29 (s, 1H), 8.08 (s, 1H), 7.90 (s, 1H), 7.62 to 7.59 (d, J = 8.6 Hz, 2H), 7.35 to 7.33 (d, J = 8.6 Hz, 2H), 6.54 (s, 1H), 6.05 (s, 1H), 3.61 (s, 3H), 1.22 (s, 9H); MS $[M+H]^+$ = 472.2; LCMS RT = 2.43 min.

Example 296: Preparation of N-{4-[4-amino-6-(1,3-oxazol-5-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-(3-tert-butylisoxazol-5-yl)urea



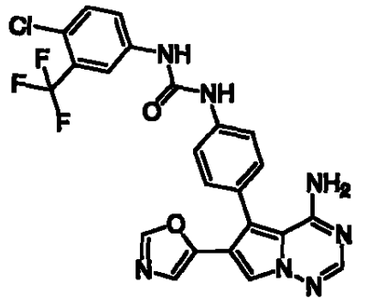
The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting Intermediate AB for Intermediate X and by substituting phenyl (3-tert-butylisoxazol-5-yl)carbamate for phenyl (4-*tert*-butylpyridin-2-yl)carbamate. ^{1}H-NMR (DMSO-d_6) δ 10.21 (s, 1H), 9.07 (s, 1H), 8.29 (s, 1H), 8.09 (s, 1H), 7.90 (s, 1H), 7.62 to 7.60 (d, J = 8.6 Hz, 2H), 7.38 to 7.35 (d, J = 8.5 Hz, 2H), 6.55 (s, 1H), 6.07 (s, 1H), 1.26 (s, 9H); MS $[M+H]^+$ = 459.1; LCMS RT = 2.65 min.

Example 297: Preparation of N-{4-[4-amino-6-(1,3-oxazol-5-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-[3-(trifluoromethoxy)phenyl]urea



The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting Intermediate AB for Intermediate X and by substituting phenyl [3-(trifluoromethoxy)phenyl]carbamate for phenyl (4-*tert*-butylpyridin-2-yl)carbamate. ^{1}H-NMR (DMSO-d_6) δ 9.11 (s, 1H), 9.02 (s, 1H), 8.30 (s, 1H), 8.08 (s, 1H), 7.90 (s, 1H), 7.71 (s, 1H), 7.62 to 7.60 (d, J = 8.4 Hz, 2H), 7.42 to 7.38 (t, J = 8.1 Hz, 1H), 7.36 to 7.34 (d, J = 8.7 Hz, 2H), 7.32 to 7.29 (d, J = 9.1 Hz, 1H), 6.96 to 6.93 (d, J = 10.6, 1H), 6.55 (s, 1H); MS $[M+H]^+$ = 496.1; LCMS RT = 2.89 min.

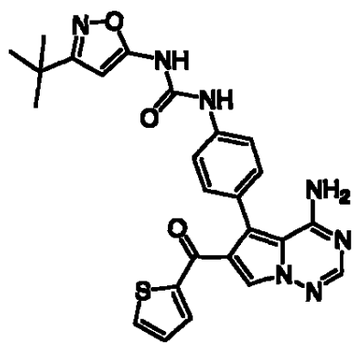
Example 298: Preparation of N-[4-[4-amino-6-(1,3-oxazol-5-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl]-N'-[4-chloro-3-(trifluoromethyl)phenyl]urea



The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting Intermediate AB for Intermediate X and by substituting phenyl [4-chloro-3-(trifluoromethyl)phenyl]carbamate for phenyl (4-*tert*-butylpyridin-2-yl)carbamate. ^{1}H-NMR (DMSO-d_6) δ 9.26 (s, 1H), 9.08 (s, 1H), 8.30

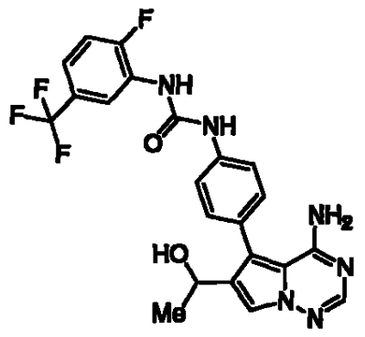
(s, 1H), 8.12 (s, 1H), 8.09 (s, 1H), 7.90 (s, 1H), 7.64 to 7.61 (m, 4H), 7.37 to 7.35 (d, J = 8.5 Hz, 2H), 6.55 (s, 1H); MS $[M+H]^+$ = 514.1; LCMS RT = 3.02 min.

Example 299: Preparation of N-{4-[4-amino-6-(2-thienylcarbonyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-(3-tert-butylisoxazol-5-yl)urea



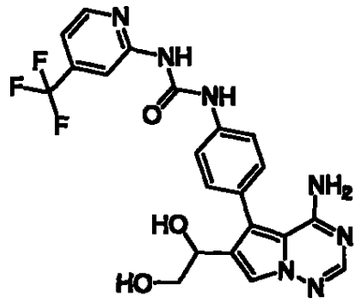
The procedure used for the preparation of Example 287 was used to prepare the title compound by substituting 2-thienylmagnesium bromide for methylmagnesium bromide. ^{1}H-NMR (DMSO-d_6) 8.26 (s, 1H), 7.98 (dd, J = 1, 4 Hz, 1H), 7.96 (s, 1H), 7.75 (dd, J = 1, 3 Hz), 7.53 (d, J = 6 Hz, 2H), 7.30 (d, J = 6 Hz, 2H), 7.19 (dd, J = 3, 4 Hz, 1H), 6.05 (s, 1H) 1.25 (s, 9H); MS $[M+H]^+$ = 502.1; LCMS RT = 2.98 min.

Example 300: Preparation of N-{4-[4-amino-6-(1-hydroxyethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea



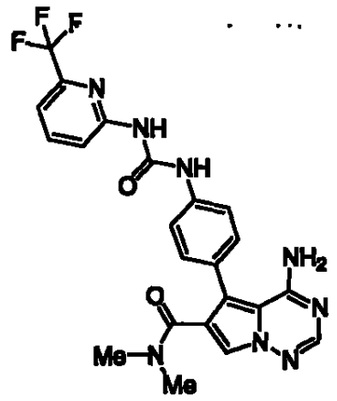
The procedure used for the preparation of Example 269 was used to prepare the title compound by substituting Example 1 for Example 51. ^{1}H-NMR (DMSO-d_6) δ 9.41 (s, 1H), 9.01 (d, J = 3 Hz, 1H), 8.62 (d, J = 3, 8 Hz, 1H), 7.81 (s, 1H), 7.77 (s, 1H), 7.61 (d, J = 9 Hz, 2H), 7.47 to 7.54 (m, 1H), 7.38 to 7.42 (m, 1H), 7.35 (d, J = 9 Hz, 2H); MS $[M+H]^+$ =475.1; LCMS RT =2.59 min.

Example 301: Preparation of N-[4-[4-amino-6-(1,2-dihydroxyethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl]-N'-[4-(trifluoromethyl)pyridin-2-yl]urea



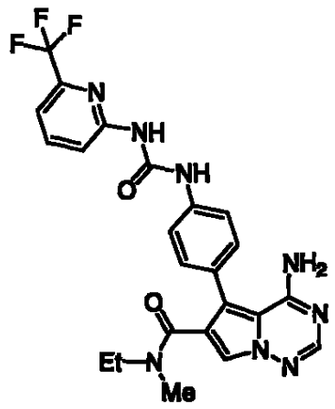
Methanesulfonamide (65 mg, 0.683 mmol) was dissolved in a 1:1 solution of tert-Butanol: water (5 mL) and treated with AD-mix β (1.0 g). The mixture was then treated with Example 222 (0.3 g, 0.683 mmol) and the reaction was stirred at room temperature overnight. After completion, the solution was treated with solid sodium sulfite (1.5 g) and stirred for 1 hour. The reaction was then transferred to a sep. funnel and the crude product was extracted with EtOAc. The organic layer was washed with water and saturated NaCl solution. The solution was then dried over $MgSO_4$, filtered and concentrated under reduced pressure. No purification was needed for the title compound isolated as 0.3 g of a tan solid (0.634 mmol, 93 % yield). ^{1}H-NMR (DMSO-d_6) δ 9.88 (bs, 1H), 9.76 (bs, 1H), 8.53 (d, J = 5.7 Hz, 1H), 8.06 (s, 1H), 7.82 (s, 1H), 7.63 (s, 1H), 7.61 (d, J = 8.8 Hz, 2H), 7.37-7.35 (m, 3H), 5.03 (d, J = 4.6 Hz, 2H), 4.65 (t, J = 5.8 Hz, 1H), 4.47-4.43 (m, 1H), 3.45-3.38 (m, 2H); MS $[M+H]^+$ = 474.0; LCMS RT = 2.13 min.

Example 302: Preparation of 4-amino-N,N-dimethyl-5-{4-[({[6-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



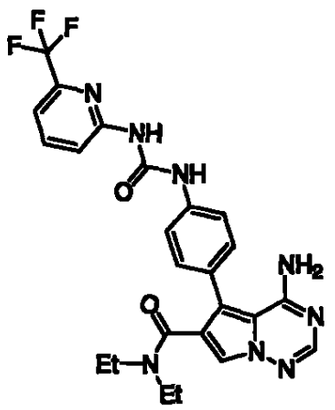
The procedure used for the preparation of Example 69 was used to prepare the title compound by substituting Intermediate AH for Intermediate G and dimethylamine for cyclopropylamine. The reaction was stirred for 16 h and was purified by HPLC (20-85% acetonitrile in water). ^{1}H NMR (DMSO-d_6) δ 9.87 (s, 1H), 9.68 (s, 1H), 8.05 to 7.96 (m, 2H), 7.89 (s, 1 H), 7.85 (s, 1 H), 7.57 to 7.52 (m, 2H), 7.49 (dd, J = 6.6, 1.6 Hz, 1 H), 7.32 to 7.27 (m, 2H), 2.81 (s, 3H), 2.64 (s, 3H); MS $[M+H]^+$ = 485.0; LCMS RT = 2.43 min.

Example 303: Preparation of 4-amino-N-ethyl-N-methyl-5-{4-[({[6-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



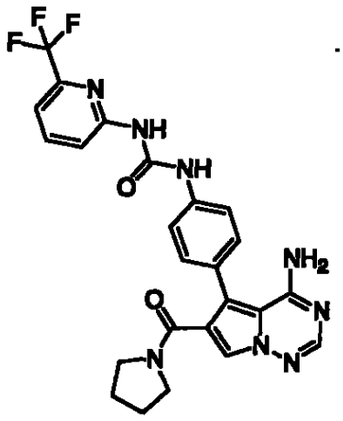
The procedure used for the preparation of Example 69 was used to prepare the title compound by substituting Intermediate AH for Intermediate G and N-ethyl-N-methylamine for cyclopropylamine. The reaction was stirred for 16 h and was purified by HPLC (20-85% acetonitrile in water). ^{1}H NMR (DMSO-d_6) δ 9.86 (s, 1H), 9.68 (s, 1H), 8.05 to 7.96 (m, 2H), 7.89 (s, 1H), 7.85 (s, 1H), 7.56 to 7.46 (m, 3H), 7.30 (d, J = 8.1 Hz, 2H), 3.31 and 3.06 (diastereomeric quartets, 2H), 2.79 and 2.58 (diastereomeric singlets, 3H), 0.93 and 0.81 (diastereomeric triplets, 3H); MS $[M+H]^+$ = 499.1; LCMS RT = 2.55 min.

Example 304: Preparation of 4-amino-N,N-diethyl-5-{4-[({[6-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



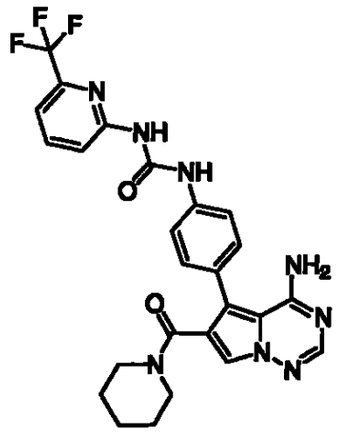
The procedure used for the preparation of Example 69 was used to prepare the title compound by substituting Intermediate AH for Intermediate G and diethylamine for cyclopropylamine. The reaction was stirred for 16 h and was purified by HPLC (20-85% acetonitrile in water). ^{1}H NMR (DMSO-d_6) δ 9.85 (s, 1H), 9.67 (s, 1H), 8.05 to 7.96 (m, 2H), 7.89 (s, 1H), 7.85 (s, 1H), 7.55 to 7.46 (m, 3H), 7.33 to 7.28 (m, 2H), 3.32 and 3.02 (diastereomeric quartets, 2H), 0.94 and 0.82 (diastereomeric triplets, 3H); MS $[M+H]^+$ = 513.1; LCMS RT = 2.64 min.

Example 305: Preparation of N-{4-[4-amino-6-(pyrrolidin-1-ylcarbonyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-[6-(trifluoromethyl)pyridin-2-yl]urea



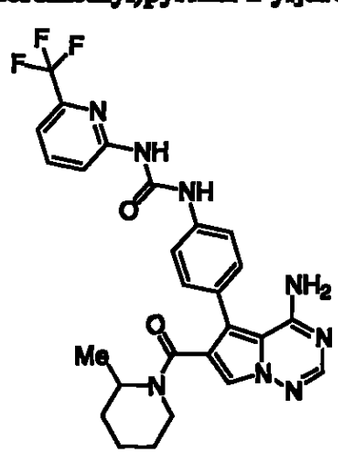
The procedure used for the preparation of Example 69 was used to prepare the title compound by substituting Intermediate AH for Intermediate G and pyrrollidine for cyclopropylamine. The reaction was stirred for 16 h and was purified by HPLC (20-85% acetonitrile in water). ^{1}H NMR (DMSO-d_6) δ 9.86 (s, 1H), 9.67 (s, 1H), 8.04 to 7.98 (m, 2H), 7.91 (s, 1H), 7.89 (s, 1H), 7.56 to 7.46 (m, 3H), 7.34 to 7.29 (m, 2H), 3.32 (t, J = 6.4 Hz, 2H), 3.11 (t, J = 6.4 Hz, 2H), 1.77 to 1.60 (m, 4H); MS $[M+H]^+$ = 511.1; LCMS RT = 2.53 min.

Example 306: Preparation of N-{4-[4-amino-6-(piperidin-1-ylcarbonyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-[6-(trifluoromethyl)pyridin-2-yl]urea



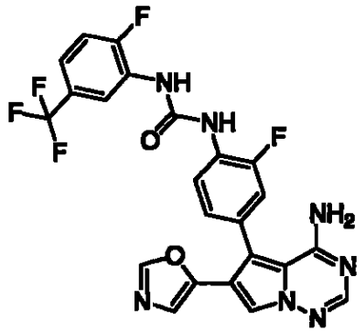
The procedure used for the preparation of Example 69 was used to prepare the title compound by substituting Intermediate AH for Intermediate G and piperidine for cyclopropylamine. The reaction was stirred for 16 h and was purified by HPLC (20-85% acetonitrile in water). ^{1}H NMR (DMSO-d_6) δ 9.86 (s, 1H), 9.68 (s, 1H), 8.04 to 7.98 (m, 2H), 7.89 (s, 1H), 7.83 (s, 1H), 7.58 to 7.47 (m, 3H), 7.33 to 7.28 (m, 2H), 3.43 (br s, 2 H), 3.04 (br s, 2H), 1.43 to 1.31 (m, 4H), 0.98 (br s, 2H); MS $[M+H]^+$ = 525.1; LCMS RT = 2.73 min.

Example 307: Preparation of N-(4-{4-amino-6-[(2-methylpiperidin-1-yl)carbonyl]pyrrolo[2,1-f][1,2,4]triazin-5-yl}phenyl)-N'-[6-(trifluoromethyl)pyridin-2-yl]urea



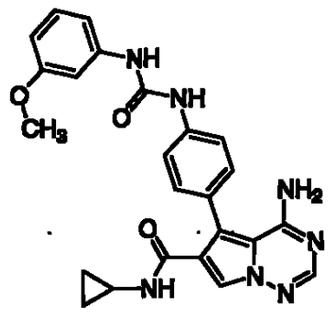
The procedure used for the preparation of Example 69 was used to prepare the title compound by substituting Intermediate AH for Intermediate G and piperidine for cyclopropylamine. The reaction was stirred for 16 h and was purified by HPLC (20-85% acetonitrile in water). ^{1}H NMR (DMSO-d_6) δ 9.85 (s, 1H), 9.68 (s, 1H), 8.05 to 7.97 (m, 2H), 7.89 (s, 1H), 7.83 (s, 1H), 7.58 to 7.47 (m, 3H), 7.33 to 7.27 (m, 2H), 2.69 to 2.60 (m, 1H), 2.50 (br s, 2H), 1.50 to 1.31 (m, 4H), 0.99 to 0.90 (m, 5H); MS $[M+H]^+$ = 539.1; LCMS RT = 2.81 min.

Example 308: Preparation of N-[4-[4-amino-6-(1,3-oxazol-5-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]-2-fluorophenyl}-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea



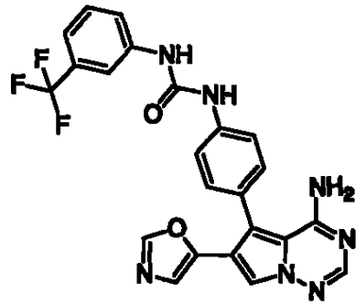
The procedure used for the preparation of Example 276 was used to prepare the title compound by Intermediate AL for Intermediate 7. ^{1}H-NMR (DMSO-d_6) δ 9.46 (s, 1H), 9.32 (s, 1H), 8.65 to 8.64 (d, J = 7.4 Hz, 1H), 8.35 to 8.30 (t, J = 8.5 Hz, 1H), 8.30 (s, 1H), 8.09 (s, 1H), 7.90 (s, 1H), 7.53 to 7.48 (m, 1H), 7.42 to 7.39 (m, 1H), 7.37 to 7.34 (d, J = 12.0 Hz, 1H), 7.21 to 7.19 (d, J = 8.4 Hz, 1H), 6.62 (s, 1H); MS $[M+H]^+$ = 516.1; LCMS RT = 3.01 min.

Example 309: Preparation of 4-amino-N-cyclopropyl-5-[4-({[(3-methoxyphenyl)amino]carbonyl}amino)phenyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting Intermediate W for Intermediate X and phenyl (3-methoxyphenyl)carbamate for phenyl (4-*tert*-butylpyridin-2-yl)carbamate. The reaction was heated at reflux overnight in THF. ^{1}H NMR (DMSO-d_6) δ 8.81 (s, 1H), 8.75 (s, 1H), 8.04 (s, 1H), 7.92 (br s, 1H), 7.88 (s, 1H), 7.88 (d, J = 4.3 Hz, 1H), 7.54 to 7.48 (m, 2H), 7.31 to 7.23 (m, 2H), 7.21 to 7.12 (m, 2H), 6.96 to 6.90 (m, 1H), 6.55 (ddd, J = 8.1, 2.7, 0.7 Hz, 1H), 4.66 (br s, 1H), 3.73 (s, 3H), 2.70 to 2.62 (m, 1H), 0.64 to 0.58 (m, 2H), 0.44 to 0.38 (m, 2H); MS $[M+H]^+$ = 458.1; LCMS RT = 2.38 min.

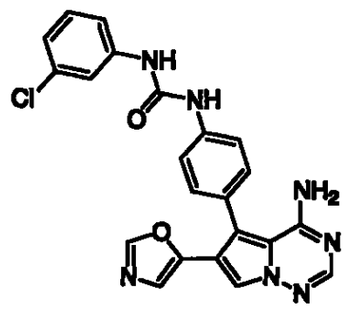
Example 310: Preparation of N-{4-[4-amino-6-(1,3-oxazol-5-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-[3-(trifluoromethyl)phenyl]urea



The procedure used for the preparation of Example 3 was used to prepare the title compound by substituting Intermediate AO for Intermediate C and 3-(trifluoromethyl)aniline for 4-fluoro-3-(trifluoromethyl)aniline. ^{1}H-NMR (DMSO-d_6) δ 9.23 to 9.16 (br s, 2H), 8.28 (s, 1H), 8.07 (s, 1H), 7.89 (s, 1H), 7.72 (s, 1H),

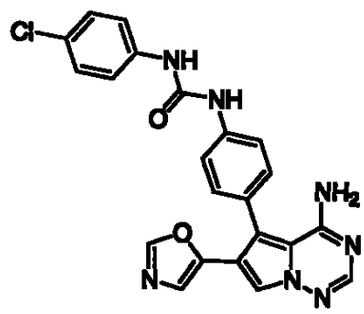
7.63 to 7.61 (d, J = 8.6 Hz, 2H), 7.34 to 7.28 (m, 4H), 7.01 to 6.99 (d, J = 7.1 Hz, 1H), 6.55 (s, 1H); MS $[M+H]^+$ = 480.0; LCMS RT = 2.84 min.

Example 311: Preparation of N-{4-[4-amino-6-(1,3-oxazol-5-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-(3-chlorophenyl)urea



The procedure used for the preparation of Example 3 was used to prepare the title compound by substituting Intermediate AO for Intermediate C and 3-chloroaniline for 4-fluoro-3-(trifluoromethyl)aniline. ^{1}H-NMR (DMSO-d_6) δ 8.29 (s, 1H), 8.08 (s, 1H), 8.04 (s, 1H), 7.90 (s, 1H), 7.68 to 7.66 (m, 3H), 7.51 to 7.47 (t, J = 8.1 Hz, 1H), 7.34 to 7.32 (d, J = 8.6 Hz, 2H), 7.30 to 7.28 (d, J = 8.4 Hz, 1H), 6.56 (s, 1H); MS $[M+H]^+$ = 446.1; LCMS RT = 2.72 min.

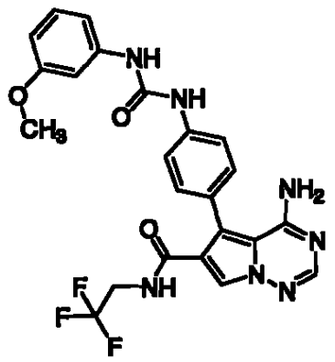
Example 312: Preparation of N-{4-[4-amino-6-(1,3-oxazol-5-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-(4-chlorophenyl)urea



The procedure used for the preparation of Example 3 was used to prepare the title compound by substituting Intermediate AO for Intermediate C and 4-chloroaniline for 4-fluoro-3-(trifluoromethyl)aniline. ^{1}H-NMR (DMSO-d_6) δ 8.93

(s, 1H), 8.90 (s, 1H), 8.29 (s, 1H), 8.08 (s, 1H), 7.90 (s, 1H), 7.61 to 7.59 (d, J = 8.6 Hz, 2H), 7.50 to 7.48 (d, J = 9.1 Hz, 2H), 7.35 to 7.32 (m, 4H), 6.55 (s, 1H); MS $[M+H]^+$ = 446.1; LCMS RT = 2.65 min.

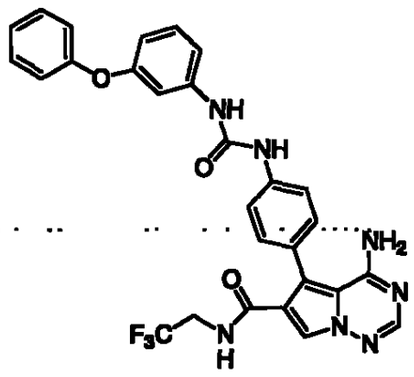
Example 313: Preparation of 4-amino-5-[4-({[(3-methoxyphenyl)amino]carbonyl}amino)phenyl]-N-(2,2,2-trifluoroethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



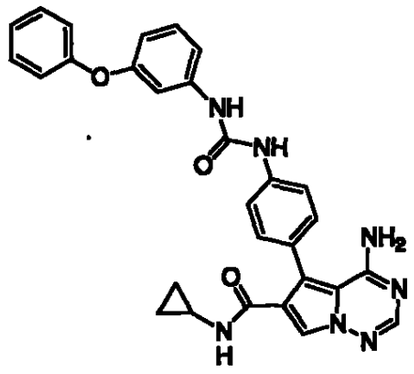
The procedure used for the preparation of Example 73 was used to prepare the title compound by substituting Intermediate M for Intermediate X and phenyl (3-methoxyphenyl)carbamate for phenyl (4-*tert*-butylpyridin-2-yl)carbamate. The reaction was heated at reflux overnight in THF. ^{1}H NMR (DMSO-d_6) δ 8.79 (s, 1H), 8.72 (s, 1H), 8.48 (dd, J = 6.4, 6.4 Hz, 1H), 8.17 (s, 1H), 8.00 (br s, 1H), 7.91 (s, 1H), 7.52 to 7.47 (m, 2H), 7.30 to 7.23 (m, 2H), 7.21 to 7.12 (m, 2H), 6.96 to 6.90 (m 1H), 6.54 (ddd, J = 8.2, 2.6, 0.8 Hz, 1H), 5.08 (br s, 1H), 4.02 to 3.90 (m, 2H), 3.73 (s, 3H); MS $[M+H]^+$ = 500.2; LCMS RT = 2.61 min.

The following further examples can be synthesized according to the synthetic procedures outlined above:

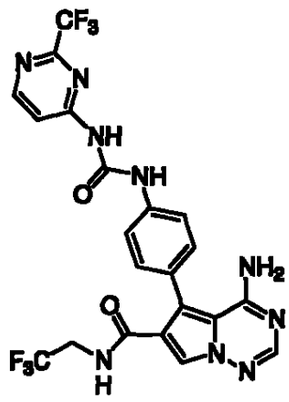
4-amino-5-[4-({[(3-phenoxyphenyl)amino]carbonyl}amino)phenyl]-N-(2,2,2-trifluoroethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



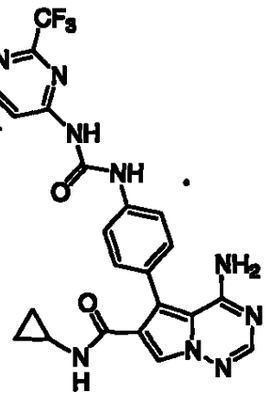
4-amino-N-cyclopropyl-5-[4-({[(3-phenoxyphenyl)amino]carbonyl}amino)phenyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



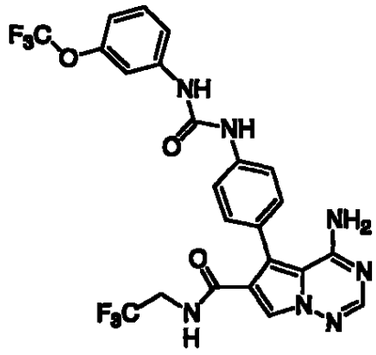
4-amino-N-(2,2,2-trifluoroethyl)-5-{4-[({[2-(trifluoromethyl)pyrimidin-4-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



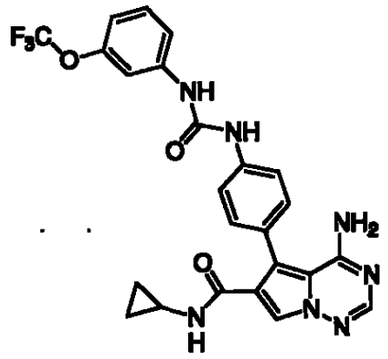
4-amino-N-cyclopropyl-5-{4-[({[2-(trifluoromethyl)pyrimidin-4-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



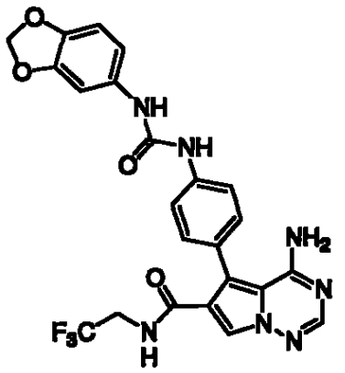
4-amino-N-(2,2,2-trifluoroethyl)-5-{4-[({[3-(trifluoromethoxy) phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



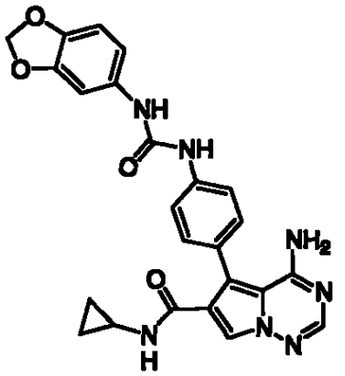
4-amino-N-cyclopropyl-5-{4-[({[3-(trifluoromethoxy) phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



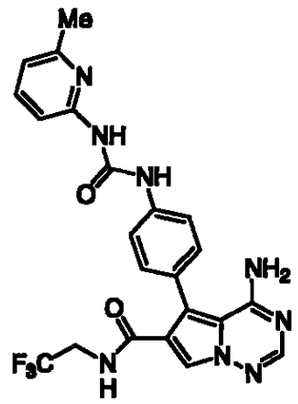
4-amino-5-(4-{[(1,3-benzodioxol-5-ylamino)carbonyl]amino}phenyl)-N-(2,2,2-trifluoroethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



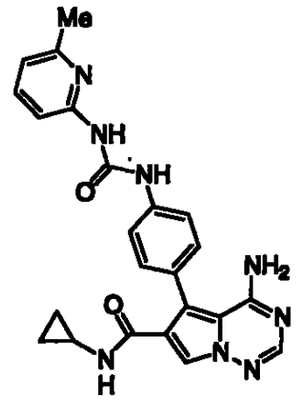
4-amino-5-(4-{[(1,3-benzodioxol-5-ylamino)carbonyl]amino}phenyl)-N-cyclopropylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



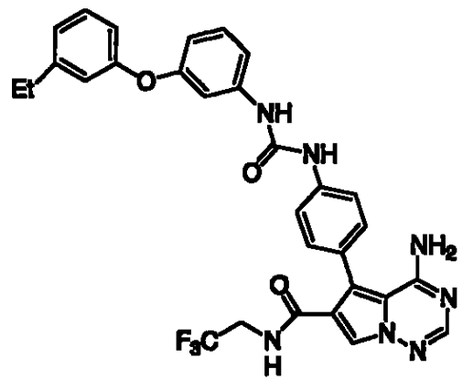
4-amino-5-[4-({[(6-methylpyridin-2-yl)amino]carbonyl}amino)phenyl]-N-(2,2,2-trifluoroethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



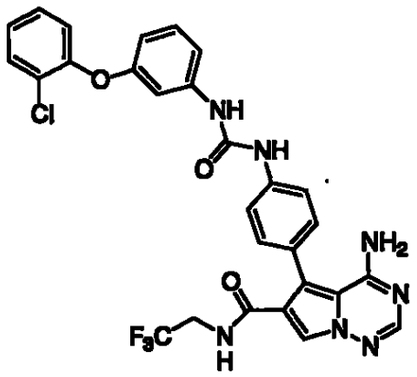
4-amino-N-cyclopropyl-5-[4-({[(6-methylpyridin-2-yl)amino]carbonyl}amino)phenyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



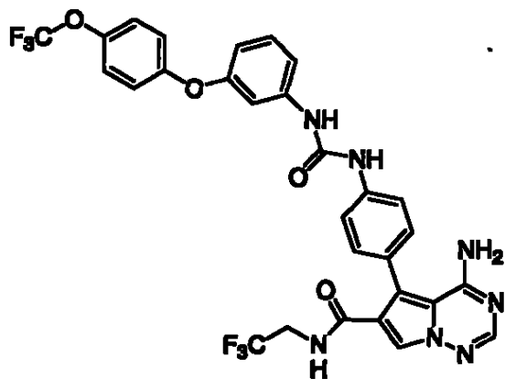
4-amino-5-{4-[({[3-(3-ethylphenoxy)phenyl]amino}carbonyl)amino]phenyl}-N-(2,2,2-trifluoroethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



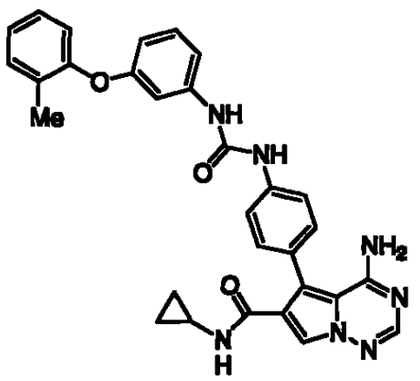
4-amino-5-{4-[({[3-(2-chlorophenoxy)phenyl]amino}carbonyl)amino]phenyl}-N-(2,2,2-trifluoroethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



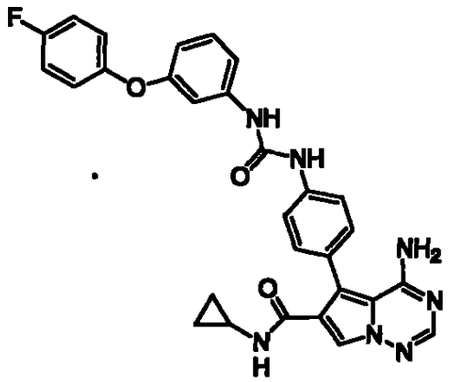
4-amino-N-(2,2,2-trifluoroethyl)-5-(4-{[({3-[4-(trifluoromethoxy)phenoxy]phenyl}amino)carbonyl]amino}phenyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



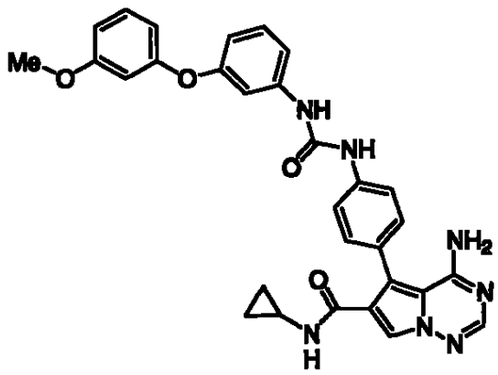
4-amino-N-cyclopropyl-5-{4-[({[3-(2-methylphenoxy)phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



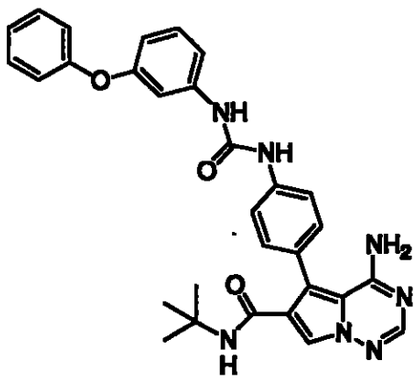
4-amino-N-cyclopropyl-5-{4-[({[3-(4-fluorophenoxy)phenyl] amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



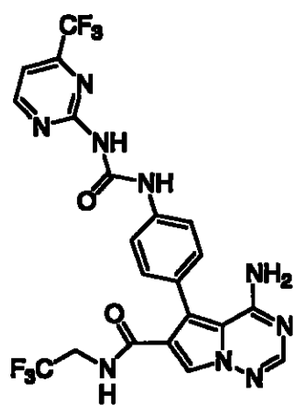
4-amino-N-cyclopropyl-5-{4-[({[3-(3-methoxyphenoxy) phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



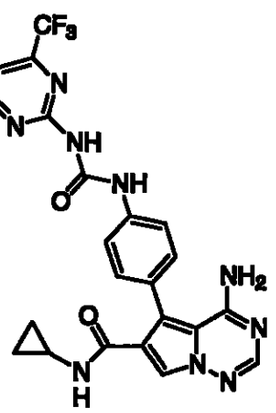
4-amino-N-(tert-butyl)-5-[4-({[(3-phenoxyphenyl)amino] carbonyl}amino)phenyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



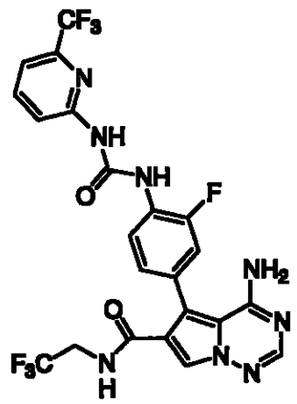
4-amino-N-(2,2,2-trifluoroethyl)-5-[4-[({[4-(trifluoromethyl)pyrimidin-2-yl]amino}carbonyl)amino]phenyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



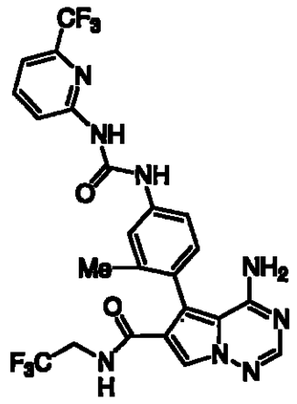
4-amino-N-cyclopropyl-5-[4-[({[4-(trifluoromethyl)pyrimidin-2-yl]amino}carbonyl)amino]phenyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



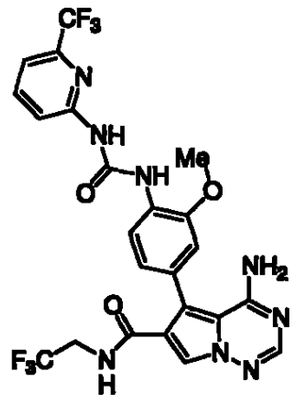
4-amino-5-{3-fluoro-4-[({[6-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}-N-(2,2,2-trifluoroethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



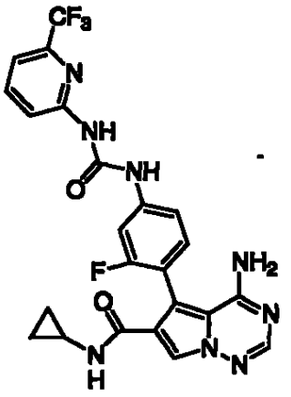
4-amino-5-{2-methyl-4-[({[6-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}-N-(2,2,2-trifluoroethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



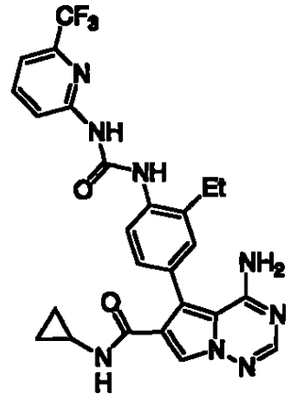
4-amino-5-{3-methoxy-4-[({[6-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}-N-(2,2,2-trifluoroethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



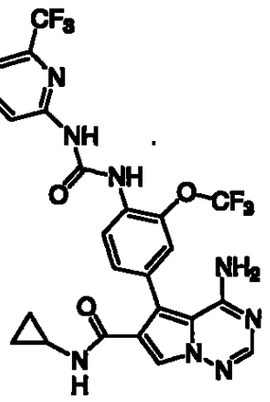
4-amino-N-cyclopropyl-5-{2-fluoro-4-[({[6-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



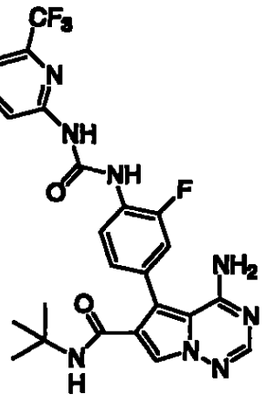
4-amino-N-cyclopropyl-5-{3-ethyl-4-[({[6-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



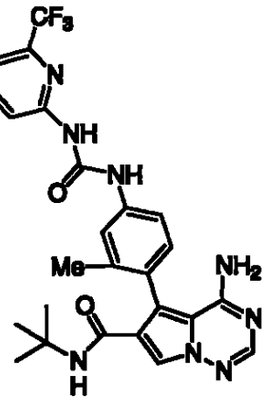
4-amino-N-cyclopropyl-5-{3-(trifluoromethoxy)-4-[({[6-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



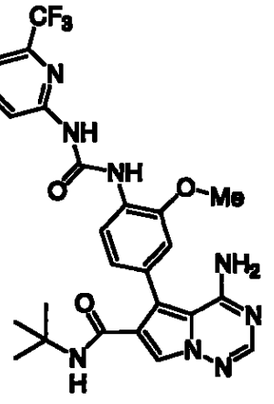
4-amino-N-(tert-butyl)-5-{3-fluoro-4-[({[6-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



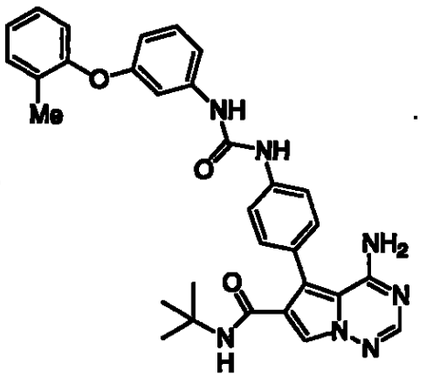
4-amino-N-(tert-butyl)-5-{2-methyl-4-[({[6-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



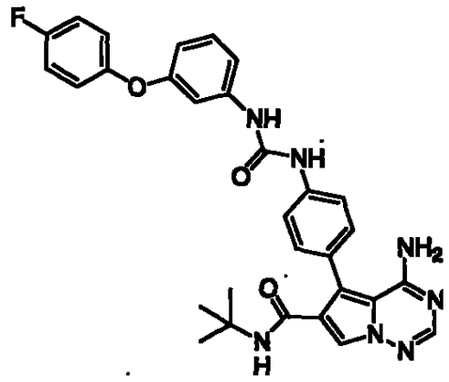
4-amino-N-(tert-butyl)-5-{3-methoxy-4-[({[6-(trifluoromethyl)pyridin-2-yl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-*f*][1,2,4]triazine-6-carboxamide



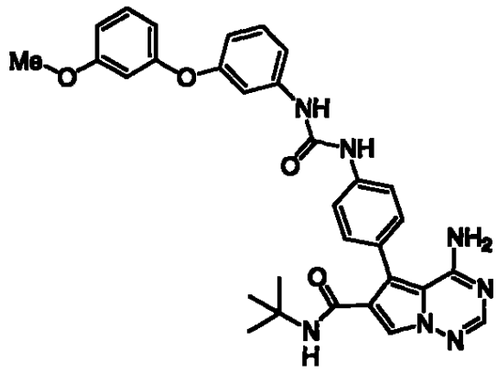
4-amino-N-(tert-butyl)-5-{4-[({[3-(2-methylphenoxy)phenyl]amino}carbonyl)amino]phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide



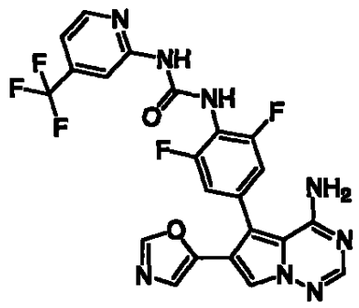
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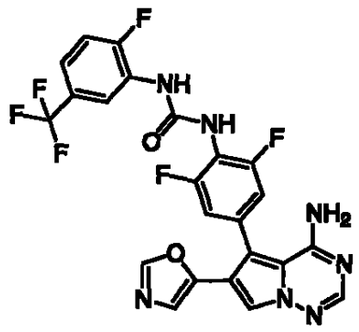
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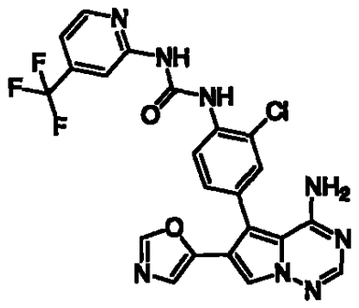
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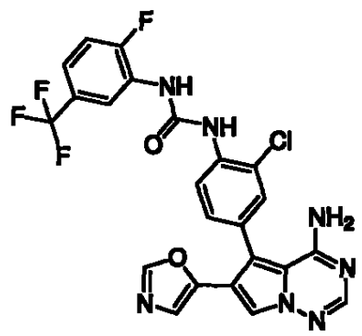
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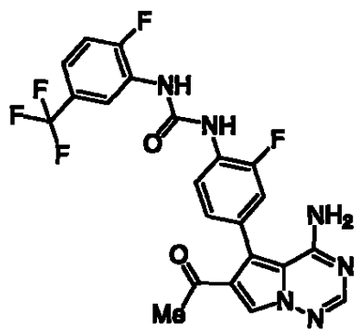
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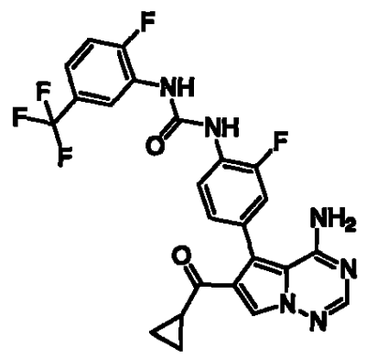
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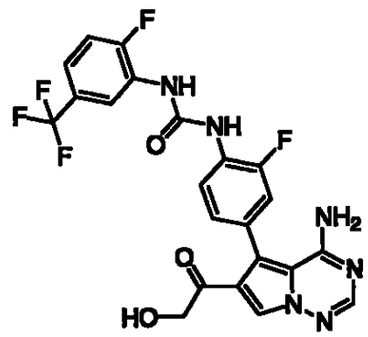
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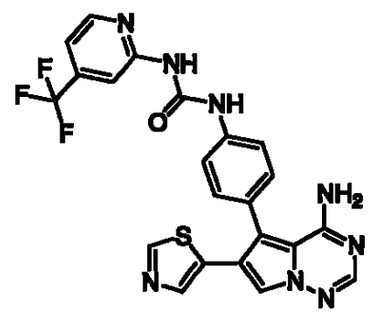
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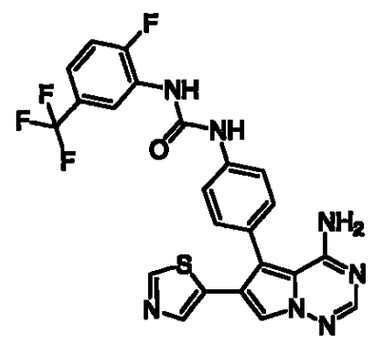
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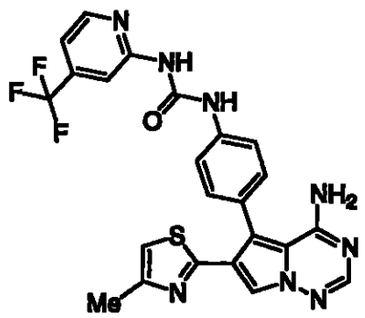
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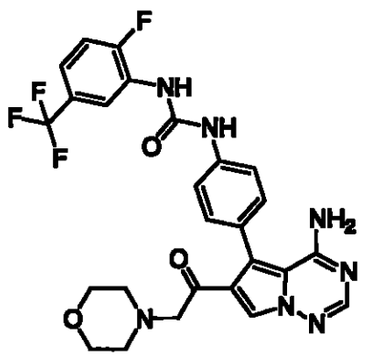
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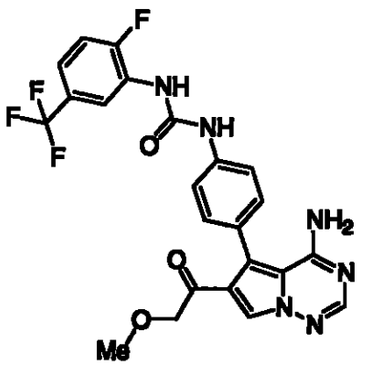
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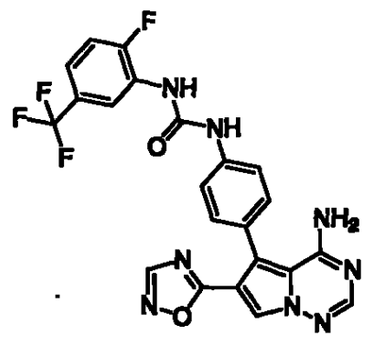
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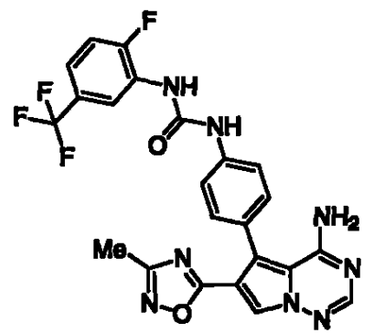
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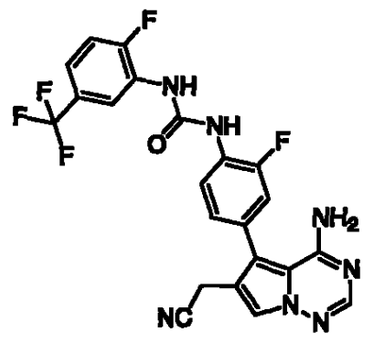
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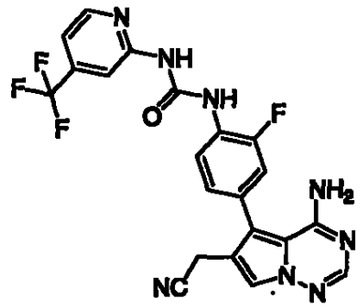
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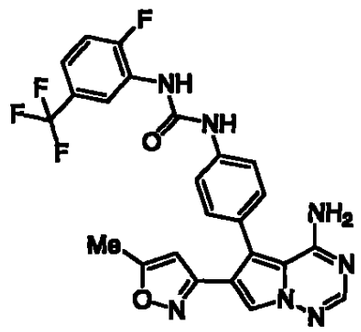
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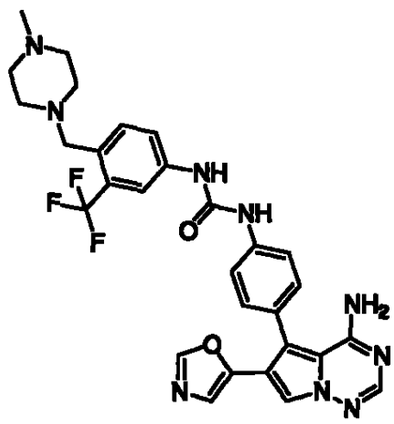
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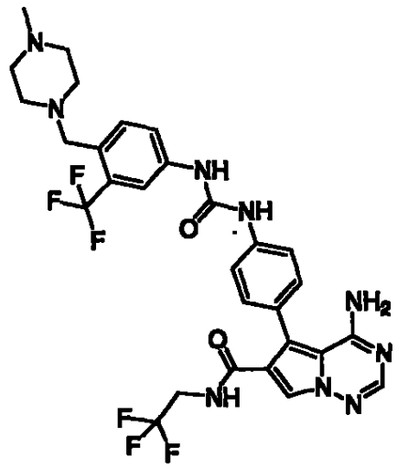
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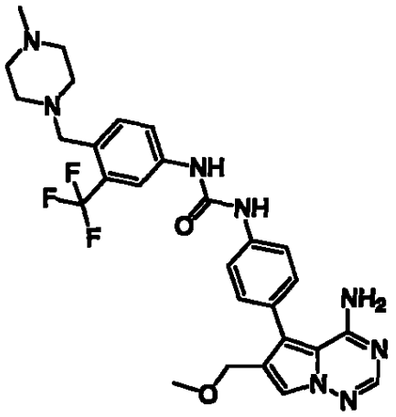
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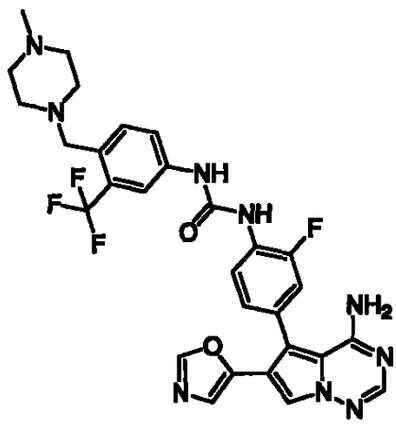
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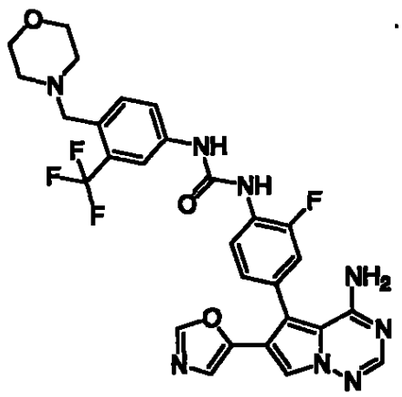
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N-[4-[4-amino-6-(methoxymethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}-N'-[4-[(4-methylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenyl]urea



N-{4-[4-amino-6-(1,3-oxazol-5-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]-2-fluorophenyl}-N'-[4-[(4-methylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenyl]urea



N-[4-[4-amino-6-(1,3-oxazol-5-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]-2-fluorophenyl}-N'-[4-(morpholin-4-ylmethyl)-3-(trifluoromethyl)phenyl]urea

B. Evaluation of physiological activity

The *in vitro* effect of the compounds according to the invention can be demonstrated in the following assays:

Growth Factor Stimulated p-ERK assay in HUVECs

Exponentially growing human endothelial HUVECs cells (human umbilical vein endothelial cells, cat# CC-2517, Cambrex, Walkersville, MD) were seeded at twenty five thousand cells/well in 96 well plates in EBM-2 MV medium with growth factors (cat# CC-3202, Cambrex) and grown at 37°C in 5% CO_2. Sixteen hours post-plating, the cells were changed to serum-free medium (RPMI 1640 containing 0.1% BSA (bovine serum albumin) and compounds were added at different concentrations for 2 hrs, after which the cells were stimulated for 10 min with 50 ng/ml of either VEGF (vascular endothelial growth factor, Protein Sciences, Meriden, CT) or bFGF (basic fibroblast growth factor cat# PHG0026, Biosource International, Camarillo, CA). The rest of the assay was performed per manufacturer indications for the ERK1/2 Bioplex assay (cat#171-304004, Bio-Rad, Hercules, CA). After removing culture medium by aspiration, the cells were quickly rinsed with 100 µl of cell wash buffer A to stop treatment reaction. Eighty microliters of cell lysis buffer were then immediately added to each well of the 96 well plate which was put on ice. Cells in each well were lysed by pipetting up and down 5 times with a multi-channel pipet. The plate was then agitated on a microtiter plate shaker at 300 rpm for 20 min at 4°C. Cellular debris were pelleted by centrifugation at 4500 g for 15 min at 4°C and the supernatant was collected. Forty five microliters of supernatant was diluted with an equal volume of Bio-Plex phosphoprotein assay Buffer B, The coupled and color coated beads were added into a 96 well filter plate, and the prepared lysates were added. The beads and lysate mixture was incubated at room temperature for 15-18 hrs. The following day, the plate was vacuum-filtered and then washed 3x. Twenty-five microliters of detection antibody solution were added to each well and the plate was then incubated for 30 min at room temperature. The plate was then vaccum-filtered and washed as described previously. Fifty microliters of streptavidin-PE solution was added to each well, the plate was incubated for 10 min at room temperature and then was then vaccum-filtered and washed as described above. One

hundred twenty-five microliters of resuspension buffer was added to each well and data were acquired on the Luminex 100 instrument (Bio-Rad). Compounds of examples 1, 8, 9, 12, 23, 27, 30, 32, 49, 59 and 70 demonstrate an inhibition greater than 50% @ 100 nM in the VEGF stimulated Phospho-ERK in HUVEC assay. Compounds of examples 11, 22, 24, 26, 29, 37, 39, 41, 47, 66, 75, 85, 93, 99, 100, 131, 143, 146 and 168 demonstrate an inhibition greater than 50% @ 1 μM but less than 50% @ 100 nM in the VEGF stimulated Phospho-ERK in HUVEC assay. Compounds of examples 14, 18, 62, 96, 98, 104 and 140 demonstrate an inhibition greater than 50% @ 10 μM but less than 50% @ 100 nM and 1 μM in the VEGF stimulated Phospho-ERK in HUVEC assay.

BRDU Growth Factor Stimulated Proliferation of HUVEC

Exponentially growing human umbilical vein endothelial cells (HUVEC; Cat# CC-2519A, Cambrex, Walkersville, MD) were seeded at two thousand cells/well into Collagen IV-coated 96 well plates (Cat# 35-4429, Becton Dickinson, Bedford, MA) in assay media containing RPMI-1640 (Cat# 11875-093, Gibco, Carlsbad, CA), 0.5% charcoal-stripped serum (Cat# SH30068.03, HyClone, Logan, Utah), and 1% N-2 supplement (Cat# 17502-048, Gibco, Carlsbad, CA). Fours hours after incubating the plates at 37°C in 5% CO_2, the cells were treated with different concentrations of compound (diluted in assay media with a final DMSO concentration=0.1%) and then were immediately stimulated with 80 ng/ml of vascular endothelial growth factor (VEGF, Cat# 100-20, PeproTech, Rocky Hill, NJ) or 1.5 ng/ml of basic fibroblast growth factor (bFGF, Catt# 100-18B, PeproTech, Rocky Hill, NJ). Treated cells were incubated for 3 days at 37°C in 5% CO_2. DNA synthesis was measured via the incorporation of bromodeoxyuridine (BrdU) into newly synthesized DNA using the Amersham Cell Proliferation BioTrack ELISA system (Cat# RPN250, Amersham, Piscataway, NJ). Diluted BrdU solution (20 μl of stock BrdU diluted 1:20 fold into assay media) was added to each well and incubation proceeded for 6 hours at 37°C in 5% CO_2. The media was removed and the cells were fixed according to the specifications of the Amersham assay kit for 30 minutes at room temperature. After removing the fixative, blocking buffer (supplied by Amersham kit; 200 μl/well) was added and the plates were stored at 4°C

overnight. The blocking buffer was aspirated and peroxidase-labeled anti-BrdU antibody (supplied by Amersham kit; 100 µl/well) was added and incubated for 3 hours at room temperature. The plates were washed three times with wash buffer (supplied by Amersham kit; 300 µl/well/wash). Immediately following the washes, 100 µl of the TMB-substrate was dispensed into each well and the plates were further incubated for 30 minutes at room temperature. The reaction was terminated by the addition of 25 µl of 1M H_2SO_4. Plates were read immediately at 450 nm using a SpectraMAX 250 spectrophotometer plate reader (Molecular Devices, Sunnyvale, CA). The software utilized was SoftMAX pro v.2.4.1.

Compounds of examples 70, 101, 218 and 226 demonstrate an IC_{50} of less than 10 nM in the VEGFR stimulated HUVEC proliferation assay. Compounds of examples 103, 151, 155, 157, 159, 162, 223, 233, 234, 239 and 243 demonstrate an IC_{50} greater than 10 nM but less than 100 nM in the VEGFR stimulated HUVEC proliferation assay. Compounds of examples 30, 99, 102, 152, 240 and 247 demonstrate an IC_{50} greater than 100 nM but less than 500 nM in the VEGFR stimulated HUVEC proliferation assay. Compounds of examples 100 and 163 demonstrate an IC_{50} greater than 500 nM but less than 2 µM in the VEGFR stimulated HUVEC proliferation assay.

Compounds of examples 70, 99, 101, 103, 151 and 223 demonstrate an IC_{50} of less than 100 nM in the FGFR stimulated HUVEC proliferation assay. Compounds of examples 30, 102, 152, 155, 157, 159, 162, 218, 226, 233, 234, 239, 243 and 247 demonstrate an IC_{50} greater than 100 nM but less than 500 nM in the FGFR stimulated HUVEC proliferation assay. Compound of example 240 demonstrates an IC_{50} greater than 500 nM but less than 1 µM in the FGFR stimulated HUVEC proliferation assay.

Tumor Cell Proliferation

Human tumor cells (e.g., HCT116 or MDA-MB-231 cells), are seeded in a Costar 96-well plate at $3.0x10^3$ cells/well and grown in 150 µl of RPMI complete media (Invitrogen Corporation, Grand Island, NY) containing 10% fetal bovine serum

(Hyclone, Logan, Utah) at 37 °C for 16 h in an incubator with 5% CO_2. To each well, 50 µl of additional growth media containing 40 µM to 18 nM concentrations of compound with 0.4% DMSO is added. Cells are grown for another 72 h at 37 °C with 5% CO_2. 20 µl of Alamar Blue (Trek Diagnostic Systems, Inc., Cleveland, Ohio) reagent is added to each well and incubated for 3 h at 37 °C. Plates are read in a SpectraMax Gemini (Molecular Devices, CA) with 544 nm excitation and 590 nm emission wavelength. IC_{50} values are determined by linear regression analysis of log drug concentration versus percent inhibition.

Compounds of examples 25, 70, 93, 155, 235 and 237 demonstrate an IC_{50} of less than 500 nM in the HCT116 proliferation assay. Compounds of examples 59, 69, 71, 76, 156, 159, 161, 162, 223, 239, 241, 256 and 257 demonstrate an IC_{50} greater than 500 nM but less than 1.5 µM in the HCT116 proliferation assay. Compounds of examples 30, 73, 74, 82, 99, 100, 102, 149, 157, 163, 217, 225, 226, 232, 233, 234, 240, 242, 243, 247, 248, 254 and 255 demonstrate an IC_{50} greater than 1.5 µM but less than 5 µM in the HCT116 proliferation assay. Compounds of examples 84, 94, 103, 153 and 218 demonstrate an IC_{50} greater than 5 µM but less than 10 µM in the HCT116 proliferation assay.

Compounds of examples 25, 70, 71, 155 and 156 demonstrate an IC_{50} of less than 500 nM in the MDA-MB-231 proliferation assay. Compounds of examples 59, 82, 93, 99, 149, 159, 217, 223, 235, 239, 248, 251, 255, 256 and 257 demonstrate an IC_{50} greater than 500 nM but less than 1.5 µM in the MDA-MB-231 proliferation assay. Compounds of examples 69, 73, 74, 76, 94, 100, 157, 161, 162, 163, 225, 226, 232, 233, 234, 237, 240, 241, 242, 243, 247 and 254 demonstrate an IC_{50} greater than 1.5 µM but less than 5 µM in the MDA-MB-231 proliferation assay. Compounds of examples 102, 103, 153 and 218 demonstrate an IC_{50} greater than 5 µM but less than 10 µM in the MDA-MB-231 proliferation assay.

<u>p-Histone3</u>

Compounds were assayed for the inhibition of histone 3 phosphorylation in colon carcinoma (HCT116). Briefly, 20,000 cells/well were seeded in a 96-well black-walled, poly-d-lysine plates in RPMI + 10% FBS and incubated at 37°C in 5%

CO_2 overnight. The following day, the cells were treated with compounds for 24 hours at 37°C. Following compound treatment; plates were centrifuged at 1000 rpm for 2 minutes and washed twice with 100 µl of cold sterile TBS. Cells were then fixed with cold 3.7% formaldehyde in TBS (4°C for 1 hour) and then permeabolized with 0.1% Triton-X-100 in TBS (room temperature for 30 minutes). Plates were then washed with of 0.25% BSA-TBS and blocked with BSA solution for 1 hour at room temperature while shaking. The supernatant was removed and replaced with diluted primary antibody (anti-phospho-histone 3, serine 10, Cell Signaling) at 1:250 in 0.25% BSA-TBS and incubated overnight at 4°C. The plates were washed and treated with diluted secondary antibody (anti-rabbit Eu-labeled) at 1:10000 in 0.25% BSA-TBS (room temperature for 1 hour). The antibody solution was removed from each well and washed eight times. The wash buffer was replaced with 50 µl pre-warmed enhancement solution and mixed on the orbital shaker for 10 minutes. Fluorescence was detected with a Victor V Fluorescence Detector. The data are expressed as percent inhibition: % inhibition = 100 –((Signal with inhibitor-background)/(Signal without inhibitor-background)) x 100. Compounds of examples 88, 92, 139, 164, 165, 171, 176 and 177 demonstrate an IC_{50} of less than 500 nM in the p-histone3 assay. Compounds of examples 7, 13, 59, 167 and 204 demonstrate an IC_{50} greater than 500 nM but less than 1 µM in the p-histone3 assay.

The *in vivo* effect of the compounds according to the invention can be demonstrated in tumor xenograft experiments, such as described in Wilhelm, S. *et al. Cancer Res.* 2004, *64*, 7099-09.

C. Operative examples relating to pharmaceutical compositions

The compounds according to the invention can be converted into pharmaceutical preparations as follows:

Tablet:

Composition:

100 mg of the compound of Example 1, 50 mg of lactose (monohydrate), 50 mg of maize starch (native), 10 mg of polyvinylpyrrolidone (PVP 25) (from BASF, Ludwigshafen, Germany) and 2 mg of magnesium stearate.

Tablet weight 212 mg, diameter 8 mm, curvature radius 12 mm.

Preparation:

The mixture of active component, lactose and starch is granulated with a 5% solution (m/m) of the PVP in water. After drying, the granules are mixed with magnesium stearate for 5 min. This mixture is moulded using a customary tablet press (tablet format, see above). The moulding force applied is typically 15 kN.

Suspension for oral administration:

Composition:

1000 mg of the compound of Example 1, 1000 mg of ethanol (96%), 400 mg of Rhodigel (xanthan gum from FMC, Pennsylvania, USA) and 99 g of water.

A single dose of 100 mg of the compound according to the invention is provided by 10 ml of oral suspension.

Preparation:

The Rhodigel is suspended in ethanol and the active component is added to the suspension. The water is added with stirring. Stirring is continued for about 6 h until the swelling of the Rhodigel is complete.

Solution for intravenous administration 1:

Composition: 100-200 mg of the compound of Example 1, 15 g polyethylenglykol 400 and 250 g water optionally with up to 15 % Cremophor EL, and optionally up to 15% ethyl alcohol, and optionally up to 2 equivalents of a pharmaceutically suitable acid such as citric acid or hydrochloric acid.

Preparation:

The compound of Example 1 and the polyethylenglykol 400 are dissolved in the water with stirring. The solution is sterile filtered (pore size 0.22 µm) and filled into heat sterilized infusion bottles under aseptical conditions. The infusion bottles are being sealed with rubber seals.

Solution for intravenous administration 2:

Composition: 100-200 mg of the compound of Example 1, saline solution, optionally with up to 15 % by weight of Cremophor EL, and optionally up to 15% by weight of ethyl alcohol, and optionally up to 2 equivalents of a pharmaceutically suitable acid such as citric acid or hydrochloric acid.

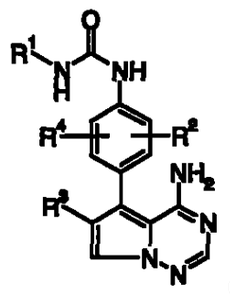
Preparation:

The compound of Example 1 is dissolved in the saline solution with stirring. Optionally Cremophor EL, ethyl alcohol or acid are added. The solution is sterile filtered (pore size 0.22 µm) and filled into heat sterilized infusion bottles under aseptical conditions. The infusion bottles are being sealed with rubber seals.

It should be apparent to one of ordinary skill in the art that changes and modifications can be made to this invention without departing from the spirit or scope of the invention as it is set forth herein.

Claims

1. A compound of formula (I)



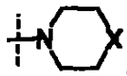
(I),

wherein

R^1 is selected from the group consisting of aryl, benzyl, and heteroaryl,

wherein aryl and heteroaryl can be optionally substituted with 0, 1, 2, 3 or 4 substituents independently selected from the group consisting of

- $(C_1\text{-}C_4)$alkyl, wherein $(C_1\text{-}C_4)$alkyl can be substituted with 0, 1, 2 or 3 halogen, 0 or 1 heterocyclyl, or 0 or 1 $(C_1\text{-}C_3)$alkoxy, wherein

  $(C_1\text{-}C_3)$alkoxy can be optionally substituted with $(C_1\text{-}C_3)$alkylamino,
- $(C_1\text{-}C_3)$alkoxy, wherein $(C_1\text{-}C_3)$alkoxy can be optionally substituted with $(C_1\text{-}C_3)$alkylamino,
- halogen,
- trifluoromethyl,
- trifluoromethoxy,
- $(C_3\text{-}C_6)$cycloalkyl,
- phenyl optionally substituted with 1 or 2 halogen,
-  , wherein X is CH_2, O, S or $NR^{1\text{-}1}$, and wherein $R^{1\text{-}1}$ is hydrogen or $(C_1\text{-}C_6)$alkyl,
- nitro,
- cyano,

- (C_1-C_3)alkylthio,
- trifluoromethylthio,
- (C_1-C_3)alkylcarbonyl,
- (C_1-C_6)alkoxycarbonyl, and
- phenoxy, wherein phenoxy can optionally be substituted with 0, 1 or 2 substituents independently selected from the group consisting of (C_1-C_6)alkyl, (C_1-C_6)alkoxy, trifluoromethoxy, and halogen,

and

wherein benzyl can be substituted with 0, 1, 2 or 3 groups selected from halogen, (C_1-C_3)alkyl, and (C_1-C_3)alkoxy;

R^2 is selected from the group consisting of hydrogen, halogen, (C_1-C_4)alkyl and (C_1-C_4)alkoxy;

R^3 is selected from the group consisting of

- carboxyl,
- formyl,
- (C_1-C_6)alkylcarbonyl optionally substituted with 0, 1, 2, or 3 groups selected from fluorine, chlorine, hydroxy, (C_1-C_6)alkoxy, and heterocycle,
- (C_3-C_6)cycloalkylcarbonyl,
- (C_1-C_6)alkoxycarbonyl optionally substituted with 0, 1, 2, or 3 groups selected from amino, and (C_1-C_6)alkoxycarbonyl,
- aminocarbonyl,
- (C_1-C_6)alkylaminocarbonyl, wherein (C_1-C_6)alkylaminocarbonyl can optionally be substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of (C_3-C_6)cycloalkyl, halogen, amino, (C_1-C_6)alkylamino, hydroxy, (C_1-C_6)alkoxy, (C_1-C_6)alkoxycarbonyl, (C_1-C_6)alkylthio, (C_1-C_6)alkoxycarbonylamino, and methylsulfonyl, and wherein

(C_1-C_6)alkylaminocarbonyl can optionally be substituted with or 0 or 1 heterocyclyl, wherein heterocyclyl can optionally be substituted with 0 or 1 (C_1-C_6)alkyl, and wherein (C_1-C_6)alkylaminocarbonyl can optionally be substituted with 0 or 1 phenyl, wherein phenyl can optionally be substituted with 0 or 1 halogen, (C_1-C_6)alkyl, or (C_1-C_6)alkoxy,

- heterocyclylcarbonyl optionally substituted with 0 or 1 amino, (C_1-C_6)alkylamino, cycloalkyl, or (C_1-C_6)alkyl, wherein (C_1-C_6)alkyl can optionally be substituted with 0 or 1 amino or (C_1-C_6)alkylamino,
- (C_1-C_6)alkyl optionally substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of

a) hydroxyl,

b) amino,

c) (C_1-C_6)alkylamino, wherein (C_1-C_6)alkylamino can be substituted with 0, 1, 2, 3 or 4 substituents independently selected from the group consisting of halogen, amino, alkylamino, methoxy, methylthio, and methylsulfonyl,

d) arylamino, wherein arylamino can be substituted with 0, 1 or 2 substituents independently selected from the group consisting of (C_1-C_6)alkyl, (C_1-C_6)alkoxy, and trifluoromethyl,

e) heterocyclyl, wherein heterocyclyl can be substituted with 0, 1 or 2 (C_1-C_6)alkyl, wherein (C_1-C_6)alkyl can be substituted with 0, 1 or 2 hydroxy, methoxy or pyridyl,

f) imidazolyl,

g) pyridylamino,

h) (C_1-C_3)alkoxy optionally substituted by fluoro up to the perfluoro level, or by heterocycle, wherein heterocycle can optionally be substituted by 0 or 1 (C_1-C_6)alkyl,

i) (C_1-C_3)alkoxy(C_2-C_3)alkoxy, and

j) (C_1-C_6)alkoxycarbonyl,

k) (C_3-C_6)cycloalkyl,

l) cyano,

- (C_1-C_6)alkoxy optionally substituted with 1, 2 or 3 substituents

independently selected from the group consisting of amino, (C_1-C_6)alkylamino, and heterocyclyl, wherein heterocyclyl can be substituted with 0, 1, 2 or 3 (C_1-C_6)alkyl,

- (C_3-C_6)cycloalkylaminocarbonyl optionally substituted with (C_1-C_3)alkyl,
- cyano,
- heteroaryl, wherein heteroaryl can be substituted with 0, 1, 2, or 3 groups independently selected from the group consisting of

q) (C_1-C_6)alkyl, wherein (C_1-C_6)alkyl can be subsituted with 0, 1, 2, or 3 halogen, 0 or 1 heterocyclyl, 0 or 1 alkylamino, or 0 or 1 hydroxy or methoxy,

r) halogen,

s) amino,

t) alkylamino,

u) (C_1-C_6)alkoxycarbonyl, and

v) (C_3-C_6)cycloalkyl,

- heteroarylcarbonyl, which can be substituted with 0, 1, 2, or 3 groups independently selected from the group consisting of (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl and halogen,
- heterocyclyl, wherein heterocyclyl can be substituted with 0, 1, 2, or 3 groups independently selected from the group consisting of (C_1-C_6)alkyl and (C_1-C_6)alkoxycarbonyl; and

R^4 is selected from the group consisting of hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy and halogen;

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein

R^1 is selected from the group consisting of phenyl and monocyclic heteroaryl having 5 or 6 ring atoms,

wherein phenyl and heteroaryl can be optionally substituted with 0, 1, 2, 3 or 4 substituents independently selected from the group consisting of

- (C_1-C_4)alkyl, wherein (C_1-C_4)alkyl can be substituted with 0, 1, 2 or 3 halogen, 0 or 1 pyrrolidinyl, 0 or 1 morpholinyl, or 0 or 1 (C_1-C_3)alkoxy wherein
  (C_1-C_3)alkoxy can be optionally substituted with (C_1-C_3)alkylamino,
- (C_1-C_3)alkoxy, wherein (C_1-C_3)alkoxy can be optionally substituted with (C_1-C_3)alkylamino,
- halogen,
- trifluoromethyl,
- trifluoromethoxy,
- (C_3-C_6)cycloalkyl,
- phenyl optionally substituted with 1 or 2 halogen,
- trifluoromethylthio;

R^2 is selected from the group consisting of hydrogen, halogen, (C_1-C_4)alkyl and (C_1-C_4)alkoxy;

R^3 is selected from the group consisting of

- carboxyl,
- formyl,
- (C_1-C_6)alkylcarbonyl optionally substituted with 0, 1, 2, or 3 groups selected from fluorine, chlorine, hydroxy, (C_1-C_6)alkoxy, and monocyclic heterocycle having 5 or 6 ring atoms,
- (C_3-C_6)cycloalkylcarbonyl,

- (C_1-C_6)alkoxycarbonyl optionally substituted with 0, 1, 2, or 3 groups selected from amino, and (C_1-C_6)alkoxycarbonyl,
- aminocarbonyl,
- (C_1-C_6)alkylaminocarbonyl, wherein (C_1-C_6)alkylaminocarbonyl can optionally be substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of (C_3-C_6)cycloalkyl, halogen, amino, (C_1-C_6)alkylamino, hydroxy, (C_1-C_6)alkoxy, (C_1-C_6)alkoxycarbonyl, (C_1-C_6)alkylthio, (C_1-C_6)alkoxycarbonylamino, and methylsulfonyl, and wherein (C_1-C_6)alkylaminocarbonyl can optionally be substituted with 0 or 1 hydroxyl or 0 or 1 monocyclic heterocyclyl having 5 or 6 ring atoms, wherein heterocyclyl can optionally be substituted with 0 or 1 (C_1-C_6)alkyl, and wherein (C_1-C_6)alkylaminocarbonyl can optionally be substituted with 0 or 1 phenyl, wherein phenyl can optionally be substituted with 0 or 1 halogen or (C_1-C_6)alkyl,
- monocyclic heterocyclylcarbonyl having 5 or 6 ring atoms, optionally substituted with 0 or 1 amino, (C_1-C_6)alkylamino, (C_3-C_6)cycloalkyl, or (C_1-C_6)alkyl, wherein (C_1-C_6)alkyl can optionally be substituted with 0 or 1 amino or (C_1-C_6)alkylamino,
- (C_1-C_6)alkyl optionally substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of

  a) hydroxyl,

  b) amino,

  c) (C_1-C_6)alkylamino, wherein (C_1-C_6)alkylamino can be substituted with 0, 1, 2, 3 or 4 substituents independently selected from the group consisting of halogen, amino, alkylamino, methoxy, methylthio, and methylsulfonyl,

  e) monocyclic heterocyclyl having 5 or 6 ring atoms, wherein heterocyclyl can be substituted with 0, 1 or 2 (C_1-C_6)alkyl, wherein (C_1-C_6)alkyl can be substituted with 0, 1 or 2 hydroxy, methoxy or pyridyl,

  f) imidazolyl,

h) (C_1-C_3)alkoxy optionally substituted by fluoro up to the perfluoro level, or by monocyclic heterocycle having 5 or 6 ring atoms, wherein heterocycle can optionally be substituted by 0 or 1 (C_1-C_6)alkyl,

i) (C_1-C_3)alkoxy(C_2-C_3)alkoxy, and

j) (C_1-C_6)alkoxycarbonyl,

k) (C_3-C_6)cycloalkyl,

l) cyano,

- (C_3-C_6)cycloalkylaminocarbonyl optionally substituted with (C_1-C_3)alkyl,
- cyano,
- heteroaryl, wherein heteroaryl can be substituted with 0, 1, 2, or 3 groups independently selected from the group consisting of

a) (C_1-C_6)alkyl, wherein (C_1-C_6)alkyl can be subsituted with 0, 1, 2, or 3 halogen, 0 or 1 monocyclic heterocyclyl having 5 or 6 ring atoms, 0 or 1 alkylamino, or 0 or 1 hydroxy or methoxy,

b) halogen,

e) (C_1-C_6)alkoxycarbonyl, and

f) (C_3-C_6)cycloalkyl,

- monocyclic heteroarylcarbonyl having 5 or 6 ring atoms,
- monocyclic heterocyclyl having 5 or 6 ring atoms, wherein heterocyclyl can be substituted with 0, 1, 2, or 3 groups independently selected from the group consisting of (C_1-C_6)alkyl and (C_1-C_6)alkoxycarbonyl; and

R^4 is selected from the group consisting of hydrogen and halogen;

or a pharmaceutically acceptable salt thereof.

3. The compound of claim 1, wherein

R^1 is selected from the group consisting of phenyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, pyridinyl, and pyrimidinyl,

wherein phenyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, pyridinyl, and pyrimidinyl can be optionally substituted with 0, 1, 2, 3 or 4 substituents independently selected from the group consisting of

- (C_1-C_4)alkyl, wherein (C_1-C_4)alkyl can be substituted with 0, 1, 2 or 3 halogen,
- (C_1-C_3)alkoxy, wherein (C_1-C_3)alkoxy can be optionally substituted with (C_1-C_3)alkylamino,
- halogen,
- trifluoromethyl,
- trifluoromethoxy,
- cyclopropyl,
- phenyl optionally substituted with 1 or 2 halogen;

R^2 is selected from the group consisting of hydrogen, fluoro and chloro;

R^3 is selected from the group consisting of

- (C_1-C_6)alkylcarbonyl optionally substituted with 0, 1, 2, or 3 groups selected from fluorine, chlorine, hydroxy, (C_1-C_6)alkoxy, piperazinyl, morpholinyl, pyrrolidinyl, and piperidinyl,
- cyclopropylcarbonyl,
- aminocarbonyl,
- (C_1-C_6)alkylaminocarbonyl, wherein (C_1-C_6)alkylaminocarbonyl can optionally be substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of (C_3-C_6)cycloalkyl, halogen, amino, (C_1-C_6)alkylamino, hydroxy, (C_1-C_6)alkoxy, (C_1-C_6)alkoxycarbonyl, (C_1-C_6)alkylthio, (C_1-C_6)alkoxycarbonylamino, and methylsulfonyl, and

wherein (C_1-C_6)alkylaminocarbonyl can optionally be substituted with 0 or 1 hydroxyl, piperazinyl, morpholinyl, pyrrolidinyl or piperidinyl, wherein piperazinyl, morpholinyl, pyrrolidinyl or piperidinyl can optionally be substituted with 0 or 1 (C_1-C_6)alkyl, and wherein (C_1-C_6)alkylaminocarbonyl can optionally be substituted with 0 or 1 phenyl, wherein phenyl can optionally be substituted with 0 or 1 halogen or (C_1-C_6)alkyl,

- heterocyclylcarbonyl selected from piperazinylcarbonyl, morpholinylcarbonyl, pyrrolidinylcarbonyl or piperidinylcarbonyl, optionally substituted with 0 or 1 amino, (C_1-C_6)alkylamino, (C_3-C_6)cycloalkyl, or (C_1-C_6)alkyl, wherein (C_1-C_6)alkyl can optionally be substituted with 0 or 1 amino or (C_1-C_6)alkylamino,
- (C_1-C_6)alkyl optionally substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of

a) hydroxyl,

c) (C_1-C_6)alkylamino, wherein (C_1-C_6)alkylamino can be substituted with 0, 1, 2, 3 or 4 substituents independently selected from the group consisting of halogen, alkylamino, and methoxy,

e) piperazinyl, morpholinyl, pyrrolidinyl or piperidinyl, wherein piperazinyl, morpholinyl, pyrrolidinyl or piperidinyl can be substituted with 0, 1 or 2 (C_1-C_6)alkyl, wherein (C_1-C_6)alkyl can be substituted with 0, 1 or 2 hydroxy or methoxy,

f) imidazolyl,

h) (C_1-C_3)alkoxy optionally substituted by fluoro up to the perfluoro level, or by monocyclic heterocycle having 5 or 6 ring atoms, wherein heterocycle can optionally be substituted by 0 or 1 (C_1-C_6)alkyl,

i) (C_1-C_3)alkoxy(C_2-C_3)alkoxy, and

j) (C_1-C_6)alkoxycarbonyl,

k) (C_3-C_6)cycloalkyl,

l) cyano,

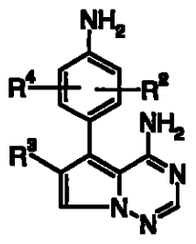
- (C_3-C_6)cycloalkylaminocarbonyl optionally substituted with
  (C_1-C_3)alkyl,
- cyano,
- pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, imidazolyl or pyrimidinyl, wherein pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, imidazolyl or pyrimidinyl can be substituted with 0, 1, 2, or 3 groups independently selected from the group consisting of
  a) (C_1-C_6)alkyl, wherein (C_1-C_6)alkyl can be subsituted with 0, 1, 2, or 3 halogen, 0 or 1 alkylamino, or 0 or 1 methoxy,
  b) halogen, and
  f) (C_3-C_6)cycloalkyl,
- pyrazolylcarbonyl, oxazolylcarbonyl, isoxazolylcarbonyl, thiazolylcarbonyl, pyridinylcarbonyl or pyrimidinylcarbonyl; and

R^4 is selected from the group consisting of hydrogen and fluoro;

or a pharmaceutically acceptable salt thereof.

4. A process for preparing a compound of claim 1, wherein

a compound of formula (II)



(II)

wherein R^2, R^3 and R^4 have the meaning indicated in claim 1,

is reacted with an isocyanate compound of formula (III)

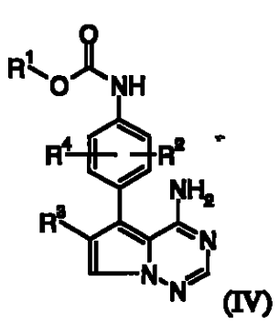
R^1-NCO (III)

or with an carbamate of formula (VI)

R^1-NH-C(O)-OPh (VI),

wherein R^1 has the meaning indicated in claim 1; or

a compound of formula (IV)



(IV)

wherein R^1, R^2, R^3 and R^4 have the meaning indicated in claim 1,

is reacted with an amine of formula (V)

R^1-NH_2 (V),

wherein R^1 has the meaning indicated in claim 1.

5. A compound of claim 1 for the treatment or prevention of disorders.

6. A pharmaceutical composition comprising a compound of claim 1.

7. The pharmaceutical composition of claim 6 in combination with at least one pharmaceutically acceptable, pharmaceutically safe carrier or excipient.

8. A process for preparing the pharmaceutical composition of claim 7, comprising combining at least one compound of claim 1 with at least one pharmaceutically acceptable, pharmaceutically safe carrier or excipient, mixing the combination and bringing the combination into a suitable administration form.

9. A use of the compound of claim 1 for manufacturing a pharmaceutical composition for the treatment of proliferative disorders.

10. A pharmaceutical composition of Claim 6 or 7 for the treatment or prevention of proliferative disorders.

11. A method of treating a disease or condition in a mammal, comprising administering to a mammal in need thereof a therapeutically effective amount of a compound of formula (I).

12. The method of claim 11, wherein the disease or condition is cancer.

13. The method of claim 11, wherein said therapeutically effective amount of a compound of formula (I) exhibits an effect on angiogenesis.

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Derivados de pirrolotriazina útiles para tratar trastornos hiper-proliferativos y enfermedades asociadas con angiogénesis

La presente invención se refiere a nuevos compuestos de pirrozolotriazina, composiciones farmacéuticas que contienen tales compuestos y el uso de esos compuestos y composiciones para la prevención y/o tratamiento de trastornos hiper-proliferativos y enfermedades asociadas con la angiogénesis.

Antecedentes de la Invención

Para apoyar el crecimiento progresivo del tumor más allá del tamaño de 1-2 mm^3, se reconoce que las células tumorales necesitan un estroma funcional, una estructura de apoyo que consiste en fibroblasto, células del músculo liso, células endoteliales, proteínas de la matriz extracelular, y factores solubles (Folkman, J., *Semin Oncol*, 2002. 29(6 Suppl 16), 15-8). Los tumores inducen la formación de tejidos estromales a través de la secreción de factores de crecimiento solubles tales como PDGF y factor de crecimiento transformante beta (TGF-beta), , los cuales a su vez estimulan la secreción de factores complementarios por células huésped tales como factor de crecimiento fibroblástico (FGF), factor de crecimiento epidérmico (EGF), y factor de crecimiento endotelial vascular (VEGF). Estos factores estimulatorios inducen la formación de nuevos vasos sanguíneos, o angiogénesis, la cual lleva oxígeno y nutrientes al tumor y le permite desarrollarse y aporta una vía para la metástasis. Se cree que algunas terapias dirigidas a inhibir la formación del estroma, inhibirán el desarrollo de tumores epiteliales a partir de una amplia variedad de tipos histológicos. (George, D. *Semin Oncol*, 2001. 28(5 Supl 17), 27-33; Shaheen, R.M., et al., *Cancer Res*, 2001. 61(4), 1464-8; Shaheen, R.M., et al. *Cancer Res*, 1999. 59(21), 5412-6). Sin embargo, debido a la naturaleza compleja y los factores de crecimiento múltiple involucrados en el proceso de angiogénesis y avance del tumor, un agente que apunta a una vía simple puede tener eficacia limitada. Es deseable aportar tratamiento contra una cantidad de vía de señalización claves utilizadas por los tumores para inducir la angiogénesis en el estroma huésped. Estos incluyen PDGF, un potente estimulador de formación del estroma (Ostman, A. y C.H. Heldin, *Adv Cancer Res*, 2001, 80, 1-38), FGF, un quimio-atractivo y mitógeno

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para fibroblastos y células endoteliales, y VEGF, un potente regulador de vascularización.

Un regulador principal de la angiogénesis y la vasculogénesis tanto en el desarrollo embriónico como en las enfermedades dependientes angiogénicas es el factor de crecimiento endotelial vascular (VEGF; también denominado factor de permeabilidad vascular, VPF). El VEGF representa una familia de isoformas de mitógenos que existen en formas homodiméricas debido al empalme de ARN alternativo. Se informa que las isoformas de VEGF son específicas para células endoteliales vasculares (para revisiones, ver: Ferrara et al. *Endocr. Rev.* 1992, *13*, 18; Neufield et al. *FASEB J.* 1999, *13*, 9).

Se informa que la expresión de VEGF está inducida por hipoxia (Shweiki et al. *Nature* 1992, *359*, 843), como así también por una variedad de citoquinas y factores de crecimiento, tales como interleuquina-1, interleuquina-6, factor de crecimiento epidérmico y factor de crecimiento transformante. A la fecha, se ha informado que los miembros de la familia VEGF y de la VEGF se unen a uno o más de las tres tirosina quinasas del receptor de transmembrana (Mustonen et al. *J. Cell Biol.*, 1995, *129*, 895), el receptor-1 de VEGF (también conocido como flt-1 (tirosina quinasa-1 del tipo fms)), el VEGFR-2 (también conocido como receptor que contiene el dominio inserto de quinasa (KDR); el análogo murino de KDR se conoce como quinasa-1 de hígado fetal (flk-1)), y el VEGFR-3 (también conocido como flt-4). El KDR y el flt-1 han demostrado tener diferentes propiedades de transducción de señal (Waltenberger et al. *J. Biol. Chem.* 1994, *269*, 26988); Park et al. *Oncogene* 1995, *10*, 135). De este modo, el KDR se somete a una fuerte fosforilación de tirosina dependiente del ligando en células intactas, por lo que el flt-1 muestra una débil respuesta. De este modo, se cree que la unión al KDR es un requerimiento crítico para la inducción del espectro completo de respuestas biológicas mediadas por VEGF.

In vivo, el VEGF tiene una función central en la vasculogénesis, e induce la angiogénesis y la permeabilización de vasos sanguíneos. La expresión del VEGF desregulada contribuye al desarrollo de una cantidad de enfermedades que se caracterizan por los procesos de angiogénesis anormal y/o hiperpermeabilidad. Se cree que la regulación de la cascada de transducción de señal mediada por VEGF

por algunos agentes puede aportar un modo útil para el control de procesos de angiogénesis anormal y/o hiperpermeabilidad.

Los factores de crecimiento endotelial vascular (VEGF, VEGF-C, VEGF-D) y sus receptores (VEGFR2, VEGFR3) no son sólo reguladores claves de la angiogénesis tumoral sino además de la linfangiogénesis. Los VEGF, VEGF-C y VEGF-D se expresan en la mayoría de los tumores, esencialmente durante los períodos de crecimiento del tumor y, a menudo a niveles sustancialmente aumentados. La expresión de VEGF se estimula por hipoxia, citoquinas, oncogenes tales como *ras*, o por inactivación de los genes supresores del tumor (McMahon, G. *Oncologist* 2000, *5(Suppl. 1)*, 3-10; McDonald, N.Q.; Hendrickson, W.A. *Cell* 1993, *73*, 421-424).

Las actividades biológicas de los VEGFs están mediadas a través de la unión de sus receptores. El VEGFR3 (también denominado Flt-4) se expresa predominantemente sobre el endotelio linfático en tejidos adultos normales. La función del VEGFR3 es necesaria para una nueva formación del vaso linfático, pero no para el mantenimiento de los vasos linfáticos pre-existentes. El VEGFR3 además se regula por aumento sobre el endotelio de los vasos sanguíneos en tumores. Recientemente, el VEGF-C y el VEGF-D, ligandos para VEGFR3, han sido identificados como reguladores de la linfangiogénesis en mamíferos. La linfangiogénesis inducida por factores linfangiogénicos asociados al tumor podrían promover el crecimiento de nuevos vasos en el tumor, suministrando acceso de las células tumorales a la circulación sistémica. Las células que invaden los vasos linfáticos podrían encontrar su vía en el flujo sanguíneo mediante el ducto torácico. Los estudios de expresión del tumor han permitido una comparación directa de la expresión del VEGF-C, VEGF-D y VEGFR3 con factores clinicopatológicos que se relacionan directamente con la capacidad de los tumores primarios de dispersarse (por ejemplo, implicancia del nodo linfático, invasión linfática, metástasis secundaria, y libre supervivencia de la enfermedad). En muchos casos, estos estudios muestran una correlación estadística entre la expresión de los factores linfangiogénicos y la capacidad de un tumor sólido primario de producir metástasis (Skobe, M. et al. *Nature Med.* 2001, *7(2)*, 192-198; Stacker, S.A. et al.. *Nature Med.* 2001, *7(2)*, 186-

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191; Makinen, T. et al. *Nature Med.* 2001, *7(2)*, 199-205; Mandriota, S.J. et al. *EMBO J.* 2001, *20(4)*, 672-82; Karpanen, T. et al. *Cancer Res.* 2001, *61(5)*, 1786-90; Kubo, H. et al. *Blood* 2000, *96(2)*, 546-53).

La hipoxia parece ser un estímulo importante para la producción de VEGF en células malignas. La activación de la p38MAP quinasa es necesaria para la inducción del VEGF por células tumorales en respuesta a la hipoxia (Blaschke, F. et al. *Biochem. Biophys. Res. Commun.* 2002, *296*, 890-896; Shemirani, B. et al. *Oral Oncology* 2002, *38*, 251-257). Además de su implicancia en la angiogénesis a través de la regulación de la secreción del VEGF, la p38 MAP quinasa promueve la invasión de células malignas, y la migración de diferentes tipos de tumores a través de la regulación de la actividad de la colagenasa y la expresión del activador del plasminógeno uroquinasa (Laferriere, J. et al. *J. Biol. Chem.* 2001, *276*, 33762–33772; Westermarck, J. et al. *Cancer Res.* 2000, *60*, 7156–7162; Huang, S. et al. *J. Biol. Chem.* 2000, *275*, 12266–12272; Simon, C. et al. *Exp. Cell Res.* 2001, *271*, 344–355). Más aún, el VEGF activa la proteína quinasa regulada por la señal extracelular (ERK) en células endoteliales de vena umbilical humana (HUVEC) (Yu, Y.; Sato, D. *J. Cell Physiol* 1999, *178*, 235-246).

El PDGF es otro regulador clave de la formación estromal que es secretada por muchos tumores de forma parácrina y se cree que promueve el desarrollo de fibroblastos, células del músculo liso y endoteliales, promocionando la formación del estroma y la angiogénesis. El PDGF se identificó originalmente como el producto v-sis oncogen de virus de sarcoma simio (Heldin, C.H., et al., *J Cell Sci Suppl*, 1985, 3, 65-76). El factor de crecimiento se obtiene de dos cadenas de péptidos, referidas como cadenas A o B las cuales comparten 60% de homología en su secuencia de aminoácidos primaria. Las cadenas son dizulfuro entrecruzado para formar la proteína madura de 30 kDa compuesta de homo- o heterodímeros ya sean AA, BB o AB. El PDGF se encuentra a altos niveles en plaquetas, y se expresa por células endoteliales y células del músculo liso vascular. Además, la producción de PDGF se regula por aumento en condiciones de oxígeno bajas tales como las halladas en el tejido tumoral débilmente vascularizado (Kourembanas, S., et al., *Kidney Int*, 1997, 51(2), 438-43). El PDGF se une con elevada afinidad al receptor de PDGF, un

aminoácido 1106 un receptor de tirosina quinasa de transmembrana de 124 kDa (Heldin, C.H., A. Ostman, y L. Ronnstrand, *Biochim Biophys Acta*, 1998. 1378(1), 79-113). El PDGFR se halla como cadenas homo o heterodímeras que tienen 30% de homología total en su secuencia de aminoácidos y 64% de homología entre sus dominios de quinasa (Heldin, C.H., et al.. *Embo J*, 1988, 7(5), 1387-93). El PDGFR es un miembro de una familia de receptores de tirosina quinasa con dominios de quinasa empalmados que incluye el VEGFR2 (KDR), VEGFR3 (Flt4), c-Kit, y el FLT3. El receptor de PDGF se expresa esencialmente en el fibroblasto, células del músculo liso, y pericitos y en menor grado sobre neuronas, células mesangiales de riñón, células de Leydig y Schwann del sistema nervioso central. Al unirse al receptor, el PDGF induce la dimerización del receptor y se somete a la auto y transfosforilación de residuos de tirosina que aumentan la actividad de la quinasa de los receptores y promueve el reclutamiento de efectores de corriente abajo a través de la activación de los dominios de unión de la proteína de SH2. Una cantidad de moléculas de señalización forman complejos con PDGFR activado incluyendo la PI-3-quinasa, fosfolipasa C-gamma, src y GAP (proteína que activa la GTPasa para p21-ras) (Soskic, V., et al. *Biochemistry*, 1999, 38(6), 1757-64). A través de la activación de la PI-3-quinasa, el PDGF activa la trayectoria de la señalización de Rho induciendo la motilidad y migración celular, y a través de la activación de GAP, induce la mitogénesis a través de la activación del p21-ras y la trayectoria de señalización MAPK.

En los adultos, se cree que la principal función del PDGF consiste en facilitar y aumentar la proporción de cicatrización de heridas y mantener la homeostasis de los vasos sanguíneos (Baker, E.A. & D.J. Leaper, *Wound Repair Regen*, 2000. 8(5), 392-8; Yu, J., A. Moon, y H.R. Kim, *Biochem Biophys Res Commun*, 2001. 282(3), 697-700). El DPGF se halla a concentraciones elevadas en plaquetas y es un potente quimioatrayente para el fibroblasto, células del músculo liso, neutrófilos y macrófagos. Además de su función en la cicatrización de heridas, el PDGF es conocido por mantener la homeostasis vascular. Durante el desarrollo de los nuevos vasos sanguíneos, el PDGR recluta pericitos y células del músculo liso que son necesarias para la integridad muscular de los vasos. Se cree que el PDGF tienen

una función similar durante la neovascularización. Como parte de su función en la angiogénesis, el PDGF controla presión del fluido intersticial, regulando la permeabilidad de los vasos a través de su regulación de la interacción entre las células de tejido conectivo y la matriz extracelular. Al inhibir la actividad del PDGR puede disminuir la presión intersticial y facilitar el influjo de citotóxicos en tumores que mejoran la eficacia anti-tumoral de estos agentes (Pietras, K., et al. *Cancer Res*, 2002. 62(19), 5476-84; Pietras, K., et al. *Cancer Res*, 2001. 61(7), 2929-34).

El PDGF puede promover el crecimiento del tumor a través de la estimulación prácrina o autócrina de los receptores de PDGFR sobre células estromales o células tumorales directamente, o a través de la amplificación del receptor o activación del receptor por recombinación. El PDGF sobreexpresado puede transformar las células del melanoma humano y los queratinocitos (Forsberg, K., et al. *Proc Natl Acad Sci U S A.*, 1993. 90(2), 393-7; Skobe, M. & N.E. Fusenig, *Proc Natl Acad Sci U S A*, 1998. 95(3), 1050-5), dos tipos de células que no expresan los receptores de PDGF, presumiblemente por el efecto directo del PDGF sobre la formación del estroma y la inducción de la angiogénesis. Esta estimulación parácrina del estroma tumoral además se observa en carcinomas del colon, pulmón, pecho y próstata (Bhardwaj, B., et al. *Clin Cancer Res*, 1996, 2(4), 773-82; Nakanishi, K., et al. *Mod Pathol*, 1997, 10(4), 341-7; Sundberg, C., et al. *Am J Pathol*, 1997, 151(2), 479-92; Lindmark, G., et al. *Lab Invest*, 1993, 69(6), 682-9; Vignaud, J.M., et al, *Cancer Res*, 1994, 54(20), 5455-63) donde los tumores expresan el PDGF, pero no el receptor. La estimulación autócrina del crecimiento de célula tumoral, donde una gran fracción de tumores analizados expresan tanto el PDGF del ligando como el receptor, se ha reportado en glioblastomas (Fleming, T.P., et al. *Cancer Res*, 1992, 52(16), 4550-3), sarcomas del tejido blando (Wang, J., M.D. Coltrera, y A.M. Gown, *Cancer Res*, 1994, 54(2), 560-4) y cáncares de ovario (Henriksen, R., et al. *Cancer Res*, 1993, 53(19), 4550-4), próstata (Fudge, K., C.Y. Wang, y M.E. Stearns, *Mod Pathol*, 1994, 7(5), 549-54), páncreas (Funa, K., et al. *Cancer Res*, 1990, 50(3), 748-53) y pulmón (Antoniades, H.N., et al., *Proc Natl Acad Sci U S A*, 1992, 89(9), 3942-6). En menor medida se halló activación independiente del ligando del receptor pero se ha informado en leucemia mielomonocítica crónica (CMML, en inglés) donde el evento de

translocación cromosómica forma una proteína de fusión entre el TEL del factor de transcripción de tipo Ets y el receptor de PDGF. Además, las mutaciones activas en el PDGFR han sido halladas en los tumores estromales gastrointestinales en los cuales la activación de c-Kit no está involucrada (Heinrich, M.C., et al., *Science*, 2003, 9, 9).

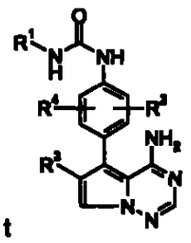
Ciertos inhibidores de PDGFR interferirán con el desarrollo estromal del tumor y se cree que inhiben el crecimiento tumoral y la metástasis.

La unión entre la actividad en los ensayos de proliferación celular del tumor *in vitro* y la actividad anti-tumoral en el estado clínico ha sido bien establecida en la técnica. Por ejemplo la utilidad terapéutica de taxol (Silvestrini et al. *Stem Cells* 1993, 11(6), 528-35), taxotere (Bissery et al. *Anti Cancer Drugs* 1995, 6(3), 339), y los inhibidores de topoisomerasa (Edelman et al. *Cancer Chemother).*

Las células protegen su ADN adoptando un complejo de orden más elevado denominado cromatina. La condensación de cromatina es evidente durante la mitosis y la muerte celular inducida por apoptosis mientras que la descondensación de cromatina es necesaria para la replicación, reparación, recombinación y transcripción. Las histonas están entre algunas de las proteínas de unión al ADN que están involucradas en la regulación de condensación del ADN; y las modificaciones pos-translacionales de las colas de la histona cumplen una función crítica en la condensación / descondensación dinámica que se produce durante el ciclo celular. La fosforilación de las colas de la histona H3 está involucrada en la transcripción y división celular (Prigent et al. *J. Cell Science* 2003, 116, 3677). Se ha informado que una cantidad de proteína quinasas fosforilan la histona h3 y estas quinasas funcionan tanto como transducción de señal como quinasas mitóticas.

Derivados de pirrolotriazina han sido descriptos como que poseen actividad inhibidora de quinasa en la Solicitud Estadounidense No. 10/289.010, Patente Estadounidense No. 6.670.357, WO 2001/19828, WO 2003/042172, WO 2004/009542, WO2004/009601, WO 2004/009784 y WO 2004/013145.

En una realización, la presente invención aporta un compuesto de fórmula (I)



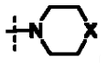
t (I),

donde

R^1 se selecciona del grupo integrado por arilo, bencilo, y heteroarilo, en donde arilo y heteroarilo pueden estar opcionalmente sustituidos con 0, 1, 2, 3 o 4 *sustituyentes seleccionados independientemente del grupo integrado por*

- alquilo (C_1-C_4), en donde alquilo (C_1-C_4) puede estar sustituido con 0, 1, 2 o 3 halógeno, 0 o 1 heterociclilo, o 0 o 1 (C_1-C_3)alcoxi, en donde

  alcoxi (C_1-C_3) puede estar opcionalmente sustituido con alquilamino (C_1-C_3),

- alcoxi (C_1-C_3), en donde alcoxi (C_1-C_3) pueden estar opcionalmente sustituidos con alquilamino (C_1-C_3),
- halógeno,
- trifluorometilo,
- trifluorometoxi,
- (C_3-C_6)cicloalquilo,
- fenilo opcionalmente sustituido con 1 o 2 halógeno,
-  , en donde X es CH_2, O, S o NR^{1-1}, y en donde R^{1-1} es hidrógeno o alquilo (C_1-C_6),
- nitro,
- ciano,
- (C_1-C_3)alquiltio,
- trifluorometiltio,
- alquil (C_1-C_3)-carbonilo,
- alcoxi (C_1-C_6)-carbonilo, y
- fenoxi, en donde fenoxi puede estar opcionalmente sustituido con 0, 1 o 2 sustituyentes seleccionados

independientemente del grupo integrado por alquilo (C_1-C_6), alcoxi (C_1-C_6), trifluorometoxi, y halógeno,

y

en donde bencilo puede estar sustituido con 0, 1, 2 o 3 grupos seleccionados de halógeno, (C_1-C_3)alquilo, y (C_1-C_3)alcoxi;

R^2 se selecciona del grupo integrado por hidrógeno, halógeno, alquilo (C_1-C_4) y alcoxi (C_1-C_4);

R^3 se selecciona del grupo integrado por

- carboxilo,
- formilo,
- alquil-(C_1-C_6)-carbonilo opcionalmente sustituido con 0, 1, 2, o 3 grupos seleccionados de flúor, cloro, hidroxi, alcoxi (C_1-C_6), y heterocicilo,
- cicloalquil-(C_3-C_6)-carbonilo,
- alcoxi-(C_1-C_6)-carbonilo opcionalmente sustituido con 0, 1, 2, o 3 grupos seleccionados de amino, y (C_1-C_6)alcoxicarbonilo,
- aminocarbonilo,
- alquilamino-(C_1-C_6)-carbonilo, en donde alquilamino-(C_1-C_6)-carbonilo puede estar opcionalmente sustituido con 0, 1, 2 o 3 sustituyentes seleccionados independientemente del grupo integrado por cicloalquilo (C_3-C_6), halógeno, amino, alquilamino (C_1-C_6), hidroxi, alcoxi (C_1-C_6), alcoxi-(C_1-C_6)-carbonilo, alquiltio (C_1-C_6), alcoxi-(C_1-C_6)-carbonilamino, y metilsulfonilo, y en donde alquilamino-(C_1-C_6)-carbonilo puede estar opcionalmente sustituido con o 0 o 1 heterociclilo, en donde heterociclilo puede estar opcionalmente sustituido con 0 o 1 alquilo (C_1-C_6), y en donde alquilamino-(C_1-C_6)-carbonilo puede estar opcionalmente sustituido con 0 o 1 fenilo, en donde fenilo puede estar opcionalmente sustituido con 0 o 1 halógeno, alquilo (C_1-C_6), o alcoxi (C_1-C_6),
- heterociclilcarbonilo opcionalmente sustituido con 0 o 1 amino, alquilamino (C_1-C_6), cicloalquilo, o alquilo (C_1-C_6), en donde alquilo (C_1-C_6) puede estar opcionalmente sustituido con 0 o 1 amino o alquilamino (C_1-C_6),

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• alquilo (C_1-C_6) opcionalmente sustituido con 0, 1, 2 o 3 sustituyentes seleccionados independientemente del grupo integrado por

a) hidroxilo,

b) amino,

c) alquilamino (C_1-C_6), en donde alquilamino (C_1-C_6) puede estar sustituido con 0, 1, 2, 3 o 4 sustituyentes seleccionados independientemente del grupo integrado por halógeno, amino, alquilamino, metoxi, metilio, y metilsulfonilo,

d) arilamino, en donde arilamino puede estar sustituido con 0, 1 o 2 sustituyentes seleccionados independientemente del grupo integrado por alquilo (C_1-C_6), alcoxi (C_1-C_6), y trifluorometilo,

e) heterociclilo, en donde heterociclilo puede estar sustituido con 0, 1 o 2 alquilo (C_1-C_6), en donde alquilo (C_1-C_6) puede estar sustituido con 0, 1 o 2 hidroxi, metoxi o piridilo,

f) imidazolilo,

g) piridilamino,

h) alcoxi (C_1-C_3) opcionalmente sustituido con fluoro hasta el nivel de perfluoro, o con heterociclo, en donde heterociclo puede estar opcionalmente sustituido con 0 o 1 alquilo (C_1-C_6),

i) alcoxi (C_1-C_3)-alcoxi (C_2-C_3), y

j) alcoxi-(C_1-C_6)-carbonilo,

k) cicloalquilo (C_3-C_6),

l) ciano,

• alcoxi (C_1-C_6) opcionalmente sustituido con 1, 2 o 3 sustituyentes

independientemente seleccionados del grupo integrado por amino, alquilamino (C_1-C_6), y heterociclilo, en donde heterociclilo puede estar sustituido con 0, 1, 2 o 3 alquilo (C_1-C_6),

• cicloalquilamino-(C_3-C_6)-carbonilo opcionalmente sustituido con alquilo (C_1-C_3),

- ciano,
- heteroarilo, en donde heteroarilo puede estar sustituido con 0, 1, 2, o 3 grupos independientemente seleccionado del grupo integrado por

a) alquilo (C_1-C_8), en donde alquilo (C_1-C_8) puede estar sustituido con 0, 1, 2, o 3 halógeno, 0 o 1 heterociclilo, 0 o 1 alquilamino, o 0 o 1 hidroxi o metoxi,

b) halógeno,

c) amino,

d) alquilamino,

e) alcoxi-(C_1-C_8)-carbonilo, y

f) cicloalquilo (C_3-C_8),

- heteroarilocarbonilo, el cual puede estar sustituido con 0, 1, 2, o 3 grupos independientemente seleccionados del grupo integrado por alquilo (C_1-C_8), cicloalquilo (C_3-C_8) y halógeno,
- heterociclilo, en donde heterociclilo puede estar sustituido con 0, 1, 2, o 3 grupos independientemente seleccionados del grupo integrado por alquilo (C_1-C_8) y alcoxi-(C_1-C_8)-carbonilo; y

R^4 se selecciona del grupo integrado por hidrógeno, alquilo (C_1-C_8), alcoxi (C_1-C_8) y halógeno;

o su sal aceptable para uso farmacéutico.

Dependiendo de su estructura, los compuestos de acuerdo con la invención pueden existir en formas estereoisoméricas (enantiómeros, diastereómeros). Por lo tanto, la invención se refiere a los enantiómeros o diastereómeros y a sus mezclas respectivas. Tales mezclas de enantiómeros y/o diastereómeros se pueden separar en constituyentes unitarios de forma estereoisomérica de manera conocida.

La invención además se refiere a tautómeros de los compuestos, dependiendo de la estructura de los compuestos.

Una sal a los fines de la invención es una sal aceptable para uso farmacéutico del compuesto de acuerdo con la invención.

Sales aceptables para uso farmacéutico de los compuestos (I) incluyen sales de adición de ácidos minerales, ácidos carboxílicos y ácidos sulfónicos, por ejemplo sales

de ácido clorhídrico, ácido bromhídrico, ácido sulfúrico, ácido fosfórico, ácido metansulfónico, ácido etansulfónico, ácido toluensulfónico, ácido bencenosulfónico, ácido naftalendisulfónico, ácido acético, ácido propiónico, ácido láctico, ácido tartárico, ácido málico, ácido cítrico, ácido maleico y ácido benzoico.

Sales aceptables para uso farmacéutico de los compuestos (I) incluyen además sales de bases habituales, tales como por ejemplo sales de metal alcalino (por ejemplo sales de sodio y potasio, sales de metal alcalinotérreo (por ejemplo sales de calcio y magnesio) y sales de amonio derivadas de amoníaco o aminas orgánicas que tienen de 1 a 16 átomos de carbono, tales como etilamina, dietilamina, trietilamina, etildiisopropilamina, monoetanolamina, dietanolamina, trietanolamina, diciclohexilamina, dimetilaminoetanol, procaína, dibencilamina, *N*-metilmorfolina, dihidroabietilamina, arginina, lisina, etilendiamina y metilpiperidina.

Solvatos a los fines de la invención son aquellas formas de los compuestos que coordinan con las moléculas de solvente para formar un complejo en estado sólido o líquido. Los hidratos son una forma específica de solvatos, donde la coordinación es con agua.

A los fines de la presente invención los sustituyentes tienen los siguientes significados, a menos que se especifique lo contrario:

Alquilo representa un radical alquilo lineal o ramificado que tiene en general 1 a 6, 1 a 4 o 1 a 3 átomos de carbono, que representan a modo ilustrativo metilo, etilo, n-propilo, isopropilo, *ter*-butilo, n-pentilo y n-hexilo.

Alcoxi en general representa un radical hidrocarbonado de cadena recta o ramificada que tiene en general 1 a 6, 1 a 4 o 1 a 3 átomos de carbono y unidos mediante un átomo de oxígeno. Ejemplos no limitantes incluyen metoxi, etoxi, propoxi, isopropoxi, butoxi, isobutoxi, pentoxi, isopentoxi, hexoxi, isohexoxi. Los términos "alcoxi" y "alquiloxi" se pueden utilizar como sinónimos.

Alquilamino representa un radical amino que tiene uno o dos (seleccionados independientemente) sustituyentes de alquilo que representan a manera ilustrativa metilamino, etilamino, n-propilamino, isopropilamino, *ter*-butilamino, n-pentilamino, n-hexilamino, *N,N*-dimetilamino, *N,N*-dietilamino, *N*-etil-*N*-metilamino, *N*-metil-*N*-

n-propilamino, *N*-isopropilo-*N*-n-propilamino, *N*-t-butilo-*N*-metilamino, *N*-etil-*N*-n-pentilamino y *N*-n-hexilo-*N*-metilamino.

Alquiltio en general representa un radical hidrocarbonado de cadena recta o ramificada que tiene 1 a 6 átomos de carbono y unidos mediante un átomo de azufre. Ejemplos no-limitantes incluyen metiltio y etiltio.

Arilamino representa un radical amino que tiene uno o dos (seleccionados independientemente) sustituyentes de arilo, que representan a modo ilustrativo fenilamino.

Aminoalquilo representa un radical alquilo radical sustituido con un grupo amino. Ejemplos no-limitantes incluyen aminometilo y aminoetilo.

Aminocarbonilo representa un grupo amida libre.

Alquilcarbonilo representa un grupo carbonilo que tienen un sustituyente alquilo. Ejemplos no-limitantes incluyen acetilo, propanoílo, butanoílo, 2-metilopropanoílo, y hexanoílo.

Alquilaminocarbonilo representa un radical aminocarbonilo (amida libre) que tiene uno o dos (seleccionados independientemente) sustituyentes de alquilo, que representan a modo ilustrativo metilaminocarbonilo, etilaminocarbonilo, n-propilaminocarbonilo, isopropilaminocarbonilo, *ter*-butilaminocarbonilo, n-pentilaminocarbonilo, n-hexilaminocarbonilo, *N,N*-dimetilaminocarbonilo, *N,N*-dietilaminocarbonilo, *N*-etil-*N*-metilaminocarbonilo, *N*-metil-*N*-n-propilaminocarbonilo, *N*-isopropilo-*N*-n-propilaminocarbonilo, *N*-t-butilo-*N*-metilaminocarbonilo, *N*-etil-*N*-n-pentilamino-carbonilo y *N*-n-hexilo-*N*-metilaminocarbonilo.

Alcoxicarbonilo representa un grupo carbonilo que tiene un sustituyente alcoxi. Representa a modo ilustrativo metoxicarbonilo, etoxicarbonilo, n-propoxicarbonilo, isopropoxicarbonilo, *ter*-butoxicarbonilo, n-pentoxicarbonilo y n-hexoxicarbonilo.

Cicloalquilo representa un radical cicloalquilo monocíclico que tiene en general 3 a 8 o 5 a 7 átomos de carbono, que representan a modo ilustrativo ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo y cicloheptilo.

Arilo representa un radical carbocíclico mono- a bicíclico, el cual es aromático al menos en un anillo, que tiene en general 6 a 10 átomos de carbono, que representan a modo ilustrativo fenilo y naftilo.

Heteroarilo representa radical mono- o bicíclico radical que tiene en general 5 a 10 o 5 o 6 átomos de anillo y hasta 5, en otra realización hasta 4 heteroátomos seleccionados del grupo integrado por nitrógeno, oxígeno y azufre, el cual es aromático al menos en un anillo. Puede estar unido mediante un átomo de carbono de anillo o un átomo de nitrógeno de anillo. Si representa un bicíclo, donde un anillo es aromático y el otro no lo es, puede unirse a cualquier anillo. Ejemplos ilustrativos son tienilo, furilo, pirrolilo, pirazolilo, tiazolilo, oxazolilo, imidazolilo, piridilo, pirimidilo, piridazinilo, indolilo, indazolilo, benzofurilo, bencimidazolilo, benzotiofenilo, quinolinilo, isoquinolinilo, 1,3-benzodioxinilo, 1,4-benzodioxinilo, o benzodioxolilo.

Heteroarilocarbonilo representa un residuo heteroarilo unido mediante un átomo de carbono de carbonilo.

Heterociclilo representa un radical mono- o bicíclico, en otra realización monocíclico, no-aromático, es decir saturado o parcialmente insaturado radical que tiene en general 4 a 10 o 5 a 8 átomos de anillo y hasta 3, en otra realización hasta 2 heteroátomos y/o heterogrupos seleccionados del grupo integrado por nitrógeno, oxígeno y azufre, CO, SO y SO_2. Si es bicíclico, puede ser un bicíclo fusionado o espiro-conectado. Puede estar unido mediante un átomo de carbono de anillo o un átomo de nitrógeno de anillo. Ejemplos ilustrativos son tetrahidrofuran-2-ilo, pirrolidin-2-ilo, pirrolidin-3-ilo, pirrolinilo, piperidinilo, morfolinilo, perhidroazepinilo.

Heterociclilcarbonilo representa un residuo de heterociclilo unido mediante un átomo de carbono de carbonilo.

Metilsulfonilo representa un residuo $-S(O)_2CH_3$.

Halógeno o halo representa un sustituyente seleccionado del grupo integrado por fluoro, cloro, bromo y yodo, en otra realización fluoro y cloro.

alcoxi (C_1-C_3)-alcoxi (C_2-C_3) representa un grupo de alcoxi de 2 a 3 carbonos sustituido en la posición 2 o 3 con un grupo alcoxi de 1 a 3 carbonos, que representan a modo ilustrativo 2-metoxietoxi (CH_3-O-CH_2CH_2-O-), 3-etoxipropoxi (CH_3CH_2-O-$CH_2CH_2CH_2$-O-), 2-metoxipropoxi (CH_3-O(CH_3)$CHCH_2$-O-), 2-isopropoxietoxi ($CH_3(CH_3)$CH-O-CH_2CH_2-O-) 2-metoxi-1-metiloetoxi ($CH_3OCH_2(CH_3)$CH-O-) o 3-propoxietoxi, ($CH_3CH_2CH_2$-O-CH_2CH_2-O-).

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cicloalquilamino(C_3-C_8)carbonilo opcionalmente sustituido con alquilo (C_1-C_3) representa un radical aminocarbonilo (amida libre) que tiene un (seleccionados independientemente) sustituyente de cicloalquilo que puede estar opcionalmente sustituido sobre el átomo de nitrógeno con un grupo alquilo (C_1-C_3) e independientemente sustituido sobre cualquier átomo de carbono disponible con 1 o 2 grupos alquilo (C_1-C_3), que representan a modo ilustrativo *N*-ciclopropilaminocarbonilo, *N*-ciclopropil-*N*-metilaminocarbonilo, *N*-(2-metilciclopropil)aminocarbonilo, *N*-ciclobutilaminocarbonilo, *N*-(2,2-dimetil)-ciclopropil)aminocarbonilo, ciclopentilaminocarbonilo, *N*-(3-etilciclopentil)-aminocarbonilo, *N*-ciclohexilaminocarbonilo, *N*-ciclohexil-*N*-etilaminocarbonilo, *N*-(3-propilciclohexilo)aminocarbonilo, y *N*-(4,4-dimetilciclohexil)aminocarbonilo.

Un símbolo * próximo a un enlace denota el punto de unión en la molécula. Alternativamente, una línea de puntos (—) denota un enlace mediante un radical que está unido al resto de la molécula.

Cuando prefijos tales como (C_1-C_4) se utilizan antes de los sustituyentes, significa que indican la cantidad de átomos de carbono, por ejemplo 1 a 4 en caso de (C_1-C_4).

Cuando más de un sustituyente se selecciona de un grupo, la selección puede ser independiente una de otra. A menos que se indique una cantidad máxima de sustituyentes, la sustitución puede tener lugar hasta la cantidad máxima de locaciones de sustitución disponibles, por ejemplo, en caso de halogenación al nivel perhalo.

En otra realización, la presente invención aporta un compuesto de fórmula (I), en donde

R^1 se selecciona del grupo integrado por fenilo y heteroarilo monocíclico que tiene 5 o 6 átomos de anillo,

en donde fenilo y heteroarilo pueden estar opcionalmente sustituidos con 0, 1, 2, 3 o 4 sustituyentes seleccionados independientemente del grupo integrado por

- alquilo (C_1-C_4), en donde alquilo (C_1-C_4) puede estar sustituido con 0, 1, 2 o 3 halógeno, 0 o 1 pirrolidinilo, 0 o 1 morfolinilo, o 0 o 1 alcoxi (C_1-C_3) en donde

alcoxi (C_1-C_3) puede estar opcionalmente sustituido con alquilamino (C_1-C_3),

- alcoxi (C_1-C_3), en donde alcoxi (C_1-C_3) puede estar opcionalmente sustituido con alquilamino (C_1-C_3),
- halógeno,
- trifluorometilo,
- trifluorometoxi,
- cicloalquilo (C_3-C_6),
- fenilo opcionalmente sustituido con 1 o 2 halógeno,
- trifluorometiltio;

R^2 se selecciona del grupo integrado por hidrógeno, halógeno, alquilo (C_1-C_4) y alcoxi (C_1-C_4);

R^3 se selecciona del grupo integrado por

- carboxilo,
- formilo,
- alquil(C_1-C_6)carbonilo opcionalmente sustituido con 0, 1, 2, o 3 grupos seleccionados de flúor, cloro, hidroxi, alcoxi (C_1-C_6), y heterocicio monocíclico que tiene 5 o 6 átomos de anillo,
- cicloalquil(C_3-C_6)carbonilo,
- alcoxi(C_1-C_6)carbonilo opcionalmente sustituido con 0, 1, 2, o 3 grupos seleccionados de amino, y alcoxi(C_1-C_6)carbonilo,
- aminocarbonilo,
- alquilamino(C_1-C_6)carbonilo, en donde alquilamino(C_1-C_6)carbonilo puede estar opcionalmente sustituido con 0, 1, 2 o 3 sustituyentes seleccionados independientemente del grupo integrado por cicloalquilo (C_3-C_6), halógeno, amino, alquilamino (C_1-C_6), hidroxi, alcoxi (C_1-C_6), alcoxi(C_1-C_6)carbonilo, alquiltio (C_1-C_6), alcoxi(C_1-C_6)carbonilamino, y metilsulfonilo, y en donde alquilamino(C_1-C_6)carbonilo puede estar opcionalmente sustituido con 0 o 1 hidroxilo o 0 o 1 heterocicilo monocíclico que tiene 5 o 6 átomos de anillo, en donde heterocicilo puede estar opcionalmente sustituido con 0 o 1 alquilo (C_1-C_6),

y en donde alquilamino(C_1-C_6)carbonilo puede estar opcionalmente sustituido con 0 o 1 fenilo, en donde fenilo puede estar opcionalmente sustituido con 0 o 1 halógeno o alquilo (C_1-C_6),

- heterociclilcarbonilo monocíclico que tiene 5 o 6 átomos de anillo, opcionalmente sustituido con 0 o 1 amino, alquilamino (C_1-C_6), cicloalquilo (C_3-C_6), o alquilo (C_1-C_6), en donde alquilo (C_1-C_6) puede estar opcionalmente sustituido con 0 o 1 amino o alquilamino (C_1-C_6),

- alquilo (C_1-C_6) opcionalmente sustituido con 0, 1, 2 o 3 sustituyentes seleccionados independientemente del grupo integrado por

a) hidroxilo,

b) amino,

c) alquilamino (C_1-C_6), en donde alquilamino (C_1-C_6) puede estar sustituido con 0, 1, 2, 3 o 4 sustituyentes seleccionados independientemente del grupo integrado por halógeno, amino, alquilamino, metoxi, metiltio, y metilsulfonilo,

e) heterocicilo monocíclico que tiene 5 o 6 átomos de anillo, en donde heterocicilo puede estar sustituido con 0, 1 o 2 alquilo (C_1-C_6), en donde alquilo (C_1-C_6) puede estar sustituido con 0, 1 o 2 hidroxi, metoxi o piridilo,

f) imidazolilo,

h) alcoxi (C_1-C_3) opcionalmente sustituido con fluoro hasta el nivel de perfluoro, o con heterociclo monocíclico que tiene 5 o 6 átomos de anillo, en donde heterociclo puede estar opcionalmente sustituido con 0 o 1 alquilo (C_1-C_6),

i) alcoxi (C_1-C_3)-alcoxi (C_2-C_3), y

j) alcoxi(C_1-C_6)carbonilo,

k) cicloalquilo (C_3-C_6),

l) ciano,

- cicloalquilamino(C_3-C_6)carbonilo opcionalmente sustituido con alquilo (C_1-C_3),

- ciano,

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- heteroarilo, en donde heteroarilo puede estar sustituido con 0, 1, 2, o 3 grupos independientemente seleccionado del grupo integrado por

a) (C_1-C_6)alquilo, en donde (C_1-C_6)alquilo puede estar sustituido con 0, 1, 2, o 3 halógeno, 0 o 1 heterociclilo monocíclico que tiene 5 o 6 átomos de anillo, 0 o 1 alquilamino, o 0 o 1 hidroxi o metoxi,

b) halógeno,

e) alcoxi(C_1-C_6)carbonilo, y

f) cicloalquilo (C_3-C_6),

- heteroarilocarbonilo monocíclico que tiene 5 o 6 átomos de anillo,
- heterociclilo monocíclico que tiene 5 o 6 átomos de anillo, en donde heterociclilo puede estar sustituido con 0, 1, 2, o 3 grupos independientemente seleccionados del grupo integrado por alquilo (C_1-C_6) y alcoxi(C_1-C_6)carbonilo; y

R^4 se selecciona del grupo integrado por hidrógeno y halógeno;

o su sal aceptable para uso farmacéutico.

En otra realización, la presente invención aporta un compuesto de fórmula (I), en donde

R^1 se selecciona del grupo integrado por fenilo, pirazolilo, oxazolilo, isoxazolilo, tiazolilo, piridinilo, y pirimidinilo,

en donde fenilo, pirazolilo, oxazolilo, isoxazolilo, tiazolilo, piridinilo, y pirimidinilo pueden estar opcionalmente sustituidos con 0, 1, 2, 3 o 4 sustituyentes seleccionados independientemente del grupo integrado por

- alquilo (C_1-C_4), en donde alquilo (C_1-C_4) puede estar sustituido con 0, 1, 2 o 3 halógeno,
- alcoxi (C_1-C_3), en donde alcoxi (C_1-C_3) puede estar opcionalmente sustituido con alquilamino (C_1-C_3),
- halógeno,
- trifluorometilo,
- trifluorometoxi,
- ciclopropilo,
- fenilo opcionalmente sustituido con 1 o 2 halógeno;

R^2 se selecciona del grupo integrado por hidrógeno, fluoro y cloro;

R^3 se selecciona del grupo integrado por

- alquil(C_1-C_6)carbonilo opcionalmente sustituido con 0, 1, 2, o 3 grupos seleccionados de flúor, cloro, hidroxi, alcoxi (C_1-C_6), piperazinilo, morfolinilo, pirrolidinilo, y piperidinilo,
- ciclopropilcarbonilo,
- aminocarbonilo,
- alquilamino(C_1-C_6)carbonilo, en donde alquilamino(C_1-C_6)carbonilo puede estar opcionalmente sustituido con 0, 1, 2 o 3 sustituyentes seleccionados independientemente del grupo integrado por cicloalquilo (C_3-C_6), halógeno, amino, alquilamino (C_1-C_6), hidroxi, alcoxi (C_1-C_6), alcoxi(C_1-C_6)carbonilo, alquiltio (C_1-C_6), alcoxi(C_1-C_6)carbonilamino, y metilsulfonilo, y en donde alquilamino(C_1-C_6)carbonilo puede estar opcionalmente sustituido con 0 o 1 hidroxilo, piperazinilo, morfolinilo, pirrolidinilo o piperidinilo, en donde piperazinilo, morfolinilo, pirrolidinilo o piperidinilo puede estar opcionalmente sustituido con 0 o 1 alquilo (C_1-C_6), y en donde alquilamino(C_1-C_6)carbonilo puede estar opcionalmente sustituido con 0 o 1 fenilo, en donde fenilo puede estar opcionalmente sustituido con 0 o 1 halógeno o alquilo (C_1-C_6),
- heterociclilcarbonilo seleccionado de piperazinilocarbonilo, morfolinilcarbonilo, pirrolidinilcarbonilo o piperidinilcarbonilo, opcionalmente sustituido con 0 o 1 amino, alquilamino (C_1-C_6), cicloalquilo (C_3-C_6), o alquilo (C_1-C_6), en donde alquilo (C_1-C_6) puede estar opcionalmente sustituido con 0 o 1 amino o alquilamino (C_1-C_6),
- alquilo (C_1-C_6) opcionalmente sustituido con 0, 1, 2 o 3 sustituyentes seleccionados independientemente del grupo integrado por

  a) hidroxilo,

  c) alquilamino (C_1-C_6), en donde alquilamino (C_1-C_6) puede estar sustituido con 0, 1, 2, 3 o 4 sustituyentes seleccionados independientemente del grupo integrado por halógeno, alquilamino, y metoxi,

e) piperazinilo, morfolinilo, pirrolidinilo o piperidinilo, en donde piperazinilo, morfolinilo, pirrolidinilo o piperidinilo pueden estar sustituidos con 0, 1 o 2 alquilo (C_1-C_6), en donde alquilo (C_1-C_6) puede estar sustituido con 0, 1 o 2 hidroxi o metoxi,

f) imidazolilo,

h) alcoxi (C_1-C_3) opcionalmente sustituido con fluoro hasta el nivel de perfluoro, o con heterociclo monocíclico que tiene 5 o 6 átomos de anillo, en donde heterociclo puede estar opcionalmente sustituido con 0 o 1 alquilo (C_1-C_6),

I) alcoxi (C_1-C_3)-alcoxi (C_2-C_3), y

j) alcoxi(C_1-C_6)carbonilo,

k) cicloalquilo (C_3-C_6),

l) ciano,

- cicloalquilamino(C_3-C_6)carbonilo opcionalmente sustituido con alquilo (C_1-C_3),
- ciano,
- pirazolilo, oxazolilo, isoxazolilo, tiazolilo, isotiazolilo, piridinilo, imidazolilo o pirimidinilo, en donde pirazolilo, oxazolilo, isoxazolilo, tiazolilo, isotiazolilo, piridinilo, imidazolilo o pirimidinilo puede estar sustituido con 0, 1, 2, o 3 grupos independientemente seleccionado del grupo integrado por

a) alquilo (C_1-C_6), en donde alquilo (C_1-C_6) puede estar sustituido con 0, 1, 2, o 3 halógeno, 0 o 1 alquilamino, o 0 o 1 metoxi,

b) halógeno, y

f) cicloalquilo (C_3-C_6),

- pirazolilocarbonilo, oxazolilocarbonilo, isoxazolilocarbonilo, tiazolilocarbonilo, piridinilcarbonilo o pirimidinilcarbonilo; y

R^4 se selecciona del grupo integrado por hidrógeno y fluoro;

o su sal aceptable para uso farmacéutico.

En otra realización, la presente invención aporta un compuesto de fórmula (I), en donde

R^1 se selecciona del grupo integrado por fenilo y heteroarilo monocíclico,

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en donde arilo y heteroarilo pueden estar opcionalmente sustituidos con 0, 1, 2, 3 o 4 sustituyentes seleccionados independientemente del grupo integrado por

- alquilo (C_1-C_4), en donde alquilo (C_1-C_4) puede estar sustituido con 0, 1, 2 o 3 halógeno, 0 o 1 pirrolidinilo o morfolinilo, o 0 o 1 (C_1-C_3)alcoxi en donde

  (C_1-C_3)alcoxi puede estar opcionalmente sustituido con alquilamino (C_1-C_3),

- alcoxi (C_1-C_3), en donde alcoxi (C_1-C_3) puede estar opcionalmente sustituido con alquilamino (C_1-C_3),
- halógeno,
- trifluorometilo,
- trifluorometoxi,
- cicloalquilo (C_3-C_6),
- (C_1-C_3)alquiltio, y
- fenoxi, en donde fenoxi puede estar opcionalmente sustituido con 0, 1 o 2 sustituyentes seleccionados independientemente del grupo integrado por alquilo (C_1-C_6), alcoxi (C_1-C_6), trifluorometoxi, y halógeno,

R^2 se selecciona del grupo integrado por hidrógeno, halógeno, alquilo (C_1-C_4) y alcoxi (C_1-C_4);

R^3 se selecciona del grupo integrado por

- carboxilo,
- alquil(C_1-C_6)carbonilo opcionalmente sustituido con 0, 1, 2, o 3 grupos seleccionados de flúor, cloro, hidroxi, alcoxi (C_1-C_6), y heterocicilo,
- cicloalquil(C_3-C_6)carbonilo,
- alcoxi(C_1-C_6)carbonilo,
- aminocarbonilo,
- alquilamino(C_1-C_6)carbonilo, en donde alquilamino(C_1-C_6)carbonilo puede estar opcionalmente sustituido con 0, 1, 2 o 3 sustituyentes seleccionados independientemente del grupo integrado por cicloalquilo (C_3-C_6), halógeno, alquilamino (C_1-C_6), hidroxi y alcoxi (C_1-C_6),

y en donde alquilamino(C_1-C_6)carbonilo puede estar opcionalmente sustituido con o 0 o 1 heterociclilo, en donde heterociclilo puede estar opcionalmente sustituido con 0 o 1 alquilo (C_1-C_6), y en donde *alquilamino*(C_1-C_6)carbonilo *puede estar opcionalmente sustituido con* 0 o 1 fenilo, en donde fenilo puede estar opcionalmente sustituido con 0 o 1 halógeno, alquilo (C_1-C_6), o alcoxi (C_1-C_6),

- heterociclilcarbonilo opcionalmente sustituido con 0 o 1 amino, alquilamino (C_1-C_6), cicloalquilo, o alquilo (C_1-C_6), en donde alquilo (C_1-C_6) puede estar opcionalmente sustituido con 0 o 1 amino o alquilamino (C_1-C_6),

- alquilo (C_1-C_6) opcionalmente sustituido con 0, 1, 2 o 3 sustituyentes seleccionados independientemente del grupo integrado por

a) hidroxilo,

c) alquilamino (C_1-C_6), en donde alquilamino (C_1-C_6) puede estar sustituido con 0, 1, 2, 3 o 4 sustituyentes seleccionados independientemente del grupo integrado por halógeno, amino, alquilamino, metoxi, metilio, y metilsulfonilo,

e) heterociclilo, en donde heterociclilo puede estar sustituido con 0, 1 o 2 alquilo (C_1-C_6), en donde alquilo (C_1-C_6) puede estar sustituido con 0, 1 o 2 *hidroxi, metoxi o piridilo,*

f) imidazolilo,

h) alcoxi (C_1-C_3) opcionalmente sustituido con fluoro hasta el nivel de perfluoro, o con heterociclo, en donde heterociclo puede estar opcionalmente sustituido con 0 o 1 alquilo (C_1-C_6),

l) alcoxi (C_1-C_3)-alcoxi (C_2-C_3), y

J) alcoxi(C_1-C_6)carbonilo,

k) cicloalquilo (C_3-C_6),

- cicloalquilamino(C_3-C_6)carbonilo opcionalmente sustituido con alquilo (C_1-C_3),

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- heteroarilo monocíclico que tiene 5 o 6 átomos de anillo, en donde heteroarilo puede estar sustituido con 0, 1, 2, o 3 grupos independientemente seleccionado del grupo integrado por

g) alquilo (C_1-C_6), en donde alquilo (C_1-C_6) puede estar sustituido con 0, 1, 2, o 3 halógeno, 0 o 1 heterocicilo, 0 o 1 alquilamino, o 0 o 1 hidroxi o metoxi,

h) halógeno,

i) amino,

j) alquilamino,

k) alcoxi(C_1-C_6)carbonilo, y

l) cicloalquilo (C_3-C_6),

- heteroarilocarbonilo monocíclico que tiene 5 o 6 átomos de anillo,
- heterociclilcarbonilo monocíclico que tiene 5 o 6 átomos de anillo,

en donde heterocicilo puede estar sustituido con 0, 1, 2, o 3 grupos independientemente seleccionados del grupo integrado por alquilo (C_1-C_6) y alcoxi(C_1-C_6)carbonilo; y

R^4 es hidrógeno o fluoro;

o su sal aceptable para uso farmacéutico.

En otra realización, la presente invención aporta un compuesto de fórmula (I), en donde

R^1 se selecciona del grupo integrado por fenilo, pirazolilo, oxazolilo, isoxazolilo, tiazolilo, piridinilo, y pirimidinilo,

en donde fenilo, pirazolilo, oxazolilo, isoxazolilo, tiazolilo, piridinilo, y pirimidinilo pueden estar opcionalmente sustituidos con 0, 1, 2, 3 o 4 sustituyentes seleccionados independientemente del grupo integrado por

- alquilo (C_1-C_4), en donde alquilo (C_1-C_4) puede estar sustituido con 0, 1, 2 o 3 halógeno,
- alcoxi (C_1-C_3),
- halógeno,
- trifluorometilo, y

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- fenoxi, en donde fenoxi puede estar opcionalmente sustituido con 0, 1 o 2 sustituyentes seleccionados independientemente del grupo integrado por alquilo, alcoxi (C_1-C_6), trifluorometoxi, y halógeno;

R^2 es hidrógeno, fluoro, cloro, metilo, etilo o metoxi;

R^3 se selecciona del grupo integrado por

- alcoxi(C_1-C_6)carbonilo,
- alquilamino(C_1-C_6)carbonilo, en donde alquilamino(C_1-C_6)carbonilo puede estar opcionalmente sustituido con 0, 1, 2 o 3 sustituyentes seleccionados independientemente del grupo integrado por halógeno, y
- *cicloalquilamino(C_3-C_6)carbonilo opcionalmente sustituido con* (C_1-C_3)alquilo,
- piperazinilocarbonilo, morfolinilcarbonilo, pirrolidinilcarbonilo o piperidinilcarbonilo; y

R^4 es hidrógeno;

o su sal aceptable para uso farmacéutico.

En otra realización, la presente invención aporta un compuesto de fórmula (I), en donde

R^1 se selecciona del grupo integrado por fenilo, pirazolilo, tiazolilo, piridinilo, y pirimidinilo,

en donde fenilo, pirazolilo, oxazolilo, isoxazolilo, tiazolilo, piridinilo, y pirimidinilo pueden estar opcionalmente sustituidos con 0, 1, 2, 3 o 4 sustituyentes seleccionados independientemente del grupo integrado por

- metilo, etilo, propilo o butilo, en donde metilo, etilo, propilo o butilo puede estar sustituido con 0, 1, 2 o 3 fluoro o cloro,
- fluoro o cloro,
- trifluorometilo, y
- fenoxi, en donde fenoxi puede estar opcionalmente sustituido con 0, 1 o 2 sustituyentes seleccionados

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independientemente del grupo integrado por metilo, etilo, propilo o butilo, metoxi, etoxi, propoxi, trifluorometoxi, fluoro y cloro;

R^2 es hidrógeno;

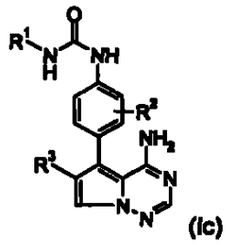
R^3 se selecciona del grupo integrado por

- metoxicarbonilo, etoxicarbonilo, propoxicarbonilo o butoxicarbonilo,
- alquilamino(C_1-C_4)carbonilo, en donde alquilamino(C_1-C_4)carbonilo puede estar opcionalmente sustituido con 0, 1, 2 o 3 fluoro, y
- ciclopropilaminocarbonilo opcionalmente sustituido con metilo, etilo o propilo,
- pirrolidinilcarbonilo o piperidinilcarbonilo; y

R^4 es hidrógeno;

o su sal aceptable para uso farmacéutico.

En otra realización, la presente invención aporta un compuesto de fórmula (Ic)



(Ic)

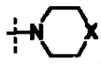
en la cual

R^1 se selecciona del grupo integrado por arilo, bencilo, y heteroarilo,

en donde arilo y heteroarilo pueden estar opcionalmente sustituidos con 1, 2, 3 o 4 sustituyentes seleccionados independientemente del grupo integrado por

- alquilo (C_1-C_4), en donde alquilo (C_1-C_4) puede estar sustituido con 0, 1, 2 o 3 halógeno, 0 o 1 pirrolidinilo, 0 o 1 morfolinilo, o 0 o 1 alcoxi (C_1-C_3) en donde alcoxi (C_1-C_3) puede estar opcionalmente sustituido con alquilamino (C_1-C_3),
- alcoxi (C_1-C_3), en donde alcoxi (C_1-C_3) pueden estar opcionalmente sustituidos con alquilamino (C_1-C_3),
- halógeno,

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- trifluorometilo,
- trifluorometoxi,
- cicloalquilo (C_3-C_6),
- fenilo opcionalmente sustituido con 1 o 2 halógeno,
-  , en donde X es CH_2, O, S o NR^{1-1}, y en donde R^{1-1} es hidrógeno o alquilo (C_1-C_6),
- nitro,
- ciano,
- alquiltio (C_1-C_3),
- trifluorometiltio,
- alquil(C_1-C_3)carbonilo,
- alcoxi(C_1-C_6)carbonilo, y
- fenoxi

y

en donde bencilo puede estar sustituido con 0, 1, 2 o 3 grupos seleccionados de halógeno, alquilo (C_1-C_3), y alcoxi (C_1-C_2);

R^2 se selecciona del grupo integrado por hidrógeno, halógeno, alquilo y alcoxi;

R^3 se selecciona del grupo integrado por

- carboxilo,
- formilo,
- alquil(C_1-C_6)carbonilo opcionalmente sustituido con 1, 2, o 3 flúor,
- alcoxi(C_1-C_6)carbonilo,
- aminocarbonilo,
- alquilamino(C_1-C_6)carbonilo, en donde alquilamino(C_1-C_6)carbonilo puede estar opcionalmente sustituido con 1, 2 o 3 sustituyentes seleccionados independientemente del grupo integrado por halógeno, amino, alquilamino, metoxi, y metilsulfonilo, y en donde alquilamino(C_1-C_6)carbonilo puede estar sustituido con 0 o 1 hidroxilo o 0 o 1 heterocicilo,
- heterocicilicarbonilo,

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- alquilo (C_1-C_6) opcionalmente sustituido con 1, 2 o 3 sustituyentes seleccionados independientemente del grupo integrado por

a) hidroxilo,

b) amino,

c) alquilamino (C_1-C_6), en donde alquilamino (C_1-C_6) puede estar sustituido con 0, 1, 2, 3 o 4 sustituyentes seleccionados independientemente del grupo integrado por halógeno, amino, alquilamino, metoxi, metilo, y metilsulfonilo,

d) arilamino, en donde arilamino puede estar sustituido con 0, 1 o 2 sustituyentes seleccionados independientemente del grupo integrado por alquilo (C_1-C_6), alcoxi (C_1-C_6), y trifluorometilo,

e) heterocicilo, en donde heterocicilo puede estar sustituido con 0, 1 o 2 alquilo (C_1-C_6), en donde alquilo (C_1-C_6) puede estar sustituido con 0, 1 o 2 metoxi o piridilo,

f) imidazolilo,

g) piridilamino,

h) alcoxi (C_1-C_3) opcionalmente sustituido con fluoro hasta el nivel de perfluoro,

i) alcoxi (C_1-C_3)-alcoxi (C_2-C_3), y

j) alcoxi(C_1-C_6)carbonilo,

- alcoxi (C_1-C_6) opcionalmente sustituido con 1, 2 o 3 sustituyentes

independientemente seleccionados del grupo integrado por amino, (C_1-C_6)alquilamino, y heterocicilo, en donde heterocicilo puede estar sustituido con 0, 1, 2 o 3 alquilo (C_1-C_3);

- cicloalquilamino(C_3-C_6)carbonilo opcionalmente sustituido con alquilo (C_1-C_3),

- ciano, y

- heteroarilo en donde heteroarilo puede estar sustituido con 0, 1, 2, o 3 grupos independientemente seleccionado del grupo integrado por

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g) alquilo (C_1-C_6), en donde alquilo (C_1-C_6) puede estar sustituido con 0, 1, 2, o 3 halógeno, 0 o 1 heterocicilo, 0 o 1 alquilamino, o 0 o 1 metoxi,

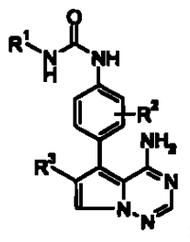
h) halógeno,

i) amino, y

j) alquilamino;

o su sal aceptable para uso farmacéutico.

En otra realización, la presente invención aporta un compuesto de fórmula (Ic):



(Ic)

en donde

R^1 se selecciona del grupo integrado por arilo y heteroarilo,

donde arilo y heteroarilo puede estar sustituido con 0, 1, 2, 3 o 4 sustituyentes seleccionados independientemente del grupo integrado por

alquilo (C_1-C_4),

alcoxi (C_1-C_3),

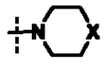
halógeno,

trifluorometilo,

trifluorometoxi,

cicloalquilo (C_3-C_6),

fenilo opcionalmente sustituido con 0, 1 o 2 halógeno, y

 , en donde X es CH_2, O, S o NR^{1-1}; y en donde R^{1-1} es hidrógeno o alquilo (C_1-C_6);

R^2 se selecciona del grupo integrado por hidrógeno, halógeno, alquilo y alcoxi;

R^3 se selecciona del grupo integrado por carboxilo, alcoxi(C_1-C_6)carbonilo, aminocarbonilo, alquilamino(C_1-C_6)carbonilo, y heterociclilcarbonilo,

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en donde alquilamino(C_1-C_8)carbonilo puede estar opcionalmente sustituido con 0, 1, 2 o 3 sustituyentes seleccionados independientemente del grupo integrado por halógeno, amino, alquilamino, metoxi y metilsulfonilo, o

R^3 es alquilo (C_1-C_8) opcionalmente sustituido con 0, 1, 2 o 3 sustituyentes seleccionados independientemente del grupo integrado por hidroxilo, amino, alquilamino (C_1-C_8), arilamino, heterocicilo, piridilo, y piridilamino,

en donde alquilamino (C_1-C_8) puede estar opcionalmente sustituido con 0, 1, 2, 3 o 4 sustituyentes seleccionados independientemente del grupo integrado por halógeno, amino, alquilamino, metoxi, metilo, y metilsulfonilo, y en donde heterocicilo puede estar opcionalmente sustituido con 0, 1 o 2 alquilo (C_1-C_8), en donde alquilo (C_1-C_8) puede estar opcionalmente sustituido con 1 o 2 metoxi o piridilo,

y en donde arilamino puede estar opcionalmente sustituido con 0, 1 o 2 sustituyentes seleccionados independientemente del grupo integrado por alquilo (C_1-C_8), alcoxi (C_1-C_8), y trifluorometilo, o

R^3 es alcoxi (C_1-C_8) opcionalmente sustituido con 0, 1, 2 o 3 sustituyentes seleccionados independientemente del grupo integrado por amino, alquilamino (C_1-C_8), y heterocicilo, en donde heterocicilo puede estar opcionalmente sustituido con 0, 1, 2 o 3 alquilo (C_1-C_8);

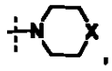
o su sal aceptable para uso farmacéutico.

En otra realización, la presente invención aporta un compuesto de fórmula (I),

en donde

R^1 se selecciona del grupo integrado por fenilo y heteroarilo mono- o bicíclico que contiene 5, 6, 9 o 10 átomos de anillo y hasta 2 heteroátomos seleccionados del grupo integrado por nitrógeno, oxígeno y azufre,

en donde fenilo y heteroarilo pueden estar sustituidos con 0, 1 o 2 sustituyentes seleccionados independientemente del grupo integrado por alquilo (C_1-C_4), alcoxi (C_1-C_3), halógeno, trifluorometilo, trifluorometoxi, cicloalquilo (C_3-C_6), fenilo opcionalmente sustituido con trifluorometilo, y


, en donde X es CH_2, O, S o NR^{1-1};

en donde R^{1-1} es hidrógeno o alquilo (C_1-C_6);

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R^2 se selecciona del grupo integrado por hidrógeno, fluoro, cloro, metilo, y metoxi;

R^3 se selecciona del grupo integrado por carboxilo, alcoxi(C_1-C_6)carbonilo, aminocarbonilo, y alquilamino(C_1-C_6)carbonilo,

en donde alquilamino(C_1-C_6)carbonilo puede estar opcionalmente sustituido con 0, 1 o 2 sustituyentes seleccionados independientemente del grupo integrado por halógeno, amino, alquilamino, metoxi y metilsulfonilo, o

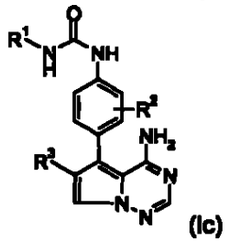
R^3 es alquilo (C_1-C_6) sustituido con amino, alquilamino (C_1-C_6), piridilo, o heterocicilo de 5 a 6 miembros que contiene 1 o 2 heteroátomos seleccionados del grupo integrado por nitrógeno, oxígeno y azufre,

en donde alquilamino (C_1-C_6) puede estar opcionalmente sustituido con 0, 1 o 2 sustituyentes seleccionados independientemente del grupo integrado por halógeno, amino, alquilamino, metoxi y metilsulfonilo, y en donde heterocicilo puede estar opcionalmente sustituido con 0, 1 o 2 alquilo (C_1-C_6), en donde alquilo (C_1-C_6) puede estar opcionalmente sustituido con 0 o 1 metoxi o piridilo, o

R^3 es alcoxi (C_1-C_6) opcionalmente sustituido con 0, 1, 2 o 3 sustituyentes seleccionados independientemente del grupo integrado por amino, alquilamino (C_1-C_6), y un heterocicilo de 5 a 6 miembros que contiene 1 o 2 heteroátomos seleccionados del grupo integrado por nitrógeno, oxígeno y azufre, en donde heterocicilo puede estar opcionalmente sustituido con 0, 1, 2 o 3 alquilo (C_1-C_6);

o su sal aceptable para uso farmacéutico.

En otra realización, la presente invención aporta un compuesto de fórmula (Ic),



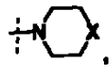
(Ic)

en la cual

R^1 se selecciona del grupo integrado por

- fenilo opcionalmente sustituido con 1-2 grupos seleccionados de

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halo, alquilo (C_1-C_4), OCF_3, CF_3, y  , en donde X es CH_2, S o NR^{1-1}, en donde R^{1-1} es hidrógeno o alquilo (C_1-C_6),

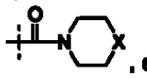
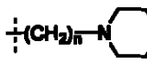
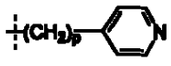
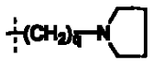
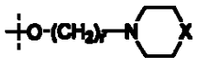
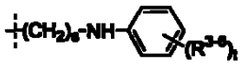
- piridilo opcionalmente sustituido con CF_3,
- pirazolilo opcionalmente sustituido con 1-2 grupos seleccionados de

alquilo (C_1-C_4), cicloalquilo (C_3-C_6), y fenilo opcionalmente sustituido con CF_3,

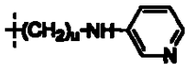
- isoxazolilo opcionalmente sustituido con alquilo (C_1-C_4),
- pirimid-4-ilo opcionalmente sustituido con alcoxi (C_1-C_3)
- indazolilo, opcionalmente sustituido en N con alquilo (C_1-C_4);

R^2 es hidrógeno;

R^3 se selecciona del grupo integrado por

- CO_2R^{3-1}
- $CONR^{3-2}R^{3-3}$
- $-(CH_2)_mNR^{3-4}R^{3-5}$
-  , en donde X es O o NH,
-  , en donde X es O o NH,
- 
- 
- 
- 

y

- 

m es 1,2 o 3

n es 1,2,o 3;

p es 1,2 o 3;

q es 2 o 3;

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r es 2 o 3

s es 1,2 o 3;

t es 0, 1 o 2;

u es 1,2 o 3;

R^{3-1} es H o alquilo (C_1-C_8);

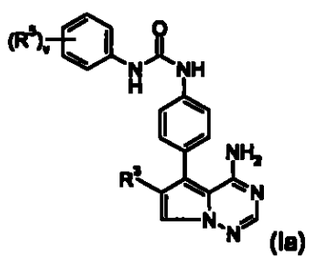
R^{3-2} y R^{3-3} están independientemente seleccionados de H y alquilo (C_1-C_8);

R^{3-4} y R^{3-5} están independientemente seleccionados de H y alquilo (C_1-C_8);

R^{3-6} es CF_3, alcoxi (C_1-C_4) o alquilo (C_1-C_4);

o su sal aceptable para uso farmacéutico.

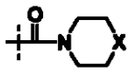
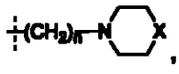
En otra realización, la presente invención aporta un compuesto de la fórmula (Ia),



(Ia)

en donde

R^3 se selecciona del grupo integrado por

-  , en donde X es O o NH,
-  , en donde X es O o NH, y
- aminocarbonilo o alquilamino (C_1-C_8) carbonilo sustituido según se describió anteriormente;

n es 1,2,o 3;

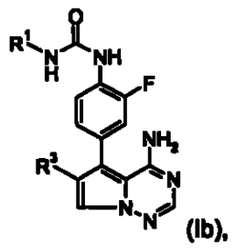
R^5 se selecciona independientemente del grupo integrado por fluoro, cloro, metilo, etilo, propilo, isopropilo, trifluorometilo, trifluorometoxi, y morfolino; y

v es 0, 1 o 2;

o su sal aceptable para uso farmacéutico.

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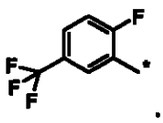
En otra realización, la presente invención aporta un compuesto de la fórmula (Ib),



(Ib),

o su sal aceptable para uso farmacéutico.

En otra realización, la presente invención aporta un compuesto de la fórmula (Ic), en donde R^1 representa



En otra realización, la presente invención aporta un compuesto de la fórmula (Ic), en donde R^3 representa etoxicarbonilo.

En otra realización, la presente invención aporta un compuesto de la fórmula (Ic), en donde R^3 es alquilamino(C_1-C_6)carbonilo,

en donde alquilamino(C_1-C_6)carbonilo puede estar opcionalmente sustituido con 1 o 2 sustituyentes seleccionados independientemente del grupo integrado por halógeno, amino, alquilamino, metoxi y metilsulfonilo, y en donde arilamino puede estar opcionalmente sustituido con 1 o 2 metoxi o trifluorometilo.

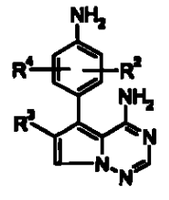
En otra realización, la presente invención aporta un compuesto según se describe como Ejemplo Operativo en la sección Ejemplos de la presente solicitud.

En otra realización, la presente invención se refiere a un compuesto capaz de ser metabolizado o hidrolizado a un compuesto de fórmula (I) en condiciones fisiológicas. Esto incluye por ejemplo derivados de ester y amida (el cual puede ser hidrolizado a los respectivos ácidos, alcoholes y aminas) como así también ortoesteres y esteres animales (los cuales se pueden hidrolizar a los respectivos

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ácidos), acetales y hemiacetales (los cuales se pueden hidrolizar a los respectivos derivados ceto, por ejemplo el grupo oxo del resto del anillo de 4-oxopirimidina).

En otra realización, la presente invención aporta un proceso para preparar un compuesto de fórmula (I), en la cual un compuesto de fórmula (II)



(II)

en donde R^2, R^3 y R^4 tienen el significado indicado anteriormente,

se hace reaccionar con un compuesto de isocianato de fórmula (III)

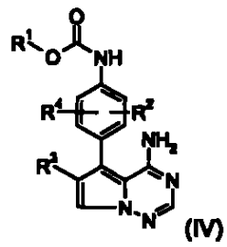
R^1-NCO (III)

o con un carbamato de fórmula (VI)

R^1-NH-C(O)-OPh (VI),

en donde R^1 tiene el significado indicado anteriormente; o

un compuesto de fórmula (IV)



(IV)

en la cual R^1, R^2, R^3 y R^4 tienen el significado indicado anteriormente,

se hace reaccionar con una amina de fórmula (V)

R^1-NH_2 (V),

en donde R^1 tiene el significado indicado anteriormente.

La preparación de los compuestos de acuerdo con la invención se puede ilustrar por medio de los siguientes esquemas de síntesis. A menos que se especifique lo contrario, los portadores sustituyentes tales como R^1 a R^3 tienen el significado indicado anteriormente.

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Los métodos para preparar pirrolotriazinas además se revelan en la Solicitud Estadounidense publicada No. 10/289.010 (Publicación No. US 2003-0186982 A1), Patente Estadounidense No. 6,670,357 (Solicitud Estadounidense No. 10/036,293), como así también los documentos WO 2003/042172, WO 2004/009542, WO2004/009601, WO 2004/009784 y WO 2004/013145, todos los cuales se incorporan a la presente como referencia en su totalidad.

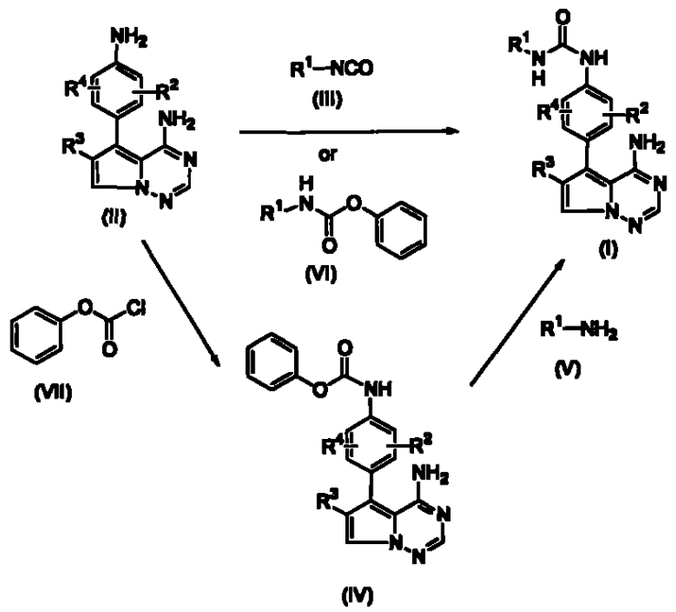
Métodos generales para la preparación de los compuestos de la invención

Los compuestos de la presente invención de Fórmula (I) se pueden preparar de manera conveniente a partir de los correspondientes compuestos de amino de Fórmula (II) por medios directos según se describe en los Esquemas de Reacción a continuación o por medio bien conocidos por los expertos en la técnica. En estos Esquemas de Reacción, a menos que se defina específicamente lo contrario, los significados de R^1-R^3, R^{3-2}, R^{3-3}, R^{3-4}, R^4 y r son idénticos a los descriptos anteriormente.

El Esquema de reacción 1 ilustra el método general para preparar compuestos de Fórmula (I) a partir de los correspondientes compuestos de amino de Fórmula (II) mediante métodos estándar de formación de urea. En este esquema, un compuesto de Fórmula (II) se deja reaccionar con, ya sea un isocianato de Fórmula (III), o más preferentemente un carbamato de Fórmula (VI), en general en un solvente inerte, para dar el compuesto de Fórmula (I) directamente. Alternativamente, la amina de Fórmula (II) se puede tratar primero con un cloroformiato de Fórmula (VII), en un solvente inerte, para dar un intermediario carbamato de Fórmula (IV). El compuesto de fórmula (IV) luego se deja reaccionar con una amina de Fórmula (V), en un solvente inerte, para dar un compuesto de Fórmula (I).

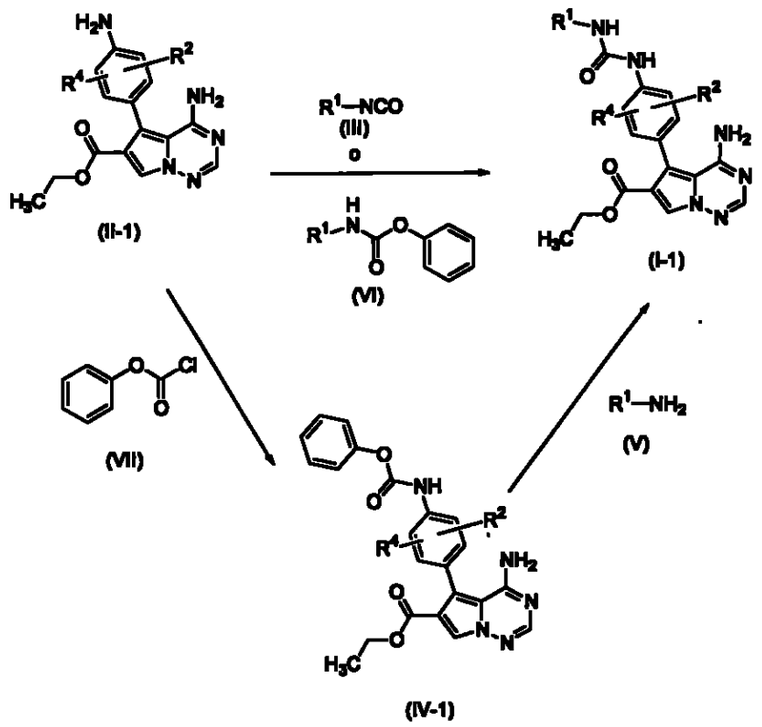
Esquema de reacción 1

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Un ejemplo más específico del método del Esquema de reacción 1 se ilustra en el Esquema de Reacción 2 a continuación. En este esquema, la amina de Fórmula (II-1) [Fórmula (II), donde R^3 es CO_2Et], se utiliza como material de partida, haciéndola reaccionar con un isocianato ((III), carbamato (VI), o en una secuencia de dos pasos utilizando (VII) seguido de (V), para dar el compuesto de Fórmula (I-1) [Fórmula (I) donde R^3 es CO_2Et]. El compuesto de fórmula (I-1) luego se puede utilizar como material de partida para preparar otros compuestos de Fórmula (I) según se muestra, por ejemplo, en el Esquema de reacción 3 a continuación.

Esquema de reacción 2

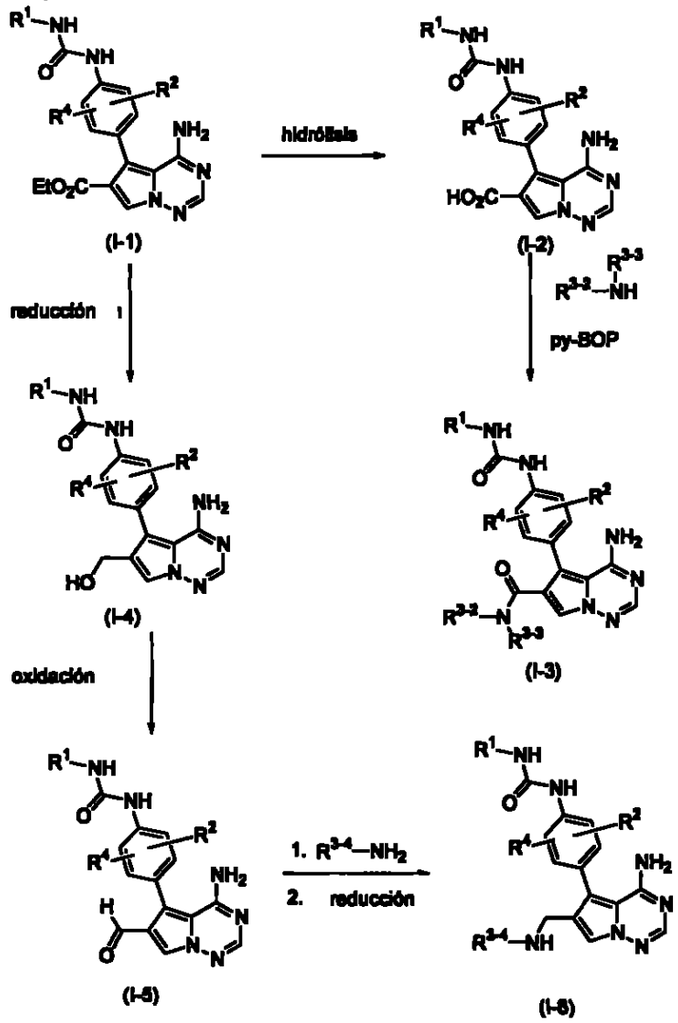


El Esquema de reacción 3 ilustra la preparación de compuestos de Fórmula (I) en la cual R^3 es una variedad de sustituyentes, partiendo del compuesto de Fórmula (I-1) en la cual R^3 es CO_2Et. Por ejemplo, la hidrólisis de (I-1), en ya sea una base acuosa o ácido, da el compuesto de ácido carboxílico de Fórmula (I-2). El acoplamiento de este ácido con una amina de Fórmula $(R^{3-2})(R^{3-3})NH$ da los compuestos de amida de Fórmula (I-3).

La reducción del ester de la fórmula (I-1) con un agente reductor tal como DIBAL, da el alcohol de Fórmula (I-4). La oxidación del alcohol por medios estándar tal como el Dess-Martin periodinano da el aldehído de Fórmula (I-5). La conversión del aldehído en un compuesto de amina de Fórmula (I-6) se logra mediante una secuencia de aminación reductora. En esta secuencia, una amina primaria de Fórmula R^{3-4}-NH_2 se agrega al compuesto de Fórmula (I-5) en presencia de ácido acético, y el compuesto intermediario de imina no se aísla pero se reduce selectivamente con un reactivo tal como triacetoxiborohidruro de sodio para dar la amina de Fórmula (I-6).

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Esquema de reacción 3



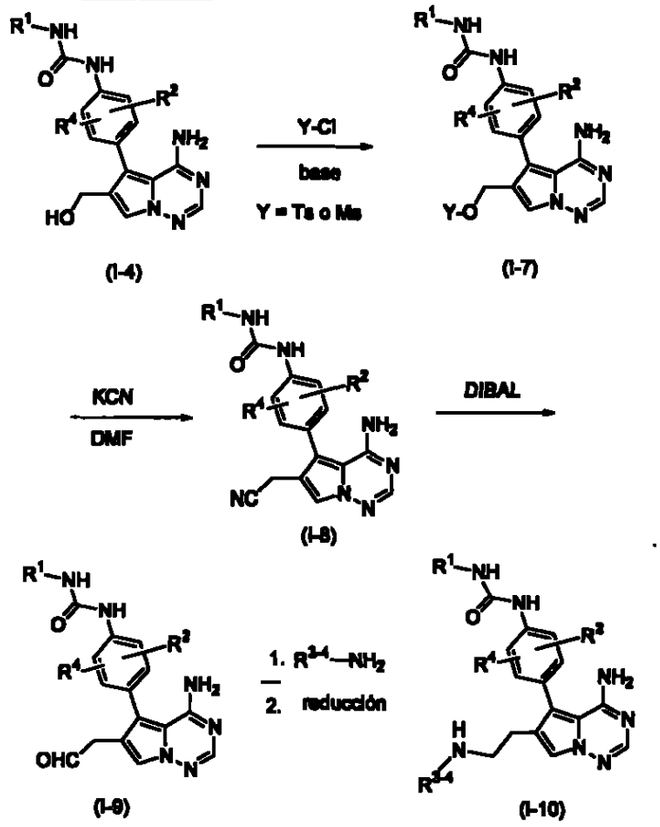
El alcohol de Fórmula (I-4) además se elabora en el Esquema de reacción 4, y el aldehído de Fórmula (I-5) se elabora también en el Esquema de reacción 5, a continuación.

En el Esquema de reacción 4, el alcohol se convierte en el aldehído homólogo por medios estándar, es decir, la conversión en un tosilato o mesilato con cloruro de tosilo o mesilo, respectivamente, y una base tal como piridina o Et_3N, para dar el intermediario de Fórmula (I-7). La reacción de (I-7) con una fuente de cianuro, por ejemplo, KCN o NaCN, en un solvente polar tal como DMF da el nitrilo de Fórmula (I-

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8). La reducción selectiva con DIBAL con elaboración hidrolítica da el aldehído de Fórmula (I-9). El aldehído de fórmula (I-9) se convierte en el compuesto de Fórmula (I-10) [(I) donde R^3 es $(R^{3-4})NHCH_2CH_2$-] por la secuencia de aminación reductora según se describe para la preparación de (I-8) en el Esquema de reacción 3.

Esquema de reacción 4

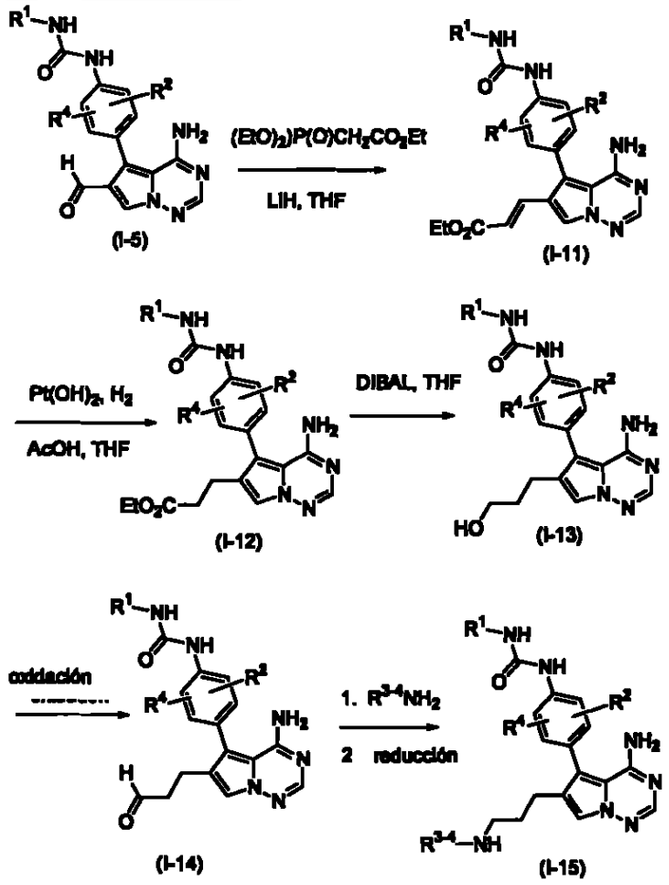


(I-4) (I-7) (I-8) (I-9) (I-10)

El aldehído de Fórmula (I-5) sirve como material de partida para la preparación de compuestos de Fórmula (I) adicionales como se muestra a continuación en el Esquema de reacción 5. Una reacción del tipo Wadsworth-Emmons de (I-5) con un ester fosfónico y una base fuerte tal como LiH da el ester insaturado de Fórmula (I-11); la reducción de este ester al compuesto saturado de Fórmula (I-12) se obtiene por hidrogenación utilizando un catalizador de óxido de platino en ácido acético. La reducción del ester a alcohol de Fórmula (I-13) es

seguida de la oxidación al compuesto de Fórmula (I-14), un homólogo de 2-carbonos del aldehído de Fórmula (I-5). La aminación reductora de (I-14), según se describió previamente en los Esquemas de Reacción 3 y 4 da el compuesto de Fórmula (I-15) [Fórmula (I) donde R^3 es $(R^{3-4})NHCH_2CH_2CH_2$-].

Esquema de reacción 5



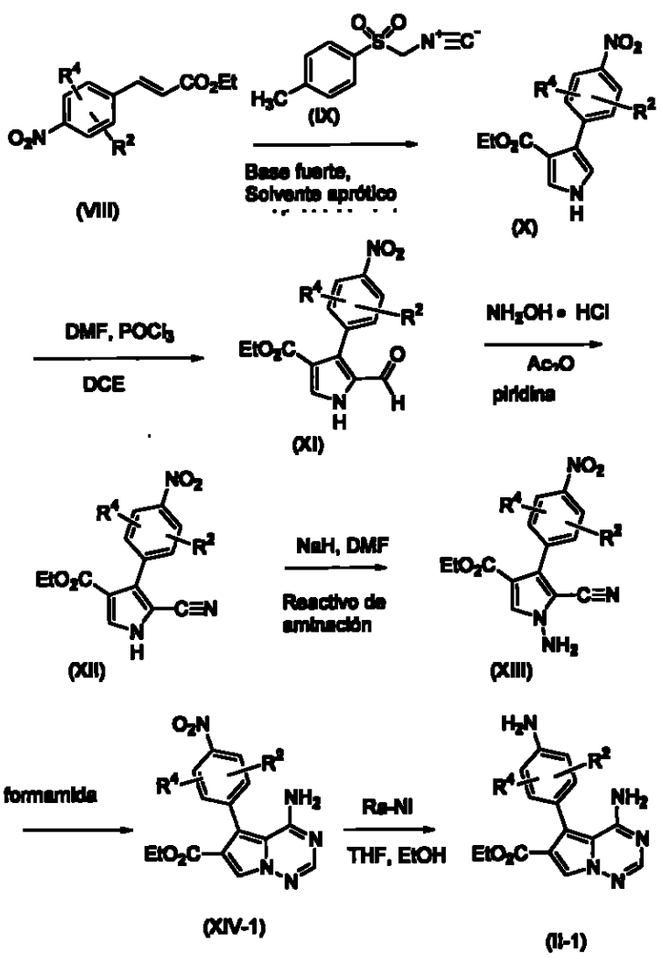
Métodos generales de preparación de intermediarios

La preparación del intermediario clave (II-1) mostrada anteriormente como material de partida para el Esquema de reacción 2, se prepara según se ilustra a continuación en el Esquema de reacción 6. Un 4-nitrocinamato de Fórmula (VIII) se deja reaccionar con el reactivo de isocianuro de Fórmula (IX) en presencia de una

base fuerte tal como hexametildisilazida de litio (LHMDS) en un solvente aprótico tal como THF, para dar el pirrol sustituido de Fórmula (X). La formilación de (X) en condiciones de Vilsmeier (por ejemplo, DMF, $POCl_3$) da el 2-formilopirrol de Fórmula (XI). El aldehído (XI) se convierte en el nitrilo de Fórmula (XII) mediante reacción con clorhidrato de hidroxilamina para formar un intermediario de oxima, el cual se deshidrata in situ a un nitrilo de Fórmula (XII), utilizando un reactivo tal como anhídrido acético. El nitrilo de Fórmula (XII) luego se N-amina utilizando una base fuerte tal como NaH y un reactivo de aminación tal como $(Ph)_2P(O)$-O-NH_2, para dar el *N*-amino nitrilo de Fórmula (XIII). La reacción de (XIII) con formamida [$HC(O)NH_2$] da el intermediario de pirrolotriazina de Fórmula (XIV-1). La reducción selectiva del sustituyente nitro del anillo de fenilo se obtiene en el paso final utilizando un catalizador tal como Raney-Níckel en THF, dando el intermediario (II-1). Estas mismas condiciones de reducción se utilizan para convertir los compuestos de adición de general fórmula (XIV), preparados según se muestra en el Esquema de reacción 8-11 a continuación, en los correspondientes intermediarios de fórmula (II).

<u>Esquema de reacción 6</u>

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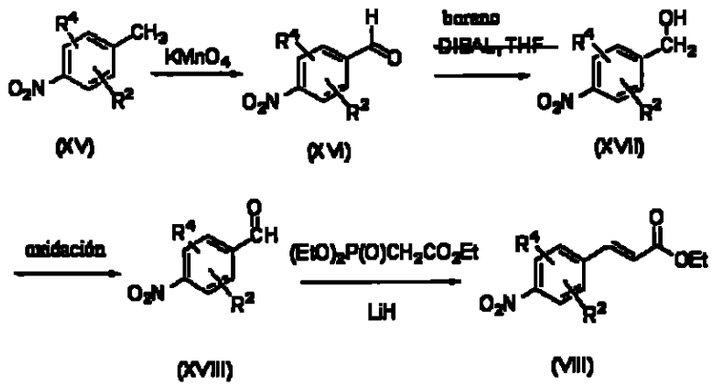


Los cinamatos de Fórmula (VIII) están o bien disponibles en el comercio o se preparan según se muestra en el Esquema de reacción 7. En esta secuencia, un nitrotolueno sustituido de Fórmula (XV) se oxida con un reactivo tal como permanganato de potasio para dar el ácido correspondiente de Fórmula (XVI); este ácido se reduce al alcohol de Fórmula (XVII) con un agente reductor tal como borano y luego se oxida al aldehído de Fórmula (XVIII) utilizando un reactivo tal como el Dess-Martin periodinano. La reacción del tipo Wadsworth-Emmons de (XVIII) que utiliza $(EtO)_2P(O)CH_2CO_2Et$ y una base fuerte tal como LiH da el cinamato de Fórmula (VIII).

Eliminado: DIBAL

Esquema de reacción 7

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(XV) (XVI) (XVII)

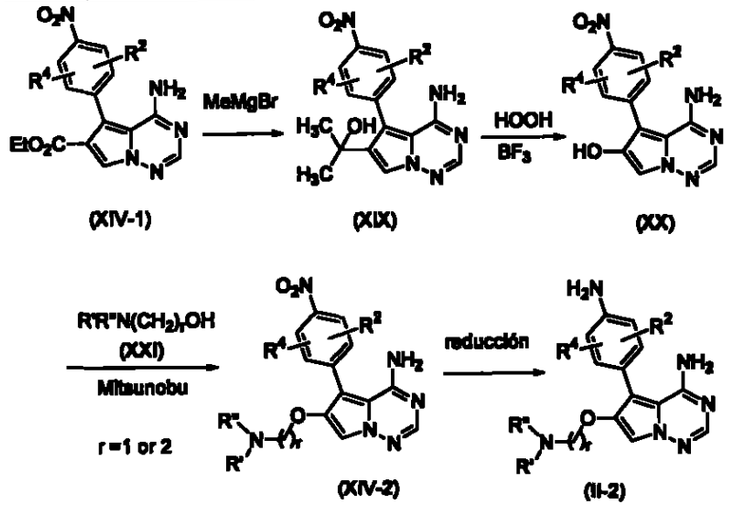
(XVIII) (VIII)

El uso del intermediario (XIV-1) para la preparación del intermediario de Fórmula (II-2) se muestra en el Esquema de reacción 8 a continuación. El compuesto de fórmula (XIV-1) se deja reaccionar con exceso del reactivo de Grignard de metilo para dar el alcohol terciario de Fórmula (XIX). Este compuesto se somete a una reagrupación oxidativa e hidrólisis utilizando peróxido de hidrógeno y un ácido Lewis, tal como BF_3, para dar el compuesto de hidroxi de Fórmula (XX). La reacción de (XX) con un alcohol sustituido de Fórmula (XXI) bajo condiciones de Mitsunobu, por ejemplo, DEAD, TPP, da el intermediario de Fórmula (XIV-2). La reducción del grupo nitro en la Fórmula (XIV-2), según se describe para la preparación de Fórmula (II-1) en el Esquema de reacción 6, da el intermediario de Fórmula (II-2) [Fórmula (II) donde R^3 es $R'R''N(CH_2)_rO$- y R'' y R' son según sed escriben en el Esquema de reacción 8].

El compuesto de Fórmula (II-2) se puede utilizar para preparar el compuesto de Fórmula (I) [donde R^3 es a grupo de Fórmula $R'R''N(CH_2)_rO$-, y R'' y R' son según

se describe en el Esquema de reacción 8] mediante la vía delineada en el Esquema de reacción 1.

Esquema de reacción 8

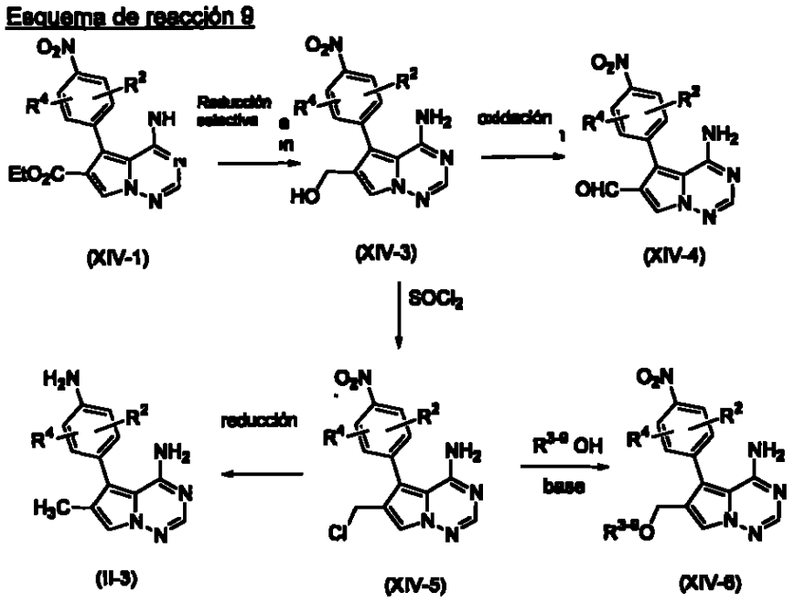


donde
R', R" se seleccionan independientemente de H y alquilo (C_1-C_6)
o
R' R" pueden estar unidos para formar un anillo heterocíclico de 5 o 6 miembros que contiene un átomo de N, O o S adicional y puede estar opcionalmente sustituido con alquilo (C_1-C_6)

El compuesto de Fórmula (XIV-1), preparado según se mostró anteriormente en el Esquema de reacción 6, se utiliza para preparar una variedad de otros intermediarios de Fórmula (IV-3) – (XIV-7) según se muestra a continuación en el Esquema de reacción 9. Por ejemplo, la reducción selectiva del grupo ester en la Fórmula (XIV-1) utilizando, por ejemplo, DIBAL in THF, da el compuesto de Fórmula (XIV-3). La oxidación del alcohol (XIV-3) al aldehído de Fórmula (XIV-4) se obtiene utilizando condiciones estándar tal como el reactivo de Dess-Martin periodinano en cloruro de metileno. El compuesto de fórmula (XIV-3) además se puede convertir en el correspondiente cloruro de Fórmula (XIV-5) con, por ejemplo, cloruro de tionilo. La reducción tanto del grupo nitro como el grupo cloro en la Fórmula (XIV-5) utilizando Ra-Ni, da el intermediario de Fórmula (II-3). La reacción de Fórmula (XIV-5) con un alcohol de Fórmula R^{3-6}-OH y una base tal como hidruro de sodio da el éter de Fórmula (XIV-6).

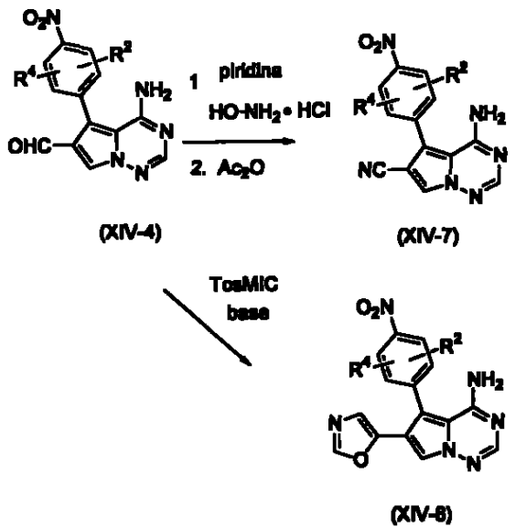
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Esquema de reacción 9



Como se muestra a continuación en el Esquema de reacción 9, el compuesto de Fórmula (XIV-4) además se puede utilizar para la preparación del nitrilo de Fórmula (XIV-7), mediante un procedimiento de dos pasos: reacción con clorhidrato de hidroxilamina y piridina, seguido de la deshidratación del intermediario de oxima utilizando anhídrido acético. El aldehído de fórmula (XIV-4) además se puede convertir en un intermediario de isoxazol de Fórmula (XIV-8) por la reacción con toslilometilisocianuro (TosMIC) en presencia de una base tal como carbonato de potasio, en un solvente prótico tal como metanol.

Esquema de reacción 10

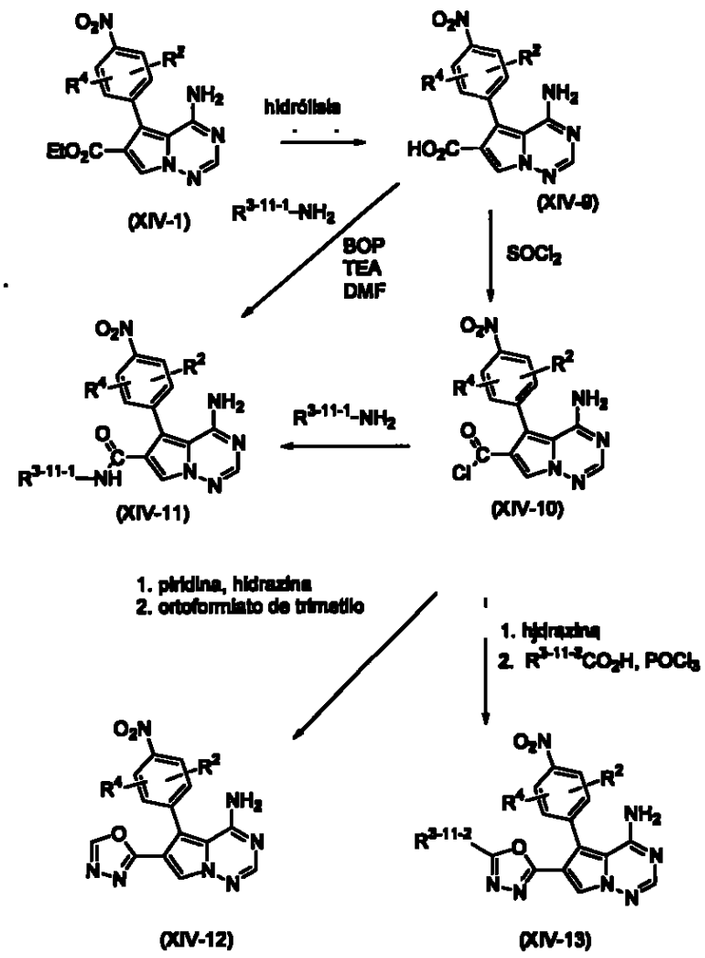


(XIV-4) (XIV-7) (XIV-8)

El intermediario de Fórmula (XIV-1) además se puede utilizar para la preparación de otras amidas y heterociclos según se muestra en el Esquema de reacción 11. La hidrólisis de (XIV-1) bajo condiciones estándar al correspondiente ácido de Fórmula (XIV-9) es seguido de la conversión en la amida de Fórmula (XIV-11), ya sea directamente utilizando una amina de fórmula R^{3-11-1}-NH_2 , BOP, y una base tal como TEA, o por conversión anterior al cloruro de ácido de Fórmula (XIV-10), el cual luego se deja reaccionar con la amina de fórmula R^{3-11-1}-NH_2. El cloruro de ácido de Fórmula (XIV-10) además se utiliza para la preparación de oxadiazoles de Fórmulas(XIV-12) y (XIV-13), por la reacción con ya sea 1) hidrazina y ortoformiato de trimetilo para dar el oxadiazol de Fórmula (XIV-12), o 2) hidrazina, un ácido carboxílico de fórmula R^{3-11-2}-CO_2H, y un agente deshidratante tal como $POCl_3$, para dar el oxadiazol sustituido de Fórmula (XIV-13).

Esquema de reacción 11

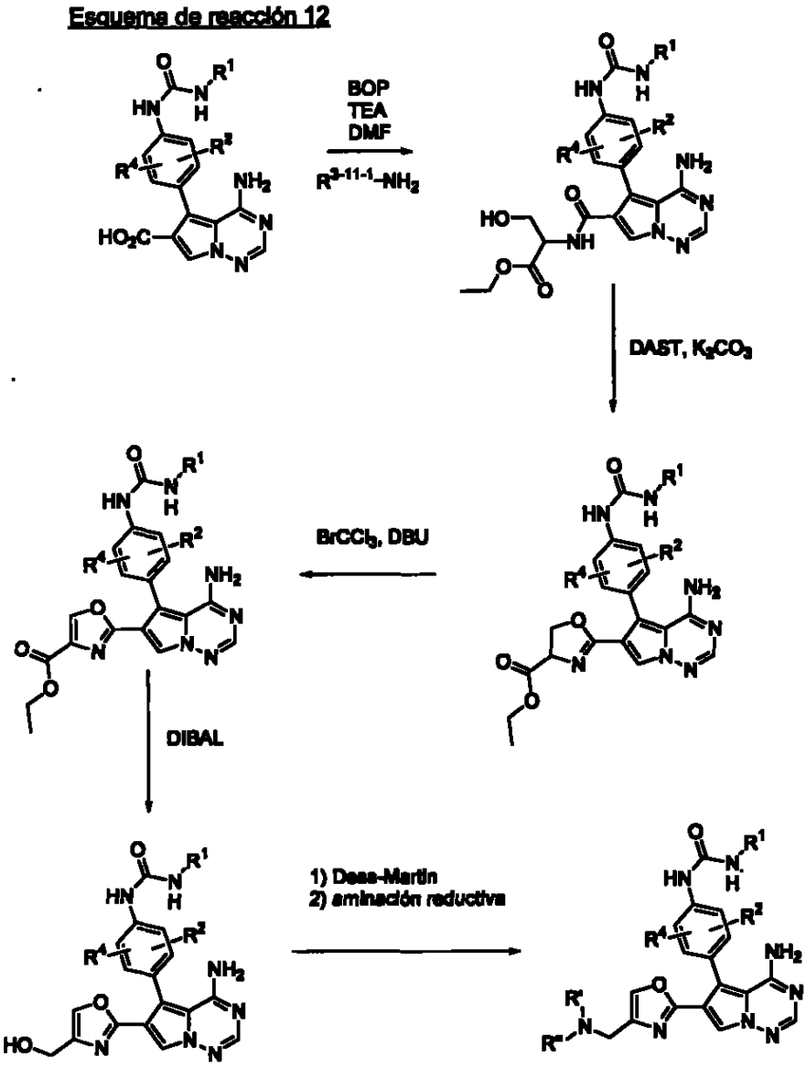
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Los intermediarios de Fórmula (XIV-1) – (XIV-13) luego se pueden reducir según se desee para dar los correspondientes compuestos de amino de Fórmula (II), y a su vez los compuestos de Fórmula (I).

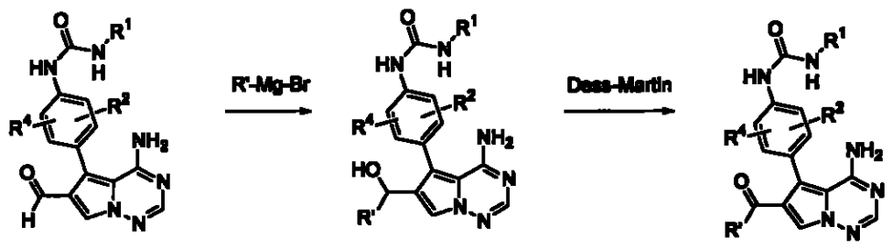
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Esquema de reacción 12



donde
R', R" se seleccionan independientemente de H y alquilo (C_1-C_6)
o
R' y R" se pueden unir para formar un anillo heterocíclico de 5 o 6 miembros que contiene un átomo de N, O o S adicional y puede estar opcionalmente sustituido con alquilo (C_1-C_6).

Esquer[illegible]



donde
R', R" se seleccionan independientemente de alquilo (C_1-C_8) sustituido y cicloalquilo (C_3-C_8)

Además debe entenderse que los materiales de partida están disponibles en el comercio o se preparan fácilmente mediante métodos estándar bien conocidos en la técnica. Tales métodos incluyen, pero sin limitación, las transformaciones mencionadas en la presente.

Si no se menciona lo contrario, las reacciones usualmente se llevan a cabo en solventes inertes orgánicos que no cambian bajo las condiciones de reacción. Estas incluyen éteres, tal como éter dietílico, 1,4dioxano o tetrahidrofurano, hidrocarburos halogenados, tal como diclorometano, triclorometano, tetracloruro de carbono, 1,2-dicloroetano, tricloroetano o tetracloroetano, hidrocarburos, tales como benceno, tolueno, xileno, hexano, ciclohexano o fracciones de aceite mineral, alcoholes, tales como metanol, etanol o iso-propanol, nitrometano, dimetilformamida o acetonitrilo. Además es posible utilizar mezclas de los solventes.

En general, las reacciones se llevan a cabo en un rango de temperatura de 0°C a 150°C, preferentemente de 0°C a 70°C. La reacciones se pueden llevar a cabo bajo presión atmosférica elevada o reducida (por ejemplo de 0,5 a 5 bar). En general, se llevan a cabo bajo presión atmosférica de aire o gas inerte, típicamente nitrógeno.

Los profármacos de esta invención en general se pueden producir mediante métodos convencionales bien conocidos en la técnica. Por ejemplo, los grupos hidroxilo se pueden convertir en esteres haciendo reaccionar los compuestos con cloruros o anhídridos de ácido carboxílico bajo condiciones estándar. Un grupo hidroxilo además se puede convertir en carbonatos haciendo reaccionar los compuestos con cloroformiatos en condiciones estándar.

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Las sales de los compuestos identificados en la presente se pueden obtener aislando los compuestos como sales de clorhidrato, preparados mediante tratamiento de la base libre con HCl anhidro en un solvente adecuado tal como THF. En general, una sal deseada de un compuesto de esta invención se puede preparar in situ durante el aislamiento final y purificación de un compuesto por medios bien conocidos en la técnica. O, una sal deseada se puede preparar haciendo reaccionar en forma separada el compuesto purificado en su forma de base libre con un ácido orgánico o inorgánico adecuado y aislando la sal formada de este modo. Estos métodos son convencionales y serían fácilmente evidentes a los expertos en la técnica.

Además, grupos sensibles o reactivos sobre el compuesto de esta invención pueden necesitar estar protegidos y desprotegidos durante cualquiera de los métodos anteriores. Los grupos protectores en general se pueden agregar y eliminarse mediante métodos convencionales bien conocidos en la técnica (ver, por ejemplo, T. W. Greene y P.G.M. Wuts, *Protective Groups in Organic Synthesis;* Wiley: New York, (1999).

Si se utilizan como compuestos activos, los compuestos de acuerdo con la invención se aíslan preferentemente en una forma más o menos pura, que está más o menos libre de residuos del procedimiento de síntesis. El grado de pureza puede estar determinado por métodos conocidos para el químico o farmacéutico (ver especialmente Remington's Pharmaceutical Sciences, 18° ed. 1990, Mack Publishing Group, Enolo). Preferentemente los compuestos tienen una pureza superior a 99% (p/p), mientras que se pueden emplear purezas mayores a 95%, 90% o 85%.

Los compuestos de acuerdo con la invención exhiben un espectro de actividad farmacocinética o farmacológica útil, imprevisible. Por lo tanto, son adecuados para su uso como medicamentos para el tratamiento y/o profilaxis de trastornos en seres humanos y animales.

Debido a sus propiedades antiproliferativas, los compuestos de acuerdo con la invención son útiles solos o en combinación con otros componentes activos para tratar y/o prevenir trastornos hiper-proliferativos mamíferos. Indicaciones mediadas

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por trastornos hiperproliferativos significa enfermedades o afecciones cuyo avance progresa, al menos en parte, mediante proliferación.

La presente invención además se refiere a un método para utilizar los compuestos o composiciones descriptas en la presente para el tratamiento o prevención de, o en la fabricación de un medicamento para tratar o prevenir, trastornos hiperproliferativos mamíferos. Este método comprende la administración a un paciente (o un mamífero) que la necesita, incluyendo un ser humano, una cantidad de un compuesto, una sal aceptable para uso farmacéutico o ester del mismo, o una composición de esta invención, la cual es efectiva para tratar o prevenir el trastorno.

La presente invención además se refiere a un método para utilizar los compuestos de esta invención como agentes profilácticos o quimiopreventivos para la prevención de los trastornos hiper-proliferativos mamíferos descriptos en la presente. Este método comprende la administración a un mamífero que la necesita, incluyendo un ser humano, una cantidad de un compuesto de esta invención, o una sal aceptable para uso farmacéutico o ester del mismo, la cual es efectiva para retardar o disminuir el inicio del trastorno.

Trastornos hiper-proliferativos incluyen pero sin estar limitados a tumores sólidos, tal como cánceres de pecho, del tracto respiratorio, cerebral, de órganos reproductores, del tracto digestivo, del tracto urinario, de ojos, de hígado, piel, cabeza y cuello, tiroides, paratiroides y sus metástasis distantes. Esos trastornos además incluyen linfomas, sarcomas y leucemias.

La presente invención además se refiere a un método para utilizar los compuestos como agentes profilácticos o quimiopreventivos para la prevención de los trastornos hiper-proliferativos mamíferos descriptos en la presente. Este método comprende la administración a un mamífero que la necesita, incluyendo un ser humano, una cantidad de un compuesto de esta invención, o una sal aceptable para uso farmacéutico o ester del mismo, la cual es efectiva para retardar o disminuir el inicio del trastorno.

Ejemplos de cáncer de pecho incluyen pero sin estar limitados a, carcinoma ductal invasivo, carcinoma lobular invasivo, carcinoma ductal in situ, y carcinoma lobular in situ.

Ejemplos de cánceres del tracto respiratorio incluyen, pero sin estar limitados a, carcinoma de pulmón de células pequeñas o células no-pequeñas, como así también adenoma bronquial y blastoma pleuropulmonar.

Ejemplos de cánceres cerebrales incluyen, pero sin estar limitados a, tronco cerebral y glioma hipoftálmico, astrocitoma cerebelar y cerebral, médulobiastoma, ependimoma, como así también tumor neuroectodérmico y pineal.

Tumores de los órganos reproductores masculinos incluyen, pero sin estar limitados a, próstata y cáncer testicular. Tumores de los órganos reproductores femeninos incluyen, pero sin estar limitados a endometrio, cervical, ovárico, vaginal, y cáncer de vulva, como así también sarcoma del útero.

Tumores del tubo digestivo incluyen, pero sin estar limitados a, cáncer anal, de colon, colorrectal, esófageo, de la vesícula biliar, gástrico, pancreático, rectal, del intestino delgado, y de las glándulas salivares.

Tumores del tracto urinario incluyen, pero sin estar limitados a, cáncer de vejiga, fálico, de riñón, de la pelvis renal, del uréter y cáncer uretral.

Cánceres de ojo incluyen, pero sin estar limitados a, melanoma intraocular y *retinoblastoma*.

Ejemplos de cánceres de hígado incluyen, pero sin estar limitados a carcinoma hepatocelular (carcinomas de células hepáticas con o sin variante fibrolamelar), colangiocarcinoma (carcinoma de vías biliares intrahepático), y mezcla de colangiocarcinoma hepatocelular.

Cánceres de piel incluyen pero sin estar limitados a, carcinoma de células escamosas, sarcoma de Kaposi, melanoma maligno, cáncer de células Merkel, y cáncer de piel no melanoma.

Cánceres de cabeza y cuello incluyen, pero sin estar limitados a cáncer laríngeo, hipofaríngeo, nasofaríngeo, orofaríngeo y cáncer del labio y la cavidad oral.

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Linfomas incluyen, pero sin estar limitados, linfoma relacionado con el SIDA, linfoma de no-Hodgkin, linfoma de células T cutáneo, enfermedad de Hodgkin, y linfoma del sistema nervioso central.

Sarcomas incluyen, pero sin estar limitados a, sarcoma del tejido blando, osteosarcoma, histiocitoma fibroso maligno, linfosarcoma, y rabdomiosarcoma.

Leucemias incluyen, pero sin estar limitados a, leucemia mieloide aguda, leucemia linfoblástica aguda, leucemia linfocítica crónica, leucemia mielógena crónica, y leucemia de células pilosas.

Estos trastornos han estado bien caracterizados en seres humanos, y además existe con una etiología similar en otros mamíferos que pueden tratarse además mediante la administración de los compuestos y/o composiciones farmacéuticas de la presente invención.

El ensayo descripto en esta solicitud es uno de los métodos por los cuales se puede determinar la actividad del compuesto que se refiere al tratamiento de los trastornos identificados en la presente.

En otra realización, la presente invención aporta un medicamento que contiene al menos un compuesto de acuerdo con la invención. En otra realización, la presente invención aporta un medicamento que contiene al menos un compuesto de acuerdo con la invención junto con una o más sustancias portadoras o excipientes seguros de acción farmacológica, por ejemplo, hidroxipropilcelulosa, y además su uso para los fines mencionados anteriormente.

El componente activo puede actuar sistémica y/o localmente. A este fin, se puede aplicar de manera adecuada, por ejemplo, por vía oral, parenteral, pulmonar, nasal, sublingual, lingual, bucal, rectal, transdérmica, conjuntival, ótica o como implante.

Para estas vías de aplicación el componente activo puede administrarse en formas de aplicación adecuadas. Un esquema de las formas de aplicación se presenta en Remington's Pharmaceutical Sciences, 18° ed. 1990, Mack Publishing Grupo, Enolo.

Formas útiles de aplicación oral incluyen las formas de aplicación que liberan el componente activo rápidamente y/o en forma modificada, tal como por ejemplo

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comprimidos (comprimidos recubiertos y no recubiertos, por ejemplo, con un recubrimiento entérico), cápsulas, comprimidos recubiertos por azúcar, gránulos, pellets, polvos, emulsiones, suspensiones, soluciones y aerosoles. Tales composiciones farmacéuticas de liberación sostenida se describen en la Parte 8, Capítulo 91 de Remington's Pharmaceutical Sciences, 18ª ed. 1990, Mack Publishing Grupo, Enolo.

La aplicación parenteral se puede llevar a cabo con la exclusión del paso de absorción (intravenosa, intraarterial, intracardiaca, intraespinal o intralumbar) o con la inclusión de una absorción (intramuscular, subcutánea, intracutánea, percutánea o intraperitoneal). Las formas útiles de aplicación parenteral incluyen preparaciones de inyección e infusión en la forma de soluciones, suspensiones, emulsiones, liofilisados, y polvos estériles. Tales composiciones farmacéuticas parenterales se describen en la Parte 8, Capítulo 84 de Remington's Pharmaceutical Sciences, 18ª ed. 1990, Mack Publishing Grupo, Enolo.

En una realización, la invención se refiere a la aplicación intravenosa (i.v.) del compuesto activo, por ejemplo, como inyección de bolo (que es una dosis simple, por ejemplo, por jeringa), infusión durante un breve período de tiempo (por ejemplo, durante hasta una hora) o infusión durante un largo período de tiempo (por ejemplo, durante más de una hora). La aplicación además se puede llevar a cabo por dosificación intermitente. El volumen aplicado puede variar dependiendo de las condiciones y usualmente es 0,5 a 30, o 1 a 20 ml para inyección de bolo, 25 a 500, o 50 a 250 ml para infusión durante un breve período de tiempo y 50 a 1000, o 100 a 500 ml durante un largo período de tiempo.

Las formas de aplicación deben ser estériles y libre de pirógenos. Pueden basarse en solventes acuosos o mezclas de solventes acuosos y orgánicos. Ejemplos are etanol, polietilenglicol (PEG) 300 o 400, soluciones acuosas que contienen ciclodextrinas o emulsionantes, tales como lecitina, Pluronic F68®, Solutol HS15® o Cremophor®. Se prefieren las soluciones acuosas.

Para aplicación intravenosa las soluciones son, en general, isotónicas y euhídricas, por ejemplo con un pH de 3 a 11, 6 a 8 o aproximadamente 7,4.

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Se pueden emplear envases de plástico o vidrio como embalajes para soluciones I.v., por ejemplo recipientes sellados de goma.. Pueden contener volúmenes líquidos de 1 a 1000, o 5 a 50 ml. La solución puede extraerse directamente del recipiente para ser aplicada al paciente. A este fin, puede ser ventajoso proveer el compuesto activo en forma sólida (por ejemplo como liofilizado) y disolverlo agregando el solvente al recipiente directamente antes de la administración.

Las soluciones para infusión se pueden envasar en forma ventajosa en envases fabricados de vidrio o plástico, por ejemplo botellas o envases plegables tales como bolsas. Pueden contener volúmenes líquidos de 1 a 1000, o 50 a 500 ml.

Formas adecuadas para otras vías de aplicación incluyen por ejemplo formas farmacéuticas inhalantes (incluyendo inhaladores de polvo, nebulizadores), gotas/soluciones nasales, atomizadores; comprimidos o cápsulas a ser administradas por vía lingual, sublingual o bucal, supositorios, preparaciones oculares, cápsulas vaginales, suspensiones acuosas (lociones, mezclas agitables), suspensiones lipofílicas, ungüentos, cremas, leche, pastas, polvos limpiadores o implantes.

Los componentes activos se pueden convertir en las formas de aplicación mencionadas de una manera conocida per se. Esto se lleva a cabo utilizando excipientes adecuados para uso farmacéutico, no tóxicos, inertes. Estos incluyen entre otros vehículos (por ejemplo celulosa microcristalina), solventes (por ejemplo polietilenglicoles líquidos), emulsionantes (por ejemplo dodecil sulfato de sodio), agentes dispersantes (por ejemplo polivinilpirrolidona), biopolímeros sintéticos y naturales (por ejemplo, albúmina), estabilizantes (por ejemplo antioxidantes tales como ácido ascórbico), colorantes (por ejemplo pigmentos inorgánicos tales como óxidos de hierro) o correctores del sabor y/u olor.

Para uso humano, en el caso de la administración oral, se recomienda administrar dosis desde 0,001 a 100 mg/kg, o desde 0,01 a 20 mg/kg. En el caso de administración parenteral tal como, por ejemplo, por vía intravenosa o por vía nasal mediante membranas mucosas, por vía bucal o por inhalación, se recomienda utilizar dosis de 0,001 a 0,60 mg/kg, en particular 0,01 a 30 mg/kg.

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A pesar de esto, puede ser necesario en ciertas circunstancias apartarse de las cantidades mencionadas, es decir como una función del peso corporal, vía de aplicación, comportamiento individual hacia el componente activo, modo de preparación y tiempo o intervalo en el cual la aplicación tiene lugar. Por ejemplo, puede ser suficiente en algunos casos utilizar menos de la cantidad mínima mencionada anteriormente, mientras en otros casos el límite superior mencionado deberá ser excedido. En el caso de la aplicación de cantidades más grandes, puede ser aconsejable dividirlas en una pluralidad de dosis individuales esparcidas a lo largo del día.

Los porcentajes en los ensayos y ejemplos que siguen son, a menos que se indique lo contrario, en peso; las partes son en peso. Las relaciones de solvente, relaciones de dilución y concentraciones informadas para soluciones líquido/líquido se basan cada una de ellas en el volumen.

A. Ejemplos

Métodos Generales de Preparación

A menos que se indique lo contrario, el término "concentrado bajo presión reducida" se refiere al uso de un evaporador rotatorio Buchi a aproximadamente 15 mm de Hg.

La cromatografía de capa delgada (TLC) se llevó a cabo sobre placas Whatman® de 250 µm 60A F-254 de gel de sílice pre-recubiertas de vidrio negro. La visualización de las placas se efectuó mediante una o más de las siguientes técnicas: (a) iluminación ultravioleta, (b) exposición al vapor de yodo, (c) inmersión de la placa en una solución al 10% de ácido fosfomolíbdico en etanol seguido de calentamiento, y/o (d) inmersión de la placa en solución de sulfato de cerio seguido de calentamiento. La cromatografía de columna (cromatografía flash) se llevó a cabo utilizando gel de sílice de malla de 230-400 EM Science®.

"Bloque agitador" se refiere al uso de un agitador modelo BTS3000 de J-Kem Scientific a una velocidad de 150-180.

Espectros de resonancia magnética nuclear (RMN) de protones (^{1}H) se midieron con un espectrómetro Varian 400 Mercury Plus (400 MHz) con Me_4Si (δ 0,00) o solvente protonado residual ($CHCl_3$ δ 7,26; MeOH δ 3,30; DMSO δ 2,49)

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como estándar. Los espectros de RMN de carbono (^{13}C) se midieron con un espectrómetro Varian 400 Mercury Plus (400 MHz) (100 MHz) con solvente ($CDCl_3$ δ 77,0; d_3-MeOD; δ 49,0; d_6-DMSO δ 39,5) como estándar.

Los espectros de masa por electroasperslón – HPLC (HPLC ES-MS) para caracterización se obtuvieron utilizando un sistema Gilson HPLC equipado con un detector de longitud de onda variable colocado a 254 nm, una columna YMC pro C-18 (2 x 23 mm, 120A), y espectrómetro de masa de entrampamiento de iones Finnigan LCQ con ionización por electroasperslón. Los espectros se barrieron de 120-1200 amu utilizando un ion variable de acuerdo con la cantidad de iones en la fuente. Los eluyentes fueron A: 2% de acetonitrilo en agua con 0,02% de TFA y B: 2% de agua en acetonitrilo con 0,018% de TFA. La elución del gradiente del 10% de B a 95% durante 3,5 minutos a una velocidad de flujo de 1,0 mL/min se utilizó con una retención inicial de 0,5 minutos y una retención final a 95% de B de 0,5 minutos. El tiempo de corrida total fue de 6,5 minutos.

La cromatografía liquida de alta resolución preparativa (HPLC), cuando fue necesario, se corrió utilizando ya sea un Gilson 215 Liquid Handler con una bomba Gilson 322 y un detector Gilson UV-VIS-155 colocado a 254 nm o una bomba Shimadzu LC-8A con un detector Shimadzu SPD-10A colocado a 220 nM ambos equipados con una columna YMC Pac ProC18 (150 x 20 mm). El eluyente A es acetonitrilo con 0,01% de ácido trifluoroacético y el eluyente B es agua con 0,01% ácido trifluoroacético. Típicamente, se corrió un gradiente de 10% de A / 90% de B a 90% de A / 10% de B durante un período de 15-25 min. Las fracciones de interés se recolectaron y el solvente se eliminó al vacío para dar el compuesto final en forma de una sal de ácido trifluoroacético.

La HPLC que utiliza una columna quiral se puede utilizar para separar enantiómeros. Las condiciones analíticas utilizaron una columna Chiralcel OD-H® (4.6 x 150 mm) sobre un Shimadzu HPLC. 30% de Eluyente A = Hexano (0,1 % de Et_3N) y 70% de eluyente B = 1:1 MeOH-EtOH (0,1 % de Et_3N) durante 15 min. con una velocidad de flujo de 1,0 ml/min, detección por UV a 235 nm. Las condiciones preparativas utilizaron una columna Chiralcel OD® (20 x 150 mm) sobre un Gilson 215 HPLC. 30% de eluyente A = Hexano (0,1 % de Et_3N) y 70% de eluyente B = 1:1

MeOH-EtOH (0,1% de Et_3N) durante 15 min. con una velocidad de flujo de 1,0 ml/min, detección por UV a 235 nm utilizando aproximadamente 75 mg del material por inyección.

El medio de crecimiento RPMI se obtuvo de GIBCO®.

Los nombres IUPAC se generaron utilizando el ACD/Name Versión 7.0 de Advanced Chemistry Development (EE.UU.).

Abreviaturas y siglas

^{1}H-RMN	espectroscopia de resonancia magnética nuclear de protones
^{31}P-RMN	espectroscopia de resonancia magnética nuclear de fósforo
AcOH	ácido acético
$(Ac)_2O$	anhídrido acético
abs	absoluto
ac	acuoso/a
ap	aproximado
atm	atmósfera
br	ancho
BOP	hexafluorofosfato de benzotriazol-1-iloxi-tris(dimetilamino)fosfonio
Bu	butilo
ACN	acetonitrilo
Ac_2O	anhídrido acético
AcOH	ácido acético
Celite ®	marca de tierra de diatomeas de Celite Corp.
CD_3CN	acetonitrilo-d_3
CD_3OD	metanol-d_4
d	doblete
DCE	dicloroetano
DCM	diclorometano
dd	doblete de dobletes
DIBAL	hidruro de diisobutilaluminio
DMF	*N,N*-dimetilformamida

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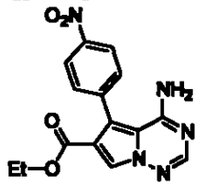
DMSO	dimetilsulfóxido
DMSO-d_6	dimetilsulfóxido-d_6
equiv	equivalente(s)
ES-MS	espectrometría de masa - electroaspersión
Et_3N	trietilamina
Et_2O	éter dietílico
EtOAc	acetato de etilo
EtOH	etanol
FBS	*suero fetal bovino*
g	gramo(s)
h	hora(s)
HPLC	cromatografía líquida de alta resolución
Hz	hertz
J	constante de acoplamiento de RMN
L	litro(s)
LCMS	cromatografía líquida-espectrometría de masa
LHMDS	hexametildisilazida de litio
M	molar
Me	metilo
MeOH	metanol
mg	miligramo(s)
MHz	megahertz
min	minuto(s)
mL	mililitro
mmol	*milimol*
MPLC	cromatografía líquida de presión media
MS	espectrometría de masa
Ms	metanosulfonilo
N	normal
nM	nanomolar
Pr	propilo

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py-BOP	hexafluorofosfato de benzotriazol-1-il-oxitripirrolidinfosfonio
q	cuarteto
Ra-Ni	Níquel Raney
R_f	*factor de retención* TLC
Sal de Rochelle	tartrato de sodio y potasio
RPMI	Roswell Park Memorial Institute
TR	tiempo de retención
ta	temperatura ambiente
s	singulete
t	triplete
TEA	trietilamina
TFA	ácido trifluoroacético
THF	tetrahidrofurano
TLC	cromatografía en capa delgada
TosMIC	isocianuro de toslmetilo
TPP	trifenilfosfina
Ts	*p*-toluensulfonilo
v/v	proporción volumen en volumen
v/v/v	proporción volumen en volumen en volumen
µl	*microlitro*
µm	micrometro

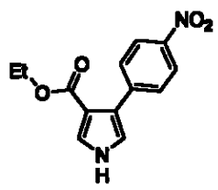
Preparación de Intermediarios

Intermediario A: Preparación de 4-amino-5-(4-nitrofenil)pirrolo[2,1-f][1,2,4]triazin-6-carboxilato de etilo



Paso 1: Preparación de 4-(4-nitrofenil)-1*H*-pirrol-3-carboxilato de etilo

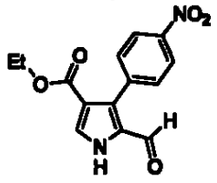
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A una solución 1M de hexametildisilazida de litio en THF (102,4 ml, 102,4 mmol) enfriada a –77°C se agregó gota a gota 1-[(isocianometil)sulfonil]-4-metilbenceno (20,0 g, 102,4 mmol) como una solución en THF (100 ml) durante 30 min. La solución se dejó agitar otros 15 min, y luego se agregó gota a gota (2E)-3-(4-nitrofenil)acrilato de etilo (22,66 g, 102,4 mmol) como una solución en THF (250 ml) durante 1 h. La reacción se dejó entibiar a temperatura ambiente durante 17 h. Se agregó $NaHCO_3$ acuoso saturado (200 ml) a la mezcla de reacción seguido de EtOAc (500 ml). La solución se transfirió a un embudo de separación, y la capa orgánica se aisló y se lavó con H_2O (100 ml). Las capas orgánicas se retro extrajeron con EtOAc (2 x 150 ml). Las capas orgánicas combinadas se recolectaron, se secaron ($MgSO_4$), se concentraron sobre gel de sílice, y se purificaron por cromatografía de columna (100% CH_2Cl_2 saltando a 95:5 v/v CH_2Cl_2-EtOAc) para dar 16,85 g del compuesto anterior en forma de un sólido naranja/amarillo (63,98 mmol, rendimiento 62%). ^{1}H-RMN (DMSO-d_6) δ 11,78 (br s, 1H), 8,19 a 8,15 (m, 2H), 7,76 a 7,73 (m, 2H), 7,57 a 7,56 (m, 1H), 7,22 a 7,21 (m, 1H), 4,18 a 4,13 (q, J = 7,1 Hz, 2H), 1,21 (t, J = 7,1 Hz, 3H); LCMS TR = 2,90 min; TLC R_f = 0,47 (95:5 v/v CH_2Cl_2-EtOAc).

Paso 2: Preparación de 5-formil-4-(nitrofenil)-1*H*-pirrol-3-carboxilato de etilo

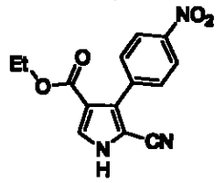


A una solución de DCE (100 ml) se agregó DMF (14,96 ml, 194,4 mmol), la cual se enfrió en un baño salitre helado. A medida que se agregó lentamente $POCl_3$ (18,12 ml, 194,4 mmol) se formó un precipitado blanco. La solución se dejó entibiar a temperatura ambiente mientras se agitó vigorosamente durante 30 min. La suspensión se enfrió nuevamente en un baño salitre helado. Se agregó 4-(4-nitrofenil)-1*H*-pirrol-3-carboxilato de etilo (46,00 g, 176,8 mmol) en forma de una suspensión en DCE (500 ml). La reacción procedió mientras se enfrió en un baño salitre helado durante 1 h, y luego se dejó entibiar a temperatura ambiente durante

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17 h. Se agregó a la reacción acetato de sodio (79,75 g, 972,2 mmol) en agua (600 ml), y la solución se calentó a 80°C durante 1 h. Al enfriarse a temperatura ambiente la solución se transfirió a un embudo de separación y la capa orgánica se aisló mientras que la capa acuosa se retro extrajo con CH_2Cl_2 (2 x 150 ml). Las capas orgánicas combinadas se recolectaron, se secaron ($MgSO_4$), se filtraron, y se concentraron hasta sequedad. El material bruto se calentó a reflujo en tolueno (2 L) y a la solución caliente se agregó hexanos (200 ml). La solución se dejó enfriar lentamente, y durante los siguientes 2 días se formaron los cristales. Los cristales se recolectaron, se lavaron con Et_2O (500 ml), y se secaron al vacío para dar 25,53 g del compuesto anterior en forma de agujas doradas (88,57 mmol, rendimiento 50%). ^{1}H-RMN (DMSO-d_6) δ 12,94 (br s, 1H), 9,29 (d, *J* = 0,8 Hz, 1H), 8,25 a 8,22 (m, 2H), 7,81 (d, *J* = 2,7 Hz, 1H), 7,74 a 7,71 (m, 2H), 4,12 a 4,08 (q, *J* = 7,1 Hz, 2H), 1,15 a 1,11 (t, *J* = 7,0 Hz, 3H); **LCMS TR** = 2,75 min; **TLC** R_f = 0,16 (95:5 v/v CH_2Cl_2–EtOAc).

Paso 3: Preparación de 5-ciano-4-(nitrofenil)-1*H*-pirrol-3-carboxilato de etilo

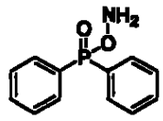


A una solución de piridina (400 ml) se agregó 5-formil-4-(nitrofenil)-1*H*-pirrol-3-carboxilato de etilo (24,55 g, 85,17 mmol) seguido de clorhidrato de hidroxilamina (6,51 g, 93,7 mmol). La solución se agitó a temperatura ambiente durante 2 h, se agregó anhídrido acético (17,68 ml, 187,4 mmol), y la solución se calentó a 80 °C durante 17 h. Al enfriarse a temperatura ambiente la mezcla de reacción se concentró parcialmente al vacío y luego se diluyó con EtOAc (300 ml) y H_2O (300 ml). La solución se transfirió a un embudo de separación, y la capa orgánica se aisló mientras que las capas orgánicas se retro extrajeron con EtOAc (2 x 100 ml). Las capas orgánicas combinadas se recolectaron, se secaron (Na_2SO_4), se filtraron, y se concentraron hasta sequedad. El material bruto luego se trituró con CH_2Cl_2–Et_2O (1:1 v/v, 300 ml). El sólido se recolectó, se lavó con Et_2O (150 ml), y se secó al vacío

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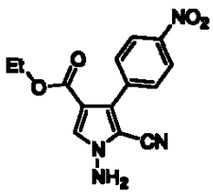
para dar 18,94 g del compuesto anterior en forma de un sólido color blanco esponjoso (66,40 mmol, rendimiento 78%). ^{1}H-RMN (DMSO-d_6) δ13,24 (br s, 1H), 8,30 a 8,27 (m, 2H), 7,92 (s, 1H), 7,74 a 7,71 (m, 2H), 4,16 a 4,10 (q, J = 7,2 Hz, 2H), 1,18 a 1,15 (t, J = 7,0 Hz, 3H); LCMS TR = 2,97 min; TLC R_f = 0,20 (95:5 v/v CH_2Cl_2-EtOAc).

Paso 4: Preparación de óxido de (aminooxi)(difenil)fosfina



Al clorhidrato de hidroxilamina (15,86 g, 228,2 mmol) en H_2O (35 ml) enfriado en un baño salitre helado se agregó NaOH 7,1 N (27,4 ml, 194,4 mmol) seguido de 1,4-dioxano (100 ml). La solución se agitó vigorosamente durante 15 min y luego óxido de clorodifenilfosfina (20,00 g, 84,52 mmol) se agregó como una solución en 1,4-dioxano (100 ml). La solución se agitó otros 15 min hasta que se formó un precipitado blanco el se filtró. El sólido se suspendió en NaOH 0,25 N (250ml) mientras que se agitó en un baño salitre helado durante 1 h. El sólido luego se recolectó, se lavó con H_2O (100 ml), y se secó completamente al vacío para dar 7,09 g del compuesto anterior en forma de un polvo color blanco (30,4 mmol, rendimiento 36%). ^{1}H-RMN (DMSO-d_6) δ 7,72 a 7,67 (m, 4H), 7,50 a 7,40 (m, 6H); ^{31}P-RMN (DMSO-d_6) δ 23,11 (br s, 1P).

Paso 5: Preparación de 1-amino-5-ciano-4-(nitrofenil)-1*H*-pirrol-3-carboxilato de etilo



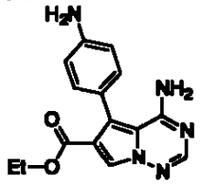
A una solución de DMF (625 ml) se agregó 5-ciano-4-(nitrofenil)-1*H*-pirrol-3-carboxilato de etilo (17,97 g, 63,00 mmol) seguido de NaH, 60% de dispersión en aceite mineral (3,02 g, 75,59 mmol). La solución se agitó a temperatura ambiente durante 15 min y luego se agregó óxido de (aminooxi)(difenil)fosfina (17,63 g, 75,59

mmol), y la solución se calentó a 80 °C durante 17 h. Al enfriarse a temperatura ambiente se agregó $NaHCO_3$ acuoso saturado (500 ml) seguido de EtOAc (400 ml), el cual se transfirió a un embudo de separación y la capa orgánica se aisló mientras que la capa acuosa se retro extrajo con EtOAc (2 x 200ml). Las capas orgánicas combinadas se recolectaron, se secaron (Na_2SO_4), se filtraron, y se concentraron hasta sequedad. El material bruto luego se trituró con CH_2Cl_2-hexanos (1:1 v/v 400 ml). El sólido se recolectó, se lavó con hexanos (100 ml), se secó al vacío, suspended en EtOAc el cual se calentó a reflujo durante 15 min, y luego se filtró. El filtrado se concentró al vacío y luego se secó al vacío para dar 14,15 g del compuesto anterior en forma de un polvo color amarillo (47,12 mmol, rendimiento 75%). ^{1}H-RMN (DMSO-d_6) δ 8,29 a 8,27 (m, 2H), 7,73 (s, 1H), 7,71 a 7,69 (m, 2H), 6,71 (br s, 2H), 4,14 a 4,09 (q, J = 7,1 Hz, 2H), 1,17 a 1,14 (t, J = 7,1 Hz, 3H); LCMS TR = 2,91 min; TLC R_f = 0,30 (95:5 v/v CH_2Cl_2-EtOAc).

Paso 6: Preparación del compuesto del título

A una solución de formamida (74,9 ml, 1,88 mol) se agregó 1-amino-5-ciano-4-(nitrofenil)-1*H*-pirrol-3-carboxilato de etilo (14,15 g, 47,12 mmol). La solución se calentó a 195 °C durante 2 h y luego se dejó enfriar a temperatura ambiente durante 17 h. El sólido cristalino se recolectó y se lavó con EtOAc (2 x 100ml) y luego con H_2O (100ml). El sólido se secó al vacío para dar 10,20 g del compuesto anterior en forma de un sólido cristalino bronce (31,16 mmol, rendimiento 66%). ^{1}H-RMN (DMSO-d_6) 8,27 a 8,25 (m, 2H), 8,20 (s, 1H), 8,05 (br s, 1H), 7,97 (s, 1H), 7,66 a 7,64 (m, 2H), 5,52 (br s, 1H), 4,10 a 4,05 (q, J = 7,1 Hz, 2H), 1,11 a 1,07 (t, J = 7,1 Hz, 3H); EM $[M+H]^+$ = 328; LCMS TR = 2,51 min; TLC R_f = 0,20 (3:1 v/v CH_2Cl_2-EtOAc).

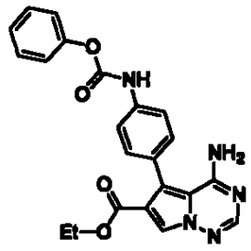
Intermediario B: Preparación de 4-amino-5-(4-aminofenil)pirrolo[2,1-*f*]-[1,2,4]triazin-6-carboxilato de etilo



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Se agregó níquel Raney a un matraz conteniendo 20 ml de EtOH abs. El catalizador se trituró con EtOH abs (3 x 20 ml). Una suspensión de 4-amino-5-(4-nitrofenil)pirrolo[2,1-f][1,2,4]triazin-6-carboxilato de etilo (4,0 g, 12,2 mmol) en EtOH abs (600 ml)/THF (200 ml) se agregó al matraz con el catalizador. El matraz se evacuó y se llenó nuevamente con gas de hidrógeno (3x) y la reacción luego se colocó bajo una atmósfera de hidrógeno (1 atm) y se dejó agitar a temperatura ambiente durante toda la noche. La reacción se filtró a través de un taco de Celite® y se lavó con cantidades copiosas de EtOH/THF (3:1) para dar 3,60 g del compuesto anterior en forma de un sólido color marrón (rendimiento 98%) ^{1}H-RMN (DMSO-d_6) δ 8,05 (s, 1H), 8,04 (br s, 2H), 7,88 (s, 1H), 7,01 (d, J = 8,0 Hz, 2H), 6,61 (d, J = 8,0 Hz, 2H), 5,31 (br s, 2H), 4,07 (q, J = 7,4 Hz, 2H), 1,12 (t, J = 7,2 Hz, 3H); EM $[M+H]^+$ = 298; LCMS TR = 1,64 min; TLC R_f = 0,30 (Acetona/ CH_2Cl_2 1:3).

Intermediario C: Preparación de 4-amino-5-[4-[(fenoxicarbonil)-amino]fenil]pirrolo[2,1-f][1,2,4]triazin-6-carboxilato de etilo

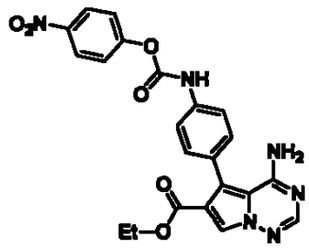


A una solución agitada del intermediario B (1,0 g, 3,4 mmol) en THF (33 ml) se agregó piridina (0,33 ml, 4,0 mmol), luego cloroformiato de fenilo (0,42 ml, 3,4 mmol) a -40 °C. Parte del sólido precipitó. La mezcla se agitó a temperatura ambiente durante 2 h. luego se agregó más cloroformiato de fenilo (0,02 ml, 0,10 mmol) y la mezcla se agitó a temperatura ambiente durante otra media hora. La reacción se filtró, se lavó con agua (3 x 5 ml) y EtOAc-hexanos (9:1 v/v)(3 x 5 ml) para dar el compuesto anterior en forma de un sólido color amarillo claro (600 mg, 43%). El filtrado se concentró al vacío y además se purificó por cromatografía de columna (30:70:1 a 80:20:1 v/v/v EtOAc-hexanos-NH_4OH) para dar más del compuesto del título (570 mg, 40%). ^{1}H-RMN (DMSO-d_6) δ 10,42 (s, 1H), 8,13 (s, 1H), 8,06 (br s, 1H), 7,93 (s, 1H), 7,58 (d, J = 8,4 Hz, 2H), 7,46 a 7,39 (m, 2H), 7,35 (d, J = 8,5 Hz,

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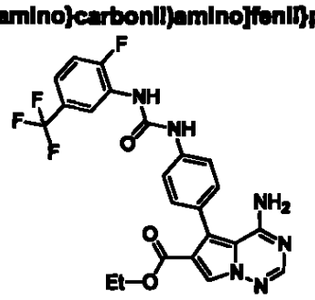
2H), 7,29 a 7,21 (m, 3H), 5,07 (br s, 1H), 4,08 (q, *J* = 7,2 Hz, 2H), 1,08 (t, *J* = 7,2 Hz, 3H); EM $[M+H]^+$ = 418; LCMS TR = 2,81 min.

Intermediario D: Preparación de 4-amino-5-(4-{[(4-nitrofenoxi)-carbonil]amino}fenil)pirrolo[2,1-*f*][1,2,4]triazin-6-carboxilato de etilo



El procedimiento utilizado para la preparación del intermediario C se utilizó para preparar el compuesto del título sustituyendo 4-nitrocloroformiato de fenilo con cloroformiato de fenilo. ^{1}H-RMN (DMSO-d_6) δ10,66 (s, 1H), 8,32 (d, *J* = 9,3 Hz, 2H), 8,16 (s, 1H), 7,95 (s, 1H), 7,61 (d, *J* = 8,8 Hz, 2H), 7,56 (d, *J* = 8,9 Hz, 2H), 7,38 (d, *J* = 8,9 Hz, 2H), 4,07 (q, *J* = 7,2 Hz, 2H), 1,09 (t, *J* = 7,2 Hz, 3H); EM $[M+H]^+$ = 463; LCMS TR = 3,29 min.

Intermediario E: Preparación de 4-amino-5-{4-[({[2-fluoro-5-(trifluorometil)-fenil]amino}carbonil)amino]fenil}pirrolo[2,1-*f*][1,2,4]triazin-6-carboxilato de etilo

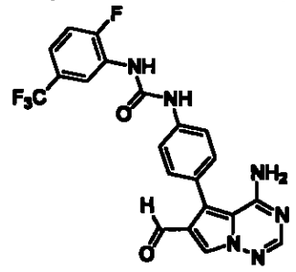


A una suspensión del intermediario C (210 mg, 0,45 mmol) en THF:DMF 4:1 (8 ml) se agregó Et_3N (0,20 ml, 1,4 mmol) y 2-fluoro-5-(trifluorometil)anilina (0,18 ml, 1,36 mmol). Esta se agitó a temperatura ambiente hasta que la reacción se completó al cabo de la cual la reacción se evaporó hasta sequedad y se purificó mediante HPLC (10-90% de ACN/H_2O) para dar el producto en forma de un sólido color amarillo (80 mg, 35%). ^{1}H-RMN (DMSO-d_6) δ 9,33 (s, 1H), 8,97 (d, *J* = 4,0 Hz, 1H), 8,62 (d, *J* = 12,0 Hz, 1H), 8,12 (s, 1H), 8,11 (br s, 1H), 7,92 (s, 1H), 7,6-7,3 (m, 5H),

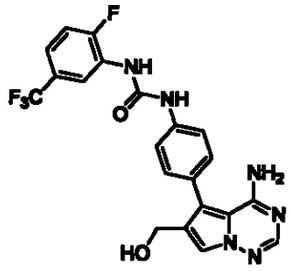
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4,10 (q, *J* = 8,0 Hz, 2H), 1,11 (t, *J* = 8,0 Hz, 3H); EM $[M+H]^+$ = 503; LCMS TR = 3,50 min; TLC R_f = 0,40 (3:1 v/v CH_2Cl_2-Acetona).

Intermediario F: Preparación de *N*-[4-(4-amino-6-formilpirrolo[2,1-f][1,2,4]-triazin-5-il)fenil]-N'-[2-fluoro-5-(trifluorometil)fenil]urea



Paso 1: · Preparación de *N*-(4-[4-amino-6-(hidroximetil)pirrolo[2,1-f][1,2,4]triazin-5-il]fenil)-N'-[2-fluoro-5-(trifluorometil)fenil]urea



A una solución de THF (8,0 ml) se agregó el intermediario E (80,0 mg, 0,16 mmol) seguido de DIBAL (0,8 ml, 0,8 mmol, solución 1,0M en THF). La reacción se agitó a temperatura ambiente con agregado de DIBAL (2,4 ml, 2,4 mmol, solución 1,0M en THF) en tres lotes hasta que la HPLC indicó la terminación de la reacción. La reacción se diluyó con EtOAc y se templó con sal de Rochelle acuosa saturada. La reacción se extrajo con EtOAc (4x). La capa orgánica se secó (Na_2SO_4) y se evaporó para dar un aceite bruto que se purificó mediante HPLC (10-90% de ACN/H_2O) dando un sólido color amarillo (40,0 mg, 55%). ^{1}H-RMN (CD_3CN) δ 8,61 (d, *J*= 8,0 Hz, 1H), 7,80 (s, 1H), 7,66-7,60 (m, 3H), 7,42-7,32 (m, 4H), 4,50 (s, 2H); EM $[M+H]^+$ = 461; LCMS TR = 2,87 min.

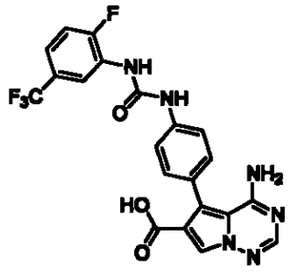
Paso 2: Preparación del compuesto del título

N-(4-[4-amino-6-(hidroximetil)pirrolo[2,1-f][1,2,4]triazin-5-il]fenil)-N'-[2-fluoro-5-(trifluorometil)fenil]urea (40,0 mg, 0,09 mmol) se disolvió en THF (5,0 ml) y a esto se

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agregó reactivo de Dess-Martin Periodinano (44,0 mg, 0,10 mmol). La reacción se agitó a temperatura ambiente hasta que la HPLC indicó la terminación de la reacción. La reacción se diluyó con EtOAc y se lavó con $NaHCO_3/Na_2S_2O_3$ acuoso saturado 1:1 (3x). La capa acuosa se retro extrajo con EtOAc (2x). La capa orgánica se secó (Na_2SO_4) y se evaporó para dar un aceite bruto que se purificó mediante HPLC (10-90% de ACN/H_2O) para dar un sólido color amarillo (35,0 mg, 88%). ^{1}H-RMN (CD_3OD) δ 9,76 (s, 1H), 8,61 (d, J = 8,0 Hz, 1H), 8,11 (s, 1H), 7,87 (s, 1H), 7,65 (d, J = 8,0 Hz, 1H), 7,46 (d, J = 8,0 Hz, 1H), 7,30 (d, J = 8,0 Hz, 1H); EM $[M+H]^+$ = 459; LCMS TR = 2,95 min.

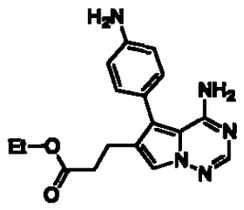
Intermediario G: Preparación del ácido 4-amino-5-{4-[({[2-fluoro-5-(trifluorometil)fenil]amino}carbonil)amino]fenil}pirrolo[2,1-f][1,2,4]triazin-6-carboxílico



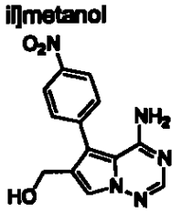
A una solución del Intermediario E (720,0 mg, 1,433 mmol) en 5 ml de MeOH y 3 ml de THF se agregó NaOH 1M (3,58 ml, 3,58 mmol) y la reacción se dejó agitar a 60 °C durante 12 h. La mezcla de reacción se enfrió y se dividió entre $CHCl_3$ y buffer de sulfato pH 2. La capa orgánica se lavó con salmuera, se secó (Na_2SO_4) y se concentró para dar un sólido color marrón (623 mg, 92% de rendimiento). ^{1}H-RMN (DMSO-d_6) δ 12,17 (bs, 1H), 9,34 (s, 1H), 8,98 (d, J = 2 Hz, 1H), 8,62 (dd, J = 2 Hz, 8 Hz, 1H), 8,07 (3, 1H), 8,0 (bs, 1H), 7,91 (s, 1H), 7,53 (d, J = 8Hz, 2 H), 7,55-7,45 (m, 1H), 7,42-7,35 (m, 1H), 7,32 (d, J = 8 Hz, 2H), 5,0 (bs, 1H); EM $[M+H]^+$ = 475,2; LCMS TR = 2,56min; TLC R_f = 0,26 (1:1:0,02 v/v/v THF:CH_2Cl_2:MeOH).

Intermediario H: Preparación de 3-[4-amino-5-(4-aminofenil)pirrolo[2,1-f]-[1,2,4]triazin-6-il]propanoato de etilo

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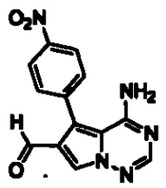


Paso 1: Preparación de [4-amino-5-(4-nitrofenil)pirrolo[2,1-f][1,2,4]triazin-6-il]metanol



A una solución de THF (10 ml) se agregó el intermediario A (500 mg, 1,53 mmol) seguido de DIBAL (3 ml, 3 mmol, solución 1,0M en tolueno). La reacción se agitó a temperatura ambiente durante 1 h. Se agregó DIBAL adicional (1,5 ml, 1,5 mmol, solución 1,0M en tolueno) y se agitó a temperatura ambiente durante otra hora. La reacción se diluyó con EtOAc y se templó con sal de Rochelle acuosa saturada. La reacción se extrajo con EtOAc (4x). La capa orgánica se secó (Na_2SO_4) y se evaporó para dar un sólido bruto (435 mg, 100%) que se utilizó directamente en el próximo paso sin purificación posterior. ^{1}H-RMN (DMSO-d_6) δ 8,29 (d, J= 9,2 Hz, 2H), 7,89 (s, 1H), 7,73 (s, 1H), 7,67 (d, J= 9,3 Hz, 2H), 5,07 (t, J= 5,5 Hz, 1H), 4,38 (d, J= 5,2 Hz, 2H); EM $[M+H]^+$ = 286; LCMS TR = 0,59 min.

Paso 2: Preparación de 4-amino-5-(4-nitrofenil)pirrolo[2,1-f][1,2,4]triazin-6-carbaldehído

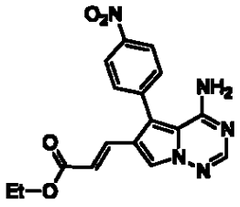


A una solución de THF (80 ml) se agregó 4-amino-5-(4-nitrofenil)pirrolo[2,1-f][1,2,4]triazin-6-il]metanol (435 mg, 1,53 mmol) seguido de Reactivo Dess-Martin Periodinano (4 ml, 1,89 mmol, 15% en peso en CH_2Cl_2). La reacción se agitó a

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temperatura ambiente hasta que la HPLC indicó la terminación de la reacción (5 h). La reacción se diluyó con EtOAc y se lavó con $NaHCO_3/Na_2S_2O_3$ acuoso saturado (1:1 v/v) (3x). La capa acuosa se retro extrajo con EtOAc (2x). La capa orgánica se secó (Na_2SO_4) y se evaporó para dar un sólido bruto de color amarillo (433mg, 100%) que se utilizó directamente en el próximo paso sin purificación posterior. ^{1}H-RMN (DMSO-d_6) 9,79 (s, 1H), 8,39 (s, 1H), 8,29 (d, J= 8,7 Hz, 2H), 8,00 (s, 1H), 7,73 (d, J= 8,8 Hz, 2H); EM $[M+H]^+$ = 284; LCMS TR = 2,48 min.

Paso 3: Preparación de (2E)-3-[4-amino-5-(4-nitrofenil)pirrolo[2,1-f][1,2,4]triazin-6-il]acrilato de etilo



A una suspensión de hidruro de litio (68 mg, 4,0 mmol) en THF (5 ml) bajo atmósfera de N_2 se agregó fosfonoacetato de trietilo (498 mg, 2,22 mmol). La mezcla se agitó a temperatura ambiente durante 30 min y a la mezcla de reacción se agregó una suspensión de 4-amino-5-(4-nitrofenil)pirrolo[2,1-f][1,2,4]triazin-6-carbaldehído (433 mg, 1,53 mmol) en THF (15 ml). La mezcla se calentó a reflujo durante 2 h. Después se enfrió a temperatura ambiente, se agregó lentamente $NaHCO_3$ acuoso seguido de EtOAc. La capa orgánica se recolectó y la capa acuosa se retro extrajo con EtOAc (2x). Las capas orgánicas combinadas se secaron (Na_2SO_4) y se evaporaron para dar un sólido bruto de color amarillo que se purificó por cromatografía de columna (10:90 a 90:10 v/v EtOAc-hexanos) para dar el compuesto del título (460 mg, 69%). ^{1}H-RMN (CD_3OD) δ 8,42 (d, J = 8,0 Hz, 2H), 8,17 (s, 1H), 7,88 (s, 1H), 7,66 (d, J = 8,0 Hz, 2H), 7,43 (d, J = 16 Hz, 1H), 6,36 (d, J = 16 Hz, 1H), 4,16 (q, J = 7,1 Hz, 2H), 1,23 (t, J = 7,1 Hz, 3H); EM $[M+H]^+$ = 354; LCMS TR = 3,12 min.

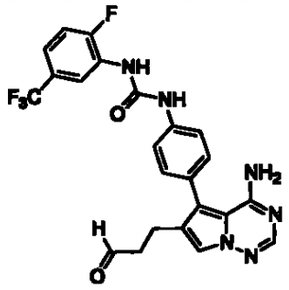
Paso 4: Preparación del compuesto del título

Una suspensión de PtO_2 (16 mg, 0,070 mmol) en ácido acético (0,5 ml) se agregó a una suspensión de (2E)-3-[4-amino-5-(4-nitrofenil)pirrolo[2,1-f][1,2,4]triazin-

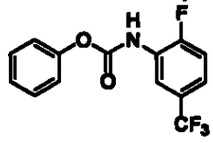
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6-il]acrilato de etilo (144 mg, 0,408 mmol) en ácido acético (2 ml) bajo atmósfera de N_2. El matraz se evacuó y se llenó nuevamente con gas de hidrógeno (3x) y la reacción procedió bajo una atmósfera de hidrógeno (1 atm) durante 1 día. Se agregó PtO_2 adicional (50 mg, 0,22 mmol) en ácido acético (0,5 ml) y la reacción procedió bajo atmósfera de H_2 durante otro día. La reacción se filtró a través de un taco de celite y se lavó con MeOH. Se evaporó hasta sequedad, se diluyó con EtOAc y se lavó con Na_2CO_3 acuoso. La capa acuosa se retro extrajo con EtOAc (2x). La capa orgánica se secó (Na_2SO_4), se filtró, y se evaporó hasta sequedad para dar el compuesto anterior en forma de un sólido color amarillo (120 mg, rendimiento 90%). ^{1}H-RMN (CD_3OD) δ 7,70 (s, 1H), 7,47 (s, 1H), 7,12 (d, J = 8,3 Hz, 2H), 6,84 (d, J = 8,3 Hz, 2H), 4,06 (q, J = 7,8 Hz, 2H), 2,82 (t, J = 7,8 Hz, 2H), 2,48 (t, J = 7,7 Hz, 2H), 1,18(t, J = 7,8 Hz, 3H); EM $[M+H]^+$ = 326; LCMS TR = 1,20 min.

Intermediario I: Preparación de *N*-{4-[4-amino-6-(3-oxopropil)pirrolo[2,1-f]-[1,2,4]triazin-5-il]fenil}-N'-[2-fluoro-5-(trifluorometil)fenil]urea



Paso 1: Preparación de [2-fluoro-5-(trifluorometil)fenil]carbamato de fenilo

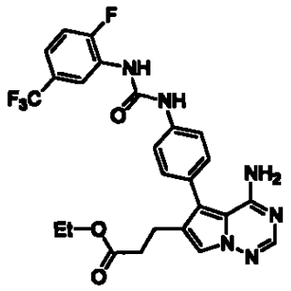


A una solución agitada de 2-fluoro-5-(trifluorometil)anilina (3,00 g, 16,7 mmol) en THF (80 ml) se agregó piridina (2,71 ml, 33,5 mmol), seguido de cloroformiato de fenilo (3,15 ml, 25,1 mmol) a temperatura ambiente. Parte del sólido precipitó. La mezcla se agitó a temperatura ambiente durante toda la noche. Se agregó agua a la reacción y se extrajo con EtOAc. La solución orgánica se lavó con agua (2x) y se secó sobre $MgSO_4$ y luego se filtró. El filtrado se concentró al vacío y se purificó por

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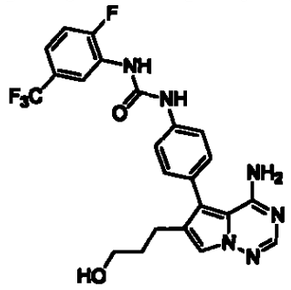
cromatografía de columna (10:90 a 30:70 v/v EtOAc-hexanos) para dar el compuesto del título (3,1 g, 62%). ^{1}H-RMN (DMSO-d_6) δ 10,36 (br s, 1H), 8,15 (d, J = 7,1 Hz, 1H), 7,59 a 7,47 (m, 2H), 7,46 a 7,38 (m, 2H), 7,30 a 7,20 (m, 3H); TLC R_f = 0,39 (9:1 v/v hexanos-EtOAc).

Paso 2: Preparación de 3-(4-amino-5-{4-[({[2-fluoro-5-(trifluorometil)fenil]amino}carbonil)amino]fenil}pirrolo[2,1-f][1,2,4]triazin-6-il)-propanoato de etilo



A una solución de THF (2,0 ml) se agregó el intermediario H (80 mg, 0,25 mmol) seguido de [2-fluoro-5-(trifluorometil)fenil]carbamato de fenilo (74 mg, 0,25 mmol) y trietilamina (34 µl, 0,25 mmol). La reacción se agitó a 0 °C y se dejó entibiar lentamente a temperatura ambiente durante toda la noche. La solución se concentró al vacío hasta sequedad y luego se purificó por cromatografía de columna (5:95 a 50:50 v/v EtOAc-hexanos) para dar el compuesto del título (66 mg, 50%). ^{1}H-RMN (CD_3OD) δ 8,62 (d, J = 7,4 Hz, 1H), 7,74 (s, 1H), 7,63 (d, J = 8,6 Hz, 2H), 7,52 (s, 1H), 7,40 a 7,31 (m, 4H), 4,06 (q, J = 7,0 Hz, 2H), 2,84 (t, J = 7,5 Hz, 2H), 2,50 (t, J = 7,4 Hz, 2H), 1,18 (t, J = 7,0 Hz, 3H); EM $[M+H]^+$ = 531; LCMS TR = 3,29 min.

Paso 3: Preparación de *N*-{4-[4-amino-6-(3-hidroxipropil)pirrolo[2,1-f]-[1,2,4]triazin-5-il]fenil}-*N'*-[2-fluoro-5-(trifluorometil)fenil]urea



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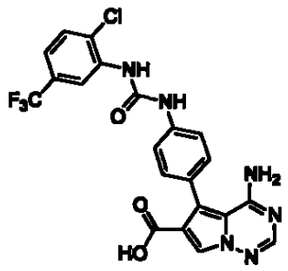
A una solución de THF (6 ml) se agregó 3-(4-amino-5-[4-[([[2-fluoro-5-(trifluorometil)fenil]amino}carbonil)amino]fenil}pirrolo[2,1-f][1,2,4]triazin-6-il)propanoato de etilo (62 mg, 0,12 mmol) seguido de DIBAL (0,6 ml, 0,6 mmol, solución 1,0M en tolueno). La reacción se agitó a temperatura ambiente durante 1 hora. Se agregó DIBAL adicional (1,2 ml, 1,2 mmol, solución 1,0M en tolueno) y se agitó a temperatura ambiente durante otra hora. La reacción se diluyó con EtOAc y se templó con sal de Rochelle acuosa saturada. La reacción se extrajo con EtOAc (4x). Las capas orgánicas combinadas se secaron (Na_2SO_4), se filtraron, y se evaporaron hasta sequedad para dar un sólido bruto de color amarillo (56 mg, 96%) que se utilizó directamente en el próximo paso sin purificación posterior. ^{1}H-RMN (CD_3OD) δ 8,62 (d, J = 7,6 Hz, 1H), 7,74 (s, 1H), 7,61 (d, J = 7,6 Hz, 2H), 7,52 (s, 1H), 7,38 a 7,31 (m, 4H), 3,50 (t, J = 7,1 Hz, 2H), 2,61 (t, J = 7,8 Hz, 2H), 1,77 a 1,65 (m, 2H); EM $[M+H]^+$ = 489; LCMS TR = 2,50 min.

Paso 4: Preparación del compuesto del título

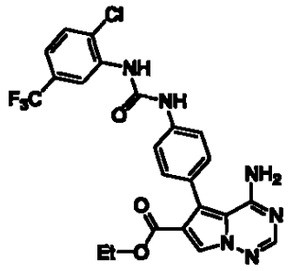
A una solución de THF (5 ml) se agregó *N*-(4-[4-amino-6-(3-hidroxipropil)pirrolo[2,1-f][1,2,4]triazin-5-il]fenil}-N'-[2-fluoro-5-trifluorometil)fenil] urea (55 mg, 0,11 mmol) seguido de reactivo Dess-Martin Periodinano (0,29 ml, 0,14 mmol, 15% en peso en CH_2Cl_2). La reacción se agitó hasta que la HPLC indicó la terminación de la reacción (2 h). La reacción se diluyó con EtOAc y se lavó con $NaHCO_3$/$Na_2S_2O_3$ acuoso saturado 1:1 (3x). La capa acuosa se retro extrajo con EtOAc (2x). Las capas orgánicas combinadas se secaron (Na_2SO_4), se filtraron, y se evaporaron para dar un sólido bruto de color amarillo (53mg, 96%) que se utilizó sin purificación posterior. ^{1}H-RMN (DMSO-d_6) δ 9,35 (s, 1H), 8,98 (s, 1H), 8,62 (d, J = 7,2 Hz, 1H), 7,80 (s, 1H), 7,62 a 7,28 (m, 6H), 2,71 (t, J = 7,5 Hz, 2H), 2,41 (t, J = 7,4 Hz, 2H); EM $[M+H]^+$ = 487; LCMS TR = 2,62 min.

Intermediario J: Preparación de ácido 4-amino-5-[4-[([[2-cloro-5-(trifluorometil)fenil]amino}carbonil)amino]fenil}pirrolo[2,1-f][1,2,4]triazin-6-carboxílico

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Paso 1: Preparación de 4-amino-5-{4-[({[2-cloro-5-(trifluorometil)fenil]-amino}carbonil)amino]fenil}pirrolo[2,1-f][1,2,4]triazin-6-carboxilato de etilo



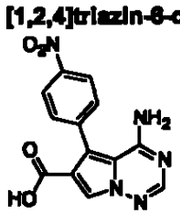
A una solución de DCE (5 ml) se agregó el intermediario B (300 mg, 1,01 mmol) seguido de 2-cloro-1-isocianato-4-(trifluorometil)benceno (0,32 ml, 2,12 mmol). La reacción se agitó bajo N_2 a temperatura ambiente durante 1 h, y luego se agregó HCl 2N ac (0,50 ml, 1,01 mmol) a la reacción seguido de DMF (5 ml). La solución se calentó a 80 °C durante 1 h. Al enfriarse a temperatura ambiente la solución se diluyó con EtOAc, se transfirió a un embudo de separación, y se lavó con saturado $NaHCO_3$ ac. La capa ac se retro extrajo con EtOAc. Las capas orgánicas combinadas se recolectaron, se secaron, se concentraron, y se purificaron por cromatografía de columna (95:5 v/v CH_2Cl_2-MeOH). Las fracciones resultantes conteniendo el producto se concentraron y se trituraron usando CH_2Cl_2 y hexanos. El producto se filtró y se secó al vacío para dar 408 mg del compuesto anterior en forma de un sólido color blanco (0,79 mmol, rendimiento 78%). ^{1}H-RMN (DMSO-d_6) δ 9,72 (s, 1H), 8,67 (s, 1H), 8,64 (s, 1H), 8,13 (s, 1H), 8,08 (br s, 1H), 7,93 (s, 1H), 7,72 (d, J = 8,5 Hz, 1H), 7,56 (d, J = 8,8 Hz, 2H), 7,39 a 7,36 (m, 1H), 7,34 (d, J = 8,6 Hz, 2H), 5,10 (br s, 1H), 4,09 (q, J = 7,0 Hz, 2H), 1,12 (t, J = 7,1 Hz, 3H); EM $[M+H]^+$ = 519; LCMS TR = 3,58 min; TLC R_f = 0,26 (95:5 v/v CH_2Cl_2-MeOH).

Paso 2: Preparación del compuesto del título

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A una solución de MeOH (20 ml) y THF (50 ml) se agregó 4-amino-5-{4-[({[2-cloro-5-(trifluorometil)fenil]amino}carbonil)amino]fenil}pirrolo[2,1-*f*][1,2,4]triazin-6-carboxilato de etilo (381 mg, 0,73 mmol) seguido de NaOH 1N ac (7,34 ml, 7,34 mmol). La reacción luego se calentó bajo N_2 a 60 °C durante 17 h. Al enfriarse a temperatura ambiente la solución luego se evaporó parcialmente en evaporador rotativo y luego se trató con HCl 1N (7,34 ml, 7,34 mmol). Se formó un precipitado, el cual se recolectó y se lavó con agua dando 324 mg del compuesto anterior en forma de un sólido color blanco (0,66 mmol, rendimiento 90%). ^{1}H-RMN (DMSO-d_6) δ 12,29 (br s, 1H), 9,75 (s, 1H), 8,69 (s, 1H), 8,63 (s, 1H), 8,08 (s, 1H), 8,03 (br s, 1H), 7,92 (s, 1H), 7,72 (d, J = 8,3 Hz, 1H), 7,55 (d, J = 8,4 Hz, 2H), 7,37 (m, 1H), 7,33 (d, J = 8,6 Hz, 2H), 5,05 (br s, 1H); EM $[M+H]^+$ = 491; LCMS TR = 3,15 min; TLC R_f < 0,1 (5:4:1 v/v/v CH_2Cl_2-EtOAc-MeOH).

Intermediario K: Preparación de ácido 4-amino-5-(4-nitrofenil)pirrolo[2,1-*f*]-[1,2,4]triazin-6-carboxílico



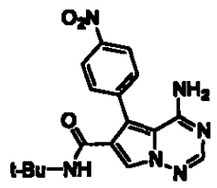
Una suspensión del intermediario A (1,04 g, 3,16 mmol) en EtOH (10 ml), THF (5 ml) y NaOH 1N (5,56ml, 5,56 mmol) se agitó a 80 °C durante 6 h. La solución homogénea se enfrió a temperatura ambiente y se trató gota a gota con HCl 1N (5,56 ml). La reacción se concentró al vacío y el sólido resultante se trituró con agua para dar el compuesto anterior en forma de un sólido color tostado. EM $[M+H]^+$ = 300,2; LCMS TR = 1,37 min.

Intermediario L: Preparación de 4-amino-5-(4-aminofenil)-*N*-(*ter*-butil)-pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida



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Paso 1: Preparación de 4-amino-*N*-(*ter*-butil)-5-(4-nitrofenil)-pirrolo[2,1-*f*]-[1,2,4]triazin-6-carboxamida



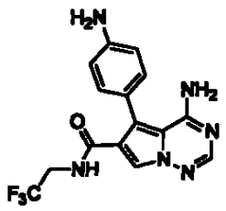
A una solución de tolueno (10 ml) se agregó trimetil aluminio 2M en hexanos (1,37 ml, 2,75 mmol) seguido de 2-metilopropan-2-amina (0,14 ml, 1,37 mmol). La solución se agitó a temperatura ambiente durante 15 min y luego se agregó el intermediario A (300 mg, 0,92 mmol). La solución se calentó a 110 °C durante 17 h. Al enfriarse a temperatura ambiente se agregó HCl 1N lentamente hasta que cesó el burbujeo. Se agregó EtOAc seguido de una cuidadosa adición de $NaHCO_3$ ac. La solución se transfirió a un embudo de separación, la capa orgánica se recolectó y la fase acuosa se retro extrajo con EtOAc (3 x 20 ml). Las capas orgánicas combinadas se secaron ($MgSO_4$), se concentraron, y se purificaron por cromatografía de columna (50:45:5 v/v/v CH_2Cl_2/EtOAc/MeOH) para dar 181 mg del compuesto anterior (0,51 mmol, rendimiento 56%). ^{1}H-RMN (DMSO-d_6) 8,25 (d, J = 8,9 Hz, 2H), 8,16 (s, 1H), 7,94 (s, 1H), 7,59 (d, J = 8,8 Hz, 2H), 7,39 (s, 1H) 1,25 (s, 9H); EM $[M+H]^+$ = 355; LCMS TR = 2,42 min.

Paso 2: Preparación del compuesto del título

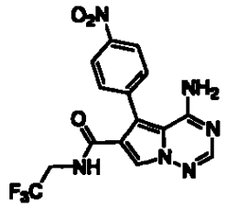
El procedimiento utilizado para la preparación del intermediario B se utilizó para preparar el compuesto del título sustituyendo 4-amino-*N*-(*ter*-butil)-5-(4-nitrofenil)pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida con el intermediario A. ^{1}H-RMN (DMSO-d_6) δ 7,91 (s, 1H), 7,89 (br s, 1H), 7,84 (s, 1H), 7,07 (d, J = 8,2 Hz, 2H), 6,69 (d, J = 8,3 Hz, 2H), 6,15 (s, 1H), 5,44 (s, 2H), 5,04 (br s, 1H), 1,14 (s, 9H); EM $[M+H]^+$ = 325; LCMS TR = 1,38 min; TLC R_f = 0,15 (95:5 v/v CH_2Cl_2-MeOH).

Intermediario M: Preparación de 4-amino-5-(4-aminofenil)-*N*-(2,2,2-trifluoroetil)pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida

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Paso 1: Preparación de 4-amino-5-(4-nitrofenil)-*N*-(2,2,2-trifluoroetil)-pirrolo[2,1-f][1,2,4]triazin-6-carboxamida



A una solución de cloruro de tionilo (15 ml) se agregó el intermediario K (495 mg, 1,73 mmol) el cual se calentó a 50 °C durante 3 h. Al enfriarse a temperatura ambiente la mezcla de reacción se concentró hasta sequedad fileteando con THF. La mezcla de reacción luego se diluyó con sal clorhidrato de 2,2,2-trifluoro-etilamina (587 mg, 4,33 mmol) y trietilamina (1,15 ml, 8,66 mmol) en THF (8 ml) y se agitó a temperatura ambiente durante toda la noche. La solución se evaporó en evaporador rotativo hasta sequedad, se diluyó con EtOAc (50 ml), se transfirió a un embudo de separación, y se lavó con agua (50 ml). La capa acuosa se retro extrajo con EtOAc (4 x 20 ml), se secó (Na_2SO_4), se filtró, y se concentró hasta sequedad, luego se trituró con EtOAc/MeOH. El producto se recolectó para dar 490 mg del compuesto anterior en forma de un sólido color amarillo (rendimiento 74%). ^{1}H-RMN (DMSO-d_6) δ 8,77 (t, J = 6,2 Hz, 1H), 8,29 (s, 1H), 8,23 (d, J = 8,9 Hz, 2H), 7,97 (s, 1H), 7,59 (d, J = 8,9 Hz, 2H), 3,97 a 3,91 (m, 2H); EM $[M+H]^+$ = 381,1; LCMS TR = 2,33 min).

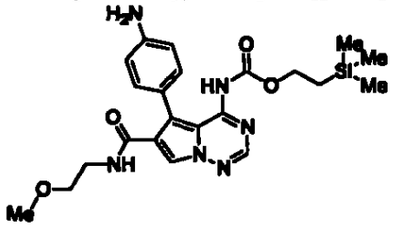
Paso 2: Preparación del compuesto del título

El procedimiento utilizado para la preparación del intermediario B se utilizó para preparar el compuesto del título sustituyendo 4-amino-5-(4-nitrofenil)-*N*-(2,2,2-trifluoroetil)pirrolo[2,1-f][1,2,4]triazin-6-carboxamida con el intermediario A. ^{1}H-RMN

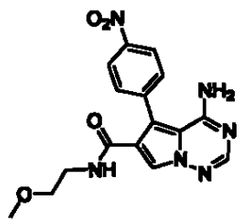
446

(CD_3OD) δ 8,00 (s, 1H), 7,81 (s, 1H), 7,17 (d, J = 8,5 Hz, 2H), 6,84 (d, J = 8,6 Hz, 2H), 4,03 a 3,85 (m, 2H); EM $[M+H]^+$ = 351,2; **LCMS TR** = 1,14 min.

Intermediario N: Preparación de (5-(4-aminofenil)-6-[[(2-metoxietil)-amino]carbonil]pirrolo[2,1-*f*][1,2,4]triazin-4-il)carbamato de 2-(trimetilsilil)-etilo

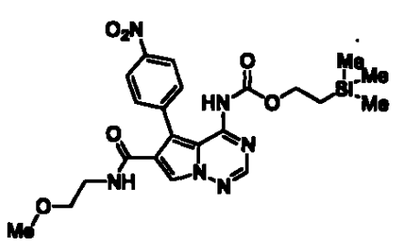


Paso 1: Preparación de 4-amino-*N*-(2-metoxietil)-5-(4-nitrofenil)-pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida



El procedimiento utilizado para la preparación de 4-amino-*N*-(*ter*-butil)-5-(4-nitrofenil)pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida (Intermediario L Paso 1) se utilizó para preparar el compuesto del título sustituyendo 2-metoxietanamina con 2-metilpropan-2-amina. ^{1}H-RMN (DMSO-d_6) δ 8,22 (d, J = 8,7 Hz, 2H), 8,16 (s, 1H), 8,11 (t, J = 5,6 Hz, 1H), 7,93 (s, 1H), 7,58 (d, J = 8,9 Hz, 2H), 3,26 a 3,26 (m, 2H), 3,21 (s, 3H), 3,16 a 3,14 (m, 2H); EM $[M+H]^+$ = 357; **LCMS TR** = 1,83 min.

Paso 2: Preparación de [6-[[(2-metoxietil)amino]carbonil]-5-(4-nitrofenil)pirrolo[2,1-*f*][1,2,4]triazin-4-il]carbamato de 2-(trimetilsilil)etilo



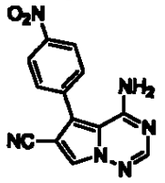
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A una solución de DMF (100 ml) se agregó 4-amino-*N*-(2-metoxietil)-5-(4-nitrofenil)pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida (4,03g, 11,3 mmol) seguido de 60% de NaH en peso en aceite mineral (1,13g, 28,3 mmol). La solución se agitó durante 15 min y se agregó luego carbonato de 4-nitrofenilo 2-(trimetilsilil)etilo (3,52 g, 12,4 mmol). La solución se agitó bajo N_2 durante 2 h. Se agregó MeOH a la reacción hasta que cesó el burbujeo y luego se agregó EtOAc (50 ml). La solución se transfirió a un embudo de separación y se lavó con NaOH 1N (20 ml) y agua (20 ml). La capa orgánica se recolectó, se secó (Na_2SO_4), y se purificó por cromatografía de columna para dar 3,60 g del compuesto anterior (7,15 mmol, rendimiento 63%). ^{1}H-RMN ($CDCl_3$) δ 8,38 (d, *J* = 8,5 Hz, 2H), 8,16 (s, 1H), 8,14 (s, 1H), 7,69 (d, *J* = 8,5 Hz, 2H), 5,87 a 5,86 (*m*, 1H), 4,17 (t, *J* = 8,3 Hz, 2H), 3,48 a 3,46 (*m*, 2H), 3,36 (t, *J* = 5,0 Hz 2H), 3,21 (s, 3H), 0,93 (t, *J* = 8,1 Hz 2H), -0,01 (s, 9H); EM $[M+H]^+$ = 501; LCMS TR = 3,17 min.

Paso 3: Preparación del compuesto del título

El procedimiento utilizado para la preparación del Intermediario B se utilizó para preparar el compuesto del título sustituyendo [6-[[(2-metoxietil)amino]carbonil]-5-(4-nitrofenil)pirrolo[2,1-*f*][1,2,4]triazin-4-il]carbamato de 2-(trimetilsilil)etilo con el Intermediario A. ^{1}H-RMN (DMSO-d_6) δ 8,26 (s, 1H), 8,23 (s, 1H), 8,16 (s, 1H), 7,42 (br s, 1H), 7,04 (d, *J* = 8,3 Hz, 2H), 6,61 (d, *J* = 8,3 Hz, 2H), 5,36 (br s, 2H), 3,99 (t, *J* = 8,3 Hz, 2H), 3,29 a 3,25 (m, 4H), 3,18 (s, 3H), 0,88 a 0,84 (m, 2H), -0,01 (s, 9H); EM $[M+H]^+$ = 471; LCMS TR = 3,04 min.

Intermediario O: Preparación de 4-amino-5-(4-nitrofenil)pirrolo[2,1-*f*]-[1,2,4]triazin-6-carbonitrilo

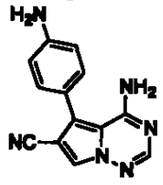


A una solución de piridina (8,75 ml) se agregó 4-amino-5-(4-nitrofenil)pirrolo[2,1-*f*][1,2,4]triazin-6-carbaldehído (Intermediario H, Paso 2) (500 mg, 1,77 mmol) seguido de clorhidrato de hidroxilamina (135 mg, 1,94 mmol). La

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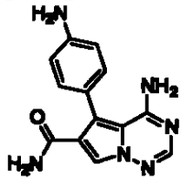
solución se agitó a temperatura ambiente durante 1 h, se agregó anhidrido acético (,366 ml, 3,88 mmol), y la solución se calentó a 80 °C durante 17 h. Al enfriarse a temperatura ambiente la mezcla de reacción luego se evaporó parcialmente en evaporador rotativo y luego se diluyó con EtOAc (50 ml) y H_2O (50 ml). La solución se transfirió a un embudo de separación, y la capa orgánica se aisló mientras que las capas orgánicas se retro extrajeron con EtOAc (2 x 25 ml). Las capas orgánicas combinadas se recolectaron, se secaron (Na_2SO_4), se filtraron, y se concentraron hasta sequedad para dar un sólido color marrón. Esto demostró ser una relación 1:1 del compuesto del título y *N*-[6-ciano-5-(4-nitro-fenil)-pirrolo[2,1-*f*][1,2,4]triazin-4-il]-acetamida. ^{1}H-RMN (DMSO-d_6) δ 10,67 (s, 1H), 8,96 (s, 1H), 8,62 (s, 1H), 8,57(s, 1H), 8,40 a 8,30 (m, 4H), 8,05 (s, 1H), 7,79 a 7,68 (m, 4H), 1,74 (s, 3H); EM $[M+H]^+$ = 281,2, 323,0; LCMS TR = 2,48 min.

Intermediario P: Preparación de 4-amino-5-(4-aminofenil)pirrolo[2,1-*f*]-[1,2,4]triazin-6-carbonitrilo



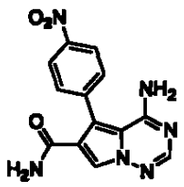
El procedimiento utilizado para la preparación del Intermediario B se utilizó para preparar el compuesto del título sustituyendo el Intermediario O con el Intermediario A ^{1}H-RMN (CD_3OD) δ 8,29 (s, 1H), 7,98 (s, 1H), 7,57 (d, *J* = 9,0 Hz, 2H), 7,33 (d, *J* = 9,0 Hz, 2H); EM $[M+H]^+$ = 251,3; LCMS TR = 0,40 min.

Intermediario Q: Preparación de 4-amino-5-(4-aminofenil)pirrolo[2,1-*f*]-[1,2,4]triazin-6-carboxamida



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Paso 1: Preparación de 4-amino-5-(4-nitrofenil)pirrolo[2,1-*f*][1,2,4]-triazin-6-carboxamida

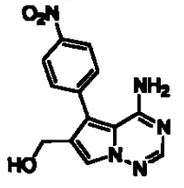


Una mezcla del intermediario O (80 mg, 0,29 mmol) en ácido sulfúrico (1 ml) se agitó a temperatura ambiente durante toda la noche. La mezcla de reacción se templó lentamente con solución de bicarbonato de sodio saturado hasta que cesó la evolución gaseosa. La mezcla de reacción luego se extrajo con EtOAc (3 x 5 ml) y THF (3 x 5 ml), se secó (Na_2SO_4), se filtró, y se concentró hasta sequedad para dar un sólido color marrón. ^{1}H-RMN (CD_3OD) δ 8,22 (d, *J* = 9,0 Hz, 2H), 8,04 (s, 1H), 7,80 (s, 1H), 7,59 (d, *J* = 8,6 Hz, 2H); EM $[M+H]^+$ = 299,1; LCMS TR = 1,15 min.

Paso 2: Preparación del compuesto del título

El procedimiento utilizado para la preparación del intermediario B se utilizó para preparar el compuesto del título sustituyendo 4-amino-5-(4-nitrofenil)pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida con el intermediario A. ^{1}H-RMN (CD_3OD) □8,26 (s, 1H), 8,02 (s, 1H), 7,98 (br s, 2H), 7,53 (d, *J* = 9,0 Hz, 2H), 7,33 (d, *J* = 9,0 Hz, 2H); EM $[M+H]^+$ = 269,3; LCMS TR = 0,19 min.

Intermediario R: Preparación de [4-amino-5-(4-nitrofenil)pirrolo[2,1-*f*]-[1,2,4]triazin-6-il]metanol

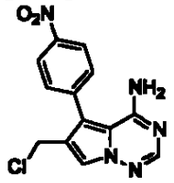


A una solución de THF (10 ml) se agregó el intermediario A (500 mg, 1,53 mmol) seguido de DIBAL (3 ml, 3 mmol, solución 1,0 M en tolueno). La reacción se agitó a temperatura ambiente durante 1 h. Se agregó DIBAL adicional (1,5 ml, 1,5

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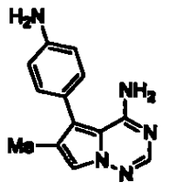
mmol, solución 1,0 M en tolueno) y se continuó con la agitación a temperatura ambiente durante otra hora. La reacción se diluyó con EtOAc y se templó con sal de Rochelle acuosa saturada. La reacción se extrajo con EtOAc (4x). La capa orgánica se secó (Na_2SO_4) y se evaporó para dar un sólido bruto (435 mg, 100%) que se utilizó directamente en el próximo paso sin purificación posterior. ^{1}H-RMN (DMSO-d_6) δ 8,29 (d, J= 9,2 Hz, 2H), 7,89 (s, 1H), 7,73 (s, 1H), 7,67 (d, J= 9,3 Hz, 2H), 5,07 (t, J= 5,5 Hz, 1H), 4,38 (d, J= 5,2 Hz, 2H); EM $[M+H]^+$ = 286; LCMS TR = 0,59 min.

Intermediario S: Preparación de 6-(clorometil)-5-(4-nitrofenil)pirrolo[2,1-*f*]-[1,2,4]triazin-4-amina



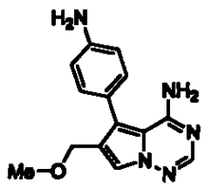
Una mezcla del intermediario R (522 mg, 1,83 mmol) en cloruro de tionilo (10 ml) se agitó a 50 °C durante 1 h. Luego se concentró hasta sequedad para dar un sólido color marrón. ^{1}H-RMN (DMSO-d_6) δ 8,37 (d, J = 8,9 Hz, 2H), 8,19 (s, 1H), 8,16 (s, 1H), 7,74 (d, J = 8,9 Hz, 2H), 4,70 (s, 2H); EM $[M+H]^+$ = 304,3; LCMS TR = 2,44 min.

Intermediario T: Preparación de 5-(4-aminofenil)-6-metilpirrolo[2,1-*f*][1,2,4]-triazin-4-amina

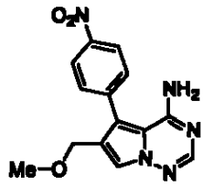


El procedimiento utilizado para la preparación del intermediario B se utilizó para preparar el compuesto del título sustituyendo el intermediario S con el intermediario A. ^{1}H-RMN (CD_3OD) δ 7,74 (s, 1H), 7,52 (s, 1H), 7,13 (d, J = 8,2 Hz, 2H), 6,86 (d, J = 8,5 Hz, 2H), 2,11 (s, 3H); EM $[M+H]^+$ = 240,3; LCMS TR = 1,06 min.

Intermediario U: Preparación de 5-(4-aminofenil)-6-(metoximetil)pirrolo[2,1-*f*][1,2,4]triazin-4-amina



Paso 1: Preparación de 6-(metoximetil)-5-(4-nitrofenil)pirrolo[2,1-f][1,2,4]triazin-4-amina



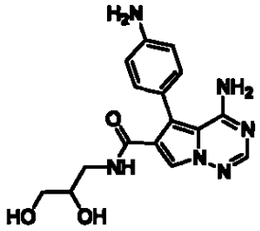
A una solución de cloruro de tionilo (20 ml) se agregó el intermediario R (873 mg, 3,06 mmol) el cual se calentó a reflujo bajo N_2 durante 2 h. Al enfriarse a temperatura ambiente la mezcla de reacción se evaporó por evaporador rotativo hasta sequedad mezclando con CH_2Cl_2. La mezcla de reacción luego se diluyó con MeOH (20 ml) y luego se agregó 60% en peso de NaH con aceite mineral (489 mg, 12,2 mmol). La solución se calentó a reflujo durante 6 h. Al enfriarse a temperatura ambiente la solución se evaporó por evaporador rotativo hasta sequedad, se diluyó con EtOAc (50 ml), se transfirió a un embudo de separación, y se lavó con agua (50 ml). La capa acuosa se retro extrajo con EtOAc (4 x 20 ml), se secó ($MgSO_4$), se filtró, y se purificó por cromatografía de columna (95:5 v/v CH_2CL_2:MeOH). Las fracciones limpias resultantes se combinaron, se evaporaron, y se trituraron con CH_2Cl_2/éter dietílico. El producto se recolectó para dar 470 mg del compuesto anterior en forma de un sólido color amarillo (1,57 mmol, rendimiento 51%). ^{1}H-RMN (DMSO-d_6) δ 8,30 (d, *J* = 8,9 Hz, 2H), 7,91 (s, 1H), 7,84 (s, 1H), 7,65 (d, *J* = 8,9 Hz, 2H), 4,29 (s, 2H), 3,21 (s, 3H); EM $[M+H]^+$ = 300; LCMS TR = 2,07 min; TLC R_f = 0,54 (95:5 v/v CH_2Cl_2-MeOH).

Paso 2: Preparación del compuesto del título

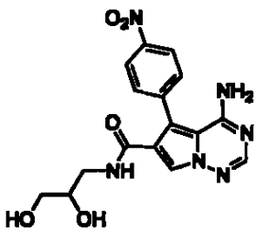
452

El procedimiento utilizado para la preparación del intermediario B se utilizó para preparar el compuesto del título sustituyendo 6-(metoximetil)-5-(4-nitrofenil)pirrolo[2,1-*f*][1,2,4]triazin-4-amina con el intermediario A. ^{1}H-RMN (DMSO-d_6) δ 7,79 (s, 1H), 7,67 (s, 1H), 7,03 (d, J = 8,4 Hz, 2H), 6,64 (d, J = 8,7 Hz, 2H), 5,30 (s, 2H),), 4,24 (s, 2H), 3,19 (s, 3H); EM $[M+H]^+$ = 270; LCMS TR = 0,26 min; TLC R_f = 0,30 (95:5 v/v CH_2Cl_2-MeOH).

Intermediario V: Preparación de 4-amino-5-(4-aminofenil)-*N*-(2,3-dihidroxipropil)pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida



Paso 1: Preparación de 4-amino-*N*-(2,3-dihidroxipropil)-5-(4-nitrofenil)pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida



A una solución del intermediario K (550 mg, 1,84 mmol), 3-amino-1,2-propanodiol (251 mg, 2,76 mmol), trietilamina (1,0 ml, 7,4 mmol), y DMF (20 ml) se agregó py-BOP (1051 mg, 2,02 mmol) y la reacción se dejó agitar durante 1 hora. La mezcla de reacción se concentró al vacío y el residuo se trituró primero con agua y luego con 30% de etanol acuoso para dar 318 mg del compuesto anterior en forma de un sólido naranja/amarillo (rendimiento 47%). EM $[M+H]^+$ = 373,2; LCMS TR = 1,21.

Paso 2: Preparación del compuesto del título

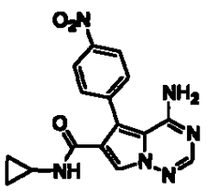
453

El procedimiento utilizado para la preparación del Intermediario B se utilizó para preparar el compuesto del título sustituyendo 4-amino-*N*-(2,3-dihidroxipropil)-5-(4-nitrofenil)pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida con el Intermediario A. ^{1}H-RMN (DMSO-d_6) δ 8,02 (s, 1H), 7,84 (s, 1H), 7,28 (t, *J* = 6 Hz, 1H) 7,02 (d, *J* = 8 Hz, 2H), 5,34 (s, 2H), 5,05 (bs, 1H), 4,75 (bs, 1H), 4,52 (bs, 1H), 4,38 a 3,43 (m. 1H), 3,36 a 3,16 (m, 3H), 3,03 a 2,85 (m, 1H). EM $[M+H]^+$ = 343,2; LCMS TR = 1,02 min.

Intermediario W: Preparación de 4-amino-5-(4-aminofenil)-*N*-ciclopropil-pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida



Paso 1: Preparación de 4-amino-*N*-ciclopropil-5-(4-nitrofenil)-pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida



El procedimiento utilizado para la preparación de 4-amino-*N*-(*ter*-butil)-5-(4-nitrofenil)pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida (Intermediario L Paso 1) se

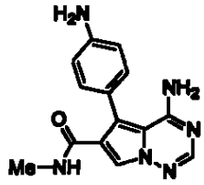
454

utilizó para preparar el compuesto del título sustituyendo ciclopropilamina con 2-metilopropan-2-amina. ^{1}H-RMN (DMSO-d_6) δ 8,23 (d, J = 8,8 Hz, 2H), 8,14 (s, 1H), 8,13 (br s, 1H), 7,93 (d, J = 8,4 Hz, 2H), 7,58 (s, 1H), 2,67 a 2,59 (m, 1H), 0,62 a 0,54 (m, 2H), 0,46 a 0,41 (m, 2H); EM $[M+H]^+$ = 339,2; LCMS TR = 1,40 min.

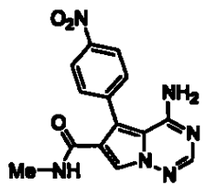
Paso 2: Preparación del compuesto del título

El procedimiento utilizado para la preparación del Intermediario B se utilizó para preparar el compuesto del título sustituyendo 4-amino-*N*-ciclopropil-5-(4-nitrofenil)pirrolo[2,1-f][1,2,4]triazin-6-carboxamida con el Intermediario A. ^{1}H-RMN (CD_3OD) δ 7,68 (s, 1H), 7,58 (s, 1H), 7,07 (s, 1H), 6,73 (d, J = 8,6 Hz, 2H), 6,33 (d, J = 8,3 Hz, 2H), 5,05 (s, 2H), 2,38 a 2,28 (m, 1H), 0,34 a 0,24 (m, 2H), 0,067 a -0,032 (m, 2H); EM $[M+H]^+$ = 309,3; LCMS TR = 0,23 min.

Intermediario X: Preparación de 4-amino-5-(4-aminofenil)-*N*-metilpirrolo[2,1-f][1,2,4]triazin-6-carboxamida



Paso 1: Preparación de 4-amino-*N*-metil-5-(4-nitrofenil)pirrolo[2,1-f][1,2,4]triazin-6-carboxamida



A una solución de cloruro de tionilo (10 ml) se agregó el intermediario K (300 mg, 1,00 mmol) el cual se calentó a 50 °C durante 3 h. Al enfriarse a temperatura ambiente la mezcla de reacción se evaporó por evaporador rotativo hasta sequedad mezclando con THF. La mezcla de reacción luego se diluyó con 2M metilamina en THF (40 ml) y se agitó a temperatura ambiente durante toda la noche. La solución se

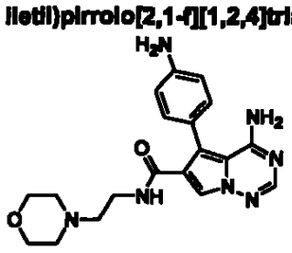
455

evaporó por evaporador rotativo hasta sequedad, se diluyó con EtOAc (50 ml), se transfirió a un embudo de separación, y se lavó con agua (50 ml). La capa acuosa se retro extrajo con EtOAc (4 x 20 ml), se secaron (Na_2SO_4), se filtraron, y se evaporó por evaporador rotativo hasta sequedad. luego se trituró con EtOAc/MeOH. El producto se recolectó para dar 240 mg del compuesto anterior en forma de un sólido color amarillo (240 mg, rendimiento 76%). ^{1}H-RMN (DMSO-d_6) □8,22 (d, J = 8,9 Hz, 2H), 8,15 (s, 1H), 7,94 (s, 1H), 7,58 (d, J = 8,9 Hz, 2H), 3,60 a 3,55 (m, 1H), 2,62 (d, J = 4,6 Hz, 3H); EM $[M+H]^+$ = 313,2; LCMS TR = 0,58 min).

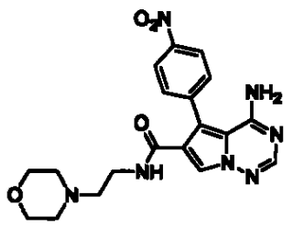
Paso 2: Preparación del compuesto del título

El procedimiento utilizado para la preparación del intermediario B se utilizó para preparar el compuesto del título sustituyendo 4-amino-*N*-metil-5-(4-nitrofenil)pirrolo[2,1-f][1,2,4]triazin-6-carboxamida con el intermediario A. ^{1}H-RMN (DMSO-d_6) □8,00 (s, 1H), 7,84 (s, 1H), 7,00 (d, J = 8,4 Hz, 2H), 6,61 (d, J = 8,5 Hz, 2H), 5,31 (s, 2H), 4,19 a 4,12 (m, 1H), 2,59 (d, J = 4,6 Hz, 3H); EM $[M+H]^+$ = 281,3; LCMS TR = 1,03 min

Intermediario Y: Preparación de 4-amino-5-(4-aminofenil)-*N*-(2-morfolin-4-iletil)pirrolo[2,1-f][1,2,4]triazin-6-carboxamida



Paso 1: Preparación de 4-amino-*N*-(2-morfolin-4-iletil)-5-(4-nitrofenil)pirrolo[2,1-f][1,2,4]triazin-6-carboxamida



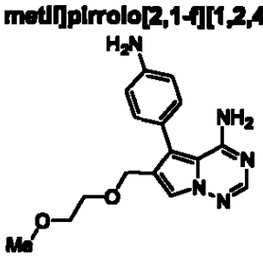
456

El procedimiento utilizado para la preparación de 4-amino-*N*-metil-5-(4-nitrofenil)pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida (Intermediario X Paso 1) se utilizó para preparar el compuesto del título sustituyendo 2-morfolin-4-il-etilamina con metilamina. ^{1}H-RMN (CD_3OD) □ 8,34 (d, *J* = 8,8 Hz, 2H), 8,07 (s, 1H), 7,89 (s, 1H), 7,69 (d, *J* = 8,8 Hz, 2H), 3,66 a 3,61 (m, 4H), 3,39 (t, *J* = 6,6 Hz, 2H), 2,49 a 2,40 (m, 6H); EM $[M+H]^+$ = 412,2; LCMS TR = 0,26 min.

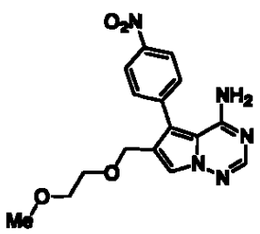
Paso 2: Preparación del compuesto del título

El procedimiento utilizado para la preparación del Intermediario B se utilizó para preparar el compuesto del título sustituyendo 4-amino-*N*-(2-morfolin-4-iletil)-5-(4-nitrofenil)pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida con el Intermediario A. ^{1}H-RMN (CD_3OD) □8,04 (br s, 2H), 7,99 (s, 1H), 7,80 (s, 1H), 7,20 (d, *J* = 8,4 Hz, 2H), 6,85 (d, *J* = 8,4 Hz, 2H), 3,64 a 3,57 (m, 4H), 3,42 a 3,36 (m, 2H), 2,35 a 2,27 (m, 6H); EM $[M+H]^+$ = 382,3; LCMS TR = 0,17 min.

Intermediario Z: Preparación de 5-(4-aminofenil)-6-[(2-metoxietoxi)-metil]pirrolo[2,1-*f*][1,2,4]triazin-4-amina



Paso 1: Preparación de 6-[(2-metoxietoxi)metil]-5-(4-nitrofenil)-pirrolo[2,1-*f*][1,2,4]triazin-4-amina



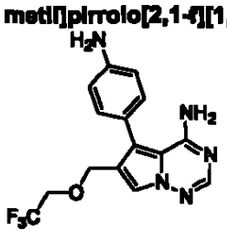
457

El procedimiento utilizado para la preparación de 6-(metoximetil)-5-(4-nitrofenil)pirrolo[2,1-f][1,2,4]triazin-4-amina (Intermediario U Paso 1) se utilizó para preparar el compuesto del título sustituyendo 2-metoxi-etanol con metanol. ^{1}H-RMN (CD_3OD) □ 8,35 (d, *J* = 8,7 Hz, 2H), 7,85 (s, 1H), 7,77 (s, 1H), 7,75 (d, *J* = 8,7 Hz, 2H), 4,45 (s, 2H), 3,59 a 3,49 (m, 4H), 3,33 (s, 3H); EM $[M+H]^+$ = 344,1; LCMS TR = 2,14 min.

Paso 2: Preparación del compuesto del título

El procedimiento utilizado para la preparación del Intermediario B se utilizó para preparar el compuesto del título sustituyendo 6-[(2-metoxietoxi)metil]-5-(4-nitrofenil)pirrolo[2,1-f][1,2,4]triazin-4-amina con el intermediario A. ^{1}H-RMN (CD_3OD) □7,74 (s, 1H), 7,65 (s, 1H), 7,17 (d, *J* = 8,5 Hz, 2H), 6,81 (d, *J* = 8,5 Hz, 2H), 4,42 (s, 2H), 3,57 a 3,47 (m, 4H), 3,32 (s, 3H); EM $[M+H]^+$ = 314,3; LCMS TR = 0,25 min.

Intermediario AA: Preparación de 5-(4-aminofenil)-6-[(2,2,2-trifluoroetoxi)-metil]pirrolo[2,1-f][1,2,4]triazin-4-amina



Paso 1: Preparación de 5-(4-nitrofenil)-6-[(2,2,2-trifluoroetoxi)-metil]pirrolo[2,1-f][1,2,4]triazin-4-amina



El procedimiento utilizado para la preparación de 6-(metoximetil)-5-(4-nitrofenil)pirrolo[2,1-f][1,2,4]triazin-4-amina (Intermediario U Paso 1) se utilizó para preparar el compuesto del título sustituyendo 2,2,2-trifluoro-etanol con metanol. ^{1}H-

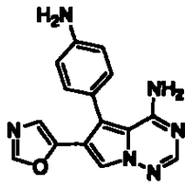
458

RMN (Acetona-d_6) δ 8,36 (d, J = 8,6 Hz, 2H), 7,89 (s, 1H), 7,85 (s, 1H), 7,81 (d, J = 8,6 Hz, 2H), 4,68 (s, 2H), 4,04 a 3,94 (m, 2H); EM $[M+H]^+$ = 368,3; LCMS TR = 2,68 min.

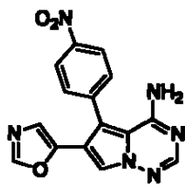
Paso 2: Preparación del compuesto del título

El procedimiento utilizado para la preparación del intermediario B se utilizó para preparar el compuesto del título sustituyendo 5-(4-nitrofenil)-6-[(2,2,2-trifluoroetoxi)metil]pirrolo[2,1-f][1,2,4]triazin-4-amina con el intermediario A. ^{1}H-RMN (CD_3OD) δ 7,75 (s, 1H), 7,65 (s, 1H), 7,15 (d, J = 8,6 Hz, 2H), 6,81 (d, J = 8,6 Hz, 2H), 4,53 (s, 2H), 3,93 a 3,72 (m, 2H); EM $[M+H]^+$ = 338,2; LCMS TR = 1,69 min.

Intermediario AB: Preparación de 5-(4-aminofenil)-6-(1,3-oxazol-5-il)pirrolo[2,1-f][1,2,4]triazin-4-amina



Paso 1: Preparación de 5-(4-nitrofenil)-6-(1,3-oxazol-5-il)pirrolo-[2,1-f][1,2,4]triazin-4-amina



A una solución de 4-amino-5-(4-nitrofenil)pirrolo[2,1-f][1,2,4]triazin-6-carbaldehído (intermediario H, Paso 2) (692 mg, 2,44 mmol) se agregó isocianuro de asilmetilo (477 mg, 2,44 mmol) y carbonato de potasio (338 mg, 2,44 mmol) en MeOH. La solución se dejó agitar a reflujo durante toda la noche. La solución se secó y se diluyó con EtOAc (50 ml) y THF (50 ml). Se agregó agua (50 ml) a la mezcla de reacción. La solución se transfirió a un embudo de separación, y la capa

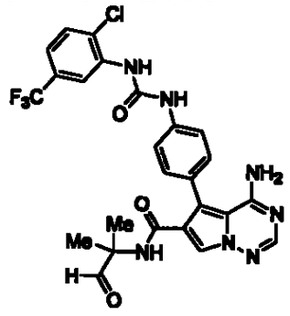
459

orgánica se aisló y se lavó con salmuera (50 ml). Las capas orgánicas se retro extrajeron con EtOAc (2 x 50 ml). Las capas orgánicas combinadas se recolectaron, se secaron (Na_2SO_4), se concentraron sobre gel de sílice, y se purificaron por cromatografía de columna (100% CH_2Cl_2 saltando a 95:5 v/v CH_2Cl_2-EtOAc) para dar 310 mg del compuesto anterior en forma de un sólido color amarillo (rendimiento 39%). ^{1}H-RMN (DMSO-d_6) δ 11,70 (s, 1H), 8,31 (d, *J* = 8,5 Hz, 2H), 8,28 (s, 1H), 8,17 (s, 1H), 7,66 (d, *J* = 7,1 Hz, 2H), 6,75 (s, 1H); EM $[M+H]^+$ = 323,2; LCMS TR = 2,57 min.

Paso 2: Preparación del compuesto del título

El procedimiento utilizado para la preparación del intermediario B se utilizó para preparar el compuesto del título sustituyendo 5-(4-nitrofenil)-6-(1,3-oxazol-5-il)pirrolo[2,1-f][1,2,4]triazin-4-amina con el intermediario A. ^{1}H-RMN (CD_3OD) □8,11 (s, 1H), 7,91 (s, 1H), 7,79 (s, 1H), 7,15 (d, *J* = 8,6 Hz, 2H), 6,87 (d, *J* = 8,6 Hz, 2H), 6,45 (s, 1H); EM $[M+H]^+$ = 293,2; LCMS TR = 1,23 min.

Intermediario AC: Preparación de 4-amino-5-[4-[({[2-cloro-5-(trifluorometil)fenil]amino}carbonil)amino]fenil]-*N*-(1,1-dimetil-2-oxoetil)-pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida

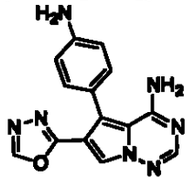


El procedimiento utilizado para la preparación del intermediario F (Paso 2) se utilizó para preparar el compuesto del título sustituyendo 4-amino-5-[4-[({[2-cloro-5-(trifluorometil)fenil]amino}carbonil)amino]fenil]-*N*-(2-hidroxi-1,1-dimetiletil)-pirrolo[2,1-f][1,2,4]triazin-6-carboxamida con *N*-[4-[4-amino-6-(hidroximetil)-pirrolo[2,1-f][1,2,4]triazin-5-il]fenil]-N'-[2-fluoro-5-(trifluorometil)-fenil]urea. ^{1}H-RMN (DMSO-d_6) δ 9,69 (s, 1H), 9,21 (s, 1H), 8,65 (s, 1H), 8,62 (d, *J* = 2,1 Hz, 1H), 8,23 (s, 1H), 8,20 (s, 1H), 7,90 (s, 1H), 7,70 (d, *J* = 8,8 Hz, 1H), 7,53 (d, *J* = 9,1 Hz, 2H), 7,35 (dd, *J* = 8,8,

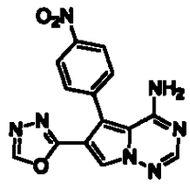
460

1,6 Hz, 1H), 7,30 (d, *J* = 8,6 Hz, 2H), 3,30 (s, 6H); EM $[M+H]^+$ = 560,1; LCMS TR = 3,36 min.

Intermediario AD: Preparación de 5-(4-aminofenil)-6-(1,3,4-oxadiazol-2-il)-pirrolo[2,1-f][1,2,4]triazin-4-amina



Paso 1: Preparación de 5-(4-nitrofenil)-6-(1,3,4-oxadiazol-2-il)-pirrolo[2,1-f][1,2,4]triazin-4-amina



A una solución de cloruro de tionilo (5 ml) se agregó el intermediario K (183 mg, 0,613 mmol) el cual se calentó a 50 °C durante 3 h. Al enfriarse a temperatura ambiente la mezcla de reacción se evaporó por evaporador rotativo hasta sequedad mezclando con THF. La mezcla de reacción luego se diluyó con piridina (5 ml), se agregó hidrazina (100 mg, 3,15 mmol), y se agitó a temperatura ambiente durante toda la noche. La solución se evaporó por evaporador rotativo hasta sequedad, se diluyó con trimetoxi-metano (10 ml), y se agitó a reflujo durante 5 horas. La solución se evaporó por evaporador rotativo hasta sequedad, y se purificó por HPLC para dar el compuesto del título (27 mg, 14%); ^{1}H-RMN (CD_3OD) □8,71 (s, 1H), 8,24 (d, *J* = 9,1 Hz, 2H), 8,20 (s, 1H), 7,84 (s, 1H), 7,73 (d, *J* = 8,9 Hz, 2H); EM $[M+H]^+$ = 324,2; LCMS TR = 2,07 min.

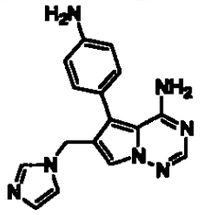
Paso 2: Preparación del compuesto del título

El procedimiento utilizado para la preparación del intermediario B se utilizó para preparar el compuesto del título sustituyendo 5-(4-nitrofenil)-6-(1,3,4-oxadiazol-2-il)pirrolo[2,1-f][1,2,4]triazin-4-amina con el intermediario A. ^{1}H-RMN (CD_3OD)

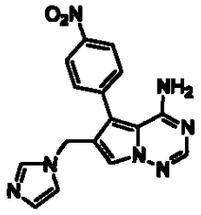
461

□8,64 (s, 1H), 8,06 (s, 1H), 7,75 (s, 1H), 7,08 (d, *J* = 8,7 Hz, 2H), 6,66 (d, *J* = 8,9 Hz, 2H); EM $[M+H]^+$ = 294,2; LCMS TR = 0,21 min.

Intermediario AE: Preparación de 5-(4-amino-fenil)-6-imidazol-1-ilmetil-pirrolo[2,1-f][1,2,4]triazin-4-ilamina



Paso 1: Preparación de 6-imidazol-1-ilmetil-5-(4-nitro-fenil)-pirrolo-[2,1-f][1,2,4]triazin-4-ilamina



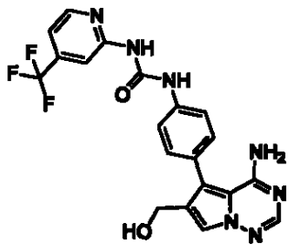
El procedimiento utilizado para la preparación de 6-(metoximetil)-5-(4-nitrofenil)pirrolo[2,1-f][1,2,4]triazin-4-amina (Intermediario U Paso 1) se utilizó para preparar el compuesto del título sustituyendo imidazol con metanol. ^{1}H-RMN (Acetona-d_6) δ 8,22 (d, *J* = 8,8 Hz, 2H), 7,77 (s, 1H), 7,66 (s, 1H), 7,54 (d, *J* = 8,8 Hz, 2H), 7,27 (s, 1H), 6,82 (s, 1H), 6,73 (s, 1H), 5,14 (s, 2H); EM $[M+H]^+$ = 336,0; LCMS TR = 0,25 min.

Paso 2: Preparación del compuesto del título

El procedimiento utilizado para la preparación del Intermediario B se utilizó para preparar el compuesto del título sustituyendo 6-imidazol-1-ilmetil-5-(4-nitro-fenil)-pirrolo[2,1-f][1,2,4]triazin-4-ilamina con el Intermediario A. EM $[M+H]^+$ = 306,0; LCMS TR = 1,02 min.

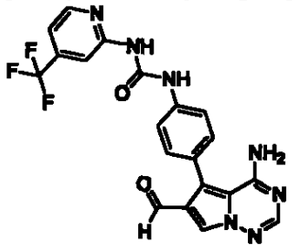
Intermediario AF: Preparación de N-(4-[4-amino-6-(hidroximetil)pirrolo[2,1-f][1,2,4]triazin-5-il]fenil)-N'-[4-(trifluorometil)piridin-2-il]urea

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El ejemplo 51 (0,25 g, 0,515 mmol) se suspendió en THF (5 ml) y se trató con solución 1M de DIBAL en THF (2 ml, 2,06 mmol). La solución resultante se agitó a temperatura ambiente durante 3 horas y se templó con solución de NH_4Cl saturado. La mezcla se agitó durante 1 hora. La mezcla se transfirió a un embudo de separación y el producto bruto se extrajo con EtOAc. La capa orgánica luego se lavó con agua y solución de NaCl saturado. La capa orgánica luego se secó sobre $MgSO_4$, se filtró y se concentró bajo presión reducida. El sólido remanente luego se trituró con EtOAc y se filtró dando 0,22 g del producto en forma de un sólido color tostado (0,496 mmol, 96% de rendimiento). ^{1}H-RMN (DMSO) δ11,66 (s, 1H), 9,86 (s, 1H), 9,73 (s, 1H), 8,53 (d, *J* = 8,7 Hz, 1H), 8,05 (s, 1H), 7,82 (s, 1H), 7,65 (s, 1H), 7,61 (d, *J* = 6,6 Hz, 2H), 7,38-7,35 (m, 3H), 4,95 (t, *J* = 5,2 Hz, 1H), 4,37 (d, *J* = 5,1 Hz, 2H); EM $[M+H]^+$ = 444,0; LCMS TR = 2,3 min.

Intermediario AG: Preparación de N-[4-(4-amino-6-formilpirrolo[2,1-*f*]-[1,2,4]triazin-5-il)fenil]-N'-[4-(trifluorometil)piridin-2-il]urea

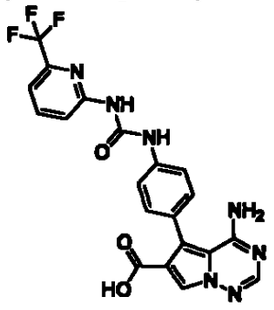


El intermediario AF (1,9 g, 4,29 mmol) se suspendió en THF (20 ml) y se trató con Dess-Martin periodinano (2,0 g , 4,71 mmol). La mezcla se agitó a temperatura ambiente durante toda la noche y se templó con solución de $NHCO_3$ saturado con $Na_2S_2O_3$. La mezcla se agitó durante 1 hora luego se transfirió a un embudo de

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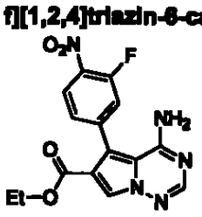
separación. El producto bruto se extrajo con EtOAc y se lavó con agua y solución de NaCl saturado. La capa orgánica luego se secó sobre $MgSO_4$, se filtró y se concentró bajo presión reducida. El sólido remanente luego se trituró con EtOAc y se filtró dando 1,6 g del producto en forma de un sólido color tostado (4,06 mmol, 95% de rendimiento). ^{1}H-RMN (DMSO) δ10,05 (bs, 1H), 9,82 (s, 1H), 9,72 (s, 1H), 8,52 (d, J = 5,1 Hz, 1H), 8,26 (s, 1H), 8,07 (s, 1H), 7,95 (s, 1H), 7,64 (d, J = 8,6 Hz, 2H), 7,44 (d, J = 8,6 Hz, 2H), 7,35 (d, J = 5,8 Hz, 1H); EM $[M+H]^+$ = 442,0; LCMS TR = 2,81 min.

Intermediario AH: Preparación de ácido 4-amino-5-{4-[({[6-(trifluorometil)-piridin-2-il]amino}carbonil)amino]fenil}pirrolo[2,1-f][1,2,4]triazin-6-carboxílico



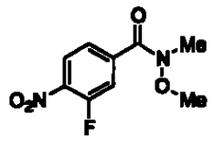
El procedimiento utilizado para la preparación del Intermediario G se utilizó para preparar el compuesto del título sustituyendo el Ejemplo 144 con el Intermediario E. ^{1}H-RMN (DMSO) δ10,29 (bs, 1H), 8,03 a 7,96 (m, 3H), 7,86 (s, 1H), 7,53 (d, J = 8,5 Hz, 2H), 7,45 (d, J = 7,0 Hz, 1H), 7,33 (d, J = 8,6 Hz, 2H); EM $[M+H]^+$ = 458,1; LCMS TR = 2,51 min.

Intermediario AI: Preparación de 4-amino-5-(3-fluoro-4-nitrofenil)-pirrolo[2,1-f][1,2,4]triazin-6-carboxilato de etilo



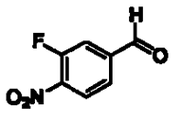
Paso 1: Preparación de 3-fluoro-N-metoxi-N-metil-4-nitrobenzamida

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A una solución de CH_2Cl_2 (1L) se agregó ácido 3-fluoro-4-nitrobenzoico (100 g, 540 mmol) y EDCI (155,3 g, 810 mmol) seguido de NMM (178 ml, 1,62 mol) y clorhidrato de N-metoximetanamina (79,0 g, 810 mmol). La solución se dejó agitar bajo N_2 a temperatura ambiente durante 17 horas. La mezcla de reacción luego se diluyó con HCl 1N (1 L), se transfirió a un embudo de separación, y se separó. La fase orgánica se lavó con NaOH 1N (2 x 500 ml) y agua (250 ml). Todas las capas acuosas se retro extrajeron con EtOAc (2 x 500 ml). Las capas orgánicas se combinaron, se secaron ($MgSO_4$), se filtraron, y se concentraron al vacío para dar 102,3 g del compuesto anterior en forma de un sólido color amarillo (448 mmol, rendimiento 83%). ^{1}H-RMN (DMSO-d_6) δ 8,22 a 8,18 (t, *J* = 8,0 Hz, 1H), 7,79 a 7,76 (d, *J* = 11,5 Hz, 1H), 7,60 a 7,58 (d, *J* = 8,3 Hz, 1H), 3,58 (s, 3H), 3,28 (s, 3H); EM $[M+H]^+$ = 229,1; LCMS TR = 2,27 min.

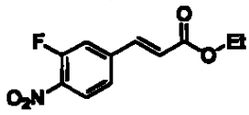
Paso 2: Preparación de 3-fluoro-4-nitrobenzaldehído de etilo



A una solución de THF (800 ml) enfriada en un baño de sal/agua helado se agregó 3-fluoro-N-metoxi-N-metil-4-nitrobenzamida seguido de la adición de DIBAL 1 M en THF mediante un embudo de adición durante 30 min. La solución se dejó agitar bajo N_2 durante 1 hora. La mezcla de reacción luego se diluyó cuidadosamente con HCl 1N (500 ml) y EtOAc (500 ml), se transfirió un embudo de separación, y se separó. La fase orgánica se lavó con HCl 1N (3 x 250 ml), NaOH 1N (2 x 250 ml), y agua (250 ml). Todas las capas acuosas se retro extrajeron con EtOAc (2 x 250 ml). Las capas orgánicas se combinaron, se secaron ($MgSO_4$), se filtraron, y se concentraron al vacío para dar 67 g del compuesto anterior (396 mmol, rendimiento 88%). ^{1}H-RMN (DMSO-d_6) δ 10,06 (s, 1H), 8,36 a 8,32 (t, *J* = 7,8 Hz, 1H), 8,06 a 8,03(d, *J* = 11,2 Hz, 1H), 7,95 a 7,93 (d, *J* = 9,1 Hz, 1H).

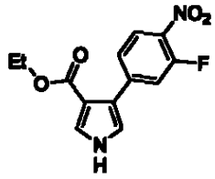
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Paso 3: Preparación de (2E)-3-(3-fluoro-4-nitrofenil)acrilato de etilo



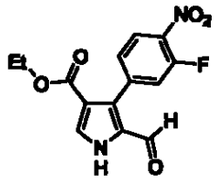
El procedimiento utilizado para la preparación del Intermediario H Paso 3 se utilizó para preparar el compuesto del título sustituyendo 3-fluoro-4-nitrobenzaldehído de etilo con 4-amino-5-(4-nitrofenil)pirrolo[2,1-f][1,2,4]triazin-6-carbaldehído. ^{1}H-RMN (DMSO-d_6) δ 8,17 a 8,13 (t, *J* = 8,2 Hz, 1H), 8,04 a 8,01 (d, *J* = 12,7 Hz, 1H), 7,79 a 7,77 (d, *J* = 8,4 Hz, 1H), 7,71 a 7,67 (d, *J* = 16,1 Hz, 1H), 6,93 a 6,87 (d, *J* = 15,9 Hz, 1H), 4,24 a 4,18 (q, *J* = 7,1 Hz, 2H), 1,29 a 1,25 (t, *J* = 7,1 Hz, 3H); **LCMS TR** = 3,16.

Paso 4: Preparación de 4-(3-fluoro-4-nitrofenil)-1H-pirrol-3-carboxilato de etilo



El procedimiento utilizado para la preparación del Intermediario A Paso 1 se utilizó para preparar el compuesto del título sustituyendo (2E)-3-(3-fluoro-4-nitrofenil)acrilato de etilo con (2E)-3-(4-nitrofenil)acrilato. ^{1}H-RMN (DMSO-d_6) δ 11,86 (s, 1H), 8,10 a 8,06 (t, *J* = 8,5 Hz, 1H), 7,74 a 7,71 (d, *J* = 13,5 Hz, 1H), 7,57 a 7,54 (m, 2H), 7,31 a 7,30 (m, 1H), 4,18 a 4,13 (q, *J* = 7,1 Hz, 2H), 1,25 a 1,21 (t, *J* = 7,0 Hz, 3H); **LCMS TR** = 3,05 min.

Paso 5: Preparación de 4-(3-fluoro-4-nitrofenil)-5-formil-1H-pirrol-3-carboxilato de etilo

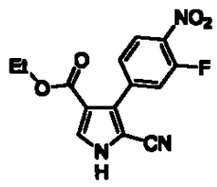


El procedimiento utilizado para la preparación del Intermediario A Paso 2 se utilizó para preparar el compuesto del título sustituyendo 4-(3-fluoro-4-nitrofenil)-1H-

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pirrol-3-carboxilato de etilo con 4-(4-nitrofenil)-1*H*-pirrol-3-carboxilato de etilo. ^{1}H-RMN (DMSO-d_6) δ 12,99 (s, 1H), 9,33 (s, 1H), 8,17 a 8,13 (t, *J* = 8,2 Hz, 1H), 7,81 a 7,74 (m, 2H), 7,52 a 7,50 (d, *J* = 6,6 Hz, 1H), 4,13 a 4,07 (q, *J* = 7,2 Hz, 2H), 1,16 a 1,13 (t, *J* = 7,0 Hz, 3H); **LCMS TR** = 2,92.

Paso 6: Preparación de 5-ciano-4-(3-fluoro-4-nitrofenil)-1H-pirrol-3-carboxilato de etilo



El procedimiento utilizado para la preparación del Intermediario A Paso 3 se utilizó para preparar el compuesto del título sustituyendo 4-(3-fluoro-4-nitrofenil)-5-formil-1H-pirrol-3-carboxilato de etilo con 5-formil-4-(nitrofenil)-1*H*-pirrol-3-carboxilato. ^{1}H-RMN (DMSO-d_6) δ13,29 (s, 1H), 8,22 a 8,18 (t, *J* = 8,2 Hz, 1H), 7,91 (s, 1H), 7,74 a 7,71 (d, *J* = 10,9 Hz, 1H), 7,51 a 7,50 (d, *J* = 6,5 Hz, 1H), 4,16 a 4,10 (q, *J* = 7,0 Hz, 2H), 1,18 a 1,15 (t, *J* = 7,0 Hz, 3H).

Paso 7: Preparación de 1-amino-5-ciano-4-(3-fluoro-4-nitrofenil)-1H-pirrol-3-carboxilato de etilo



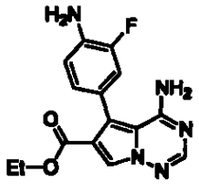
El procedimiento utilizado para la preparación del Intermediario A Paso 5 se utilizó para preparar el compuesto del título sustituyendo etilo 5-ciano-4-(3-fluoro-4-nitrofenil)-1H-pirrol-3-carboxilato con 5-ciano-4-(nitrofenil)-1*H*-pirrol-3-carboxilato de etilo. ^{1}H-RMN (DMSO-d_6) δ8,23 8,21 (t, *J* = 8,3 Hz, 1H), 7,72 (s, 1H), 7,69 (d, *J* = 1,8 Hz, 1H), 7,49 a 7,47 (d, *J* = 8,5 Hz, 1H), 6,72 (s, 2H).

Paso 8: Preparación del compuesto del título

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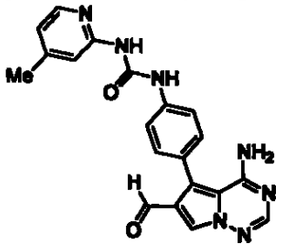
A una solución de EtOH (75 ml) se agregó 1-amino-5-ciano-4-(3-fluoro-4-nitrofenil)-1H-pirrol-3-carboxilato de etilo (1,68 g, 5,28 mmol) y acetato de formamidina (5,49 g, 52,8 mmol). La solución se calentó a 80 °C durante 17 h. Al enfriarse a temperatura ambiente la solución se trató con agua y se formó un precipitado el cual se filtró y se lavó con agua adicional. El sólido luego se suspendió en DCM y Et_2O. El sólido se recolectó y se lavó con Et_2O dando 1,22 g de un sólido color amarillo-naranja (3,52 mmol, rendimiento 67%). ^{1}H-RMN (DMSO-d_6) δ 8,20 (s, 1H), 8,18 a 8,14 (t, *J* = 8,2 Hz, 1H), 7,97 (a, 1H), 7,66 a 7,63 (d, *J* = 12,4 Hz, 1H), 7,41 a 7,39 (d, *J* = 8,4 Hz, 1H), 4,12 a 4,07 (q, *J* = 7,0 Hz, 2H), 1,13 a 1,10 (t, *J* = 7,0 Hz, 3H); EM $[M+H]^+$ = 346,2; LCMS TR = 2,77 min.

Intermediario AJ: Preparación de 4-amino-5-(4-amino-3-fluorofenil)pirrolo[2,1-f][1,2,4]triazin-6-carboxilato de etilo



El procedimiento utilizado para la preparación del intermediario B se utilizó para preparar el compuesto del título sustituyendo el intermediario 2 con el intermediario A. ^{1}H-RMN (DMSO-d_6) δ8,07 (s, 1H), 7,90 (s, 1H), 7,04 a 7,01 (d, *J* = 12,3 Hz, 1H), 6,86 a 6,85 (m, 2H), 6,81 a 6,77 (m, 1H), 5,36 (s, 2H), 4,11 a 4,06 (q, *J* = 7,1 Hz, 2H), 1,15 a 1,11 (t, *J* = 7,0 Hz, 3H); EM $[M+H]^+$ = 316,1; LCMS TR = 2,16 min.

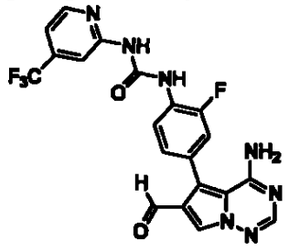
Intermediario AK: Preparación de N-[4-(4-amino-6-formilpirrolo[2,1-f]-[1,2,4]triazin-5-il)fenil]-N'-(4-metilpiridin-2-il)urea



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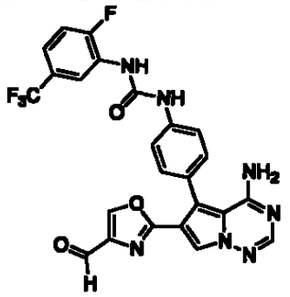
El procedimiento utilizado para la preparación del intermediario F se utilizó para preparar el compuesto del título sustituyendo el Ejemplo 258 con el intermediario E. ^{1}H-RMN (DMSO-d_6) δ 10,90 (s, 1H), 9,74 (s, 1H), 9,48 (s, 1H), 8,26 (s, 1H), 8,15 a 8,14 (d, *J* = 5,2 Hz, 1H), 7,96 (s, 1H), 7,68 a 7,66 (d, *J* = 8,6 Hz, 2H), 7,45 a 7,43 (d, *J* = 8,4 Hz, 2H), 7,28 (s, 1H), 6,87 a 6,85 (m, 1H), 2,30 (s, 3H); EM $[M+H]^+$ = 386,1; LCMS TR = 2,09 min.

Intermediario AL: Preparación de N-[4-(4-amino-6-formilpirrolo[2,1-*f*]-[1,2,4]triazin-5-il)-2-fluorofenil]-N'-[4-(trifluorometil)piridin-2-il]urea



El procedimiento utilizado para la preparación del intermediario F se utilizó para preparar el compuesto del título sustituyendo el Ejemplo 242 con el intermediario E. ^{1}H-RMN (DMSO-d_6) δ10,16 (s, 1H), 10,13 a 10,08 (br s, 1H), 9,76 (s, 1H), 8,55 a 8,54 (d, *J* = 5,3 Hz, 1H), 8,34 a 8,29 (t, *J* = 8,6 Hz, 1H), 8,28 (s, 1H), 8,01 (s, 1H), 7,97 (s, 1H), 7,48 a 7,45 (d, *J* = 11,2 Hz, 1H), 7,39 a 7,38 (d, *J* = 5,7 Hz, 1H), 7,29 a 7,27 (d, *J* = 8,1 Hz, 1H); EM $[M+H]^+$ = 459,9; LCMS TR = 2,96 min.

Intermediario AM: Preparación de N-(4-[4-amino-6-(4-formil-1,3-oxazol-2-il)-pirrolo[2,1-*f*][1,2,4]triazin-5-il]fenil)-N'-[2-fluoro-5-(trifluorometil)fenil]urea

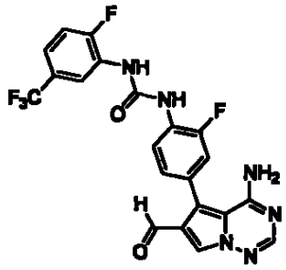


El procedimiento utilizado para la preparación del intermediario F se utilizó para preparar el compuesto del título sustituyendo el Ejemplo 237 con el

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Intermediario E. ^{1}H-RMN (DMSO-d_6) δ9,79 (s, 1H), 9,37 (s, 1H), 8,97 (s, 1H), 8,87 (s, 1H), 8,63 a 8,61 (d, J = 7,5 Hz, 1H), 8,34 (s, 1H), 7,96 (s, 1H), 7,60 a 7,58 (d, J = 8,6 Hz, 2H), 7,53 a 7,48 (m, 1H), 7,42 a 7,40 (m, 3H); EM $[M+H]^+$ = 526,1; LCMS TR = 2,93 min.

Intermediario AN: Preparación de N-[4-(4-amino-6-formilpirrolo[2,1-f][1,2,4]triazin-5-il)-2-fluorofenil]-N'-[2-fluoro-5-(trifluorometil)fenil]urea



El procedimiento utilizado para la preparación del Intermediario F se utilizó para preparar el compuesto del título sustituyendo el Ejemplo 249 con el Intermediario E. ^{1}H-RMN (DMSO-d_6) δ9,75 (s, 1H), 9,45 (s, 1H), 9,33 (s, 1H), 8,65 a 8,64 (d, J = 7,1 Hz, 1H), 8,34 a 8,29 (m, 2H), 7,97 (s, 1H), 7,54 a 7,40 (m, 3H), 7,27 a 7,25 (d, J = 9,4 Hz, 1H); EM $[M+H]^+$ = 477,1; LCMS TR = 3,07 min.

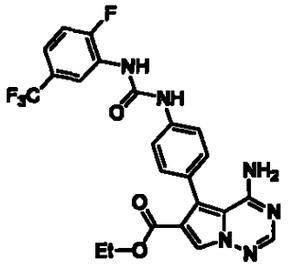
Intermediario AO: Preparación de {4-[4-amino-6-(1,3-oxazol-5-il)pirrolo[2,1-f][1,2,4]triazin-5-il]fenil}carbamato de fenilo



El procedimiento utilizado para la preparación del Intermediario C se utilizó para preparar el compuesto del título sustituyendo el Intermediario AB con el Intermediario B. ^{1}H-RMN (DMSO-d_6) δ 10,48 (s, 1H), 8,29 (s, 1H), 8,09 (s, 1H), 7,90 (s, 1H), 7,67 a 7,65 (d, J = 8,4 Hz, 2H), 7,45 a 7,38 (m, 4H), 7,28 a 7,23 (m, 3H), 6,54 (s, 1H); EM $[M+H]^+$ = 413,1; LCMS TR = 2,51 min.

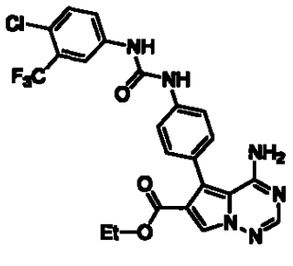
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Ejemplo 1: Preparación de 4-amino-5-{4-[({[2-fluoro-5-(trifluorometil)-fenil]amino}carbonil)amino]fenil}pirrolo[2,1-*f*][1,2,4]triazin-6-carboxilato de etilo



A una solución de DCE (2 ml) se agregó el intermediario B (75 mg, 0,25 mmol) seguido de 1-fluoro-2-isocianato-4-(trifluorometil)benceno (52 mg, 0,25 mmol). La reacción se agitó a temperatura ambiente durante 2 horas. La solución se concentró al vacío hasta sequedad y luego se purificó por HPLC preparativa (10-90% de ACN/H_2O con 0,1% de TFA). Las fracciones resultantes se transfirieron a un embudo de separación, se diluyeron con EtOAc (20 ml), se lavaron con $NaHCO_3$ acuoso saturado (20 ml) y H_2O (20 ml). La capa orgánica se aisló, se secó ($MgSO_4$), se filtró, y se concentró hasta sequedad para dar 30 mg del compuesto anterior (0,060 mmol, rendimiento 24%) ^{1}H-RMN (DMSO-d_6) δ9,33 (s, 1H), 8,95 (d, *J* = 2,3 Hz, 1H), 8,63 a 8,61 (m, 1H), 8,13 (s, 1H), 8,07 (br s, 1H), 7,93 (s, 1H), 7,56 a 7,53 (m, 2H), 7,51 a 7,48 (m, 1H), 7,40 (br s, 1H), 7,34 a 7,32 (m, 2H), 5,09 (br s, 1H), 4,11 a 4,06 (q, *J* = 6,9 Hz, 2H), 1,13 a 1,10 (t, *J* = 7,1 Hz, 3H); EM $[M+H]^+$ = 503; LCMS TR = 3,22 min; TLC R_f = 0,15 (95:5 v/v CH_2Cl_2-MeOH).

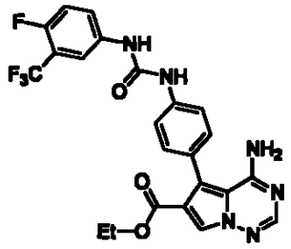
Ejemplo 2: Preparación de 4-amino-5-{4-[({[4-cloro-3-(trifluorometil)-fenil]amino}carbonil)amino]fenil}pirrolo[2,1-*f*][1,2,4]triazin-6-carboxilato de etilo



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El procedimiento utilizado para la preparación del Ejemplo 1 se utilizó para preparar el compuesto del título sustituyendo 1-cloro-4-isocianato-2-(trifluorometil)benceno con 1-fluoro-2-isocianato-4-(trifluorometil)benceno y purificando por cromatografía de columna (5:4:1 v/v/v CH_2Cl_2-EtOAc-MeOH). ^{1}H-RMN (DMSO-d_6) δ9,22 (br s, 1H), 9,02 (br s, 1H), 8,12 (s, 1H), 8,11 (d, *J* = 2,4 Hz, 1H), 7,92 (s, 1H), 7,63 (d, *J* = 2,3 Hz, 1H), 7,62 (s, 1H), 7,55 a 7,53 (m, 2H), 7,32 a 7,30 (m, 2H), 4,10 a 4,05 (q, *J* = 7,1 Hz, 2H), 1,12 a 1,09 (t, *J* = 7,0 Hz, 3H); EM $[M+H]^+$ = 519; LCMS TR = 3,06 min; TLC R_f = 0,48 (5:4:1 v/v/v CH_2Cl_2-EtOAc-MeOH).

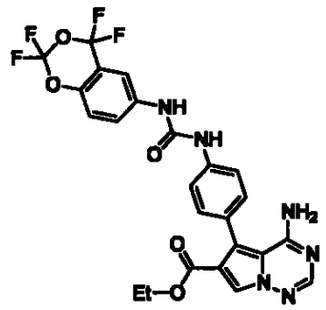
Ejemplo 3: Preparación de 4-amino-5-{4-[({[4-fluoro-3-(trifluorometil)-fenil]amino}carbonil)amino]fenil}pirrolo[2,1-f][1,2,4]triazin-6-carboxilato de etilo



A una solución de THF (1 ml) se agregó el intermediario C (55 mg, 0,13 mmol) seguido de 4-fluoro-3-(trifluorometil)anilina (30 µl, 0,24 mmol) y trietilamina (55 µl, 0,40 mmol). La reacción se agitó a 40°C durante 48 horas. La solución se concentró al vacío hasta sequedad y luego se purificó por HPLC preparativa (10-100% de ACN/H_2O con 0,1% de TFA). Las fracciones resultantes se combinaron, se concentraron al vacío, se diluyeron con EtOAc (5 ml), y se lavaron con Na_2CO_3 acuoso saturado (5 ml). La capa acuosa se retro extrajo con EtOAc (5 ml). La capa orgánica se combinó, se secó (Na_2SO_4), se filtró, y se concentró hasta sequedad para dar 37 mg del compuesto anterior (0,074 mmol, rendimiento 56%). ^{1}H-RMN (CD_3OD) δ 8,08 (s, 1H), 7,92 (dd, *J* = 6,4, 2,7 Hz, 1H), 7,84 (s, 1H), 7,69 a 7,62 (m, 1H), 7,57 (d, *J* = 8,3 Hz, 2H), 7,36 (d, *J* = 8,7 Hz, 2H), 7,26 (t, *J* = 8,7 Hz, 1H), 4,10 (q, *J* = 7,1 Hz, 2H), 1,16 (t, *J* = 7,1 Hz, 3H); EM $[M+H]^+$ = 503; LCMS TR = 3,02 min.

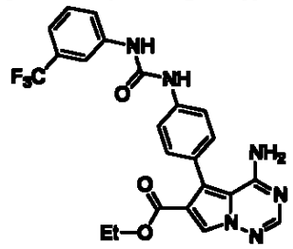
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Ejemplo 4: Preparación de 4-amino-5-[4-({[(2,2,4,4-tetrafluoro-4*H*-1,3-benzodioxin-6-il)amino]carbonil}amino)fenil]pirrolo[2,1-f][1,2,4]triazin-6-carboxilato de etilo



El procedimiento utilizado para la preparación del Ejemplo 3 se utilizó para preparar el compuesto del título sustituyendo el intermediario D con el intermediario C, y 2,2,4,4-tetrafluoro-4*H*-1,3-benzodioxin-6-amina con 4-fluoro-3-(trifluorometil)anilina. ^{1}H-RMN (CD_3OD) δ 8,38 (s, 1H), 8,02 (s, 1H), 8,01 (d, *J* = 2,2 Hz, 1H), 7,67 (dd, *J* = 8,5, 2,2 Hz, 1H), 7,62 (d, *J* = 8,2 Hz, 2H), 7,42 (d, *J* = 8,2 Hz, 2H), 7,24 (d, *J* = 8,4 Hz, 1H), 4,17 (q, *J* = 7,2 Hz, 2H), 1,16 (t, *J* = 7,2 Hz, 3H); EM $[M+H]^+$ = 547; LCMS TR = 3,29 min.

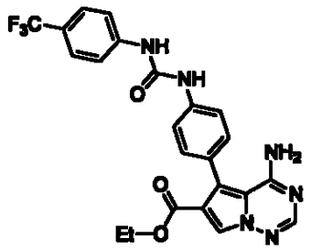
Ejemplo 5: Preparación de 4-amino-5-{4-[({[3-(trifluorometil)fenil]-amino}carbonil)amino]fenil}pirrolo[2,1-f][1,2,4]triazin-6-carboxilato de etilo



El procedimiento utilizado para la preparación del Ejemplo 3 se utilizó para preparar el compuesto del título sustituyendo 3-(trifluorometil)anilina con 4-fluoro-3-(trifluorometil)anilina. ^{1}H-RMN (CD_3OD) δ 8,08 (s, 1H), 7,93 (br s, 1H), 7,84 (s, 1H), 7,63 (d, *J* = 8,4 Hz, 1H), 7,58 (d, *J* = 8,7 Hz, 2H), 7,48 (t, *J* = 8,0 Hz, 1H), 7,38 (d, *J* =

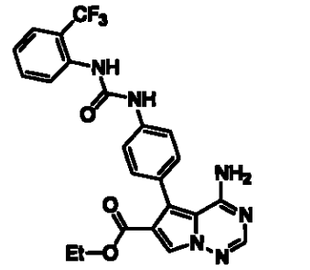
8,4 Hz, 2H), 7,30 (d, *J* = 8,2 Hz, 1H), 4,10 (q, *J* = 7,3 Hz, 2H), 1,16 (t, *J* = 7,3 Hz, 3H); EM $[M+H]^+$ = 485; LCMS TR = 3,43 min.

Ejemplo 6: Preparación de 4-amino-5-{4-[({[4-(trifluorometil)fenil]amino}-carbonil)amino]fenil}pirrolo[2,1-*f*][1,2,4]triazin-6-carboxilato de etilo



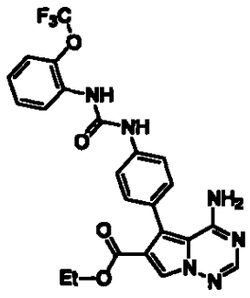
El procedimiento utilizado para la preparación del Ejemplo 3 se utilizó para preparar el compuesto del título sustituyendo 4-(trifluorometil)anilina con 4-fluoro-3-(trifluorometil)anilina. ^{1}H-RMN (CD_3OD) δ 8,07 (s, 1H), 7,83 (s, 1H), 7,66 (d, *J* = 8,3 Hz, 2H), 7,60 a 7,55 (m, 4H), 7,36 (d, *J* = 8,6 Hz, 2H), 4,14 (q, *J* = 7,2 Hz, 2H), 1,16 (t, *J* = 7,2 Hz, 3H); EM $[M+H]^+$ = 485; LCMS TR = 3,47 min.

Ejemplo 7: Preparación de 4-amino-5-{4-[({[2-(trifluorometil)fenil]amino}-carbonil)amino]fenil}pirrolo[2,1-*f*][1,2,4]triazin-6-carboxilato de etilo



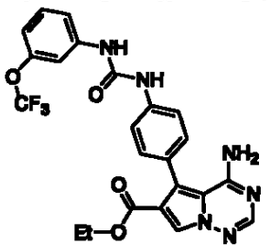
El procedimiento utilizado para la preparación del Ejemplo 3 se utilizó para preparar el compuesto del título sustituyendo 2-(trifluorometil)anilina con 4-fluoro-3-(trifluorometil)anilina. ^{1}H-RMN (CD_3OD) δ 8,07 (s, 1H), 7,96 (d, *J* = 8,7 Hz, 1H), 7,83 (s, 1H), 7,70 a 7,56 (m, 4H), 7,37 (d, *J* = 8,7 Hz, 2H), 7,30 (t, *J* = 7,9 Hz, 1H), 4,11 (q, *J* = 7,1 Hz, 2H), 1,16 (t, *J* = 7,1 Hz, 3H); EM $[M+H]^+$ = 485; LCMS TR = 2,80 min.

Ejemplo 8: Preparación de 4-amino-5-{4-[({[2-(trifluorometoxi)fenil]amino}-carbonil)amino]fenil}pirrolo[2,1-*f*][1,2,4]triazin-6-carboxilato de etilo



El procedimiento utilizado para la preparación del Ejemplo 3 se utilizó para preparar el compuesto del título sustituyendo 2-(trifluorometoxi)anilina con 4-fluoro-3-(trifluorometil)anilina. ^{1}H-RMN (CD_3OD) δ 8,26 (dd, *J* = 8,5, 2,1 Hz, 1H), 8,07 (s, 1H), 7,83 (s, 1H), 7,59 (d, *J* = 8,6 Hz, 2H), 7,40 a 7,28 (m, 4H), 7,14 a 7,07 (m, 1H), 4,08 (q, *J* = 7,2 Hz, 2H), 1,16 (t, *J* = 7,2 Hz, 3H); EM $[M+H]^+$ = 501; LCMS TR = 3,07 min.

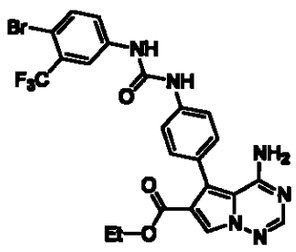
Ejemplo 9: Preparación de 4-amino-5-{4-[({[3-(trifluorometoxi)fenil]amino}-carbonil)amino]fenil}pirrolo[2,1-f][1,2,4]triazin-6-carboxilato de etilo



El procedimiento utilizado para la preparación del Ejemplo 3 se utilizó para preparar el compuesto del título sustituyendo 3-(trifluorometoxi)anilina con 4-fluoro-3-(trifluorometil)anilina. ^{1}H-RMN (CD_3OD) δ 8,07 (s, 1H), 7,83 (s, 1H), 7,64 (br s, 1H), 7,56 (d, *J* = 8,4 Hz, 2H), 7,39 a 7,28 (m, 5H), 4,10 (q, *J* = 7,1 Hz, 2H), 1,57 (t, *J* = 7,1 Hz, 3H); EM $[M+H]^+$ = 501; LCMS TR = 3,08 min.

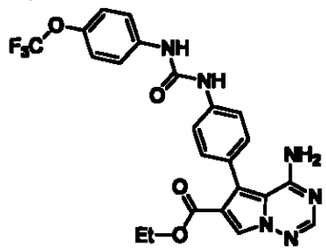
Ejemplo 10: Preparación de 4-amino-5-{4-[({[4-bromo-3-(trifluorometil)fenil]-amino}carbonil)amino]fenil}pirrolo[2,1-f][1,2,4]triazin-6-carboxilato de etilo

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El procedimiento utilizado para la preparación del Ejemplo 3 se utilizó para preparar el compuesto del título sustituyendo 4-bromo-3-(trifluorometil)anilina con 4-fluoro-3-(trifluorometil)anilina. ^{1}H-RMN (CD_3OD) δ 8,07 (s, 1H), 8,01 (d, *J* = 2,5 Hz, 1H), 7,83 (s, 1H), 7,68 (d, *J* = 8,8 Hz, 1H), 7,60 a 7,54 (m, 3H), 7,36 (d, *J* = 8,5 Hz, 2H), 4,08 (q, *J* = 7,2 Hz, 2H), 1,16 (t, *J* = 7,2 Hz, 3H); EM $[M+H]^+$ = 563; LCMS TR = 3,19 min.

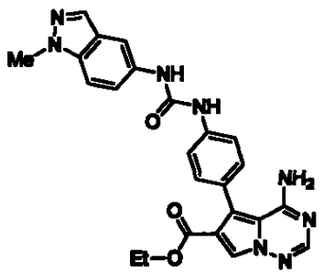
Ejemplo 11: Preparación de 4-amino-5-{4-[({[4-(trifluorometoxi)fenil]amino}-carbonil)amino]fenil}pirrolo[2,1-*f*][1,2,4]triazin-6-carboxilato de etilo



El procedimiento utilizado para la preparación del Ejemplo 3 se utilizó para preparar el compuesto del título sustituyendo 4-(trifluorometoxi)anilina con 4-fluoro-3-(trifluorometil)anilina. ^{1}H-RMN (CD_3OD) δ 8,07 (s, 1H), 7,83 (s, 1H), 7,57 (d, *J* = 7,3 Hz, 2H), 7,54 (d, *J* = 6,8 Hz, 2H), 7,35 (d, *J* = 8,5 Hz, 2H), 7,20 (d, *J* = 8,8 Hz, 2H), 4,10 (q, *J* = 7,2 Hz, 2H), 1,14 (t, *J* = 7,2 Hz, 3H); EM $[M+H]^+$ = 501; LCMS TR = 3,11 min.

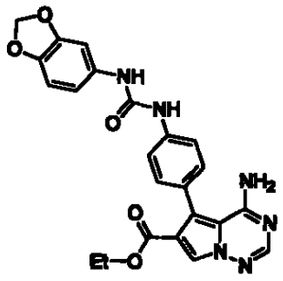
Ejemplo 12: Preparación de 4-amino-5-[4-({[(1-metil-1*H*-indazol-5-il)amino]-carbonil}amino)fenil]pirrolo[2,1-*f*][1,2,4]triazin-6-carboxilato de etilo

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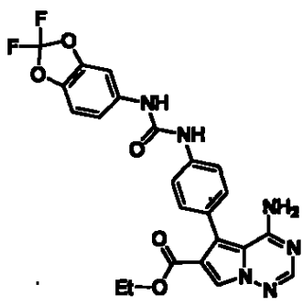
El procedimiento utilizado para la preparación del Ejemplo 3 se utilizó para preparar el compuesto del título sustituyendo 1-metil-1*H*-indazol-5-amina con 4-fluoro-3-(trifluorometil)anilina. ^{1}H-RMN (CD_3OD) δ 8,12 (s, 1H), 7,93 (d, *J* = 5,6 Hz, 2H), 7,91 (s, 1H), 7,59 a 7,51 (m, 3H), 7,36 (d, *J* = 8,6 Hz, 1H), 7,29 (d, *J* = 8,6 Hz, 2H), 4,07 (q, *J* = 7,2 Hz, 2H), 4,00 (s, 3H), 1,09 (t, *J* = 7,2 Hz, 3H); EM $[M+H]^+$ = 471; LCMS TR = 2,90 min.

Ejemplo 13: Preparación de 4-amino-5-(4-[[(1,3-benzodioxol-5-ilamino)-carbonil]amino)fenil)pirrolo[2,1-*f*][1,2,4]triazin-6-carboxilato de etilo



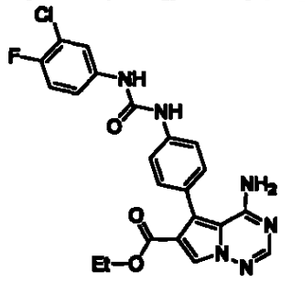
El procedimiento utilizado para la preparación del Ejemplo 3 se utilizó para preparar el compuesto del título sustituyendo 1,3-benzodioxol-5-amina con 4-fluoro-3-(trifluorometil)anilina. ^{1}H-RMN (CD_3OD) δ 8,08 (s, 1H), 7,84 (s, 1H), 7,55 (d, *J* = 9,0 Hz, 2H), 7,35 (d, *J* = 9,0 Hz, 2H), 7,13 (t, *J* = 1,4Hz, 1H), 6,92 (br s, 1H), 6,76 (d, *J* = 1,2 Hz, 2H), 5,92 (s, 2H), 4,08 (q, *J* = 7,1 Hz, 2H), 1,16 (t, *J* = 7,1 Hz, 3H); EM $[M+H]^+$ = 461; LCMS TR = 3,04 min.

Ejemplo 14: Preparación de 4-amino-5-[4-({[(2,2-difluoro-1,3-benzodioxol-5-il)amino]carbonil}amino)fenil]pirrolo[2,1-*f*][1,2,4]triazin-6-carboxilato de etilo



El procedimiento utilizado para la preparación del Ejemplo 3 se utilizó para preparar el compuesto del título sustituyendo 2,2-difluoro-1,3-benzodioxol-5-amina con 4-fluoro-3-(trifluorometil)anilina. ^{1}H-RMN (CD_3OD) δ 8,08 (s, 1H), 7,84 (s, 1H), 7,59 (d, *J* = 2,1 Hz, 1H), 7,56 (d, *J* = 8,9 Hz, 2H), 7,36 (d, *J* = 8,9 Hz, 2H), 7,12 (d, *J* = 8,7 Hz, 1H), 7,03 (dd, *J* = 8,7, 2,1 Hz, 1H), 6,92 (br s, 1H), 4,09 (q, *J* = 7,2 Hz, 2H), 1,15 (t, *J* = 7,2 Hz, 3H); EM $[M+H]^+$ = 497; LCMS TR = 3,44 min.

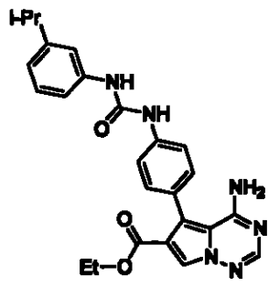
Ejemplo 15: Preparación de 4-amino-5-[4-({[(3-cloro-4-fluorofenil)amino]-carbonil}amino)fenil]pirrolo[2,1-f][1,2,4]triazin-6-carboxilato de etilo



El procedimiento utilizado para la preparación del Ejemplo 3 se utilizó para preparar el compuesto del título sustituyendo 3-cloro-4-fluoroanilina con 4-fluoro-3-(trifluorometil)anilina. ^{1}H-RMN (CD_3OD) δ 8,08 (s, 1H), 7,84 (s, 1H), 7,73 (dd, *J* = 6,3, 2,4 Hz, 1H), 7,56 (d, *J* = 8,8 Hz, 2H), 7,36 (d, *J* = 8,4 Hz, 2H), 7,33 a 7,27 (m, 1H), 7,17 (t, *J* = 9,2 Hz, 1H), 4,09 (q, *J* = 7,1 Hz, 2H), 1,16 (t, *J* = 7,1 Hz, 3H); EM $[M+H]^+$ = 469; LCMS TR = 3,37 min.

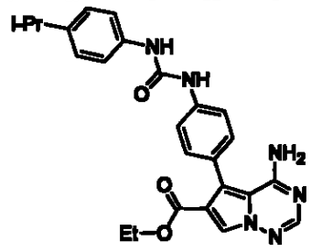
Ejemplo 16: Preparación de 4-amino-5-[4-({[(3-isopropilfenil)amino]carbonil}-amino)fenil]pirrolo[2,1-f][1,2,4]triazin-6-carboxilato de etilo

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El procedimiento utilizado para la preparación del Ejemplo 3 se utilizó para preparar el compuesto del título sustituyendo 3-isopropilanilina con 4-fluoro-3-(trifluorometil)anilina. ^{1}H-RMN (CD_3OD) δ 8,08 (s, 1H), 7,84 (s, 1H), 7,56 (d, *J* = 8,6 Hz, 2H), 7,39 a 7,32 (m, 3H), 7,26 a 7,19 (m, 2H), 6,92 (d, *J* = 7,2 Hz, 1H), 4,15 (q, *J* = 7,1 Hz, 2H), 1,16 (t, *J* = 7,1 Hz, 3H); EM $[M+H]^+$ = 459; LCMS TR = 3,07 min.

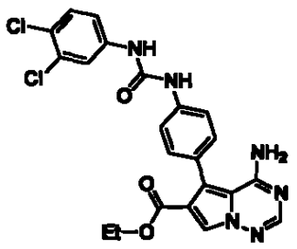
Ejemplo 17: Preparación de 4-amino-5-[4-({[(4-isopropilfenil)amino]carbonil}-amino)fenil]pirrolo[2,1-f][1,2,4]triazin-6-carboxilato de etilo



El procedimiento utilizado para la preparación del Ejemplo 3 se utilizó para preparar el compuesto del título sustituyendo 4-isopropilanilina con 4-fluoro-3-(trifluorometil)anilina. ^{1}H-RMN (CD_3OD) □8,08 (s, 1H), 7,84 (s, 1H), 7,56 (d, *J* = 8,3 Hz, 2H), 7,37 a 7,32 (m, 4H), 7,18 (d, *J* = 8,4 Hz, 2H), 4,15 (q, *J* = 7,1 Hz, 2H), 1,16 (t, *J* = 7,1 Hz, 3H); EM $[M+H]^+$ = 459; LCMS TR = 3,09 min.

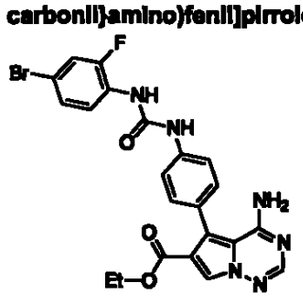
Ejemplo 18: Preparación de 4-amino-5-[4-({[(3,4-diclorofenil)amino]carbonil}-amino)fenil]pirrolo[2,1-f][1,2,4]triazin-6-carboxilato de etilo

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El procedimiento utilizado para la preparación del Ejemplo 3 se utilizó para preparar el compuesto del título sustituyendo 3,4-dicloroanilina con 4-fluoro-3-(trifluorometil)anilina. ^{1}H-RMN (CD_3OD) δ 8,09 (s, 1H), 7,84 (s, 1H), 7,82 (d, *J* = 2,1 Hz, 1H), 7,57 (d, *J* = 8,3 Hz, 2H), 7,44 a 7,29 (m, 4H), 6,92 (s, 2H), 4,15 (q, *J* = 7,2 Hz, 2H), 1,16 (t, *J* = 7,2 Hz, 3H); EM $[M+H]^+$ = 485; LCMS TR = 3,14 min.

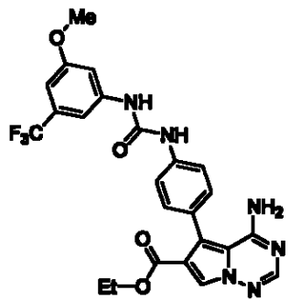
Ejemplo 19: Preparación de 4-amino-5-[4-({[(4-bromo-2-fluorofenil)amino]-carbonil}amino)fenil]pirrolo[2,1-f][1,2,4]triazin-6-carboxilato de etilo



El procedimiento utilizado para la preparación del Ejemplo 3 se utilizó para preparar el compuesto del título sustituyendo 4-bromo-2-fluoroanilina con 4-fluoro-3-(trifluorometil)anilina. ^{1}H-RMN (CD_3OD) δ 8,14 (s, 1H), 8,12 a 8,07 (m, 1H), 7,88 (s, 1H), 7,59 (d, *J* = 8,7 Hz, 2H), 7,42 a 7,27 (m, 3H), 6,92 (s, 1H), 4,15 (q, *J* = 7,1 Hz, 2H), 1,16 (t, *J* = 7,1 Hz, 3H); EM $[M+H]^+$ = 513; LCMS TR = 3,42 min.

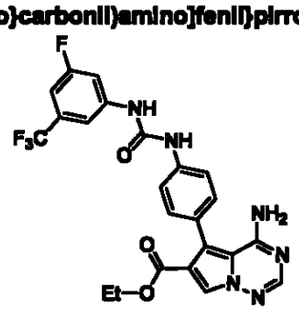
Ejemplo 20: Preparación de 4-amino-5-{4-[({[3-metoxi-5-(trifluorometil)fenil]-amino}carbonil)amino]fenil}pirrolo[2,1-f][1,2,4]triazin-6-carboxilato de etilo

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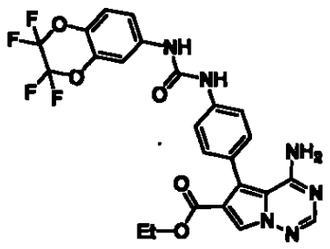
El procedimiento utilizado para la preparación del Ejemplo 3 se utilizó para preparar el compuesto del título sustituyendo 3-metoxi-5-(trifluorometil)anilina con 4-fluoro-3-(trifluorometil)anilina. ^{1}H-RMN (CD_3OD) δ 8,08 (s, 1H), 7,84 (s, 1H), 7,57 (d, *J* = 8,9 Hz, 2H), 7,40 a 7,35 (m, 4H), 6,83 (s, 1H), 4,10 (q, *J* = 7,1 Hz, 2H), 1,16 (t, *J* = 7,1 Hz, 3H); EM $[M+H]^+$ = 515; LCMS TR = 3,11 min.

Ejemplo 21: Preparación de 4-amino-5-{4-[({[3-fluoro-5-(trifluorometil)fenil]-amino}carbonil)amino]fenil}pirrolo[2,1-f][1,2,4]triazin-6-carboxilato de etilo



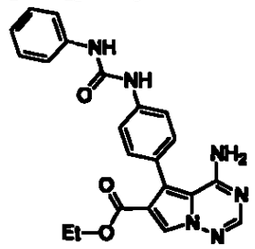
El procedimiento utilizado para la preparación del Ejemplo 3 se utilizó para preparar el compuesto del título sustituyendo 3-fluoro-5-(trifluorometil)anilina con 4-fluoro-3-(trifluorometil)anilina. ^{1}H-RMN (CD_3OD) δ 8,08 (s, 1H), 7,84 (s, 1H), 7,65 (d, *J* = 10,9 Hz, 1H), 7,59(s, 1H), 7,58 (d, *J* = 8,3 Hz, 2H), 7,38 (d, *J* = 8,5 Hz, 2H), 7,05 (d, *J* = 9,1 Hz, 1H), 4,15 (q, *J* = 7,2 Hz, 2H), 1,18 (t, *J* = 7,2 Hz, 3H); EM $[M+H]^+$ = 503; LCMS TR = 3,56 min.

Ejemplo 22: Preparación de 4-amino-5-[4-({[(2,2,3,3-tetrafluoro-2,3-dihidro-1,4-benzodioxin-6-il)amino]carbonil}amino)fenil]pirrolo[2,1-f][1,2,4]triazin-6-carboxilato de etilo



El procedimiento utilizado para la preparación del Ejemplo 3 se utilizó para preparar el compuesto del título sustituyendo 2,2,3,3-tetrafluoro-2,3-dihidro-1,4-benzodioxin-6-amina con 4-fluoro-3-(trifluorometil)anilina. ^{1}H-RMN (CD_3OD) δ 8,07 (s, 1H), 7,83 (s, 1H), 7,63 (t, J = 1,3 Hz, 1H), 7,56 (d, J = 8,7 Hz, 2H), 7,35 (d, J = 8,6 Hz, 2H), 7,20 (d, J = 1,3 Hz, 2H), 4,12 (q, J = 7,2 Hz, 2H), 1,15 (t, J = 7,2 Hz, 3H); EM $[M+H]^+$ = 547; LCMS TR = 3,66 min.

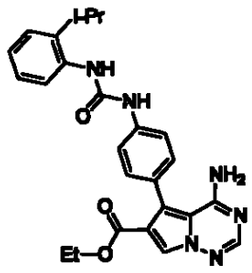
Ejemplo 23: Preparación de 4-amino-5-[4-[(anilinocarbonil)amino]fenil]-pirrolo[2,1-f][1,2,4]triazin-6-carboxilato de etilo



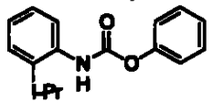
El procedimiento utilizado para la preparación del Ejemplo 3 se utilizó para preparar el compuesto del título sustituyendo anilina con 4-fluoro-3-(trifluorometil)anilina. ^{1}H-RMN (CD_3OD) δ 8,09 (s, 1H), 7,84 (s, 1H), 7,56 (d, J = 8,8 Hz, 2H), 7,44 (d, J = 8,0 Hz, 2H), 7,36 (d, J = 8,8 Hz, 2H), 7,33 a 7,27 (m, 2H), 7,03 (t, J = 7,4 Hz, 1H), 4,15 (q, J = 7,1 Hz, 2H), 1,15 (t, J = 7,1 Hz, 3H); EM $[M+H]^+$ = 417; LCMS TR = 2,53 min.

Ejemplo 24: Preparación de 4-amino-5-[4-({[(2-isopropilfenil)amino]-carbonil}amino)fenil]pirrolo[2,1-f][1,2,4]triazin-6-carboxilato de etilo

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Paso 1: Preparación de (2-isopropilfenil)carbamato de fenilo

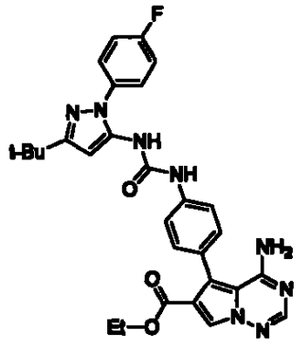


A una solución agitada de 2-isopropilanilina (200 mg, 1,5 mmol) en THF (9 ml) se agregó piridina (0,24 ml, 3,0 mmol), luego cloroformiato de fenilo (0,28 ml, 2,2 mmol) a temperatura ambiente. Parte del sólido precipitó. La mezcla se agitó a temperatura ambiente durante 4,5 h. Se agregó agua a la reacción y se extrajo con EtOAc. La solución orgánica se lavó con agua (5 ml) y se secó sobre $MgSO_4$ y luego se filtró. El filtrado se concentró al vacío y se cristalizó de EtOAc-hexanos (1:9 v/v) para dar el compuesto del título (130 mg, 34%). ^{1}H-RMN (DMSO-d_6) δ 9,45 (s, 1H), 7,44 a 7,36 (m, 2H), 7,35 a 7,28 (m, 2H), 7,25 a 7,14 (m, 5H), 3,27 (m, 1H), 1,17 (d, *J* = 6,9 Hz, 2H); TLC R_f = 0,33 (9:1 v/v hexanos-EtOAc).

Paso 2: Preparación del compuesto del título

A una solución de THF (1,5 ml) se agregó (2-isopropilfenil)carbamato de fenilo (43 mg, 0,17 mmol) seguido del intermediario B (50 mg, 0,17 mmol) y trietilamina (23 µl, 0,17 mmol). La reacción se agitó a 50 °C durante 36 horas. La solución se concentró al vacío hasta sequedad y luego se purificó por HPLC preparativa (10-100% de ACN/H_2O con 0,1% de TFA). Las fracciones resultantes se combinaron y se concentraron al vacío. Se agregó EtOAc (5 ml) y se lavó con Na_2CO_3 acuoso saturado (5 ml). La capa acuosa se retro extrajo con EtOAc (5 ml). La capa orgánica se combinó, se secó (Na_2SO_4), se filtró, y se concentró hasta sequedad para dar 19 mg del compuesto anterior (0,042 mmol, rendimiento 25%). ^{1}H-RMN (CD_3OD) δ 8,08 (s, 1H), 7,84 (s, 1H), 7,57 (d, *J* = 8,6 Hz, 2H), 7,53 a 7,49 (m, 1H), 7,38 a 7,32 (m, 3H), 7,21 a 7,16 (m, 2H), 6,92 (s, 1H), 4,09 (q, *J* = 7,1 Hz, 2H), 3,28 a 3,18 (m, 1H), 1,16 (t, *J* = 7,1 Hz, 3H); EM $[M+H]^+$ = 459; LCMS TR = 3,31 min.

Ejemplo 25: Preparación de 4-amino-5-{4-[({[3-ter-butil-1-(4-fluorofenil)-1*H*-pirazol-5-il]amino}carbonil)amino]fenil}pirrolo[2,1-*f*][1,2,4]triazin-6-carboxilato de etilo



El procedimiento utilizado para la preparación del Ejemplo 24 se utilizó para preparar el compuesto del título sustituyendo 3-*ter*-butil-1-(4-fluorofenil)-1*H*-pirazol-5-amina con 2-isopropilanilina. ^{1}H-RMN (DMSO-d_6) δ 9,15 (s, 1H), 8,44 (s, 1H), 8,12 (s, 1H), 8,05 (br s, 1H), 7,93 (s, 1H), 7,57 (dd, *J* = 9,1, 5,0 Hz, 2H), 7,49 (d, *J* = 8,6 Hz, 2H), 7,37 (t, *J* = 8,8 Hz, 2H), 7,28 (d, *J* = 9,1 Hz, 2H), 6,38 (s, 1H), 5,05 (br s, 1H), 4,02 (q, *J* = 7,1 Hz, 2H), 1,27 (s, 9H), 1,08 (t, *J* = 7,1 Hz, 3H); EM $[M+H]^+$ = 557; LCMS TR = 3,12 min.

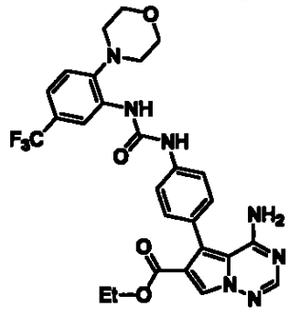
Ejemplo 26: Preparación de 4-amino-5-{4-[({[3,5-bis(trifluorometil)fenil]-amino}carbonil)amino]fenil}pirrolo[2,1-*f*][1,2,4]triazin-6-carboxilato de etilo



El procedimiento utilizado para la preparación del Ejemplo 24 se utilizó para preparar el compuesto del título sustituyendo 3,5-bis(trifluorometil)anilina durante 2-isopropilanilina. ^{1}H-RMN (CD_3OD) □ 8,11 (s, 2H), 8,09 (s, 1H), 7,86 (s, 1H), 7,60 (d,

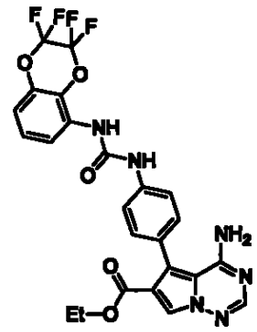
J = 8,8 Hz, 2H), 7,52 (s, 1H), 7,35 (d, *J* = 8,5 Hz, 2H), 4,07 (q, *J* = 7,1 Hz, 2H), 1,14 (t, *J* = 7,1 Hz, 3H); EM $[M+H]^+$ = 553; LCMS TR = 3,40 min.

Ejemplo 27: Preparación de 4-amino-5-(4-[({[2-morfolin-4-il-5-(trifluorometil)-fenil]amino}carbonil)amino]fenil)pirrolo[2,1-*f*][1,2,4]triazin-6-carboxilato de etilo



El procedimiento utilizado para la preparación del Ejemplo 24 se utilizó para preparar el compuesto del título sustituyendo 2-morfolin-4-il-5-(trifluorometil)anilina con 2-isopropilanilina. ^{1}H-RMN (CD_3OD) δ 8,50 (s, 1H)8,09 (s, 1H), 7,85 (s, 1H), 7,62 (d, *J* = 8,9 Hz, 2H), 7,42 a 7,29 (d, *J* = 8,7 Hz, 4H), 4,08 (q, *J* = 7,1 Hz, 2H), 3,98 a 3,93 (m, 4H), 2,98 a 2,89 (m, 4H), 1,16 (t, *J* = 7,1 Hz, 3H); EM $[M+H]^+$ = 570; LCMS TR = 3,18 min.

Ejemplo 28: Preparación de 4-amino-5-[4-({[(2,2,3,3-tetrafluoro-2,3-dihidro-1,4-benzodioxin-5-il)amino]carbonil}amino)fenil]pirrolo[2,1-*f*][1,2,4]triazin-6-carboxilato de etilo

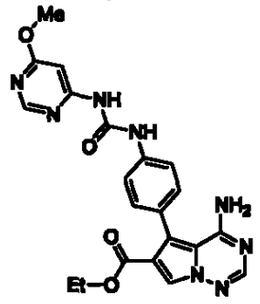


El procedimiento utilizado para la preparación del Ejemplo 24 se utilizó para preparar el compuesto del título sustituyendo 2,2,3,3-tetrafluoro-2,3-dihidro-1,4-benzodioxin-5-amina con 2-isopropilanilina. ^{1}H-RMN (CD_3OD) δ 8,10 (d, *J* = 8,0 Hz,

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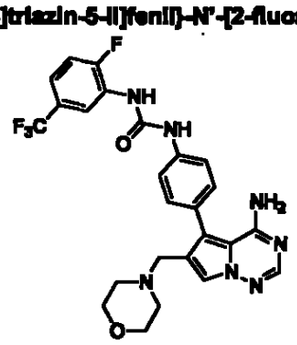
1H), 8,08 (s, 1H), 7,84 (s, 1H), 7,59 (d, *J* = 8,2 Hz, 2H), 7,38 (d, *J* = 8,2 Hz, 2H), 7,23 (t, *J* = 8,2 Hz, 1H), 6,93 (d, *J* = 8,2 Hz, 1H), 4,10 (q, *J* = 7,1 Hz, 2H), 1,16 (t, *J* = 7,1 Hz, 3H); EM $[M+H]^+$ = 547; **LCMS TR** = 3,27 min.

Ejemplo 29: Preparación de 4-amino-5-[4-({[(6-metoxipirimidin-4-il)amino]-carbonil}amino)fenil]pirrolo[2,1-*f*][1,2,4]triazin-6-carboxilato de etilo



El procedimiento utilizado para la preparación del Ejemplo 24 se utilizó para preparar el compuesto del título sustituyendo 6-metoxipirimidin-4-amina con 2-isopropilanilina. ^{1}H-RMN (DMSO-d_6) δ 9,82 (s, 1H), 9,60 (s, 1H), 8,50 (s, 1H), 8,13 (s, 1H), 7,93 (s, 1H), 7,56 (d, *J* = 8,5 Hz, 2H), 7,33 (d, *J* = 8,5 Hz, 2H), 7,09 (d, *J* = 1,1 Hz, 1H), 4,07 (q, *J* = 7,1 Hz, 2H), 3,89 (s, 3H), 1,09 (t, *J* = 7,1 Hz, 3H); EM $[M+H]^+$ = 449; **LCMS TR** = 2,94 min.

Ejemplo 30: Preparación de *N*-{4-[4-amino-6-(morfolin-4-ilmetil)pirrolo[2,1-*f*]-[1,2,4]triazin-5-il]fenil}-*N'*-[2-fluoro-5-(trifluorometil)fenil]urea

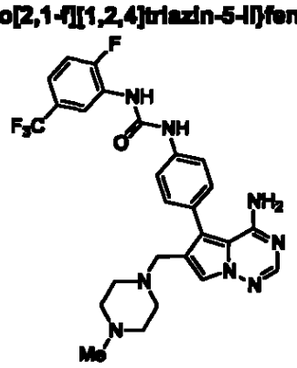


A una solución del intermediario F (40,0 mg, 0,08 mmol) en CH_2Cl_2 (3,0 ml) se agregó AcOH (0,03 ml, 0,46 mmol) y morfolina (0,01 ml, 0,11 mmol). La reacción se agitó a temperatura ambiente durante 1 hora después de lo cual se agregó

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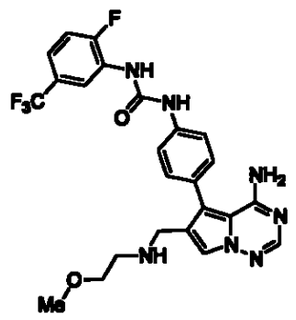
triacetoxiborohidruro de sodio (49,0 mg, 0,23 mmol). La reacción se agitó a temperatura ambiente hasta la terminación. La reacción se diluyó con CH_2Cl_2, se transfirió a un embudo de separación y se lavó con $NaHCO_3$ ac saturado (2x). La fase acuosa se retro extrajo con CH_2Cl_2 (2x). La capa orgánica se secó (Na_2SO_4) y se evaporó para dar un aceite bruto que se purificó mediante HPLC (10-90% de ACN/H_2O) para dar el compuesto del título (30 mg, 70%). ^{1}H-RMN (CD_3OD) δ 8,61 (d, J = 8,0 Hz, 1H), 7,76 (s, 1H), 7,66 (s, 1H), 7,62 (s, 1H), 7,60 (s, 1H), 7,40 (d, J = 8,0 Hz, 2H), 7,33 (d, J = 8,0 Hz, 2H), 3,65-3,62 (m, 4H), 3,48 (s, 2H), 2,40-2,36 (m, 4H); EM $[M+H]^+$ = 530; LCMS TR = 2,22 min; TLC R_f = 0,27 (1:3 v/v Acetona: CH_2Cl_2).

Ejemplo 31: Preparación de *N*-(4-[4-amino-6-[(4-metilpiperazin-1-il)metil]-pirrolo[2,1-*f*][1,2,4]triazin-5-il)fenil)-*N*'-[2-fluoro-5-(trifluorometil)fenil]urea



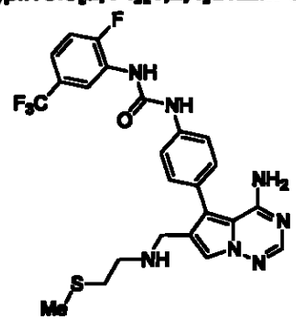
El procedimiento utilizado para la preparación del Ejemplo 30 se utilizó para preparar el compuesto del título sustituyendo 1-metilpiperazina con morfolina y purificando por TLC preparativa (20:180:1 v/v/v MeOH-CH_2Cl_2-NH_4OH). ^{1}H-RMN (CD_3OD) δ 8,61 (d, *J* = 8,0 Hz, 1H), 7,77 (s, 1H), 7,67 (s, 1H), 7,61 (d, *J* = 8,0 Hz, 2H), 7,41-7,33 (*m*, 4H), 3,53 (s, 2H), 3,35 (s, 3H), 2,50 (*br* s, 4H), 2,32 (*m*, 4H); EM $[M+H]^+$ = 543; LCMS TR = 2,15 min; TLC R_f = 0,23 (20:180:1 v/v/v MeOH-CH_2Cl_2-NH_4OH).

Ejemplo 32: Preparación de *N*-[4-(4-amino-6-[[(2-metoxietil)amino]metil)-pirrolo[2,1-*f*][1,2,4]triazin-5-il)fenil]-*N*'-[2-fluoro-5-(trifluorometil)fenil]urea



El procedimiento utilizado para la preparación del Ejemplo 30 se utilizó para preparar el compuesto del título sustituyendo 2-metoxietanamina con morfolina y purificando por MPLC (Analogix) usando 0-15% de MeOH-CH_2Cl_2. ^{1}H-RMN (CD_3OD) δ 8,61 a 8,59 (d, *J* = 7,8 Hz, 1H), 7,80 (s, 1H), 7,79 (s, 1H), 7,67 a 7,65 (d, *J* = 8,6 Hz, 2H), 7,41 a 7,39 (d, *J* = 8,6 Hz, 2H), 7,35 a 7,33 (d, *J* = 8,9 Hz, 2H), 3,99 (s, 2H), 3,48 a 3,46 (t, *J* = 5,1 Hz, 2H), 3,31 (s, 3H), 2,91 a 2,89 (t, *J* = 5,2 Hz, 2H); EM $[M+H]^+$ = 516; LCMS TR = 2,26 min; TLC R_f = 0,30 (15:85 v/v MeOH-CH_2Cl_2).

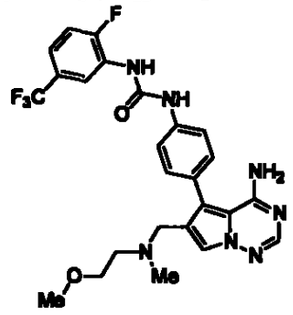
Ejemplo 33: Preparación de *N*-{4-[4-amino-6-({[2-(metiltio)etil]amino}-metil)pirrolo[2,1-*f*][1,2,4]triazin-5-il]fenil}-*N*'-[2-fluoro-5-(trifluorometil)fenil]-urea



El procedimiento utilizado para la preparación del Ejemplo 30 se utilizó para preparar el compuesto del título sustituyendo 2-(metiltio)etanamina con morfolina y purificando por MPLC (Analogix) usando 0-15% de MeOH-CH_2Cl_2. ^{1}H-RMN (CD_3OD) δ 8,62 a 8,60 (d, *J* = 7,7 Hz, 1H), 7,78 (s, 1H), 7,71 (s, 1H), 7,65 a 7,63 (d, *J* = 8,6 Hz, 2H), 7,42 a 7,40 (d, *J* = 8,5 Hz, 2H), 7,35 a 7,33 (d, *J* = 8,8 Hz, 2H), 3,80 (s, 2H), 2,75 a 2,72 (t, *J* = 6,5 Hz, 2H), 2,58 a 2,55 (t, *J* = 6,6 Hz, 2H), 1,99 (s, 3H); EM $[M+H]^+$ = 534; LCMS TR = 2,38 min; TLC R_f = 0,50 (15:85 v/v MeOH- CH_2Cl_2).

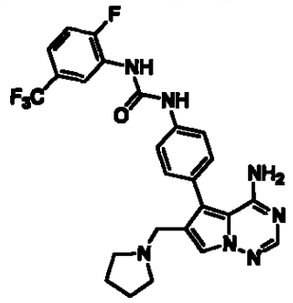
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Ejemplo 34: Preparación de *N*-[4-(4-amino-6-{[(2-metoxietil)(metil)amino]-metil}pirrolo[2,1-*f*][1,2,4]triazin-5-il)fenil]-*N'*-[2-fluoro-5-(trifluorometil)fenil]-urea



El procedimiento utilizado para la preparación del Ejemplo 30 se utilizó para preparar el compuesto del título sustituyendo 2-metoxi-*N*-metiloetanamina con morfolina y purificando por MPLC (Analogix) usando 0-15% de MeOH-CH_2Cl_2. ^{1}H-RMN (CD_3OD) δ 8,61 a 8,59 (d, *J* = 7,9 Hz, 1H), 7,80 (s, 1H), 7,78 (s, 1H), 7,66 a 7,64 (d, *J* = 8,6 Hz, 2H), 7,40 a 7,38 (d, *J* = 8,5 Hz, 2H), 7,35 a 7,32 (d, *J* = 8,9 Hz, 2H), 3,90 (s, 2H), 3,47 a 3,44 (t, *J* = 5,4 Hz, 2H), 3,29 (s, 3H), 2,79 a 2,77 (t, *J* = 5,4 Hz, 2H), 2,39 (s, 3H); EM $[M+H]^+$ = 532; LCMS TR = 2,69 min; TLC R_f = 0,16 (15:85 v/v MeOH-CH_2Cl_2).

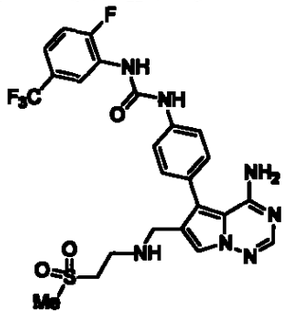
Ejemplo 35: Preparación de *N*-{4-[4-amino-6-(pirrolidin-1-ilmetil)pirrolo[2,1-*f*]-[1,2,4]triazin-5-il]fenil}-*N'*-[2-fluoro-5-(trifluorometil)fenil]urea



El procedimiento utilizado para la preparación del Ejemplo 30 se utilizó para preparar el compuesto del título sustituyendo pirrolidina con morfolina y purificando por MPLC (Analogix) usando 0-15% de MeOH-CH_2Cl_2. ^{1}H-RMN (CD_3OD) δ 8,62 a 8,60 (d, *J* = 7,8 Hz, 1H), 7,78 (s, 1H), 7,74 (s, 1H), 7,64 a 7,62 (d, *J* = 8,4 Hz, 2H),

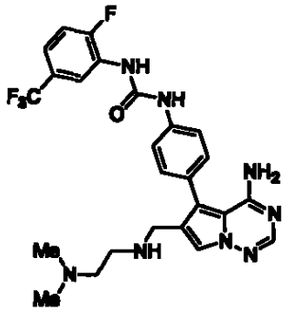
7,39 a 7,37 (d, *J* = 8,6 Hz, 2H), 7,35 a 7,33 (d, *J* = 8,8 Hz, 2H), 3,77 (s, 2H), 2,63 a 2,60 (m, 4H), 1,82 a 1,78 (m, 4H); EM $[M+H]^+$ = 514; LCMS TR = 2,69 min; TLC R_f = <0,10 (15:85 v/v MeOH-CH_2Cl_2).

Ejemplo 36: Preparación de *N*-{4-[4-amino-6-({[2-(metilsulfonil)etil]amino}-metil)pirrolo[2,1-*f*][1,2,4]triazin-5-il]fenil}-*N*'-[2-fluoro-5-(trifluorometil)fenil]-urea



El procedimiento utilizado para la preparación del Ejemplo 30 se utilizó para preparar el compuesto del título sustituyendo clorhidrato de 2-(metilsulfonil)etanamina con morfolina y purificando por MPLC (Analogix) usando 0-15% de MeOH-CH_2Cl_2. ^{1}H-RMN (CD_3OD) δ 8,62 a 8,60 (d, *J* = 7,5 Hz, 1H), 7,77 (s, 1H), 7,69 (s, 1H), 7,64 a 7,62 (d, *J* = 8,7 Hz, 2H), 7,42 a 7,40 (d, *J* = 8,9 Hz, 2H), 7,35 a 7,33 (d, *J* = 8,9 Hz, 2H), 3,77 (s, 2H), 3,22 a 3,19 (t, *J* = 6,5 Hz, 2H), 3,03 a 2,99 (t, *J* = 6,7 Hz, 2H), 2,96 (s, 3H); EM $[M+H]^+$ = 566; LCMS TR = 2,25 min; TLC R_f = 0,21 (15:85 v/v MeOH- CH_2Cl_2).

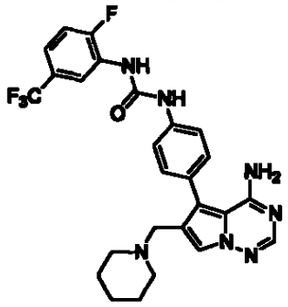
Ejemplo 37: Preparación de *N*-{4-[4-amino-6-({[2-(dimetilamino)etil]amino}-metil)pirrolo[2,1-*f*][1,2,4]triazin-5-il]fenil}-*N*'-[2-fluoro-5-(trifluorometil)fenil]-urea



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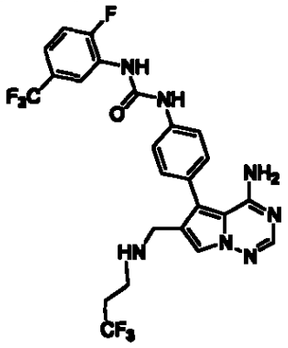
El procedimiento utilizado para la preparación del Ejemplo 30 se utilizó para preparar el compuesto del título sustituyendo *N,N*-dimetiletano-1,2-diamina con morfolina y purificando por HPLC (10-90% de ACN/H_2O). ^{1}H-RMN (CD_3OD) δ 8,62 (d, *J* = 7,4 Hz, 1H), 7,77 (s, 1H), 7,71 (s, 1H), 7,64 (d, *J* = 8,5 Hz, 2H), 7,40 (d, *J* = 8,5 Hz, 2H), 7,33 (d, *J* = 8,0 Hz, 2H), 3,73 (s, 2H), 2,61 (t, *J* = 6,5 Hz, 2H), 2,37 (t, *J* = 6,9 Hz, 2H), 2,17 (s, 6H); EM $[M+H]^+$ = 531; LCMS TR = 1,96 min.

Ejemplo 38: Preparación de *N*-{4-[4-amino-6-(piperidin-1-ilmetil)pirrolo[2,1-f]-[1,2,4]triazin-5-il]fenil}-*N'*-[2-fluoro-5-(trifluorometil)fenil]urea



El procedimiento utilizado para la preparación del Ejemplo 30 se utilizó para preparar el compuesto del título sustituyendo piperidina con morfolina y purificando mediante HPLC (10-90% de ACN/H_2O). ^{1}H-RMN (CD_3OD) δ8,63 (d, *J* = 8,2 Hz, 1H), 7,77 (s, 1H), 7,73 (s, 1H), 7,62 (d, *J* = 8,6 Hz, 2H), 7,37 (d, *J* = 8,8 Hz, 2H), 7,34 (d, *J* = 8,8 Hz, 2H), 3,50 (s, 2H), 2,36 a 2,27 (m, 4H), 1,60 a 1,50 (m, 4H), 1,40 a 1,35 (m, 2H); EM $[M+H]^+$ = 528; LCMS TR = 2,34 min.

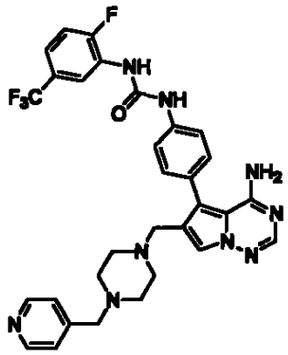
Ejemplo 39: Preparación de *N*-[4-(4-amino-6-{[(3,3,3-trifluoropropil)amino]-metil}pirrolo[2,1-f][1,2,4]triazin-5-il)fenil]-*N'*-[2-fluoro-5-(trifluorometil)fenil]-urea



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El procedimiento utilizado para la preparación del Ejemplo 30 se utilizó para preparar el compuesto del título sustituyendo 3,3,3-trifluoropropan-1-amina con morfolina y purificando por HPLC (10-90% de ACN/H_2O). ^{1}H-RMN (CD_3OD) δ8,62 (d, *J* = 7,3 Hz, 1H), 7,77 (s, 1H), 7,70 (s, 1H), 7,63 (d, *J* = 8,3 Hz, 2H), 7,39 (d, *J* = 7,9 Hz, 2H), 7,34 (d, *J* = 7,4 Hz, 2H), 3,73 (s, 2H), 2,74 (t, *J* = 7,3 Hz, 2H), 2,37 a 2,22 (m, 2H); EM $[M+H]^+$ = 556; LCMS TR = 2,41 min.

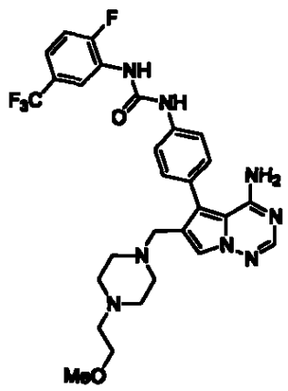
Ejemplo 40: Preparación de *N*-[4-(4-amino-6-{[4-(piridin-4-ilmetil)piperazin-1-il]metil}pirrolo[2,1-*f*][1,2,4]triazin-5-il)fenil]-*N'*-[2-fluoro-5-(trifluorometil)fenil]-urea



El procedimiento utilizado para la preparación del Ejemplo 30 se utilizó para preparar el compuesto del título sustituyendo 1-(piridin-4-ilmetil)piperazina con morfolina y purificando por HPLC (10-90% de ACN/H_2O). ^{1}H-RMN (CD_3OD) δ8,62 (d, *J* = 7,3 Hz, 1H), 8,43 (dd, *J* = 4,6, 1,6 Hz, 2H), 7,97 (s, 1H), 7,77 (s, 1H), 7,67 (s, 1H), 7,62 (d, *J* = 8,5 Hz, 2H), 7,41 a 7,31 (m, 6H), 3,54 (s, 2H), 3,51 (s, 2H), 3,32 a 3,29 (m, 4H); EM $[M+H]^+$ = 620; LCMS TR = 2,32 min.

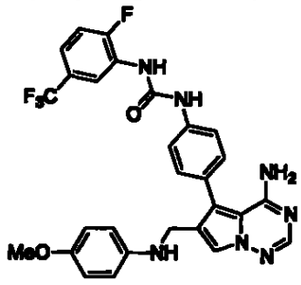
Ejemplo 41: Preparación de *N*-[4-(4-amino-6-{[4-(2-metoxietil)piperazin-1-il]metil}pirrolo[2,1-*f*][1,2,4]triazin-5-il)fenil]-*N'*-[2-fluoro-5-(trifluorometil)fenil]-urea

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El procedimiento utilizado para la preparación del Ejemplo 30 se utilizó para preparar el compuesto del título sustituyendo 1-(2-metoxietil)piperazina con morfolina y purificando por HPLC (10-90% de ACN/H_2O). ^{1}H-RMN (CD_3OD) δ8,61 (d, *J* = 7,1 Hz, 1H), 7,77 (s, 1H), 7,67 (s, 1H), 7,62 (d, *J* = 8,9 Hz, 2H), 7,39 (d, *J* = 8,9 Hz, 2H), 7,34 (d, *J* = 8,3 Hz, 2H), 3,50(s, 3H), 3,48 (t, *J* = 5,3 Hz, 2H), 3,29 (s, 2H), 2,58 a 2,38 (m, 10H); EM $[M+H]^+$ = 587; LCMS TR = 2,55 min.

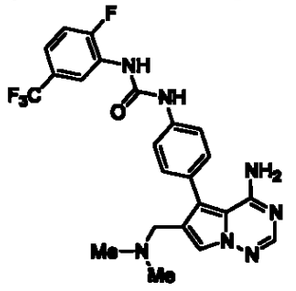
Ejemplo 42: Preparación de *N*-[4-(4-amino-8-{[(4-metoxifenil)amino]metil}-pirrolo[2,1-*f*][1,2,4]triazin-5-il)fenil]-*N'*-[2-fluoro-5-(trifluorometil)fenil]urea



El procedimiento utilizado para la preparación del Ejemplo 30 se utilizó para preparar el compuesto del título sustituyendo 4-metoxianilina con morfolina y purificando por HPLC (10-90% de ACN/H_2O). ^{1}H-RMN (CD_3OD) δ8,62 (d, *J* = 7,4 Hz, 1H), 7,75 (s, 1H), 7,65 a 7,58 (m, 3H), 7,41 (d, *J* = 8,1 Hz, 2H), 7,34 (d, *J* = 8,1 Hz, 2H), 6,70 (d, *J* = 8,8 Hz, 2H), 6,56 (d, *J* = 8,9 Hz, 2H), 4,16 (s, 2H), 3,68 (s, 3H); EM $[M+H]^+$ = 586; LCMS TR = 2,93 min.

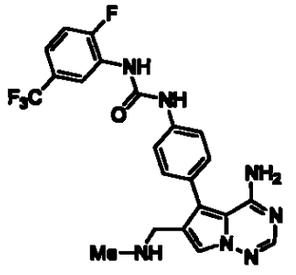
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Ejemplo 43: Preparación de *N*-(4-{4-amino-6-[(dimetilamino)metil]pirrolo[2,1-f][1,2,4]triazin-5-il}fenil)-N'-[2-fluoro-5-(trifluorometil)fenil]urea



El procedimiento utilizado para la preparación del Ejemplo 30 se utilizó para preparar el compuesto del título sustituyendo *N*-metilmetanamina con morfolina y purificando por HPLC (10-90% de ACN/H_2O). ^{1}H-RMN (CD_3OD) δ8,62 (d, *J* = 8,0 Hz, 1H), 7,78 (s, 1H), 7,70 (s, 1H), 7,63 (d, *J* = 8,6 Hz, 2H), 7,37 (d, *J* = 8,6 Hz, 2H), 7,34 (d, *J* = 8,4 Hz, 2H), 3,52 (s, 2H), 2,18 (s, 6H); EM $[M+H]^+$ = 488; LCMS TR = 2,55 min.

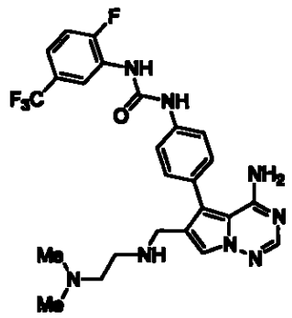
Ejemplo 44: Preparación de *N*-(4-{4-amino-6-[(metilamino)metil]pirrolo[2,1-f][1,2,4]triazin-5-il}fenil)-N'-[2-fluoro-5-(trifluorometil)fenil]urea



El procedimiento utilizado para la preparación del Ejemplo 30 se utilizó para preparar el compuesto del título sustituyendo metanamina con morfolina y purificando por HPLC (10-90% de ACN/H_2O). ^{1}H-RMN (CD_3OD) δ8,62 (d, *J* = 7,4 Hz, 1H), 7,77 (s, 1H), 7,70 (s, 1H), 7,64 (d, *J* = 8,6 Hz, 2H), 7,39 (d, *J* = 8,6 Hz, 2H), 7,34 (d, *J* = 8,5 Hz, 2H), 3,70 (s, 2H), 2,33 (s, 3H); EM $[M+H]^+$ = 474; LCMS TR = 2,55 min.

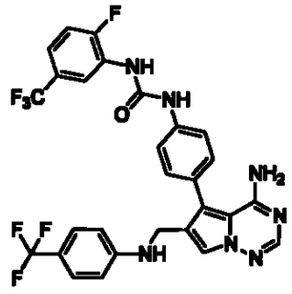
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Ejemplo 45: Preparación de *N*-(4-[4-amino-6-({[3-(dimetilamino)propil]-amino}metil)pirrolo[2,1-*f*][1,2,4]triazin-5-il]fenil}-N'-[2-fluoro-5-(trifluorometil)-fenil]urea



El procedimiento utilizado para la preparación del Ejemplo 30 se utilizó para preparar el compuesto del título sustituyendo *N,N*-dimetiletano-1,2-diamina con morfolina y purificando por HPLC (10-90% de ACN/H_2O). ^{1}H-RMN (CD_3OD) δ8,60 (d, *J* = 8,0 Hz, 1H), 7,97 (s, 1H), 7,84 (s, 1H), 7,69 (d, *J* = 8,0 Hz, 2H), 7,43 (d, *J* = 8,0 Hz, 2H), 7,35 (d, *J* = 8,8 Hz, 2H), 4,20 (s, 2H), 3,04 (t, *J* = 7,3 Hz, 2H), 2,94 (t, *J* = 7,3 Hz, 2H), 2,79 (s, 6H), 2,00 a 1,89 (m, 2H); EM $[M+H]^+$ = 545; LCMS TR = 2,28 min.

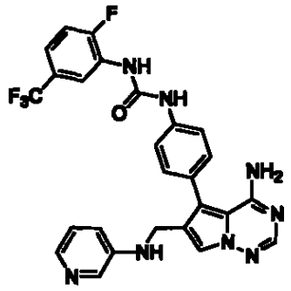
Ejemplo 46: Preparación de *N*-(4-[4-amino-6-({[4-(trifluorometil)fenil]amino}-metil)pirrolo[2,1-*f*][1,2,4]triazin-5-il]fenil}-N'-[2-fluoro-5-(trifluorometil)fenil]-urea



El procedimiento utilizado para la preparación del Ejemplo 30 se utilizó para preparar el compuesto del título sustituyendo 4-(trifluorometil)anilina con morfolina y purificando mediante HPLC (10-90% de ACN/H_2O). ^{1}H-RMN (CD_3OD) δ8,68 (d, *J* = 8,0 Hz, 1H), 7,76 (s, 1H), 7,67 a 7,62 (m, 3H), 7,43 (d, *J* = 8,8 Hz, 2H), 7,36 a 7,27

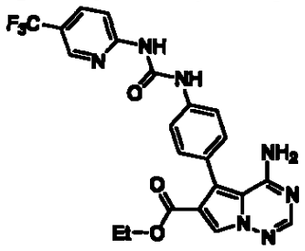
(m, 4H), 6,61 (d, *J* = 8,7 Hz, 2H), 4,67 (s, 2H); EM $[M+H]^+$ = 604; LCMS TR = 3,31 min.

Ejemplo 47: Preparación de *N*-(4-[4-amino-6-[(piridin-3-ilamino)metil]pirrolo-[2,1-*f*][1,2,4]triazin-5-il}fenil)-*N'*-[2-fluoro-5-(trifluorometil)fenil]urea

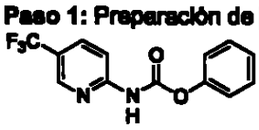


El procedimiento utilizado para la preparación del Ejemplo 30 se utilizó para preparar el compuesto del título sustituyendo piridin-3-amina con morfolina y purificando por HPLC (10-90% de ACN/H_2O). ^{1}H-RMN (CD_3OD) δ8,61 (d, *J* = 8,2 Hz, 1H), 7,82 (d, *J* = 2,9 Hz, 1H), 7,75 (s, 1H), 7,72 (dd, *J* = 5,5, 1,6 Hz, 1H), 7,64 a 7,59 (m, 3H), 7,41 (d, *J* = 7,8 Hz, 2H), 7,33 (d, *J* = 8,4 Hz, 2H), 7,09 (dd, *J* = 8,3, 4,8 Hz, 1H), 6,94 a 6,88 (m, 1H), 4,24 (s, 2H); EM $[M+H]^+$ = 537; LCMS TR = 2,08 min.

Ejemplo 48: Preparación de 4-amino-5-{4-[({[5-(trifluorometil)piridin-2-il]amino}carbonil)amino]fenil}pirrolo[2,1-*f*][1,2,4]triazin-6-carboxilato de etilo



Paso 1: Preparación de [5-(trifluorometil)piridin-2-il]carbamato de fenilo



Una solución de 5-(trifluorometil)piridin-2-amina (100 mg, 0,617 mmol) y *N,N*-diisopropiletilamina (159,5 mg, 215 µl, 1,234 mmol) en 5 ml CH_2Cl_2 se trató con

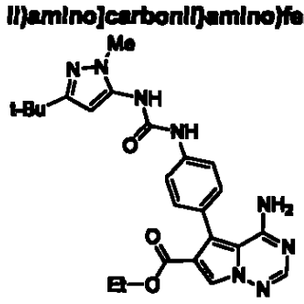
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cloroformiato de fenilo (106 mg, 85 □L, 0,68 mmol) y se dejó agitar durante 3 horas a temperatura ambiente. Se diluyó la solución con EtOAc y se lavó dos veces con HCl 1 N y 1 vez con salmuera. La capa orgánica se secó (Na_2SO_4) y se concentró para dar un sólido de color blanco. La titulación con 10% de EtOAc en hexanos dio 120 mg (69%, 0,42 mmol) del compuesto anterior en forma de un sólido color blanco. ^{1}H-RMN (DMSO-d_6) δ11,26 (s, 1H), 8,70 (s, 1H), 8,22 a 8,16 (m, 1H), 7,99 (d, J = 8 Hz, 1H), 7,45 a 7,40 (m, 2H), 7,30 a 7,20 (m, 3 H)

Paso 2: Preparación del compuesto del título

Una mezcla del intermediario B (57,9 mg, 0,195 mmol) y trietilamina en 2 ml THF se calentó a 55°C, dando una solución turbia. Se agregó [5-(trifluorometil)piridin-2-il]carbamato de fenilo (50 mg, 0,177 mmol) en forma de un sólido, y la mezcla se dejó agitar durante toda la noche. Después de 16 horas, el precipitado sólido se filtró, se lavó con acetato de etilo y se secó para dar 66 mg (77 %, 0,14 mmol) del compuesto anterior en forma de un sólido color amarillo. ^{1}H-RMN (DMSO-d_6) δ9,33 (s, 1H), 8,95 (d, *J* = 2,3 Hz, 1H), 8,63 a 8,61 (m, 1H), 8,13 (s, 1H), 8,07 (br s, 1H), 7,93 (s, 1H), 7,56 a 7,53 (m, 2H), 7,51 a 7,48 (m, 1H), 7,40 (br s, 1H), 7,34 a 7,32 (m, 2H), 5,09 (br s, 1H), 4,11 a 4,06 (q, *J* = 6,9 Hz, 2H), 1,13 a 1,10 (t, *J* = 7,1 Hz, 3H); EM $[M+H]^+$ = 486,0; LCMS TR = 3,36 min; TLC R_f = 0,46 (100% de EtOAc).

Ejemplo 49: Preparación de 4-amino-5-[4-({[(3-*ter*-butil-1-metil-1*H*-pirazol-5-il)amino]carbonil}amino)fenil]pirrolo[2,1-*f*][1,2,4]triazin-6-carboxilato de etilo

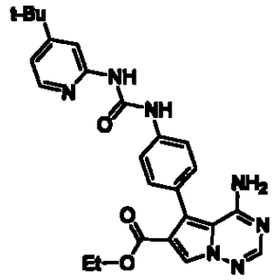


El procedimiento utilizado para la preparación del Ejemplo 48 se utilizó para preparar el compuesto del título sustituyendo 3-*ter*-butil-1-metil-1*H*-pirazol-5-amina con 5-(trifluorometil)piridin-2-amina y purificando por recristalización (EtOAc/EtOH). ^{1}H-RMN (DMSO-d_6) δ9,06 (s, 1H), 8,56 (s, 1H), 8,12 (s, 1H), 8,11-8,04 (bs, 1H), 7,92 (s, 1H), 7,53 (d, J = 8,7 Hz, 2H), 7,30 (d, J = 8,7 Hz, 2H), 6,05 (s, 1H), 5,14-5,01 (bs,

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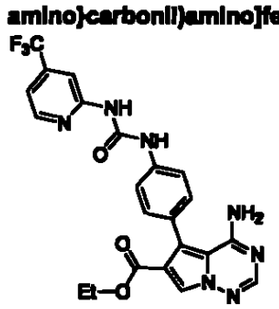
1H) 4,03 (q, J = 7,2 Hz, 2H), 1,09 (t, J = 7,2 Hz, 3H); EM $[M+H]^+$ = 477,2; LCMS TR = 2,60 min.

Ejemplo 50: Preparación de 4-amino-5-[4-({[(4-*ter*-butilpiridin-2-il)-amino]carbonil}amino)fenil]pirrolo[2,1-*f*][1,2,4]triazin-6-carboxilato de etilo



El procedimiento utilizado para la preparación del Ejemplo 48 se utilizó para preparar el compuesto del título sustituyendo 4-*ter*-butilpiridin-2-amina con 5-(trifluorometil)piridin-2-amina y purificando por HPLC (10-90% de ACN/H_2O). ^{1}H-RMN (DMSO-d_6) □10,88 (s, 1H), 9,44 (s, 1H), 8,19 (d, J = 5,7 Hz), 8,12 (s, 1H), 8,11-8,10 (bs, 1H), 7,92 (s, 1H), 7,61 (d, J = 8,4 Hz, 2H), 7,49 (s, 1H), 7,32 (d, J = 8,4 Hz, 2H) 7,09-7,03 (m, 1H), 5,01-5,18 (bs, 1H), 4,07 (q, J = 7,2 Hz, 2H), 1,25 (s, 9H), 1,08 (t, J=7,2 Hz, 3H); EM $[M+H]^+$ = 474,2; LCMS TR = 2,63 min; TLC R_f = 0,27 (3:7 v/v THF-CH_2Cl_2).

Ejemplo 51: Preparación de 4-amino-5-{4-[({[4-(trifluorometil)piridin-2-il]-amino}carbonil)amino]fenil}pirrolo[2,1-*f*][1,2,4]triazin-6-carboxilato de etilo

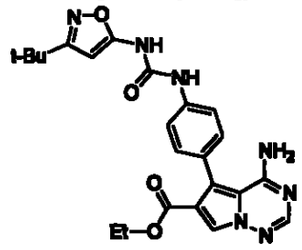


El procedimiento utilizado para la preparación del Ejemplo 48 se utilizó para preparar el compuesto del título sustituyendo 4-(trifluorometil)piridin-2-amina con 5-(trifluorometil)piridin-2-amina y purificando por cromatografía flash (1:3 v/v THF-

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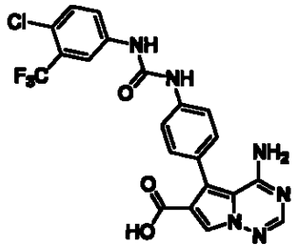
CH_2Cl_2). ^{1}H-RMN (DMSO-d_6) δ 10,19 (s, 1H), 9,89 (s, 1H), 8,52 (d, J = 5,4 Hz, 1H), 8,12 (s, 1H), 8,12 a 8,10 (m, 2H), 7,93 (s, 1H), 7,59 (d, J = 6,9 Hz, 2H), 7,48 a 7,30 (m, 3H), 5,15 a 5,10 (m, 1H), 4,06 (q, J = 7,2 Hz, 2 H), 1,11 (t, J = 7,2 Hz, 3H); EM $[M+H]^+$ = 486,1; LCMS TR = 3,33 min; TLC R_f = 0,27 (3:7 v/v THF-CH_2Cl_2).

Ejemplo 52: Preparación de 4-amino-5-[4-({[(3-*ter*-butilisoxazol-5-il)amino]-carbonil}amino)fenil]pirrolo[2,1-*f*][1,2,4]triazin-6-carboxilato de etilo



El procedimiento utilizado para la preparación del Ejemplo 48 se utilizó para preparar el compuesto del título sustituyendo 3-*ter*-butilisoxazol-5-amina con 5-(trifluorometil)piridin-2-amina y purificando lavando el precipitado formado durante la reacción (1:1 v/v EtOAC-hexanos). ^{1}H-RMN (DMSO-d_6) δ10,17 (s, 1H), 9,02 (s, 1H), 8,13 (s, 1H), 8,0-8,1 (bs, 1H), 7,93 (s, 1H), 7,54 (d, J = 8,7 Hz, 2H), 7,32 (J = 8,7 Hz, 2H), 6,07 (s, 1H), 5,2-5,0 (bs, 1H), 4,07 (q, J = 6,9 Hz, 2H), 1,25 (ms, 9H), 1,09 (t, J = 6,9 Hz, 3H); EM $[M+H]^+$ = 464,2; LCMS TR = 3,25 min; TLC R_f = 0,33 (3:7 v/v THF-CH_2Cl_2).

Ejemplo 53: Preparación de ácido 4-amino-5-{4-[({[4-cloro-3-(trifluorometil)-fenil]amino}carbonil)amino]fenil}pirrolo[2,1-*f*][1,2,4]triazin-6-carboxílico

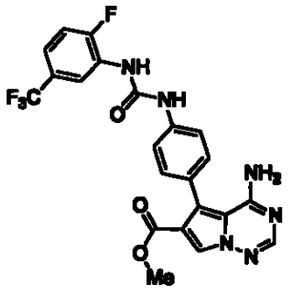


A una solución de MeOH (1,5 ml) se agregó 4-amino-5-{4-[({[4-cloro-3-(trifluorometil)fenil]amino}carbonil)amino]fenil}pirrolo[2,1-*f*][1,2,4]triazin-6-carboxilato de etilo, Ejemplo 2, (22 mg, 0,042 mmol), THF (3,0 ml), y NaOH 1N (0,42 ml, 0,42

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mmol). La reacción se calentó a 65 °C durante 17 h. Al enfriarse a temperatura ambiente la reacción se filtró a través de un tapón de celite®/Gel de sílice eluyendo con 85:15 v/v de CH_2Cl_2-MeOH. El filtrado se concentró al vacío hasta sequedad, se diluyó con CH_2Cl_2, se secó (MgSO4), se filtró, y se concentró al vacío hasta sequedad produciendo 3,8 mg del compuesto anterior (0,0077 mmol, rendimiento 18%). ^{1}H-RMN (DMSO-d_6) δ 8,18 (br s, 1H), 7,98 (br s, 1H), 7,88 (s, 1H), 7,67 (br s, 1H), 7,59 a 7,57 (d, J = 8,6 Hz, 1H), 7,53 a 7,51 (d, J = 7,7 Hz, 2H), 7,34 a 7,32 (d, J = 8,0 Hz, 2H), 6,56 (s, 1H), 5,06 (br s, 1H); EM $[M+H]^+$ = 491; LCMS TR = 3,18 min; TLC R_f = 0,20 (85:15 v/v CH_2Cl_2-MeOH).

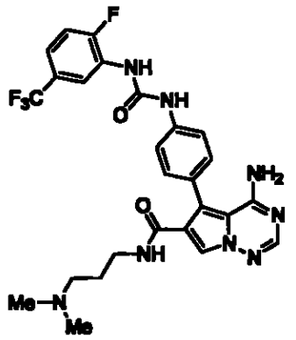
Ejemplo 54: Preparación de 4-amino-5-{4-[({[2-fluoro-5-(trifluorometil)fenil]-amino}carbonil)amino]fenil}pirrolo[2,1-f][1,2,4]triazin-6-carboxilato de metilo



A una solución de MeOH (4,0 ml) se agregó el intermediario E (30 mg, 0,060 mmol), THF (2,0 ml), y NaOH 1N (0,24 ml, 0,24 mmol). La reacción se agitó a temperatura ambiente durante 2 días. La solución se transfirió a un Biotage Samplet y se secó en un horno al vacío. El material se purificó por cromatografía flash (Biotage) eluyendo con 5:4:1 v/v/v de CH_2Cl_2-EtOAc-MeOH. Las fracciones limpias se combinaron, se concentraron al vacío hasta sequedad produciendo 14 mg del compuesto anterior (0,029mmol, rendimiento 48%). ^{1}H-RMN (DMSO-d_6) δ9,33 (s, 1H), 8,96 (d, 1H, J = 2,4 Hz), 8,63 a 8,61 (dd, 7,3 Hz, 2,4 Hz, 1H), 8,15 (s, 1H), 8,09 (br s, 1H), 7,93 (s, 1H), 7,56 a 7,54 (m, 2H), 7,50 a 7,47 (m, 1H), 7,40 (m, 1H), 7,34 a 7,32 (m, 2H), 5,09 (br s, 1H), 3,63 (s, 3H); EM $[M+H]^+$ = 489; LCMS TR = 2,85 min; TLC R_f = 0,55 (5:4:1 v/v/v CH_2Cl_2-EtOAc-MeOH).

500

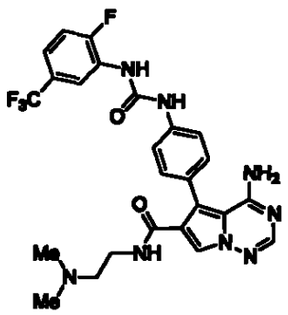
Ejemplo 55: Preparación de 4-amino-*N*-[3-(dimetilamino)propil]-5-{4-[({[2-fluoro-5-(trifluorometil)fenil]amino}carbonil)amino]fenil}pirrolo[2,1-*f*][1,2,4]-triazin-6-carboxamida



A una solución del intermediario G (41 mg, 0,09 mmol) en 0,5 ml de DMF se agregó py-BOP (32,0 mg, 0,13 mmol *N,N*-dimetilpropano-1,3-diamina (13,25 mg, 0,13 mmol) como una solución en THF, diisopropiletilamina (24,9 mg, 0,19 mmol) y 4-dimetilaminopiridina (4 mg, 0,04 mmol). Al cabo de 12 h la reacción se diluyó con 150 ml de CH_2Cl_2, se lavó con agua y salmuera, luego se secó con sulfato de sodio. Esta solución se concentró y el residuo se purificó por columna flash (20% de THF en CH_2Cl_2) para dar 25,4 mg de material impuro. La titulación con acetato de etilo dio 10,3 mg del producto deseado (0,018 mmol, 21 mg). ^{1}H-RMN (MeOD-d_4) δ 8,60 (d, J = 8 Hz, 1H), 7,97 (3, 1H), 7,84 (s, 1H), 7,65 (d, J = 9 Hz, 1H), 7,43 (d, J = 9 Hz, 2 H), 7,33 (d, J = 9 Hz, 2H), 3,25 (t, J = 7 Hz, 2H), 2,23 (t, J = 7 Hz, 2H), 2,21 (s, 6H), 1,61 (quinteto ap, J = 7 Hz, 2H); EM $[M+H]^+$ = 559,3; LCMS TR = 2,63 min; TLC R_f = 0,14 (1:2 v/v THF:CH_2Cl_2).

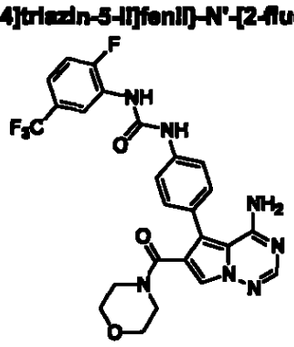
Ejemplo 56: Preparación de 4-amino-*N*-[2-(dimetilamino)etil]-5-{4-[({[2-fluoro-5-(trifluorometil)fenil]amino}carbonil)amino]fenil}pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida

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La preparación de este compuesto se describe en el Ejemplo 55, sustituyendo *N,N*-dimetiletano-1,2-diamina con *N,N*-dimetilpropano-1,3-diamina dando 23,7 mg del producto en forma de un sólido color blanco (0,044 mmol, 34 % de rendimiento). ^{1}H-RMN (CD_3OD) δ 8,62 (d, J = 8 Hz, 1H), 8,01 (s, 1H), 7,84 (s, 1H), 7,66 (d, J = 8 Hz, 1H), 7,42 (d, J = 8 Hz, 2 H), 7,35 (d, J = 8 Hz, 2H), 3,90 (t, J = 7 Hz, 2H), 2,40 (t, J = 7 Hz, 2H), 2,20 (s, 6H); EM $[M+H]^+$ = 545,2; LCMS TR = 2,13 min; TLC R_f = 0,31 (1:3:9 v/v/v 2 M NH_3 en MeOH:THF:CH_2Cl_2).

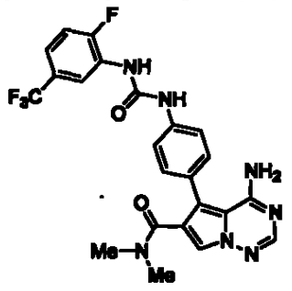
Ejemplo 57: Preparación de *N*-{4-[4-amino-6-(morfolin-4-ilcarbonil)pirrolo-[2,1-f][1,2,4]triazin-5-il]fenil}-*N'*-[2-fluoro-5-(trifluorometil)fenil]urea



Este compuesto se preparó mediante el mismo procedimiento que el Ejemplo 55, sustituyendo morfolina con N,N-dimetilpropano-1,3-diamina dando 7,2 mg del producto en forma de un sólido color blanco (0,013 mmol, 16 %). ^{1}H-RMN (CD_3OD) δ 8,62 (d, J = 8 Hz, 1H), 7,91 (s, 1H), 7,80 (s, 1H), 7,66 (d, J = 9 Hz, 1H), 7,43-7,39 (m, 2 H), 7,34 (d, J = 9 Hz, 2H), 3,26-3,45 (m, 4H), 3,2-3,0 (m, 4H), EM $[M+H]^+$ = 544,6; LCMS TR = 2,49 min; TLC R_f = 0,34 (1:2 v/v THF:CH_2Cl_2).

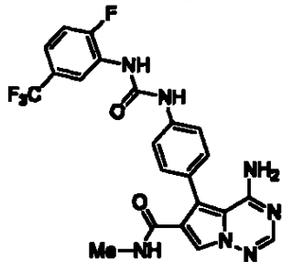
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Ejemplo 58: Preparación de 4-amino-5-{4-[({[2-fluoro-5-(trifluorometil)fenil]-amino}carbonil)amino]fenil}-*N,N*-dimetilpirrolo[2,1-f][1,2,4]triazin-6-carboxamida



Este compuesto se preparó mediante el mismo procedimiento que el Ejemplo 55, sustituyendo *N*-metilmetanamina con N,N-dimetilpropano-1,3-diamina dando 7,0 mg del producto en forma de un sólido color blanco (0,014 mmol, 17 %). ^{1}H-RMN (CD_3OD) δ 8,61 (d, J = 8 Hz, 1H), 7,85 (s, 1H), 7,79 (s, 1H), 7,60 (d, J = 9 Hz, 1H), 7,38 (d, J = 9 Hz, 2 H), 7,34 (d, J = 9 Hz, 2H), 2,93 (s, 3H), 2,72 (s, 3H), EM $[M+H]^+$ = 502,2; LCMS TR = 2,54 min; TLC R_f = 0,29 (1:2 v/v THF:CH_2Cl_2).

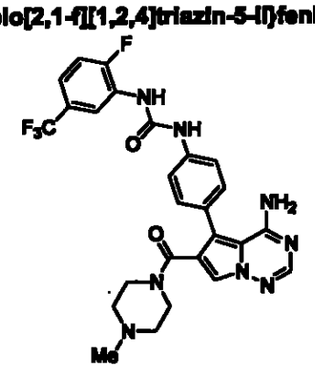
Ejemplo 59: Preparación de 4-amino-5-{4-[({[2-fluoro-5-(trifluorometil)fenil]-amino}carbonil)amino]fenil}-*N*-metilpirrolo[2,1-f][1,2,4]triazin-6-carboxamida



Este compuesto se preparó mediante el mismo procedimiento que el Ejemplo 55, sustituyendo metanamina con N,N-dimetilpropano-1,3-diamina dando mg del producto en forma de un sólido color blanco (mmol, rendimiento). ^{1}H-RMN (CD_3OD) δ 8,61 (d, J = 8 Hz, 1H), 7,85 (s, 1H), 7,97 (s, 1H), 7,83 (d, J = 9 Hz, 1H), 7,61 (d, J = 9 Hz, 2 H), 7,43-7,39 (m, 2H) 7,34 (d, J = 9 Hz, 2H), 2,93 (s, 3H); EM $[M+H]^+$ = 488,5; LCMS TR = 2,50 min; TLC R_f = 0,26 (1:2 v/v THF:CH_2Cl_2).

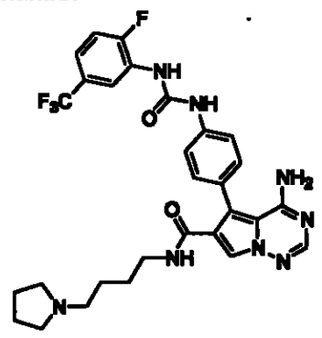
503

Ejemplo 60: Preparación de *N*-(4-{4-amino-6-[(4-metilpiperazin-1-il)carbonil]-pirrolo[2,1-*f*][1,2,4]triazin-5-il}fenil)-*N'*-[2-fluoro-5-(trifluorometil)fenil]urea



Este compuesto se preparó mediante el mismo procedimiento que el Ejemplo 55, sustituyendo 1-metilpiperazina con N,N-dimetilpropano-1,3-diamina dando 6,2 mg del producto en forma de un sólido color blanco (0,011 mmol, 9 % rendimiento). ^{1}H-RMN (CD_3OD) δ 8,62-8,59 (m, 1H), 7,88 (s, 1H), 7,80 (d, J = 9 Hz, 1H), 7,64 (d, J = 9 Hz, 2 H), 7,42-7,39 (m, 2H) 7,34 (d, J = 9 Hz, 2H), 3,65-3,57 (m, 2H), 3,56-3,50 (m, 2H), 3,20-3,11 (m, 2H), 2,13 (s, 3H); EM $[M+H]^+$ = 557,0; LCMS TR = 2,13 min; TLC R_f = 0,21 (1:1 v/v THF:CH_2Cl_2).

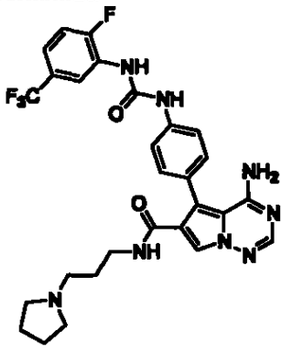
Ejemplo 61: Preparación de 4-amino-5-{4-[({[2-fluoro-5-(trifluorometil)fenil]-amino}carbonil)amino]fenil}-*N*-(4-pirrolidin-1-ilbutil)pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida



El procedimiento utilizado para la preparación del Ejemplo 55 se utilizó para preparar el compuesto del título sustituyendo 4-pirrolidin-1-ilbutan-1-amina con N,N-dimetilpropano-1,3-diamina y purificando mediante HPLC (10-90% de ACN/H_2O). ^{1}H-

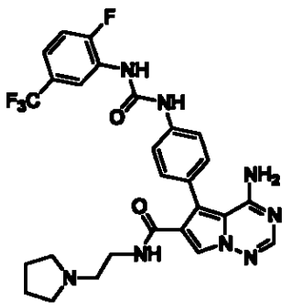
RMN (CD_3OD) δ8,61 (d, *J* = 7,4 Hz, 1H), 7,98 (s, 1H), 7,83 (s, 1H), 7,66 (d, *J* = 7,3 Hz, 2H), 7,43 (d, *J* = 8,4 Hz, 2H), 7,34 (d, *J* = 8,3 Hz, 2H), 3,24 (t, *J* = 5,8 Hz, 2H), 2,73 a 2,63 (m, 4H), 2,57 (t, *J* = 5,8 Hz, 2H), 1,86 a 1,78 (m, 4H), 1,48 a 1,39 (m, 4H); EM $[M+H]^+$ = 599; LCMS TR = 2,66 min.

Ejemplo 62: Preparación de 4-amino-5-{4-[({[2-fluoro-5-(trifluorometil)fenil]-amino}carbonil)amino]fenil}-*N*-(3-pirrolidin-1-ilpropil)pirrolo[2,1-*f*][1,2,4]-triazin-6-carboxamida



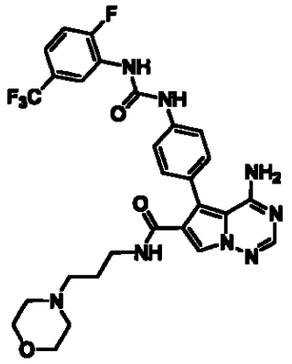
El procedimiento utilizado para la preparación del Ejemplo 55 se utilizó para preparar el compuesto del título sustituyendo 3-pirrolidin-1-ilpropan-1-amina con N,N-dimetilpropano-1,3-diamina y purificando por HPLC (10-90% de ACN/H_2O). ^{1}H-RMN (CD_3OD) δ 8,62 (d, *J* = 7,7 Hz, 1H), 8,03 (s, 1H), 7,84 (s, 1H), 7,66 (d, *J* = 8,0 Hz, 2H), 7,43 (d, *J* = 8,4 Hz, 2H), 7,35 (d, *J* = 8,2 Hz, 2H), 3,28 a 3,21 (m, 2H), 2,64 a 2,55 (m, 4H), 2,44 a 2,36 (m, 2H), 1,84 a 1,76 (m, 4H), 1,71 a 1,60 (m, 2H); EM $[M+H]^+$ = 585; LCMS TR = 2,63 min.

Ejemplo 63: Preparación de 4-amino-5-{4-[({[2-fluoro-5-(trifluorometil)fenil]-amino}carbonil)amino]fenil}-*N*-(2-pirrolidin-1-iletil)pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida



El procedimiento utilizado para la preparación del Ejemplo 55 se utilizó para preparar el compuesto del título sustituyendo 2-pirrolidin-1-iletanamina con N,N-dimetilpropano-1,3-diamina y purificando mediante HPLC (10-90% de ACN/H_2O). ^{1}H-RMN (CD_3OD) δ 8,62 (d, *J* = 7,6 Hz, 1H), 7,97 (s, 1H), 7,84 (s, 1H), 7,66 (d, *J* = 7,6 Hz, 2H), 7,43 (d, *J* = 8,2 Hz, 2H), 7,35 (d, *J* = 8,5 Hz, 2H), 3,25 a 3,20 (m, 2H), 2,64 a 2,50 (m, 6H), 1,82 a 1,74 (m, 4H); EM $[M+H]^+$ = 571; LCMS TR = 2,23 min.

Ejemplo 64: Preparación de 4-amino-5-{4-[({[2-fluoro-5-(trifluorometil)fenil]-amino}carbonil)amino]fenil}-*N*-(3-morfolin-4-ilpropil)pirrolo[2,1-*f*][1,2,4]-triazin-6-carboxamida

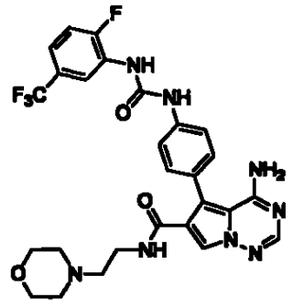


El procedimiento utilizado para la preparación del Ejemplo 55 se utilizó para preparar el compuesto del título sustituyendo 3-morfolin-4-ilpropan-1-amina con N,N-dimetilpropano-1,3-diamina y purificando por HPLC (10-90% de ACN/H_2O). ^{1}H-RMN (CD_3OD) δ8,62 (d, *J* = 7,2 Hz, 1H), 7,97 (s, 1H), 7,84 (s, 1H), 7,66 (d, *J* = 8,3 Hz, 2H), 7,44 (d, *J* = 8,3 Hz, 2H), 7,34 (d, *J* = 8,7 Hz, 2H), 3,64 (t, *J* = 3,6 Hz, 4H), 3,26 (t, *J* =

506

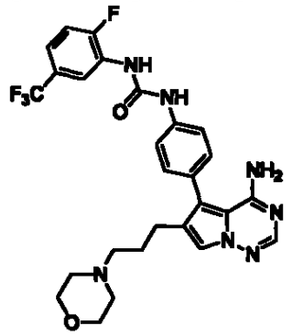
6,1 Hz, 2H), 2,43 a 2,37 (m, 4H), 2,21 (t, *J* = 7,7 Hz, 2H), 1,68 a 1,54 (m, 2H); EM $[M+H]^+$ = 601; LCMS TR = 2,21 min.

Ejemplo 65: Preparación de 4-amino-5-{4-[({[2-fluoro-5-(trifluorometil)fenil]-amino}carbonil)amino]fenil}-*N*-(2-morfolin-4-iletil)pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida



El procedimiento utilizado para la preparación del Ejemplo 55 se utilizó para preparar el compuesto del título sustituyendo 2-morfolin-4-iletanamina con N,N-dimetilpropano-1,3-diamina y purificando mediante HPLC (10-90% de ACN/H_2O). ^{1}H-RMN (CD_3OD) δ8,61 (d, *J* = 7,8 Hz, 1H), 8,03 (s, 1H), 7,84 (s, 1H), 7,69 (d, *J* = 8,4 Hz, 2H), 7,46 (d, *J* = 8,5Hz, 2H), 7,35 (d, *J* = 8,2 Hz, 2H), 3,60 (t, *J* = 5,0 Hz, 4H), 3,39 a 3,33 (m, 2H), 2,37 a 2,30 (m, 6H); EM $[M+H]^+$ = 587; LCMS TR = 2,21min.

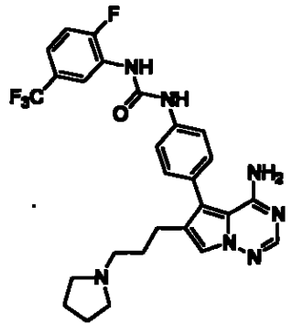
Ejemplo 66: Preparación de *N*-{4-[4-amino-6-(3-morfolin-4-ilpropil)pirrolo[2,1-*f*][1,2,4]triazin-5-il]fenil}-*N'*-[2-fluoro-5-(trifluorometil)fenil]urea



A una solución del intermediario I (53 mg, 0,11 mmol) en CH_2Cl_2 (3,0 ml) se agregó AcOH (0,036 ml, 0,63 mmol) y morfolina (0,019 ml, 0,22 mmol). La reacción

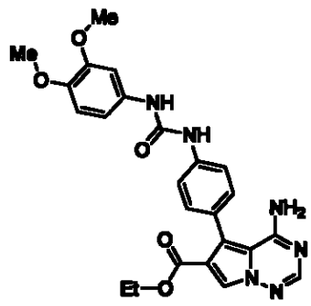
se agitó a temperatura ambiente durante 1 h después de lo cual se agregó triacetoxiborohidruro de sodio (66 mg, 0,31 mmol). La reacción se agitó a temperatura ambiente hasta la terminación. La reacción se diluyó con CH_2Cl_2, se transfirió a un embudo de separación y se lavó con $NaHCO_3$ ac saturado (2x). La fase acuosa se retro extrajo con CH_2Cl_2 (2x). La capa orgánica se secó (Na_2SO_4) y se evaporó para dar un aceite bruto que se purificó mediante HPLC (10-90% de ACN/H_2O) para dar el compuesto del título (15mg, 24%). ^{1}H-RMN (CD_3OD) δ8,62 (d, J = 7,8 Hz, 1H), 7,74 (s, 1H), 7,62 (d, *J* = 8,2 Hz, 2H), 7,53 (s, 1H), 7,38 a 7,31 (m, 4H), 3,62 (t, *J* = 5,2 Hz, 4H), 2,59 (t, *J* = 7,3 Hz, 2H), 2,38 a 2,23 (m, 6H), 1,74 a 1,62 (m, 2H); EM $[M+H]^+$ = 558; LCMS TR = 2,18 min.

Ejemplo 67: Preparación de *N*-[4-[4-amino-8-(3-pirrolidin-1-ilpropil)pirrolo-[2,1-f][1,2,4]triazin-5-il]fenil]-N'-[2-fluoro-5-(trifluorometil)fenil]urea



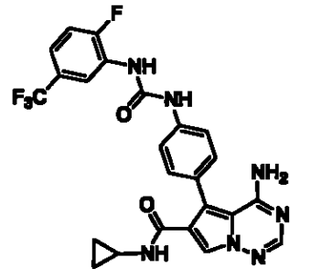
El procedimiento utilizado para la preparación del Ejemplo 66 se utilizó para preparar el compuesto del título sustituyendo pirrolidina con morfolina y purificando mediante HPLC (10-90% de ACN/H_2O). ^{1}H-RMN (CD_3OD) δ8,61 (d, J = 7,8 Hz, 1H), 7,74 (s, 1H), 7,63 (d, *J* = 8,3 Hz, 2H), 7,55 (s, 1H), 7,39 a 7,31 (m, 4H), 2,72 a 2,55 (m, 8H), 1,86 a 1,70 (m, 6H); EM $[M+H]^+$ = 542; LCMS TR = 2,15 min.

Ejemplo 68: Preparación de 4-amino-5-[4-({[(3,4-dimetoxifenil)amino]-carbonil}amino)fenil]pirrolo[2,1-f][1,2,4]triazin-6-carboxilato de etilo



El procedimiento utilizado para la preparación del Ejemplo 3 se utilizó para preparar el compuesto del título sustituyendo 3,4-dimetoxianilina con 4-fluoro-3-(trifluorometil)anilina. ^{1}H-RMN (CD_3OD) δ8,27 (s, 1H), 8,15 (s, 1H), 8,06 (s, 1H), 7,98 (s, 1H), 7,67 (d, *J* = 8 Hz, 2H), 7,39 (d, *J* = 8 Hz, 2H), 7,34 (s, 1H), 6,95 (d, *J* = 9 Hz, 1H), 6,86 (d, *J* = 9 Hz, 3H), 4,15 (q, J = 7, 2H), 3,81 (s, 3H), 3,76 (s, 3H), 1,18 (t, J = 7Hz, 3H); EM $[M+H]^+$ = 477,1 LCMS TR = 2,50 min.

Ejemplo 69: Preparación de 4-amino-*N*-ciclopropil-5-{4-[({[2-fluoro-5-(trifluorometil)fenil]amino}carbonil)amino]fenil}pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida

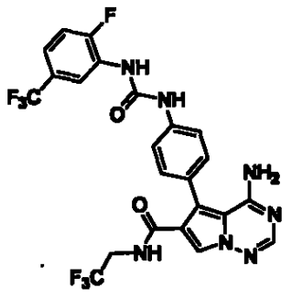


Una solución del intermediario G (50 mg, 0,105 mmol), ciclopropilamina (11 µl, 0,106 mmol), py-BOP (82 mg, 0,158 mmol) y trietilamina (22 µl, 0,158 mmol) se dejó agitar a temperatura ambiente durante 15 min y luego se concentró al vacío. El residuo se purificó por cromatografía de sílice usando 20% de THF en CH_2Cl_2 y el producto luego se trituró con 30% de metanol acuoso, dando 31,5 mg del compuesto anterior (0,061 mmol, rendimiento 71%). ^{1}H-RMN (DMSO-d_6) δ9,32 (s, 1H), 8,96 (s, 1H), 8,64 (bd, *J* = 6 Hz, 1H), 8,06 (s, 1H), 7,90 (s, 1H), 7,85 a 7,82 (m, 1H), 7,54 (d, *J* = 8 Hz, 2H), 7,53 a 7,50 (m, 2H), 7,45 a 7,35 (m, 1H), 7,31 (d, *J* = 8 Hz, 1H), 5,03

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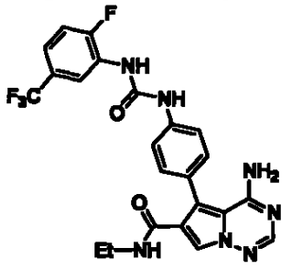
(bs, 1H), 2,63-2,59 (m 1H), 0,62 a 0,58 (m, 2H), 0,41 a 0,39 (m, 2H). EM $[M+H]^+$ = 514,2; **LCMS TR** = 3,11 min; **TLC** R_f = 0,33 (2:1 v/v CH_2Cl_2-THF).

Ejemplo 70: Preparación de 4-amino-5-{4-[({[2-fluoro-5-(trifluorometil)fenil]-amino}carbonil)amino]fenil}-*N*-(2,2,2-trifluoroetil)pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida



El procedimiento utilizado para la preparación del Ejemplo 69 se utilizó para preparar el compuesto del título sustituyendo clorhidrato de 2,2,2-trifluoroetanamina con ciclopropanamina. ^{1}H-RMN (DMSO-d_6) δ9,29 (s, 1H), 8,93 (s, 1H), 8,64-8,58 (m, 1H), 8,51 (t, J = 6 Hz, 1H), 8,18 (s, 1H), 8,00 (bs, 1H), 7,91 (s, 1H), 7,52 (d, J = 8 Hz, 2H), 7,51 a 7,46 (m, 1H), 7,40 a 7,30 (m, 1H), 7,28 (d, J = 8 Hz, 2H), 5,05 (bs, 1H), 4,00 a 3,85 (m, 2H). EM $[M+H]^+$ = 556,2; **LCMS TR** = 3,32 min; **TLC** R_f = 0,33 (CH_2Cl_2-THF 2:1 v/v).

Ejemplo 71: Preparación de 4-amino-*N*-etil-5-{4-[({[2-fluoro-5-(trifluoro-metil)fenil]amino}carbonil)amino]fenil}pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida

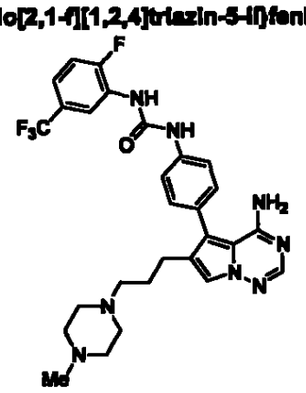


El procedimiento utilizado para la preparación del Ejemplo 69 se utilizó para preparar el compuesto del título sustituyendo etanamina con ciclopropanamina. ^{1}H-

510

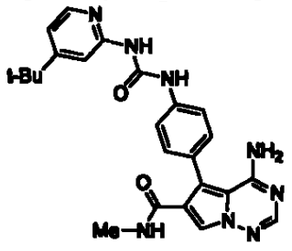
RMN (CD_3OD) δ8,62 a 8,60 (m, 1H), 7,98 (s, 1H), 7,84 (s, 1H), 7,63 (d, *J* = 9 Hz, 2H), 7,42 a 7,41 (m, 1H), 7,34 (d, *J* = 7 Hz, 2H), 1,04 (t, *J* = 7Hz, 3H); EM $[M+H]^+$ = 502,1; LCMS TR = 2,68 min; TLC R_f = 0,44 (3:2 v/v CH_2Cl_2-THF).

Ejemplo 72: Preparación de *N*-(4-{4-amino-6-[3-(4-metilpiperazin-1-il)propil]-pirrolo[2,1-*f*][1,2,4]triazin-5-il}fenil)-N'-[2-fluoro-5-(trifluorometil)fenil]urea



El procedimiento utilizado para la preparación del Ejemplo 68 se utilizó para preparar el compuesto del título sustituyendo 1-metilpiperazina con morfolina y purificando mediante HPLC (10-90% de ACN/H_2O). ^{1}H-RMN (CD_3OD) δ8,61 (d, *J* = 8,0 Hz, 1H), 7,74 (s, 1H), 7,63 (d, *J* = 8,7 Hz, 2H), 7,54 (s, 1H), 7,37 (d, *J* = 8,0 Hz, 2H), 7,34 (d, *J* = 8,1 Hz, 2H), 2,79 a 2,37 (m, 12 H), 2,47 (s, 3H), 1,75 a 1,62 (m, 2H); EM $[M+H]^+$ = 571,4; LCMS TR = 2,48.

Ejemplo 73: Preparación de 4-amino-5-[4-({[(4-*ter*-butilpiridin-2-il)amino]-carbonil}amino)fenil]-*N*-metilpirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida

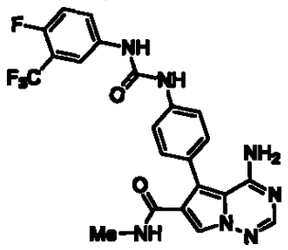


A una solución de DMF (1 ml) se agregó el intermediario X (50 mg, 0,18 mmol) seguido de (4-*ter*-butilpiridin-2-il)carbamato de fenilo (48 mg, 0,18 mmol) y trietilamina (25 µL, 0,18 mmol). La reacción se agitó a temperatura ambiente durante

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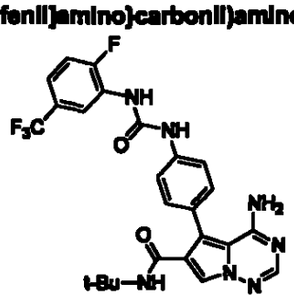
toda la noche, se concentró hasta sequedad, y se purificó por HPLC para dar 22 mg del compuesto anterior (0,04 mmol, rendimiento 26%). ^{1}H-RMN (DMSO-d_6) δ10,9 (s, 1H), 9,48 (s, 1H), 8,17 (d, *J* = 5,4 Hz, 1H), 8,06 (s, 1H), 7,88 (s, 1H), 7,02 (d, *J* = 5,0 Hz, 1H), 7,61 a 7,54 (m, 3H), 7,29 (d, *J* = 8,3 Hz, 2H), 7,04 (dd, *J* = 5,5, 1,8 Hz, 1H), 2,61 (d, *J* = 4,7 Hz, 3H), 1,25 (s, 9H); EM $[M+H]^+$ = 459,2; LCMS TR = 2,49.

Ejemplo 74: Preparación de 4-amino-5-{4-[({[4-fluoro-3-(trifluorometil)fenil]-amino}carbonil)amino]fenil}-*N*-metilpirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida



El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo [4-fluoro-3-(trifluorometil)fenil]carbamato con fenilo (4-*ter*-butilpiridin-2-il)carbamato de fenilo. ^{1}H-RMN (CD_3OD) δ7,97 (s, 1H), 7,91 (dd, *J* = 6,4, 3,0 Hz, 1H), 7,83 (s, 1H), 7,68 a 7,62 (m, 1H), 7,59 (d, *J* = 8,3 Hz, 2H), 7,40 (d, *J* = 8,3 Hz, 2H), 7,27 (t, *J* = 9,9 Hz, 1H), 2,76 (s, 3H); EM $[M+H]^+$ = 488,3; LCMS TR = 2,31.

Ejemplo 75: Preparación de 4-amino-*N*-(*ter*-butil)-5-{4-[({[2-fluoro-5-(trifluoro-metil)fenil]amino}carbonil)amino]fenil}pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida

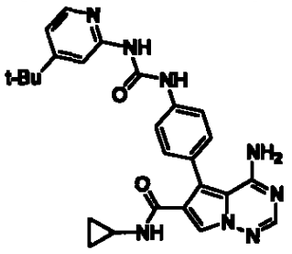


El procedimiento utilizado para la preparación del Ejemplo 69 se utilizó para preparar el compuesto del título sustituyendo 2-metilpropan-2-amina con ciclopropanamina. ^{1}H-RMN (DMSO-d_6) δ9,35 (s, 1H), 8,95 (s, 1H), 8,61 (d, *J* = 5Hz,

512

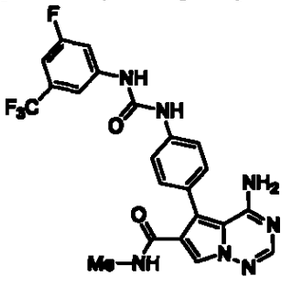
1H), 8,02 (s, 1H), 7,88 (s, 1H), 7,98 a 7,92 (m, 1H), 7,57 (d, *J* = 8 Hz, 2H), 7,45 a 7,44 (m, 1H), 7,41 a 7,36 (m, 1H), 7,34 (d, *J* = 8Hz, 2H), 6,62 (s, 1H), 1,15 (s, 9H); EM $[M+H]^+$ = 530,3; LCMS TR = 2,94 min; TLC R_f = 0,68 (3:2 v/v CH_2Cl_2-THF).

Ejemplo 76: Preparación de 4-amino-5-[4-({[(4-*ter*-butilpiridin-2-il)amino]-carbonil}amino)fenil]-*N*-ciclopropilpirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida



El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo el intermediario W con el intermediario X. ^{1}H-RMN (CD_3OD) δ8,22 (d, *J* = 6,3 Hz, 1H), 7,98 (s, 1H), 7,83 (s, 1H), 7,71 (d, *J* = 8,6 Hz, 2H), 7,42 (d, *J* = 8,6 Hz, 2H), 7,21 (s, 1H), 7,10 (dd, *J* = 5,6, 1,7 Hz, 1H), 2,72 a 2,59 (m, 1H), 1,31 (s, 9H), 0,72 a 0,62 (m, 2H), 0,42 a 0,33 (m, 2H); EM $[M+H]^+$ = 485,3; LCMS TR = 2,70.

Ejemplo 77: Preparación de 4-amino-5-[4-[({[3-fluoro-5-(trifluorometil)fenil]-amino}carbonil)amino]fenil]-*N*-metilpirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida

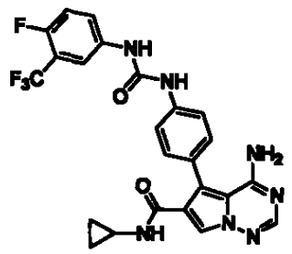


El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo [3-fluoro-5-(trifluorometil)fenil]carbamato con fenilo (4-*ter*-butilpiridin-2-il)carbamato de fenilo. ^{1}H-RMN (DMSO-d_6) δ8,04 (s, 1H), 7,88 (s, 1H), 7,70 (s, 1H), 7,61 (d, *J* = 11,0 Hz, 1H),

S13

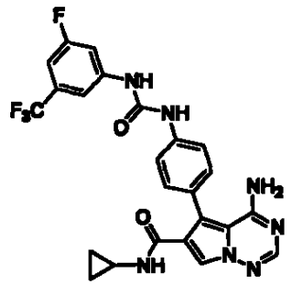
7,52 (d, *J* = 8,6 Hz, 2H), 7,29 (d, *J* = 8,6 Hz, 2H), 7,21 (d, *J* = 8,1 Hz, 1H), 3,11 a 3,08 (m, 1H), 2,62 (d, *J* = 3,4 Hz, 3H); EM $[M+H]^+$ = 488,2; LCMS TR = 3,05.

Ejemplo 78: Preparación de 4-amino-*N*-ciclopropil-5-{4-[({[4-fluoro-3-(trifluorometil)fenil]amino}carbonil)amino]fenil}pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida



El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo el intermediario W con el intermediario X y sustituyendo [4-fluoro-3-(trifluorometil)fenil]carbamato de fenilo con (4-*ter*-butilpiridin-2-il)carbamato de fenilo. ^{1}H-RMN (CD_3OD) δ7,62 (s, 1H), 7,55 (dd, *J* = 7,8, 2,8 Hz, 1H), 7,47 (a, 1H), 7,34 a 7,27 (m, 1H), 7,24 (d, *J* = 8,4 Hz, 2H), 7,03 (d, *J* = 8,4 Hz, 2H), 6,91 (t, *J* = 9,6 Hz, 1H), 2,36 a 2,24 (m, 1H), 0,39 a 0,28 (m, 2H), 0,058 a -0,027 (m, 2H); EM $[M+H]^+$ = 514,2; LCMS TR = 3,11.

Ejemplo 79: Preparación de 4-amino-*N*-ciclopropil-5-{4-[({[3-fluoro-5-(trifluorometil)fenil]amino}carbonil)amino]fenil}pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida

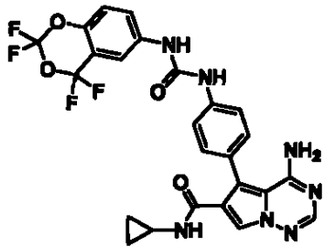


El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo el intermediario W con el intermediario X y sustituyendo [3-fluoro-5-(trifluorometil)fenil]carbamato de fenilo con (4-*ter*-

514

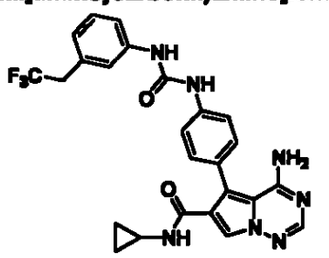
butilpiridin-2-il)carbamato de fenilo. ^{1}H-RMN (Acetona-d_6) δ7,67 (s, 1H), 7,51 (s, 1H), 7,33 (s, 1H), 7,24 (d, *J* = 1,5 Hz, 1H), 7,15 (d, *J* = 9,0 Hz, 2H), 6,92 (d, *J* = 9,0 Hz, 2H), 6,84 (d, *J* = 8,6 Hz, 1H), 2,74 a 2,69 (m, 1H), 2,29 a 2,21 (m, 1H), 0,24 a 0,15 (m, 2H), 0,045 a -0,021 (m, 2H); EM $[M+H]^+$ = 514,3; LCMS TR = 3,19.

Ejemplo 80: Preparación de 4-amino-*N*-ciclopropil-5-[4-({[(2,2,4,4-tetrafluoro-4*H*-1,3-benzodioxin-6-il)amino]carbonil}amino)fenil]pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida



El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo el intermediario W con el intermediario X y sustituyendo (2,2,4,4-tetrafluoro-4*H*-1,3-benzodioxin-6-il)carbamato de fenilo con (4-*ter*-butilpiridin-2-il)carbamato de fenilo. ^{1}H-RMN (CD_3OD) δ8,02 (d, *J* = 2,5 Hz, 1H), 7,98 (s, 1H), 7,84 (s, 1H), 7,67 (dd, *J* = 9,1, 2,8 Hz, 1H), 7,61 (d, *J* = 8,8 Hz, 2H), 7,40 (d, *J* = 8,4 Hz, 2H), 7,25 (d, *J* = 9,1 Hz, 1H), 2,72 a 2,63 (m, 1H), 0,73 a 0,65 (m, 2H), 0,42 a 0,35 (m, 2H); EM $[M+H]^+$ = 558,2; LCMS TR = 3,29.

Ejemplo 81: Preparación de 4-amino-*N*-ciclopropil-5-{4-[({[3-(2,2,2-trifluoroetil)fenil]amino}carbonil)amino]fenil}pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida

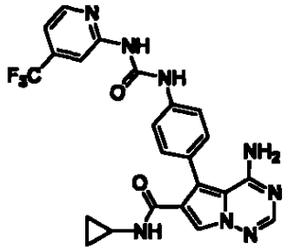


El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo el intermediario W con el intermediario

515

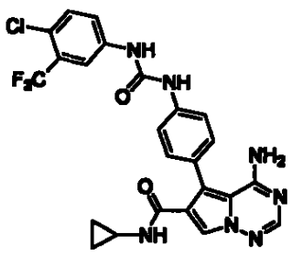
X y sustituyendo [3-(2,2,2-trifluoroetil)fenil]carbamato de fenilo con (4-*ter*-butilpiridin-2-il)carbamato de fenilo. ^{1}H-RMN (Acetona-d_6) δ7,64 (s, 1H), 7,47 (s, 1H), 7,38 (d, *J* = 4,0 Hz, 1H), 7,11 (d, *J* = 8,7 Hz, 2H), 7,06 (d, *J* = 8,7 Hz, 2H), 6,89 a 6,83 (m, 4H), 3,22 a 3,09 (m, 2H), 2,74 a 2,68 (m, 1H), 2,30 a 2,20 (m, 1H), 0,25 a 0,17 (m 2H), 0,040 a -0,027 (m, 2H); EM $[M+H]^+$ = 510,2; LCMS TR = 3,01.

Ejemplo 82: Preparación de 4-amino-*N*-ciclopropil-5-{4-[({[4-(trifluorometil)-piridin-2-il]amino}carbonil)amino]fenil}pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida



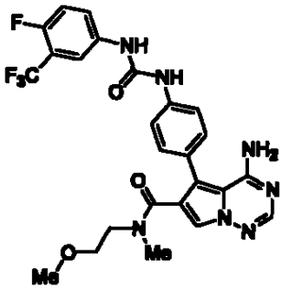
El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo el intermediario W con el intermediario X y sustituyendo [4-(trifluorometil)piridin-2-il]carbamato de fenilo con (4-*ter*-butilpiridin-2-il)carbamato de fenilo. ^{1}H-RMN (DMSO-d_6) δ8,52 (d, *J* = 5,8 Hz, 1H), 8,06 (s, 1H), 8,04 (s, 1H), 7,87 (s, 1H), 7,56 (d, *J* = 8,4 Hz, 2H), 7,34 (d, *J* = 5,0 Hz, 1H), 7,30 (d, *J* = 8,4 Hz, 2H), 3,12 a 3,09 (m, 1H), 2,68 a 2,60 (m, 1H), 0,62 a 0,55 (m 2H), 0,44 a 0,36 (m, 2H); EM $[M+H]^+$ = 497,2; LCMS TR = 2,94.

Ejemplo 83: Preparación de 4-amino-5-{4-[({[4-cloro-3-(trifluorometil)fenil]-amino}carbonil)amino]fenil}-*N*-ciclopropilpirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida



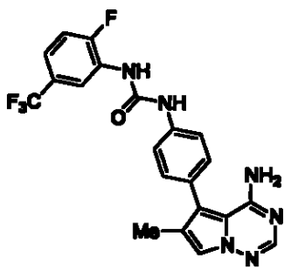
El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo el intermediario W con el intermediario X y sustituyendo [4-cloro-3-(trifluorometil)fenil]carbamato de fenilo con (4-*ter*-butilpiridin-2-il)carbamato de fenilo. ^{1}H-RMN (DMSO-d_6) δ8,11 (d, *J* = 2,4 Hz, 1H), 8,04 (s, 1H), 7,87 (s, 1H), 7,66 a 7,58 (m, 2H), 7,52 (d, *J* = 8,4 Hz, 2H), 7,26 (d, *J* = 8,4 Hz, 2H), 3,13 a 3,09 (m, 1H), 2,69 a 2,60 (m, 1H), 0,64 a 0,56 (m 2H), 0,43 a 0,37 (m, 2H); EM $[M+H]^+$ = 530,2; LCMS TR = 3,25.

Ejemplo 84: Preparación de 4-amino-5-{4-[({[4-fluoro-3-(trifluorometil)fenil]-amino}carbonil)amino]fenil}-*N*-(2-metoxietil)-*N*-metilpirrolo[2,1-*f*][1,2,4]-triazin-6-carboxamida



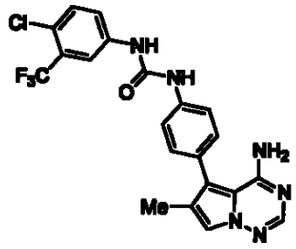
El procedimiento utilizado para la preparación del Ejemplo 69 se utilizó para preparar el compuesto del título sustituyendo 2-metoxi-*N*-metiletanamina con ciclopropanamina. ^{1}H-RMN (DMSO-d_6) δ9,07 (s, 1H), 8,98 a 8,91 (m, 1H), 8,01 a 7,97 (m, 1H), 7,90 (s, 1H), 7,87 a 7,81 (m, 1H), 7,68 a 7,60 (m, 1H), 7,59 a 7,50 (m, 2H), 7,48 a 7,40 (m, 1H), 7,17 a 7,10 (m, 1H), 3,44 a 3,40 (m, 2H), 3,25 a 3,10 (m, 5H), 2,83 (s, 3H – rotámero A), 2,65 (s, 3H – rotámero b) ; EM $[M+H]^+$ = 548,2; LCMS TR = 3,04 min; TLC R_f = 0,47 (55:40:5 v/v CH_2Cl_2-THF-EtOH).

Ejemplo 85: Preparación de *N*-[4-(4-amino-6-metilpirrolo[2,1-*f*][1,2,4]triazin-5-il)fenil]-*N'*-[2-fluoro-5-(trifluorometil)fenil]urea



El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo el intermediario T con el intermediario X y sustituyendo fenilo [2-fluoro-5-(trifluorometil)fenil]carbamato con fenilo (4-*ter*-butilpiridin-2-il)carbamato. ^{1}H-RMN (CD_3OD) δ8,61 (d, *J* = 2,6 Hz, 1H), 7,73 (s, 1H), 7,62 (d, *J* = 8,7 Hz, 2H), 7,49 (s, 1H), 7,37 a 7,31 (m, 4H), 2,14 (s, 3H); EM $[M+H]^+$ = 445,1; LCMS TR = 2,80.

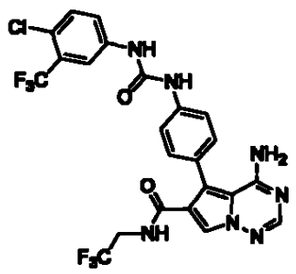
Ejemplo 86: Preparación de *N*-[4-(4-amino-6-metilpirrolo[2,1-*f*][1,2,4]triazin-5-il)fenil]-*N'*-[4-cloro-3-(trifluorometil)fenil]urea



El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo el intermediario T con el intermediario X y sustituyendo [4-cloro-3-(trifluorometil)fenil]carbamato de fenilo con (4-*ter*-butilpiridin-2-il)carbamato de fenilo. ^{1}H-RMN (CD_3OD) δ8,05 (d, *J* = 2,4 Hz, 1H), 7,73 (s, 1H), 7,67 a 7,58 (m, 3H), 7,50 (s, 1H), 7,48 (d, *J* = 8,1 Hz, 1H), 7,33 (d, *J* = 8,7 Hz, 2H), 2,18 (s, 3H); EM $[M+H]^+$ = 461,1; LCMS TR = 2,89.

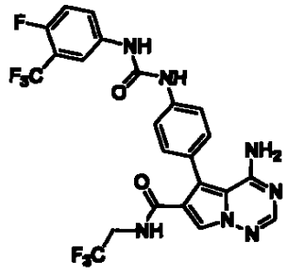
Ejemplo 87: Preparación de 4-amino-5-{4-[({[4-cloro-3-(trifluorometil)-fenil]amino}carbonil)amino]fenil}-*N*-(2,2,2-trifluoroetil)pirrolo[2,1-*f*][1,2,4]-triazin-6-carboxamida

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El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo el intermediario M con el intermediario X y sustituyendo [4-cloro-3-(trifluorometil)fenil]carbamato de fenilo con (4-*ter*-butilpiridin-2-il)carbamato de fenilo. ^{1}H-RMN (CD_3OD) δ8,04 (s, 1H), 8,00 (d, *J* = 2,4 Hz, 1H), 7,84 (s, 1H), 7,64 (dd, *J* = 8,4, 2,8 Hz, 1H), 7,59 (d, *J* = 8,4 Hz, 2H), 7,49 (d, *J* = 8,6 Hz, 1H), 7,38 (d, *J* = 8,4 Hz, 2H), 3,94 (q, *J* = 9,2 Hz, 2H); EM $[M+H]^+$ = 572,1; LCMS TR = 3,07.

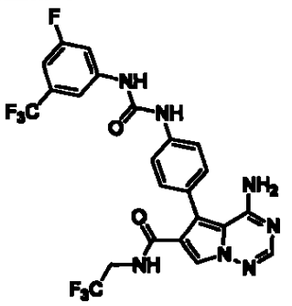
Ejemplo 88: Preparación de 4-amino-5-{4-[({[4-fluoro-3-(trifluorometil)fenil]-amino}carbonil)amino]fenil}-*N*-(2,2,2-trifluoroetil)pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida



El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo el intermediario M con el intermediario X y sustituyendo [4-fluoro-3-(trifluorometil)fenil]carbamato de fenilo con (4-*ter*-butilpiridin-2-il)carbamato de fenilo. ^{1}H-RMN (CD_3OD) δ8,04 (s, 1H), 7,90 (dd, *J* = 6,3, 2,7 Hz, 1H), 7,85 (s, 1H), 7,68 a 7,63 (m, 1H), 7,59 (d, *J* = 8,6 Hz, 2H), 7,39 (d, *J* = 8,7 Hz, 2H), 7,26 (t, *J* = 9,8 Hz, 1H), 3,94 (q, *J* = 9,2 Hz, 2H); EM $[M+H]^+$ = 556,1; LCMS TR = 2,94.

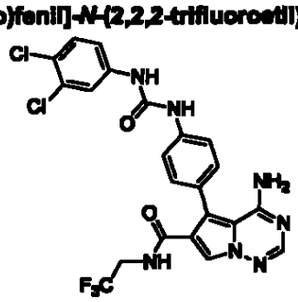
519

Ejemplo 89: Preparación de 4-amino-5-{4-[({[3-fluoro-5-(trifluorometil)fenil]-amino}carbonil)amino]fenil}-*N*-(2,2,2-trifluoroetil)pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida



El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo el intermediario M con el intermediario X y sustituyendo [3-fluoro-5-(trifluorometil)fenil]carbamato de fenilo con (4-*ter*-butilpiridin-2-il)carbamato de fenilo. ^{1}H-RMN (CD_3OD) δ8,04 (s, 1H), 7,84 (s, 1H), 7,66 a 7,53 (m, 4H), 7,38 (d, *J* = 8,7 Hz, 2H), 7,03 (d, *J* = 8,2 Hz, 1H), 3,94 (q, *J* = 9,2 Hz, 2H); EM $[M+H]^+$ = 556,1; LCMS TR = 3,02.

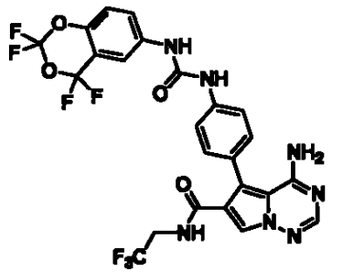
Ejemplo 90: Preparación de 4-amino-5-[4-({[[3,4-diclorofenil)amino]carbonil}-amino)fenil]-*N*-(2,2,2-trifluoroetil)pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida



El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo el intermediario M con el intermediario X y sustituyendo (3,4-diclorofenil)carbamato de fenilo con (4-*ter*-butilpiridin-2-il)carbamato de fenilo. ^{1}H-RMN (CD_3OD) δ 8,04 (s, 1H), 7,85 (s, 1H), 7,81 (d, *J* = 2,4 Hz, 1H), 7,58 (d, *J* = 8,8 Hz, 2H), 7,43 a 7,37 (m, 3H), 7,31 (dd, *J* = 8,9, 2,5 Hz, 1H), 3,94 (q, *J* = 9,2 Hz, 2H); EM $[M+H]^+$ = 538,1; LCMS TR = 2,97.

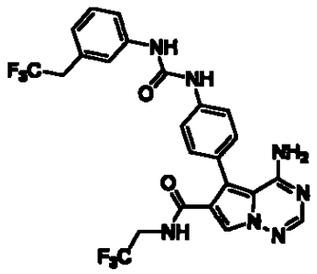
520

Ejemplo 91: Preparación de 4-amino-5-[4-({[(2,2,4,4-tetrafluoro-4*H*-1,3-benzodioxin-6-il)amino]carbonil}amino)fenil]-*N*-(2,2,2-trifluoroetil)pirrolo[2,1-f][1,2,4]triazin-6-carboxamida



El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo el intermediario M con el intermediario X y sustituyendo (2,2,4,4-tetrafluoro-4*H*-1,3-benzodioxin-6-il)carbamato de fenilo con (4-*ter*-butilpiridin-2-il)carbamato de fenilo. ^{1}H-RMN (CD_3OD) δ8,04 (s, 1H), 8,01 (d, *J* = 2,3 Hz, 1H), 7,84 (a, 1H), 7,66 (dd, *J* = 9,2, 2,8 Hz, 1H), 7,60 (d, *J* = 8,3 Hz, 2H), 7,39 (d, *J* = 8,3 Hz, 2H), 7,23 (d, *J* = 9,3 Hz, 1H), 3,94 (q, *J* = 9,2 Hz, 2H); EM $[M+H]^+$ = 600,0; LCMS TR = 3,11.

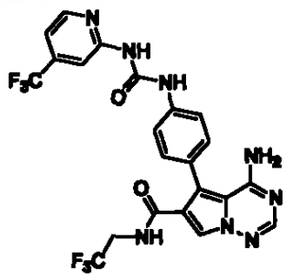
Ejemplo 92: Preparación de 4-amino-*N*-(2,2,2-trifluoroetil)-5-{4-[({[3-(2,2,2-trifluoroetil)fenil]amino}carbonil)amino]fenil}pirrolo[2,1-f][1,2,4]triazin-6-carboxamida



El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo el intermediario M con el intermediario X y sustituyendo [3-(2,2,2-trifluoroetil)fenil]carbamato de fenilo con (4-*ter*-butilpiridin-2-il)carbamato de fenilo. ^{1}H-RMN (CD_3OD) δ8,04 (s, 1H), 7,85 (s, 1H), 7,59 (d, *J* =

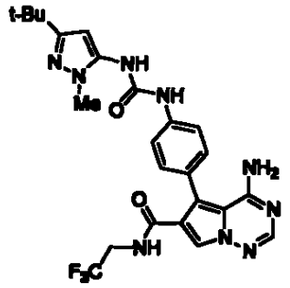
8,6 Hz, 2H), 7,46 (d, *J* = 8,6 Hz, 2H), 7,38 (d, *J* = 8,5 Hz, 2H), 7,26 (d, *J* = 8,5 Hz, 2H), 3,94 (q, *J* = 9,2 Hz, 2H), 3,42 (q, *J* = 10,2 Hz, 2H); EM $[M+H]^+$ = 552,1; LCMS TR = 2,84.

Ejemplo 93: Preparación de 4-amino-*N*-(2,2,2-trifluoroetil)-5-{4-[({[4-(trifluorometil)piridin-2-il]amino}carbonil)amino]fenil}pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida



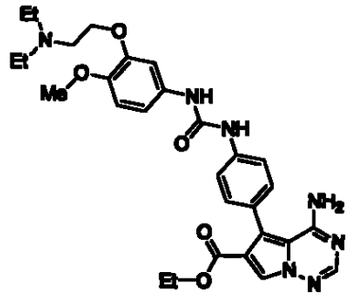
El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo el intermediario M con el intermediario X y sustituyendo [4-(trifluorometil)piridin-2-il]carbamato de fenilo con (4-*ter*-butilpiridin-2-il)carbamato de fenilo. ^{1}H-RMN (CD_3OD) δ8,54 (d, *J* = 5,1 Hz, 1H), 8,19 (s, 1H), 8,06 (br s, 1H), 7,91 (s, 1H), 7,60 (d, *J* = 8,7 Hz, 2H), 7,35 (d, *J* = 5,6 Hz, 2H), 7,31 (d, *J* = 8,9 Hz, 2H), 3,94 (q, *J* = 9,2 Hz, 2H); EM $[M+H]^+$ = 539,0; LCMS TR = 2,77.

Ejemplo 94: Preparación de 4-amino-5-[4-({[(3-*ter*-butil-1-metil-1*H*-pirazol-5-il)amino]carbonil}amino)fenil]-*N*-(2,2,2-trifluoroetil)pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida



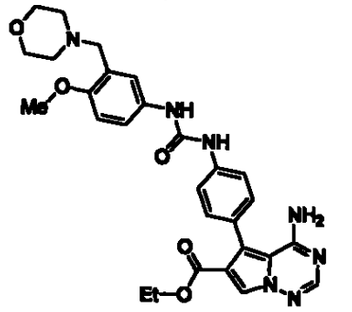
El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo el intermediario M con el intermediario X y sustituyendo (3-*ter*-butil-1-metil-1*H*-pirazol-5-il)carbamato de fenilo con (4-*ter*-butilpiridin-2-il)carbamato de fenilo. ^{1}H-RMN (CD_3OD) δ8,04 (s, 1H), 7,85 (s, 1H), 7,59 (d, *J* = 8,5 Hz, 2H), 7,39 (d, *J* = 8,7 Hz, 2H), 6,13 (s, 1H), 3,94 (q, *J* = 9,2 Hz, 2H), 3,70 (s, 3H), 1,28 (s, 9H); EM $[M+H]^+$ = 530,1; LCMS TR = 2,45.

Ejemplo 95: Preparación de 4-amino-5-{4-[({[3-[2-(dietilamino)etoxi]-4-metoxifenil}amino)carbonil]amino}fenil)pirrolo[2,1-*f*][1,2,4]triazin-6-carboxilato de etilo



El procedimiento utilizado para la preparación del Ejemplo 3 se utilizó para preparar el compuesto del título sustituyendo 3-[2-(dietilamino)etoxi]-4-metoxianilina con 4-fluoro-3-(trifluorometil)anilina. ^{1}H-RMN (CD_3OD) δ8,07 (s, 1H), 7,83 (s, 1H), 7,56 (d, *J* = 8,8 Hz, 2H), 7,33 (d, *J* = 8,9 Hz, 2H), 7,26 (s, 1H), 6,91 (d, *J* = 1,1 Hz, 2H), 4,20 a 4,10 (m, 4H), 3,81 (s, 3H), 3,16 a 2,99 (m, 2H), 2,86 a 2,74 (m, 4H), 1,18 a 1,10 (m, 9H); EM $[M+H]^+$ = 562,4; LCMS TR = 2,57.

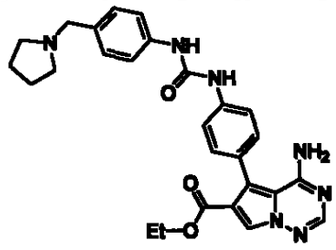
Ejemplo 96: Preparación de 4-amino-5-{4-[({[4-metoxi-3-(morfolin-4-ilmetil)-fenil]amino}carbonil)amino]fenil}pirrolo[2,1-*f*][1,2,4]triazin-6-carboxilato de etilo



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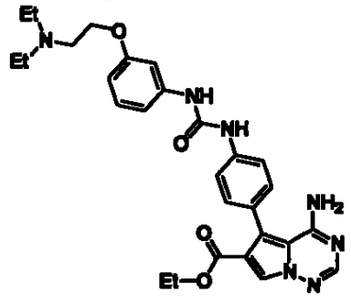
El procedimiento utilizado para la preparación del Ejemplo 3 se utilizó para preparar el compuesto del título sustituyendo 4-metoxi-3-(morfolin-4-ilmetil)anilina con 4-fluoro-3-(trifluorometil)anilina. ^{1}H-RMN (CD_3OD) δ8,11 (s, 1H), 7,91 (s, 1H), 7,50 (d, *J* = 8,5 Hz, 2H), 7,36 a 7,32 (m, 2H), 7,27 (d, *J* = 8,5 Hz, 2H), 6,89 (d, *J* = 9,6, 1H), 4,08 (q, *J* = 7,3 Hz, 2H), 3,71 (s, 2H), 3,59 a 3,53 (m, 4H), 3,28 (s, 3H), 2,39 a 2,33 (m, 4H), 1,08 (t, *J* = 7,2 Hz, 3H); EM $[M+H]^+$ = 546,2; LCMS TR = 2,47.

Ejemplo 97: Preparación de 4-amino-5-(4-[({[4-(pirrolidin-1-ilmetil)fenil]-amino}carbonil)amino]fenil)pirrolo[2,1-*f*][1,2,4]triazin-6-carboxilato de etilo



El procedimiento utilizado para la preparación del Ejemplo 3 se utilizó para preparar el compuesto del título sustituyendo 4-(pirrolidin-1-ilmetil)anilina con 4-fluoro-3-(trifluorometil)anilina. ^{1}H-RMN (CD_3OD) δ8,07 (s, 1H), 7,83 (s, 1H), 7,56 (d, *J* = 8,5 Hz, 2H), 7,47 (d, *J* = 8,5 Hz, 2H), 7,33 (t, *J* = 8,9 Hz, 4H), 4,13 (q, *J* = 7,3 Hz, 2H), 3,78 (s, 2H), 2,79 a 2,70 (m, 4H), 1,91 a 1,84 (m, 4H), 1,15 (t, *J* = 7,2 Hz, 3H); EM $[M+H]^+$ = 500,2; LCMS TR = 2,46.

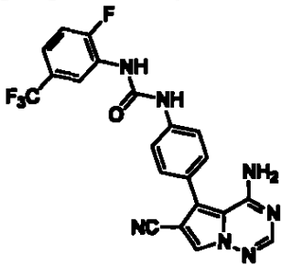
Ejemplo 98: Preparación de 4-amino-5-(4-[({3-[2-(dietilamino)etoxi]fenil}-amino)carbonil]amino}fenil)pirrolo[2,1-*f*][1,2,4]triazin-6-carboxilato de etilo



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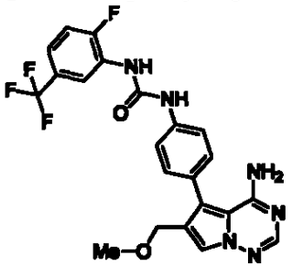
El procedimiento utilizado para la preparación del Ejemplo 3 se utilizó para preparar el compuesto del título sustituyendo 3-[2-(dietilamino)etoxi]anilina con 4-fluoro-3-(trifluorometil)anilina y purificando mediante HPLC (10-90% de ACN/H_2O). ^{1}H-RMN (CD_3OD) δ8,05 (s, 1H), 7,82 (s, 1H), 7,57 (d, *J* = 8,4 Hz, 2H), 7,35 a 7,30 (m, 3H), 7,20 (t, *J* = 8,0 Hz, 1H), 6,94 (dd, *J* = 7,9, 2,0 Hz, 1H), 6,63 (dd, *J* = 8,4, 1,9 Hz, 1H), 4,17 a 4,03 (m, 4H), 3,29 a 3,25 (m, 2H), 3,10 a 2,97 (m, 4H), 1,28 a 1,19 (m, 9H); EM $[M+H]^+$ = 532,4; LCMS TR = 2,57.

Ejemplo 99: Preparación de *N*-[4-(4-amino-8-cianopirrolo[2,1-f][1,2,4]triazin-5-il)fenil]-N'-[2-fluoro-5-(trifluorometil)fenil]urea



El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo el intermediario P con el intermediario X y sustituyendo [2-fluoro-5-(trifluorometil)fenil]carbamato de fenilo con (4-*ter*-butilpiridin-2-il)carbamato de fenilo. ^{1}H-RMN (CD_3OD) δ8,62 (d, *J* = 7,0 Hz, 1H), 8,19 (s, 1H), 7,91 (s, 1H), 7,69 (d, *J* = 8,6 Hz, 2H),7,50 (d, *J* = 8,6 Hz, 2H), 7,34 (d, *J* = 8,7 Hz, 2H); EM $[M+H]^+$ = 456,1; LCMS TR = 3,10.

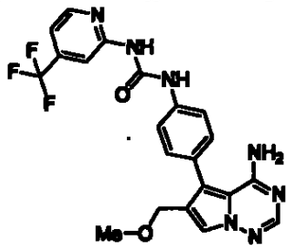
Ejemplo 100: Preparación de *N*-[4-[4-amino-8-(metoximetil)pirrolo[2,1-f][1,2,4]triazin-5-il]fenil]-N'-[2-fluoro-5-(trifluorometil)fenil]urea



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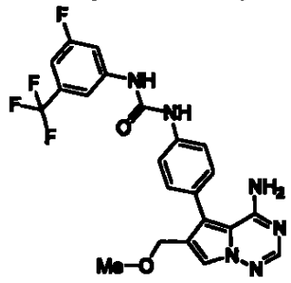
El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo el intermediario U con el intermediario X y sustituyendo [2-fluoro-5-(trifluorometil)fenil]carbamato de fenilo con (4-*ter*-butilpiridin-2-il)carbamato de fenilo. ^{1}H-RMN (CD_3OD) δ 8,61 (d, *J* = 7,6 Hz, 1H), 7,78 (s, 1H), 7,68 (s, 1H), 7,62 (d, *J* = 8,7 Hz, 2H),7,40 (d, *J* = 8,6 Hz, 2H), 7,33 (d, *J* = 8,7 Hz, 2H), 4,35 (s, 2H), 3,30 (s, 3H); EM $[M+H]^+$ = 475,2; LCMS TR = 2,81.

Ejemplo 101: **Preparación de *N*-(4-[4-amino-8-(metoximetil)pirrolo[2,1-f][1,2,4]triazin-5-il]fenil)-N'-[4-(trifluorometil)piridin-2-il]urea**



El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo el intermediario U con el intermediario X y sustituyendo fenilo [4-(trifluorometil)piridin-2-il]carbamato con fenilo (4-*ter*-butilpiridin-2-il)carbamato. ^{1}H-RMN (CD_3OD) □8,52 (d, *J* = 5,4 Hz, 1H), 7,79 (s, 1H), 7,76 (s, 1H), 7,71 a 7,67 (m, 3H),7,43 (d, *J* = 8,6 Hz, 2H), 7,28 (d, *J* = 5,3 Hz, 1H), 4,36 (s, 2H), 3,29 (s, 3H); EM $[M+H]^+$ = 456,1; LCMS TR = 2,66.

Ejemplo 102: **Preparación de *N*-(4-[4-amino-8-(metoximetil)pirrolo[2,1-f][1,2,4]triazin-5-il]fenil)-N'-[3-fluoro-5-(trifluorometil)fenil]urea**

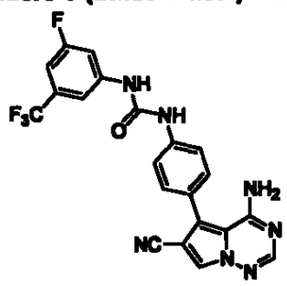


El procedimiento utilizado para la preparación del Ejemplo 76 se utilizó para preparar el compuesto del título sustituyendo el intermediario U con el intermediario

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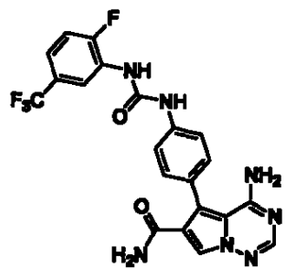
X y sustituyendo [3-fluoro-5-(trifluorometil)fenil]carbamato de fenilo con (4-*ter*-butilpiridin-2-il)carbamato de fenilo. ^{1}H-RMN (CD_3OD) δ 7,77 (s, 1H), 7,67 (s, 1H), 7,66 a 7,60 (m, 4H),7,39 (d, *J* = 8,5 Hz, 2H), 7,03 (d, *J* = 8,9 Hz, 1H), 4,34 (s, 2H), 3,20 (s, 3H); EM $[M+H]^+$ = 475,2; LCMS TR = 2,88.

Ejemplo 103: **Preparación de *N*-[4-(4-amino-6-cianopirrolo[2,1-f][1,2,4]triazin-5-il)fenil]-N'-[3-fluoro-5-(trifluorometil)fenil]urea**



El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo el intermediario P con el intermediario X y sustituyendo [3-fluoro-5-(trifluorometil)fenil]carbamato de fenilo con (4-*ter*-butilpiridin-2-il)carbamato de fenilo. ^{1}H-RMN (CD_3OD) δ8,18 (s, 1H), 7,90 (s, 1H), 7,70 a 7,62 (m, 3H),7,59 (s, 1H),□□□ (d, *J* = 8,9 Hz, 2H), 7,06 (d, *J* = 8,9 Hz, 1H); EM $[M+H]^+$ = 458,4; LCMS TR = 3,26.

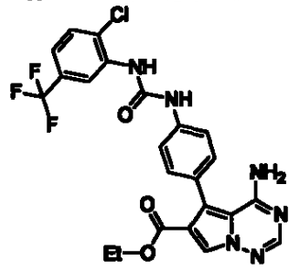
Ejemplo 104: **Preparación de 4-amino-5-{4-[({[2-fluoro-5-(trifluorometil)fenil]amino}carbonil)amino]fenil}pirrolo[2,1-f][1,2,4]triazin-6-carboxamida**



El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo el intermediario Q con el intermediario X y sustituyendo [2-fluoro-5-(trifluorometil)fenil]carbamato de fenilo con (4-*ter*-

butilpiridin-2-il)carbamato de fenilo. ^{1}H-RMN (CD_3OD) □8,61 (d, *J* = 7,9 Hz, 1H), 8,23 (s, 1H), 7,99 (s, 1H), 7,66 (d, *J* = 8,7 Hz, 2H), 7,46 (d, *J* = 8,7 Hz, 2H), 7,35 (d, *J* = 8,7 Hz, 2H); EM $[M+H]^+$ = 474,3; LCMS TR = 2,89.

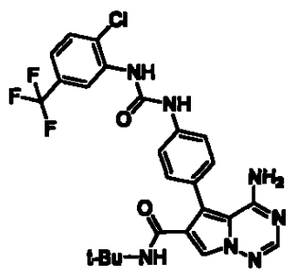
Ejemplo 105: Preparación de 4-amino-5-{4-[({[2-cloro-5-(trifluorometil)-fenil]amino}carbonil)amino]fenil}pirrolo[2,1-*f*][1,2,4]triazin-6-carboxilato de etilo



A una solución de DCE (5 ml) se agregó el intermediario B (300 mg, 1,01 mmol) seguido de 2-cloro-1-isocianato-4-(trifluorometil)benceno (0,32 ml, 2,12 mmol). La reacción se agitó bajo N_2 a temperatura ambiente durante 1 h, y luego se agregó HCl 2N ac (0,50 ml, 1,01 mmol) a la reacción seguido de DMF (5 ml). La solución se calentó durante otra hora. Al cabo del enfriamiento a ta la solución se diluyó con EtOAc, se transfirió a un embudo de separación, y se lavó con $NaHCO_3$ ac saturado. La capa acuosa se retro extrajo con EtOAc. Las capas orgánicas combinadas se recolectaron, se secaron, se concentraron, y se purificaron por cromatografía de columna (95:5 v/v CH_2Cl_2-MeOH). Las fracciones resultantes conteniendo el producto se concentraron y se trituraron utilizando CH_2Cl_2 y hexanos. El producto se filtró y se secó al vacío para dar 408 mg del compuesto anterior en forma de un sólido color blanco (0,79 mmol, rendimiento 78%). ^{1}H-RMN (DMSO-d_6) 59,72 (s, 1H), 8,67 (s, 1H), 8,64 (s, 1H), 8,13 (s, 1H), 8,08 (br s, 1H), 7,93 (s, 1H), 7,72 (d, *J* = 8,5 Hz, 1H), 7,56 (d, *J* = 8,8 Hz, 2H), 7,39 a 7,36 (m, 1H), 7,34 (d, *J* = 8,6 Hz, 2H), 5,10 (br s, 1H), 4,09 (q, *J* = 7,0 Hz, 2H), 1,12 (t, *J* = 7,1 Hz, 3H); EM $[M+H]^+$ = 519; LCMS TR = 3,58 min; TLC R_f = 0,26 (95:5 v/v CH_2Cl_2-MeOH).

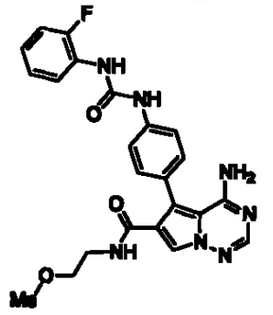
Ejemplo 106: Preparación de 4-amino-*N*-(*ter*-butil)-5-{4-[({[2-cloro-5-(trifluorometil)fenil]amino}carbonil)amino]fenil} pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida

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El procedimiento utilizado para la preparación del Ejemplo 105 se utilizó para preparar el compuesto del título sustituyendo el intermediario L con el intermediario B. ^{1}H-RMN (DMSO-d_6) δ 9,74 (s, 1H), 8,67 (s, 1H), 8,64 (d, J = 2,4 Hz, 1H), 8,03 (s, 1H), 7,89 (s, 1H), 7,72 (d, J = 7,5 Hz, 1H), 7,59 (d, J = 8,6 Hz, 2H), 7,39 (s, 1H), 7,36 (d, J = 8,7 Hz, 2H), 6,64 (s, 1H), 1,19 (s, 9H); EM $[M+H]^+$ = 546; LCMS TR = 3,09 min; TLC R_f = 0,47 (9:1 v/v CH_2Cl_2-MeOH).

Ejemplo 107: Preparación de 4-amino-5-[4-({[(2-fluorofenil)amino]-carbonil}amino)fenil]-*N*-(2-metoxietil)pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida

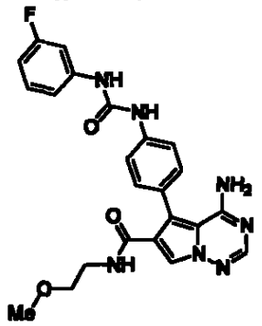


A un recipiente de EPA cargado con el intermediario N (50 mg, 0,11 mmol) se agregó CH_2Cl_2 (2 ml). Se agregó 1-fluoro-2-isocianatobenceno (15 mg, 0,11 mmol) y se agitó a temperatura ambiente durante 20 min. Luego la reacción se calentó a 42 °C y se agitó a esta temperatura durante la noche. Se corrió un TLC 3:7 v/v EtOAc-hexanos y mostró que la reacción había consumido casi todo el SM. Al recipiente se agregó TFA (100 µl). Se agitó durante toda la noche a temperatura ambiente. La LCMS mostró que se formó el producto deseado. La muestra se concentró por GeneVac y se agregó DMSO (2 ml). La muestra se purificó por LCMS Prep para dar 27,3 mg del compuesto anterior (0,059 mmol, rendimiento 58%). ^{1}H-RMN (DMSO-

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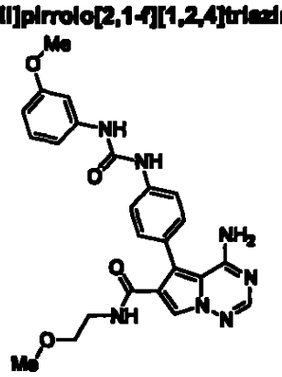
d_6) δ3,2 (s, 3H) 7,0 (m, 1H) 7,2 (t, *J* = 7,3 Hz, 1H) 7,2 (s, 1H) 7,3 (d, *J* = 7,3 Hz, 2H) 7,6 (d, *J* = 7,8 Hz, 3H) 7,6 (s, 2H) 7,9 (s, 1H) 8,2 (m, 3H) 8,6 (s, 1H) 9,2 (s, 1H). EM $[M+H]^+$ = 464; LCMS TR = 2,88 min.

Ejemplo 108: **Preparación de 4-amino-5-[4-({[(3-fluorofenil)amino]-carbonil}amino)fenil]-*N*-(2-metoxietil)pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida**



El procedimiento utilizado para la preparación del Ejemplo 107 se utilizó para preparar el compuesto del título sustituyendo 1-fluoro-3-isocianatobenceno con 1-fluoro-2-isocianatobenceno. ^{1}H-RMN (DMSO-d_6) δ3,2 (d, *J* = 11,2 Hz, 2H) 3,3 (d, *J* = 11,7 Hz, 2H) 3,3 (s, 1H) 6,8 (m, 1H) 7,1 (d, *J* = 7,8 Hz, 1H) 7,3 (d, *J* = 8,8 Hz, 1H) 7,5 (m, 4H) 7,6 (s, 2H) 7,9 (s, 1H) 8,1 (s, 2H) 9,0 (d, *J* = 19,6 Hz, 3H); EM $[M+H]^+$ = 464; LCMS TR = 2,90 min.

Ejemplo 109: **Preparación de 4-amino-*N*-(2-metoxietil)-5-[4-({[(3-metoxi-fenil)amino]carbonil}amino)fenil]pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida**

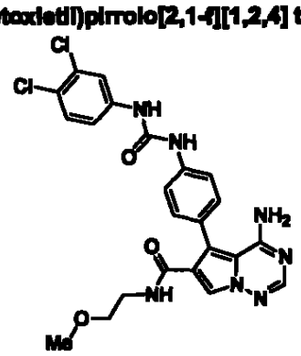


El procedimiento utilizado para la preparación del Ejemplo 107 se utilizó para preparar el compuesto del título sustituyendo 1-isocianato-3-metoxibenceno con 1-

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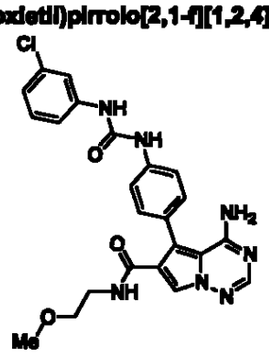
fluoro-2-isocianatobenceno. ^{1}H-RMN (DMSO-d_6) δ3,2 (s, 3H) 3,3 (m, 5H) 6,6 (d, *J* = 7,8 Hz, 1H) 7,0 (d, *J* = 8,3 Hz, 1H) 7,2 (m, 3H) 7,3 (d, *J* = 7,8 Hz, 2H) 7,6 (d, *J* = 7,8 Hz, 3H) 7,6 (s, 1H) 7,9 (s, 1H) 8,1 (s, 2H) 8,8 (s, 1H) 8,9 (s, 1H); EM $[M+H]^+$ = 476; LCMS TR = 2,84 min.

Ejemplo 110: Preparación de 4-amino-5-[4-({[(3,4-diclorofenil)amino] carbonil}amino)fenil]-*N*-(2-metoxietil)pirrolo[2,1-*f*][1,2,4] triazin-6-carboxamida



El procedimiento utilizado para la preparación del Ejemplo 107 se utilizó para preparar el compuesto del título sustituyendo 1,2-dicloro-4-isocianatobenceno con 1-fluoro-2-isocianatobenceno. ^{1}H-RMN (DMSO-d_6) δ 3,2 (s, 2H) 3,3 (d, *J* = 11,7 Hz, 2H) 3,3 (s, 1H) 7,3 (m, 4H) 7,5 (t, *J* = 8,3 Hz, 4H) 7,6 (s, 2H) 7,9 (d, *J* = 13,7 Hz, 1H) 8,1 (s, 2H) 8,0 (s, 1H) 9,1 (s, 1H); EM $[M+H]^+$ = 514; LCMS TR = 3,17 min.

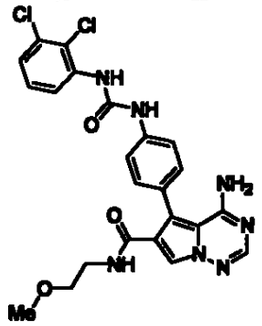
Ejemplo 111: Preparación de 4-amino-5-[4-({[(3-clorofenil)amino]-carbonil}amino)fenil]-*N*-(2-metoxietil)pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida



El procedimiento utilizado para la preparación del Ejemplo 107 se utilizó para preparar el compuesto del título sustituyendo 1-cloro-3-isocianatobenceno con 1-

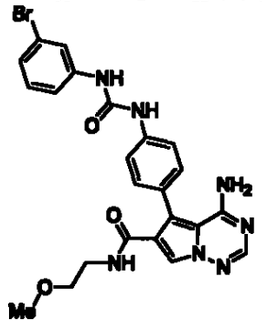
fluoro-2-isocianatobenceno. ^{1}H-RMN (DMSO-d_6) δ3,2 (s, 2H) 3,3 (d, *J* = 11,2 Hz, 3H) 3,3 (s, 2H) 7,0 (d, *J* = 6,4 Hz, 1H) 7,3 (m, 2H) 7,6 (d, *J* = 7,8 Hz, 3H) 7,6 (s, 2H) 7,7 (s, 1H) 7,9 (s, 1H) 8,1 (s, 2H) 9,0 (d, *J* = 4,9 Hz, 3H); EM [M+H]$^+$ = 480; LCMS TR = 3,02 min.

Ejemplo 112: **Preparación de 4-amino-5-[4-({[(2,3-diclorofenil)amino]-carbonil}amino)fenil]-*N*-(2-metoxietil)pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida**



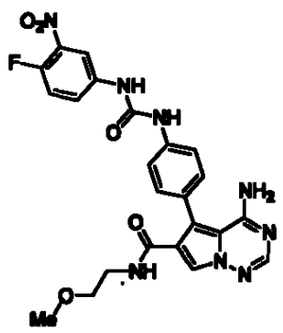
El procedimiento utilizado para la preparación del Ejemplo 107 se utilizó para preparar el compuesto del título sustituyendo 1,2-dicloro-3-isocianatobenceno con 1-fluoro-2-isocianatobenceno. ^{1}H-RMN (DMSO-d_6) δ3,2 (s, 1H) 3,3 (d, *J* = 5,9 Hz, 2H) 7,3 (s, 2H) 7,3 (d, *J* = 7,8 Hz, 4H) 7,6 (d, *J* = 8,3 Hz, 3H) 7,6 (s, 2H) 7,9 (s, 1H) 8,1 (s, 1H) 8,2 (d, *J* = 8,3 Hz, 1H) 8,5 (s, 1H) 9,7 (s, 1H); EM [M+H]$^+$ = 514; LCMS TR = 3,12 min.

Ejemplo 113: **Preparación de 4-amino-5-[4-({[(3-bromofenil)amino]-carbonil}amino)fenil]-*N*-(2-metoxietil)pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida**



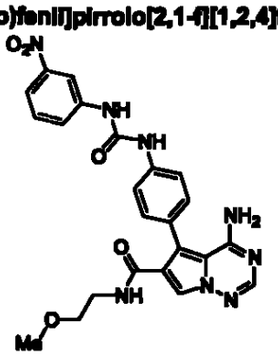
El procedimiento utilizado para la preparación del Ejemplo 107 se utilizó para preparar el compuesto del título sustituyendo 1-bromo-3-isocianatobenceno con 1-fluoro-2-isocianatobenceno. ^{1}H-RMN (DMSO-d_6) δ3,2 (s, 3H) 3,3 (m, 2H) 7,2 (d, *J* = 7,3 Hz, 1H) 7,3 (t, *J* = 7,6 Hz, 2H) 7,3 (d, *J* = 7,3 Hz, 4H) 7,6 (d, *J* = 8,3 Hz, 3H) 7,6 (s, 1H) 7,9 (s, 1H) 7,9 (s, 1H) 8,1 (s, 1H) 9,0 (s, 3H); EM $[M+H]^+$ = 524; LCMS TR = 3,04 min.

Ejemplo 114: Preparación de 4-amino-5-[4-({[(4-fluoro-3-nitrofenil)-amino]carbonil}amino)fenil]-*N*-(2-metoxietil)pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida



El procedimiento utilizado para la preparación del Ejemplo 107 se utilizó para preparar el compuesto del título sustituyendo 1-fluoro-4-isocianato-2-nitrobenceno con 1-fluoro-2-isocianatobenceno. ^{1}H-RMN (DMSO-d_6) δ 3,2 (s, 3H) 3,3 (m, 2H) 7,3 (d, *J* = 8,3 Hz, 3H) 7,5 (m, 4H) 7,7 (s, 1H) 7,7 (s, 1H) 7,9 (s, 1H) 8,1 (s, 1H) 8,5 (s, 1H) 9,1 (s, 1H) 9,3 (s, 1H); EM $[M+H]^+$ = 509; LCMS TR = 2,93 min.

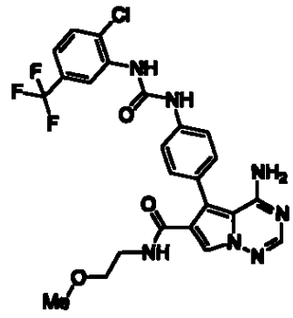
Ejemplo 115: Preparación de 4-amino-*N*-(2-metoxietil)-5-[4-({[(3-nitrofenil)amino]carbonil}amino)fenil]pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida



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El procedimiento utilizado para la preparación del Ejemplo 107 se utilizó para preparar el compuesto del título sustituyendo 1-isocianato-3-nitrobenceno con 1-fluoro-2-isocianatobenceno. ^{1}H-RMN (DMSO-d_6) δ 3,2 (s, 1H) 3,3 (d, J = 4,4 Hz, 1H) 3,3 (s, 1H) 7,3 (d, J = 7,8 Hz, 3H) 7,6 (d, J = 7,3 Hz, 5H) 7,7 (s, 2H) 7,7 (d, J = 7,8 Hz, 2H) 7,8 (d, J = 8,3 Hz, 2H) 8,0 (s, 1H) 8,1 (s, 1H) 8,6 (m, 1H) 9,1 (s, 1H) 9,3 (s, 1H); EM $[M+H]^+$ = 491; LCMS TR = 2,92 min.

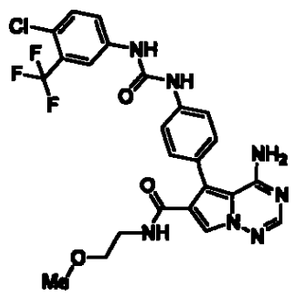
Ejemplo 116: Preparación de 4-amino-5-{4-[({[2-cloro-5-(trifluorometil)-fenil]amino}carbonil)amino]fenil}-*N*-(2-metoxietil)pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida



El procedimiento utilizado para la preparación del Ejemplo 107 se utilizó para preparar el compuesto del título sustituyendo 1-cloro-2-isocianato-4-(trifluorometil)benceno con 1-fluoro-2-isocianatobenceno. ^{1}H-RMN (DMSO-d_6) δ 3,2 (s, 2H) 3,3 (d, J = 11,7 Hz, 2H) 3,3 (s, 1H) 7,4 (dd, J = 16,9, 8,6 Hz, 3H) 7,6 (d, J = 7,8 Hz, 3H) 7,7 (s, 2H) 7,7 (d, J = 8,3 Hz, 2H) 8,0 (s, 1H) 8,1 (s, 2H) 8,7 (d, J = 12,2 Hz, 3H) 9,7 (s, 1H); EM $[M+H]^+$ = 548; LCMS TR = 3,24 min.

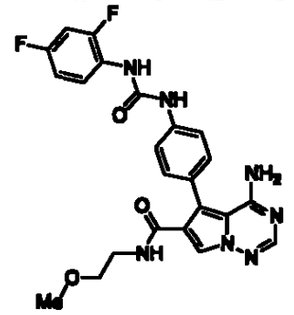
Ejemplo 117: Preparación de 4-amino-5-{4-[({[4-cloro-3-(trifluorometil)-fenil]amino}carbonil)amino]fenil}-*N*-(2-metoxietil)pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida

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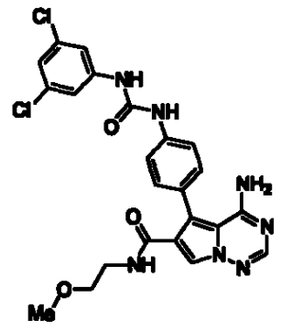
El procedimiento utilizado para la preparación del Ejemplo 107 se utilizó para preparar el compuesto del título sustituyendo 1-cloro-4-isocianato-2-(trifluorometil)benceno con 1-fluoro-2-isocianatobenceno. ^{1}H-RMN (DMSO-d_6) δ 3,2 (s, 1H) 3,3 (m, 2H) 7,3 (d, J = 7,3 Hz, 3H) 7,6 (d, J = 7,3 Hz, 3H) 7,6 (m, 4H) 7,9 (s, 1H) 8,1 (s, 3H) 9,1 (s, 1H) 9,3 (s, 2H); EM $[M+H]^+$ = 548; LCMS TR = 3,26 min.

Ejemplo 118: Preparación de 4-amino-5-[4-({[(2,5-difluorofenil)amino]-carbonil}amino)fenil]-*N*-(2-metoxietil)pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida



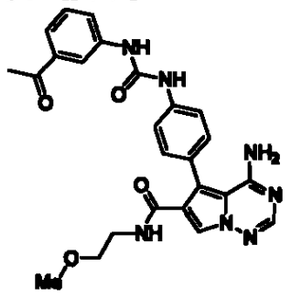
El procedimiento utilizado para la preparación del Ejemplo 107 se utilizó para preparar el compuesto del título sustituyendo 2,4-difluoro-1-isocianatobenceno con 1-fluoro-2-isocianatobenceno. ^{1}H-RMN (DMSO-d_6) δH) 6,8 (s, 1H) 7,3 (d, J = 7,8 Hz, 3H) 7,6 (d, J = 7,8 Hz, 2H) 7,6 (s, 1H) 7,9 (s, 1H) 8,1 (s, 2H) 8,8 (s, 1H) 9,3 (s, 1H); EM $[M+H]^+$ = 482; LCMS TR = 2,97 min.

Ejemplo 119: Preparación de 4-amino-5-[4-({[(3,5-diclorofenil)amino]-carbonil}amino)fenil]-*N*-(2-metoxietil)pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida



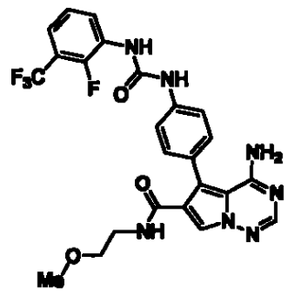
El procedimiento utilizado para la preparación del Ejemplo 107 se utilizó para preparar el compuesto del título sustituyendo 1,3-dicloro-5-isocianatobenceno con 1-fluoro-2-isocianatobenceno. ^{1}H-RMN (DMSO-d_6) δ3,2 (s, 3H) 3,3 (d, J = 17,1 Hz, 3H) 7,2 (s, 1H) 7,3 (d, J = 7,8 Hz, 3H) 7,6 (s, 6H) 7,6 (s, 2H) 8,1 (s, 2H) 9,1 (s, 1H) 9,1 (s, 1H); EM $[M+H]^+$ = 514; LCMS TR = 3,23 min.

Ejemplo 120: Preparación de 5-[4-({[[3-acetilfenil]amino]carbonil}amino)-fenil]-4-amino-*N*-(2-metoxietil)pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida



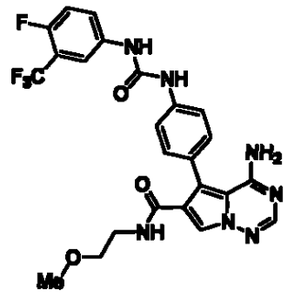
El procedimiento utilizado para la preparación del Ejemplo 107 se utilizó para preparar el compuesto del título sustituyendo 1-(3-isocianatofenil)etanona con 1-fluoro-2-isocianatobenceno. ^{1}H-RMN (DMSO-d_6) □3,2 (s, 1H) 3,3 (s, 1H) 3,3 (s, 1H) 7,3 (d, J = 7,8 Hz, 3H) 7,5 (t, J = 7,6 Hz, 2H) 7,6 (m, 7H) 7,7 (d, J = 7,3 Hz, 2H) 8,0 (s, 1H) 8,1 (d, J = 15,7 Hz, 3H) 8,9 (s, 2H) 9,0 (s, 1H); EM $[M+H]^+$ = 488; LCMS TR = 2,78 min.

Ejemplo 121: Preparación de 4-amino-5-{4-[({[2-fluoro-3-(trifluorometil)-fenil]amino}carbonil)amino]fenil}-*N*-(2-metoxietil)pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida



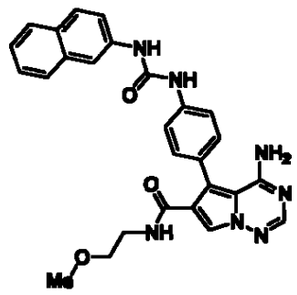
El procedimiento utilizado para la preparación del Ejemplo 107 se utilizó para preparar el compuesto del título sustituyendo 2-fluoro-1-isocianato-3-(trifluorometil)benceno con 1-fluoro-2-isocianatobenceno. ^{1}H-RMN (DMSO-d_6) δ3,2 (s, 3H) 3,3 (d, J = 16,6 Hz, 3H) 7,4 (m, 5H) 7,4 (a, 2H) 7,6 (d, J = 7,3 Hz, 4H) 7,6 (s, 2H) 7,9 (a, 1H) 8,1 (a, 2H) 8,5 (a, 2H) 8,9 (a, 1H) 9,3 (a, 2H); EM [M+H]$^+$ = 532; LCMS TR = 3,14 min.

Ejemplo 122: Preparación de 4-amino-5-{4-[({[4-fluoro-3-(trifluorometil)-fenil]amino}carbonil)amino]fenil}-*N*-(2-metoxietil)pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida



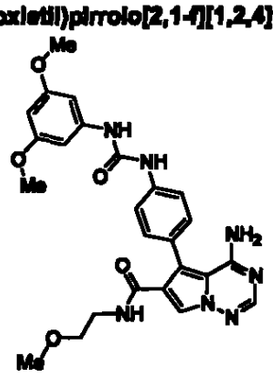
El procedimiento utilizado para la preparación del Ejemplo 107 se utilizó para preparar el compuesto del título sustituyendo 1-fluoro-4-isocianato-2-(trifluorometil)benceno con 1-fluoro-2-isocianatobenceno. ^{1}H-RMN (DMSO-d_6) □2,5 (m, 5H) 3,4 (s, 2H) 7,3 (d, J = 7,8 Hz, 2H) 7,5 (t, J = 9,5 Hz, 1H) 7,6 (d, J = 7,8 Hz, 2H) 7,6 (d, J = 4,9 Hz, 3H) 7,9 (s, 1H) 8,0 (d, J = 4,9 Hz, 1H) 8,1 (s, 1H) 9,0 (s, 1H) 9,1 (s, 1H); EM [M+H]$^+$ = 532; LCMS TR = 3,16 min.

Ejemplo 123: Preparación de 4-amino-*N*-(2-metoxietil)-5-(4-{[(2-naftilamino)carbonil]amino}fenil)pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida



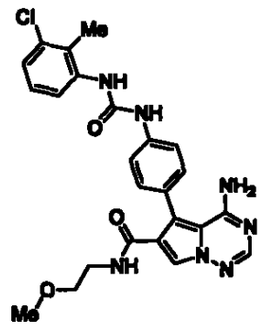
El procedimiento utilizado para la preparación del Ejemplo 107 se utilizó para preparar el compuesto del título sustituyendo 2-isocianatonaftaleno con 1-fluoro-2-isocianatobenceno. ^{1}H-RMN (DMSO-d_6) δ3,2 (s, 2H) 3,3 (d, J = 14,7 Hz, 2H) 7,4 (m, 4H) 7,5 (t, J = 7,3 Hz, 2H) 7,5 (d, J = 8,8 Hz, 2H) 7,6 (d, J = 8,3 Hz, 5H) 7,8 (m, 4H) 8,1 (s, 3H) 9,0 (s, 3H); EM $[M+H]^+$ = 496; LCMS TR = 3,07 min.

Ejemplo 124: Preparación de 4-amino-5-[4-({[(3,5-dimetoxifenil)amino]-carbonil}amino)fenil]-*N*-(2-metoxietil)pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida



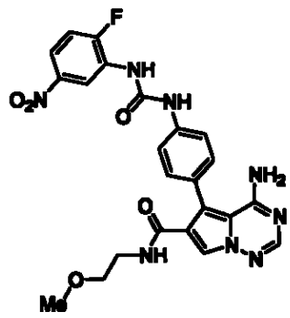
El procedimiento utilizado para la preparación del Ejemplo 107 se utilizó para preparar el compuesto del título sustituyendo 1-isocianato-3,5-dimetoxibenceno con 1-fluoro-2-isocianatobenceno. ^{1}H-RMN (DMSO-d_6) δ3,0 (s, 1H) 3,2 (s, 3H) 3,3 (m, 3H) 3,7 (s, 4H) 6,7 (s, 3H) 7,3 (d, J = 7,8 Hz, 3H) 7,5 (d, J = 7,8 Hz, 3H) 7,6 (s, 2H) 8,1 (s, 2H) 8,7 (s, 2H) 8,8 (s, 1H); EM $[M+H]^+$ = 506; LCMS TR = 2,88 min.

Ejemplo 125: Preparación de 4-amino-5-[4-({[(3-cloro-2-metilfenil)-amino]carbonil}amino)fenil]-*N*-(2-metoxietil)pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida



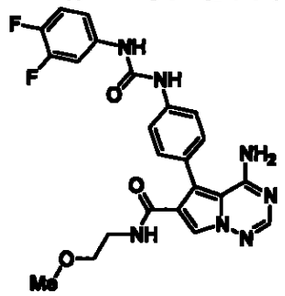
El procedimiento utilizado para la preparación del Ejemplo 107 se utilizó para preparar el compuesto del título sustituyendo 1-cloro-3-isocianato-2-metilbenceno con 1-fluoro-2-isocianatobenceno. ^{1}H-RMN (DMSO-d_6) δ2,3 (s, 3H) 2,5 (d, J = 16,6 Hz, 9H) 3,5 (s, 1H) 5,2 (s, 1H) 7,2 (m, 2H) 7,3 (d, J = 7,3 Hz, 2H) 7,6 (d, J = 7,8 Hz, 2H) 7,6 (s, 1H) 7,8 (d, J = 6,4 Hz, 1H) 7,9 (s, 1H) 8,1 (s, 1H) 8,2 (s, 1H) 9,2 (s, 1H); EM $[M+H]^+$ = 494; LCMS TR = 3,00 min.

Ejemplo 128: Preparación de 4-amino-5-[4-({[(2-fluoro-5-nitrofenil)-amino]carbonil}amino)fenil]-*N*-(2-metoxietil)pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida



El procedimiento utilizado para la preparación del Ejemplo 107 se utilizó para preparar el compuesto del título sustituyendo 1-fluoro-2-isocianato-4-nitrobenceno con 1-fluoro-2-isocianatobenceno. ^{1}H-RMN (DMSO-d_6) δ3,2 (s, 2H) 3,3 (d, J = 5,4 Hz, 1H) 3,3 (s, 1H) 7,4 (d, J = 8,3 Hz, 3H) 7,6 (t, J = 9,0 Hz, 5H) 7,7 (s, 2H) 7,9 (d, J = 11,2 Hz, 2H) 8,1 (s, 2H) 9,1 (s, 1H) 9,2 (s, 1H) 9,4 (s, 1H); EM $[M+H]^+$ = 509; LCMS TR = 2,95 min.

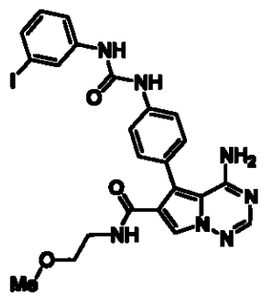
Ejemplo 127: Preparación de 4-amino-5-[4-({[(3,4-difluorofenil)amino]-carbonil}amino)fenil]-*N*-(2-metoxietil)pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida



El procedimiento utilizado para la preparación del Ejemplo 107 se utilizó para preparar el compuesto del título sustituyendo 1,2-difluoro-4-isocianatobenceno con 1-fluoro-2-isocianatobenceno. ^{1}H-RMN (DMSO-d_6) δ3,2 (s, 3H) 3,3 (m, 3H) 7,1 (d, J = 7,8 Hz, 1H) 7,3 (m, 4H) 7,6 (d, J = 8,3 Hz, 3H) 7,6 (s, 3H) 7,9 (s, 1H) 8,1 (s, 1H) 9,0 (d, J = 11,2 Hz, 3H); EM $[M+H]^+$ = 482; LCMS TR = 2,95 min.

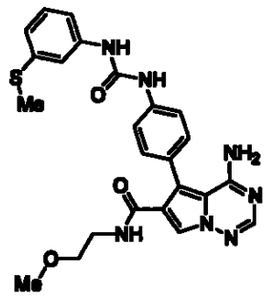
Ejemplo 128: Preparación de 4-amino-5-[4-({[(3-yodofenil)amino]-carbonil}amino)fenil]-*N*-(2-metoxietil)pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida

540



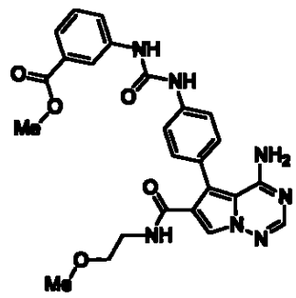
El procedimiento utilizado para la preparación del Ejemplo 107 se utilizó para preparar el compuesto del título sustituyendo 1-yodo-3-isocianatobenceno con 1-fluoro-2-isocianatobenceno. ^{1}H-RMN (DMSO-d_6) δ3,2 (s, 4H) 3,3 (m, 1H) 7,1 (t, J = 7,6 Hz, 1H) 7,3 (m, 5H) 7,5 (m, 3H) 7,6 (s, 1H) 7,9 (s, 1H) 8,0 (s, 1H) 8,1 (s, 2H) 8,9 (d, J = 18,6 Hz, 3H); EM $[M+H]^+$ = 572; LCMS TR = 3,09 min.

Ejemplo 129: Preparación de 4-amino-*N*-(2-metoxietil)-5-{4-[({[3-(metiltio)fenil]amino}carbonil)amino]fenil}pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida



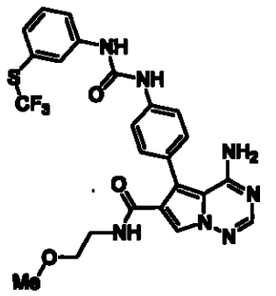
El procedimiento utilizado para la preparación del Ejemplo 107 se utilizó para preparar el compuesto del título sustituyendo 1-isocianato-3-(metiltio)benceno con 1-fluoro-2-isocianatobenceno. ^{1}H-RMN (DMSO-d_6) δ3,2 (s, 3H) 3,3 (m, 3H) 6,9 (d, J = 7,3 Hz, 1H) 7,2 (m, 3H) 7,3 (d, J = 7,3 Hz, 3H) 7,5 (s, 2H) 7,6 (d, J = 7,8 Hz, 3H) 7,6 (s, 2H) 7,9 (s, 1H) 8,1 (s, 2H) 8,6 (s, 1H) 8,9 (s, 2H); EM $[M+H]^+$ = 492; LCMS TR = 2,97 min.

Ejemplo 130: Preparación de 3-[({[4-(4-amino-6-{[(2-metoxietil)amino]-carbonil}pirrolo[2,1-*f*][1,2,4]triazin-5-il)fenil]amino}carbonil)amino]benzoato de metilo



El procedimiento utilizado para la preparación del Ejemplo 107 se utilizó para preparar el compuesto del título sustituyendo 3-isocianatobenzoato con 1-fluoro-2-isocianatobenceno de metilo. ^{1}H-RMN (DMSO-d_6) δ3,2 (s, 3H) 3,3 (m, 2H) 3,9 (s, 2H) 7,3 (d, *J* = 7,8 Hz, 3H) 7,4 (t, *J* = 7,6 Hz, 1H) 7,6 (d, *J* = 7,8 Hz, 4H) 7,6 (m, 3H) 7,9 (s, 1H) 8,1 (s, 2H) 8,2 (s, 1H) 8,9 (s, 1H) 9,0 (s, 1H); EM $[M+H]^+$ = 504; LCMS TR = 2,87 min.

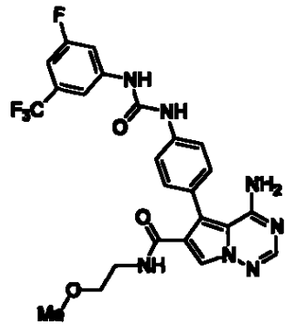
Ejemplo 131: Preparación de 4-amino-*N*-(2-metoxietil)-5-(4-[[({3-[(trifluorometil)tio]fenil}amino)carbonil]amino}fenil)pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida



El procedimiento utilizado para la preparación del Ejemplo 107 se utilizó para preparar el compuesto del título sustituyendo 1-isocianato-3-[(trifluorometil)tio]benceno con 1-fluoro-2-isocianatobenceno. ^{1}H-RMN (DMSO-d_6) □2,5 (d, *J* = 16,1 Hz, 9H) 5,2 (s, 1H) 7,3 (d, *J* = 7,3 Hz, 3H) 7,5 (t, *J* = 7,8 Hz, 1H) 7,6 (d, *J* = 6,4 Hz, 3H) 7,6 (s, 1H) 7,9 (s, 1H) 8,0 (s, 1H) 8,1 (s, 1H) 9,0 (s, 1H) 9,1 (s, 1H); EM $[M+H]^+$ = 546; LCMS TR = 3,26 min.

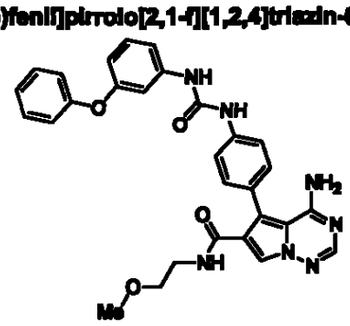
542

Ejemplo 132: **Preparación de 4-amino-5-{4-[({[3-fluoro-5-(trifluorometil)fenil]amino}carbonil)amino]fenil}-*N*-(2-metoxietil)pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida**



El procedimiento utilizado para la preparación del Ejemplo 107 se utilizó para preparar el compuesto del título sustituyendo 1-fluoro-3-isocianato-5-(trifluorometil)benceno con 1-fluoro-2-isocianatobenceno. ^{1}H-RMN (DMSO-d_6) δ 3,5 (s, 3H) 7,2 (s, 2H) 7,3 (d, *J* = 8,3 Hz, 4H) 7,6 (s, 2H) 7,8 (s, 4H) 7,7 (s, 2H) 8,1 (s, 2H) 9,1 (s, 2H) 9,3 (s, 2H); EM $[M+H]^+$ = 532; LCMS TR = 3,22 min.

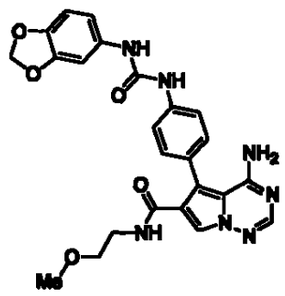
Ejemplo 133: **Preparación de 4-amino-*N*-(2-metoxietil)-5-[4-({[(3-fenoxifenil)amino]carbonil}amino)fenil]pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida**



El procedimiento utilizado para la preparación del Ejemplo 107 se utilizó para preparar el compuesto del título sustituyendo 1-isocianato-3-fenoxibenceno con 1-fluoro-2-isocianatobenceno. ^{1}H-RMN (DMSO-d_6) δ3,2 (s, 2H) 3,5 (s 2 H) 6,6 (s, 1H) 7,0 (d, *J* = 7,8 Hz, 2H) 7,2 (s, 3H) 7,3 (s, 2H) 7,3 (d, *J* = 7,8 Hz, 5H) 7,4 (s, 3H) 7,5 (s, 1H) 7,6 (s, 1H) 7,9 (s, 1H) 8,1 (s, 1H) 8,8 (d, *J* = 15,7 Hz, 3H); EM $[M+H]^+$ = 538; LCMS TR = 3,22 min.

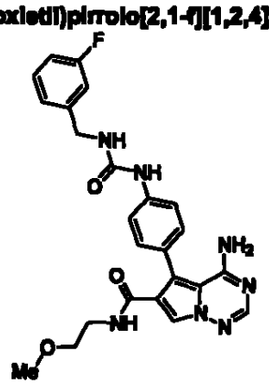
543

Ejemplo 134: **Preparación de 4-amino-5-(4-[[(1,3-benzodioxol-5-ilamino)carbonil]amino}fenil)-*N*-(2-metoxietil)pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida**



El procedimiento utilizado para la preparación del Ejemplo 107 se utilizó para preparar el compuesto del título sustituyendo 5-isocianato-1,3-benzodioxol con 1-fluoro-2-isocianatobenceno. ^{1}H-RMN (DMSO-d_6) δ3,2 (s, 2H) 6,0 (s, 5H) 6,8 (s, 2H) 7,2 (s, 2H) 7,3 (d, *J* = 7,3 Hz, 5H) 7,5 (s, 2H) 8,1 (s, 2H) 8,6 (s, 2H) 8,8 (s, 2H); EM $[M+H]^+$ = 490; LCMS TR = 2,78 min.

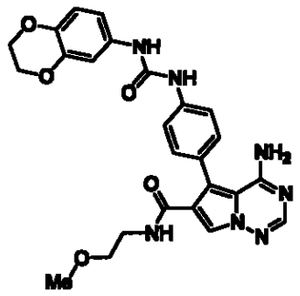
Ejemplo 135: **Preparación de 4-amino-5-[4-({[[3-fluorobencil)amino]-carbonil}amino)fenil]-*N*-(2-metoxietil)pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida**



El procedimiento utilizado para la preparación del Ejemplo 107 se utilizó para preparar el compuesto del título sustituyendo 1-fluoro-3-(isocianatometil)benceno con 1-fluoro-2-isocianatobenceno. ^{1}H-RMN (DMSO-d_6) δ4,3 (s, 3H) 6,8 (s, 2H) 7,1 (s, 1H) 7,1 (s, 4H) 7,3 (s, 4H) 7,4 (s, 1H) 7,5 (s, 4H) 7,9 (s, 1H) 8,1 (s, 2H) 8,8 (s, 2H); EM $[M+H]^+$ = 478; LCMS TR = 2,82 min.

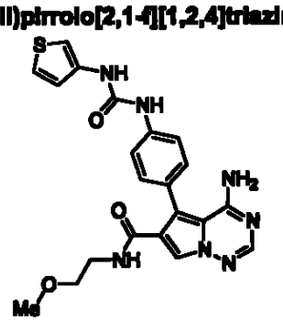
544

Ejemplo 136: Preparación de 4-amino-5-(4-{[(2,3-dihidro-1,4-benzodioxin-6-ilamino)carbonil]amino}fenil)-*N*-(2-metoxietil)pirrolo[2,1-*f*]-[1,2,4]triazin-6-carboxamida



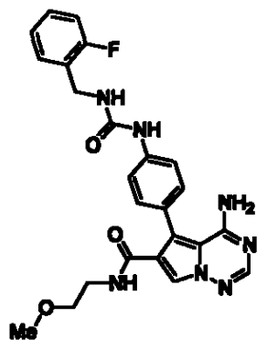
El procedimiento utilizado para la preparación del Ejemplo 107 se utilizó para preparar el compuesto del título sustituyendo 6-isocianato-2,3-dihidro-1,4-benzodioxina con 1-fluoro-2-isocianatobenceno. ^{1}H-RMN (DMSO-d_6) δ 3,0 (s, 3H) 3,2 (s, 2H) 3,5 (s, 2H) 6,8 (s, 2H) 7,1 (s, 1H) 7,3 (d, *J* = 7,3 Hz, 4H) 7,5 (s, 4H) 7,9 (s, 1H) 8,1 (s, 2H) 8,5 (s, 2H) 8,8 (s, 2H); EM $[M+H]^+$ = 504; LCMS TR = 2,78 min.

Ejemplo 137: Preparación de 4-amino-*N*-(2-metoxietil)-5-(4-{[(3-tienilamino)carbonil]amino}fenil)pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida



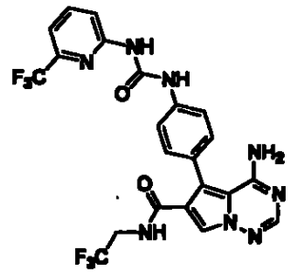
El procedimiento utilizado para la preparación del Ejemplo 107 se utilizó para preparar el compuesto del título sustituyendo 3-isocianatotiofeno con 1-fluoro-2-isocianatobenceno. ^{1}H-RMN (DMSO-d_6) δ3,0 (s, 4H) 7,3 (s, 5H) 7,6 (s, 3H) 7,9 (s, 2H) 8,1 (s, 3H) 8,8 (s, 2H) 9,0 (s, 2H); EM $[M+H]^+$ = 452; LCMS TR = 2,77 min.

Ejemplo 138: Preparación de 4-amino-5-[4-({[(2-fluorobencil)amino]-carbonil}amino)fenil]-*N*-(2-metoxietil)pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida



El procedimiento utilizado para la preparación del Ejemplo 107 se utilizó para preparar el compuesto del título sustituyendo 1-fluoro-2-(isocianatometil)benceno con 1-fluoro-2-isocianatobenceno. ^{1}H-RMN (DMSO-d_6) δ3,5 (s, 4H) 4,4 (s, 3H) 7,3 (d, J = 7,8 Hz, 9 H) 7,4 (s, 2H) 7,5 (s, H) 8,1 (s, 1H) 8,8 (s, 2H); EM $[M+H]^+$ = 476; LCMS TR = 2,82 min.

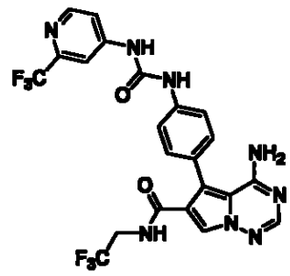
Ejemplo 139: Preparación de 4-amino-*N*-(2,2,2-trifluoroetil)-5-{4-[({[6-(trifluorometil)piridin-2-il]amino}carbonil)amino]fenil}pirrolo[2,1-*f*][1,2,4]-triazin-6-carboxamida



El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo el intermediario M con el intermediario X y sustituyendo [6-(trifluorometil)piridin-2-il]carbamato de fenilo con (4-*ter*-butilpiridin-2-il)carbamato de fenilo. ^{1}H-RMN (CD_3OD) δ 8,05 (s, 1H), 7,97 (s, 1H), 7,85 (s, 1H), 7,67 (d, J = 8,7 Hz, 2H), 7,56 (d, J = 8,7 Hz, 1H), 7,46 a 7,41 (m, 3H), 3,94 (q, J = 8,9 Hz, 2H); EM $[M+H]^+$ = 539,0; LCMS TR = 2,71.

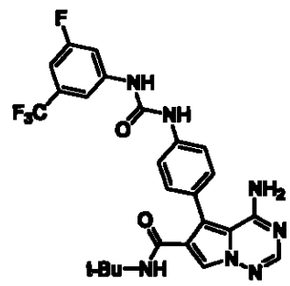
546

Ejemplo 140: Preparación de 4-amino-*N*-(2,2,2-trifluoroetil)-5-{4-[({[2-(trifluorometil)piridin-4-il]amino}carbonil)amino]fenil} pirrolo[2,1-*f*][1,2,4]-triazin-6-carboxamida



El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo el intermediario M con el intermediario X y sustituyendo [2-(trifluorometil)piridin-4-il]carbamato de fenilo con (4-*ter*-butilpiridin-2-il)carbamato de fenilo. ^{1}H-RMN (CD_3OD) δ8,47 (d, *J* = 5,9 Hz, 1H), 8,04 (s, 1H), 8,03 (d, *J* = 2,9 Hz,1H), 7,85 (s, 1H), 7,66 (dd, *J* = 5,4, 1,9 Hz, 1H), 7,62 (d, *J* = 8,9 Hz, 2H), 7,41 (d, *J* = 8,8 Hz, 2H), 3,94 (q, *J* = 9,2 Hz, 2H); EM $[M+H]^+$ = 539,0; LCMS TR = 2,56.

Ejemplo 141: Preparación de 4-amino-*N*-(*ter*-butil)-5-{4-[({[3-fluoro-5-(trifluorometil)fenil]amino}carbonil)amino]fenil} pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida

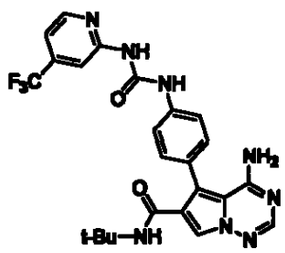


El procedimiento utilizado para la preparación del Ejemplo 105 se utilizó para preparar el compuesto del título sustituyendo el intermediario L con el intermediario B y sustituyendo 1-fluoro-3-isocianato-5-(trifluorometil)benceno con 1-cloro-2-isocianato-4-(trifluorometil)benceno. ^{1}H-RMN (DMSO-d_6) □9,34 (s, 1H), 9,14 (s, 1H),

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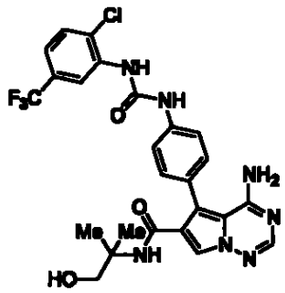
8,03 (s, 1H), 7,88 (s, 1H), 7,72 a 7,70 (m, 1H), 7,65 a 7,62 (m, 1H), 7,61 a 7,57 (m, 2H), 7,35 a 7,34 (m, 2H), 7,24 a 7,22 (m, 1H), 6,61 (m, 1H), 1,18 (s, 9H); EM $[M+H]^+$ = 530; LCMS TR = 3,09 min; TLC R_f = 0,54 (5:4:1 v/v/v CH_2Cl_2-EtOAc-MeOH).

Ejemplo 142: **Preparación de 4-amino-*N*-(*ter*-butil)-5-{4-[({[4-(trifluorometil)piridin-2-il]amino}carbonil)amino]fenil} pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida**



El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo el intermediario L con el intermediario X y sustituyendo [4-(trifluorometil)piridin-2-il]carbamato de fenilo con (4-*ter*-butilpiridin-2-il)carbamato de fenilo. ^{1}H-RMN (DMSO-d_6) δ9,91 (s, 1H), 9,76 (s, 1H), 8,54 a 8,53 (d, J = 5,1 Hz, 1H), 8,06 (s, 1H), 8,03 (s, 1H), 7,89 (s, 1H), 7,64 a 7,62 (d, J = 8,6 Hz, 2H), 7,37 a 7,35 (d, J = 8,6 Hz, 2H), 6,67 (s, 1H), 1,19 (s, 9H); EM $[M+H]^+$ = 513; LCMS TR = 2,84 min; TLC R_f = 0,37 (5:4:1 v/v/v CH_2Cl_2-EtOAc-MeOH).

Ejemplo 143: **Preparación de 4-amino-5-{4-[({[2-cloro-5-(trifluorometil)-fenil]amino}carbonil)amino]fenil}-*N*-(2-hidroxi-1,1-dimetiletil)pirrolo[2,1-*f*]-[1,2,4]triazin-6-carboxamida**

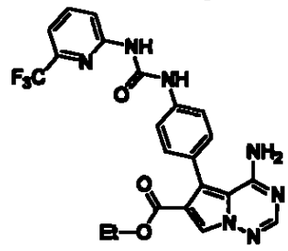


A una solución de DMF (2 ml) se agregó el intermediario J (50 mg, 0,10 mmol) seguido de benzotriazol-1-iloxitris(dimetilamino)fosfonio hexafluorofosfato (45 mg,

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0,10 mmol), 4-metilmorfolina (0,01 ml, 0,10 mmol), y 2-amino-2-metilpropan-1-ol (0,01 ml, 0,10 mmol). La solución se agitó bajo N_2 a temperatura ambiente durante 17 h. La mezcla de reacción se evaporó por evaporación rotativa y luego se purificó mediante cromatografía de columna (5:4:1 v/v/v CH_2Cl_2-EtOAc-MeOH) para dar 38 mg del compuesto anterior (0,068 mmol, rendimiento 67%) ^{1}H-RMN (DMSO-d_6) δ 9,73 (s, 1H), 8,67 (s, 1H), 8,64 (d, *J* = 2,2 Hz, 1H), 8,03 (s, 1H), 7,89 (s, 1H), 7,72 (d, *J* = 8,5 Hz, 1H), 7,59 (d, *J* = 8,6 Hz, 2H), 7,39 a 7,38 (m, 1H), 7,36 (d, *J* = 8,5 Hz, 2H), 6,52 (s, 1H), 4,77 (t, *J* = 5,8 Hz, 1H), 3,29 (d, *J* = 5,9 Hz, 2H), 1,12 (s, 6H); EM $[M+H]^+$ = 562; LCMS TR = 3,16 min; TLC R_f = 0,32 (5:4:1 v/v/v CH_2Cl_2-EtOAc-MeOH).

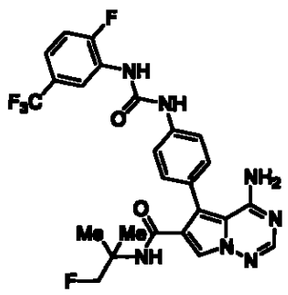
Ejemplo 144: **Preparación de 4-amino-5-{4-[({[6-(trifluorometil)piridin-2-il]amino}carbonil)amino]fenil} pirrolo[2,1-*f*][1,2,4]triazin-6-carboxilato de etilo**



El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo el intermediario B con el intermediario X y sustituyendo [6-(trifluorometil)piridin-2-il]carbamato de fenilo con (4-*ter*-butilpiridin-2-il)carbamato de fenilo. ^{1}H-RMN (DMSO-d_6) δ 9,89 (s, 1H), 9,74 (s, 1H), 8,13 (s, 1H), 8,02 a 7,97 (m, 2H), 7,92 (s, 1H), 7,55 (d, *J* = 9 Hz, 2H), 7,53 a 7,50 (m, 1H), 7,35 (d, *J* = 9 Hz, 2H), 5,12 (ba, 1H), 4,07 (q, *J* = 7 Hz, 2H), 1,09 (t, *J* = 7 Hz, 3H); EM $[M+H]^+$ = 486,0; LCMS TR = 2,92 min; TLC R_f = 0,38 (3:1 v/v CH_2Cl_2-THF).

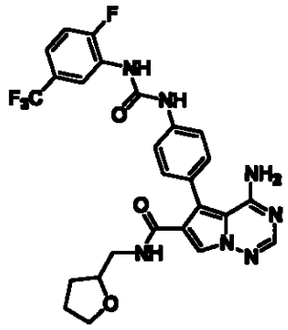
Ejemplo 145: **Preparación de 4-amino-*N*-(2-fluoro-1,1-dimetiletil)-5-{4-[({[2-fluoro-5-(trifluorometil)fenil]amino}carbonil) amino]fenil}pirrolo[2,1-*f*]-[1,2,4]triazin-6-carboxamida**

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El procedimiento utilizado para la preparación del Ejemplo 69 se utilizó para preparar el compuesto del título sustituyendo 1-fluoro-2-metilpropan-2-amina con ciclopropanamina. ^{1}H-RMN (DMSO-d_6) δ9,20 (bs, 1H), 8,60 (d, J = 7 Hz, 1H), 8,07 (s, 1H), 7,89 (s, 1H), 7,57 (d, J = 8Hz, 2H), 7,45 a 7,41 (m, 1H), 7,40 a 7,30 (m, 1H), 7,35 (d, J = 8 Hz, 2H), 6,86 (s, 1H), 5,02 (bs, 1H) 4,39 (d, J = 24 Hz, 2H), 1,15 (s, 9H); EM $[M+H]^+$ = 548,4; LCMS TR = 3,35 min; TLC R_f = 0,58 (3:2 v/v CH_2Cl_2-THF).

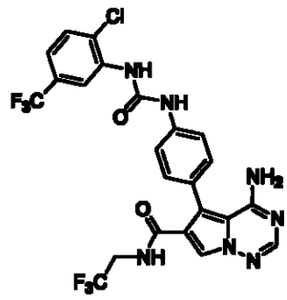
Ejemplo 148: Preparación de 4-amino-5-{4-[({[2-fluoro-5-(trifluorometil)-fenil]amino}carbonil)amino]fenil}-*N*-(tetrahidrofuran-2-ilmetil)pirrolo[2,1-*f*]-[1,2,4]triazin-6-carboxamida



El procedimiento utilizado para la preparación del Ejemplo 69 se utilizó para preparar el compuesto del título sustituyendo 1-(tetrahidrofuran-2-il)metanamina con ciclopropanamina. ^{1}H-RMN (DMSO-d_6) δ9,32 (s, 1H), 8,94 (d, J = 3 Hz, 1H), 8,63 a 8,59 (m. 1H), 8,08 (s, 1H), 7,89 (s, 1H), 7,60 a 7,55 (m, 1H), 7,54 (d, J = 8 Hz, 2H), 7,50 a 7,45 (m, 1H), 7,41 a 7,34 (m, 1H), 7,32 (d, J = 8 Hz, 2H), 5,01 (bs, 1H), 3,80 a 3,72 (m, 1H) 3,76 a 3,60 (m, 1H), 3,58 a 3,50 (m, 1H), 3,20 a 3,12 (m, 1H), 1,80 a

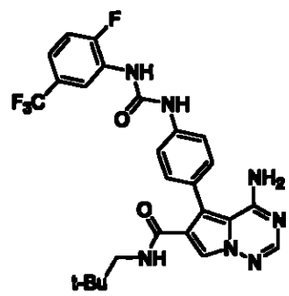
1,69 (m, 1H) ; EM $[M+H]^+$ = 558,3; LCMS TR = 3,13 min; TLC R_f = 0,29 (3:2 v/v CH_2Cl_2-THF).

Ejemplo 147: Preparación de 4-amino-5-{4-[({[2-cloro-5-(trifluorometil)-fenil]amino}carbonil)amino]fenil}-*N*-(2,2,2-trifluoroetil)pirrolo[2,1-*f*][1,2,4]-triazin-6-carboxamida



El procedimiento utilizado para la preparación del Ejemplo 143 se utilizó para preparar el compuesto del título sustituyendo 2,2,2-trifluoroetanamina con 2-amino-2-metilpropan-1-ol. ^{1}H-RMN (DMSO-d_6) δ9,70 (s, 1H), 8,67 (s, 1H), 8,64 (s, 1H), 8,52 (t, J = 6,2 Hz, 1H), 8,19 (s, 1H), 7,92 (s, 1H), 7,72 (d, J = 8,3 Hz, 1H), 7,54 (d, J = 8,7 Hz, 2H), 7,39 a 7,36 (m, 1H), 7,30 (d, J = 8,5 Hz, 2H), 3,98 a 3,91 (m, 2H); EM $[M+H]^+$ = 573; LCMS TR = 3,11 min; TLC R_f = 0,43 (5:4:1 v/v/v CH_2Cl_2-EtOAc-MeOH).

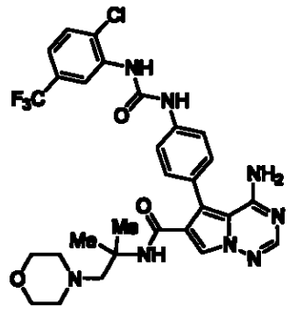
Ejemplo 148: Preparación de 4-amino-*N*-(2,2-dimetilpropil)-5-{4-[({[2-fluoro-5-(trifluorometil)fenil]amino}carbonil) amino]fenil}pirrolo[2,1-*f*][1,2,4]-triazin-6-carboxamida



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El procedimiento utilizado para la preparación del Ejemplo 69 se utilizó para preparar el compuesto del título sustituyendo 2,2-dimetilpropan-1-amina con ciclopropanamina. ^{1}H-RMN (DMSO-d_6) δ 9,33 (s, 1H), 8,94 (d, *J* = 3 Hz, 1H), 8,61 (dd, *J* = 7, 2 Hz, 1H), 8,06 (s, 1H), 7,89 (s, 1H), 7,57 (d, *J* = 9 Hz, 2H), 7,50 a 7,45 (m, 1H), 7,41 a 7,36 (m, 1H), 7,35 (d, *J* = 9 Hz, 2H) 7,26 (t, *J* = 6 Hz, 1H), 5,00 (bs, 1H), 2,91 (d, *J* = 6 Hz, 1H), 0,72 (s, 9H) ; EM $[M+H]^+$ = 544,5; LCMS TR = 3,13 min; TLC R_f = 0,51 (3:2 v/v CH_2Cl_2-THF).

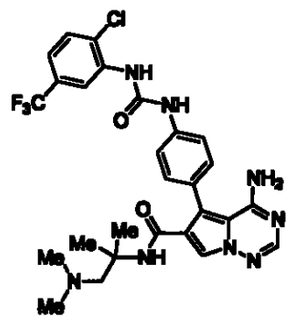
Ejemplo 149: Preparación de 4-amino-5-{4-[({[2-cloro-5-(trifluorometil)-fenil]amino}carbonil)amino]fenil}-*N*-(1,1-dimetil-2-morfolin-4-iletil)pirrolo[2,1-f][1,2,4]triazin-6-carboxamida



El procedimiento utilizado para la preparación del Ejemplo 66 se utilizó para preparar el compuesto del título sustituyendo el intermediario AC con el intermediario I. ^{1}H-RMN (CD_3OD) δ8,66 (d, *J* = 1,7 Hz, 1H), 7,95 (s, 1H), 7,83 (s, 1H), 7,72 (d, *J* = 8,8 Hz, 2H), 7,62 (d, *J* = 8,7 Hz, 1H), 7,47 (d, *J* = 8,8 Hz, 2H), 7,31 (dd, *J* = 8,5, 2,1 Hz, 1H), 3,62 a 3,53 (m, 4H), 2,44 (s, 2H), 2,42 a 2,34 (m, 4H), 1,18 (s, 6H); EM $[M+H]^+$ = 631,2; LCMS TR = 2,84.

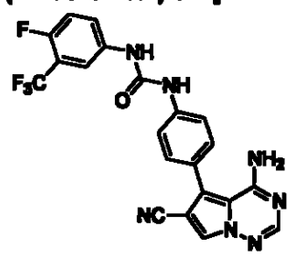
Ejemplo 150: Preparación de 4-amino-5-{4-[({[2-cloro-5-(trifluorometil)-fenil]amino}carbonil)amino]fenil}-*N*-[2-(dimetilamino)-1,1-dimetiletil]pirrolo-[2,1-f][1,2,4]triazin-6-carboxamida

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El procedimiento utilizado para la preparación del Ejemplo 66 se utilizó para preparar el compuesto del título sustituyendo el intermediario AC con el intermediario I y sustituyendo *N*-metilmetanamina con morfolina. ^{1}H-RMN (CD_3OD) δ 8,66 (s, 1H), 8,00 (s, 1H), 7,84 (s, 1H), 7,71 (d, *J* = 8,4 Hz, 2H), 7,63 (d, *J* = 8,7 Hz, 1H), 7,46 (d, *J* = 8,4 Hz, 2H), 7,32 (d, *J* = 8,9 Hz, 1H), 2,27 (s, 2H), 2,04 (s, 6H), 1,13 (s, 6H); EM $[M+H]^+$ = 456,1; EM $[M+H]^+$ = 589,4; LCMS TR = 2,50.

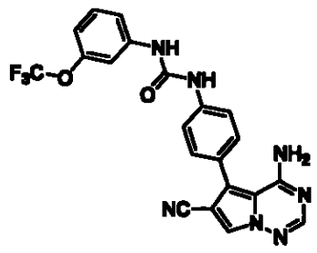
Ejemplo 151: Preparación de *N*-[4-(4-amino-6-cianopirrolo[2,1-*f*][1,2,4]-triazin-5-il)fenil]-*N'*-[4-fluoro-3-(trifluorometil)fenil]urea



El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo el intermediario P con el intermediario X y sustituyendo [4-fluoro-3-(trifluorometil)fenil]carbamato de fenilo con (4-*ter*-butilpiridin-2-il)carbamato de fenilo. ^{1}H-RMN (CD_3OD) δ 8,18 (s, 1H), 7,94 a 7,89 (m, 2H), 7,89 a 7,84 (m, 3H), 7,48 (d, *J* = 8,1 Hz, 2H), 7,26 (t, *J* = 9,9 Hz, 1H); EM $[M+H]^+$ = 456,1; LCMS TR = 3,09.

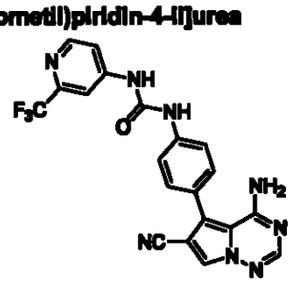
Ejemplo 152: Preparación de *N*-[4-(4-amino-6-cianopirrolo[2,1-*f*][1,2,4]-triazin-5-il)fenil]-*N'*-[3-(trifluorometoxi)fenil]urea

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El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo el intermediario P con el intermediario X y sustituyendo [3-(trifluorometoxi)fenil]carbamato de fenilo con (4-*ter*-butilpiridin-2-il)carbamato de fenilo. ^{1}H-RMN (CD_3OD) δ8,17 (s, 1H), 7,90 (s, 1H), 7,68 a 7,61 (m, 3H), 7,48 (d, *J* = 8,1 Hz, 2H), 7,40 a 7,29 (m, 2H), 6,91 (d, *J* = 8,0 Hz, 1H); EM $[M+H]^+$ = 454,1; LCMS TR = 3,11.

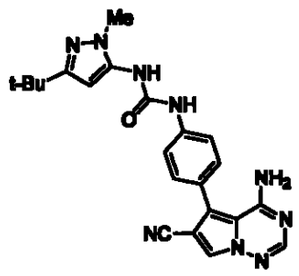
Ejemplo 153: **Preparación de *N*-[4-(4-amino-6-cianopirrolo[2,1-*f*][1,2,4]-triazin-5-il)fenil]-*N'*-[2-(trifluorometil)piridin-4-il]urea**



El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo el intermediario P con el intermediario X y sustituyendo [2-(trifluorometil)piridin-4-il]carbamato de fenilo con (4-*ter*-butilpiridin-2-il)carbamato de fenilo. ^{1}H-RMN (CD_3OD) δ 8,47 (d, *J* = 6,1 Hz, 1H), 8,18 (s, 1H), 8,05 (d, *J* = 2,2 Hz, 1H), 7,09 (s, 1H), 7,71 a 7,64 (m, 3H), 7,50 (d, *J* = 8,1 Hz, 2H); EM $[M+H]^+$ = 439,0; LCMS TR = 2,72.

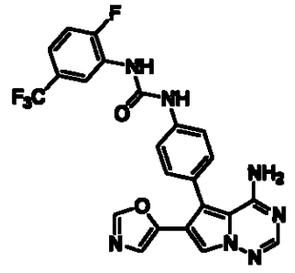
Ejemplo 154: **Preparación de *N*-[4-(4-amino-6-cianopirrolo[2,1-*f*][1,2,4]-triazin-5-il)fenil]-*N'*-(3-*ter*-butil-1-metil-1*H*-pirazol-5-il)urea**

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El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo el intermediario P con el intermediario X y sustituyendo (3-*ter*-butil-1-metil-1*H*-pirazol-5-il)carbamato de fenilo con (4-*ter*-butilpiridin-2-il)carbamato de fenilo. ^{1}H-RMN (CD_3OD) δ8,18 (s, 1H), 7,90 (s, 1H), 7,65 (d, *J* = 8,0 Hz, 2H), 7,47 (d, *J* = 8,0 Hz, 2H), 7,17 (m 1H), 7,11 (m, 1H), 6,13 (s, 1H), 3,71 (s, 3H), 1,28 (s, 9H); EM $[M+H]^+$ = 430,1; LCMS TR = 2,56.

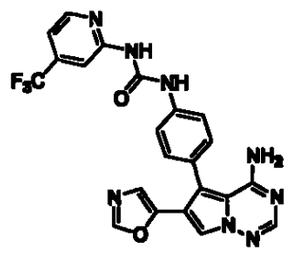
Ejemplo 155: **Preparación de *N*-(4-[4-amino-6-(1,3-oxazol-5-il)pirrolo-[2,1-f][1,2,4]triazin-5-il]fenil)-N'-[2-fluoro-5-(trifluorometil)fenil]urea**



El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo el intermediario AB con el intermediario X y sustituyendo [2-fluoro-5-(trifluorometil)fenil]carbamato de fenilo con (4-*ter*-butilpiridin-2-il)carbamato de fenilo. ^{1}H-RMN (CD_3OD) δ8,63 (d, *J* = 6,8 Hz, 1H), 8,13 (s, 1H), 7,98 (s, 1H), 7,83 (s, 1H), 7,69 (d, *J* = 8,5 Hz, 2H), 7,42 (d, *J* = 8,4 Hz, 2H), 7,35 (d, *J* = 8,3 Hz, 2H), 6,49 (s, 1H); EM $[M+H]^+$ = 498,1; LCMS TR = 2,82.

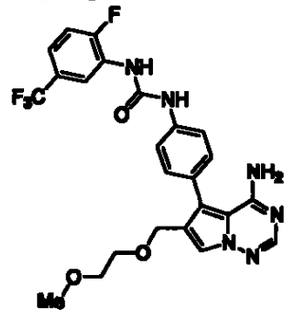
Ejemplo 156: **Preparación de *N*-(4-[4-amino-6-(1,3-oxazol-5-il)pirrolo-[2,1-f][1,2,4]triazin-5-il]fenil)-N'-[4-(trifluorometil)piridin-2-il]urea**

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El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo el intermediario AB con el intermediario X y sustituyendo [4-(trifluorometil)piridin-2-il]carbamato de fenilo con (4-*ter*-butilpiridin-2-il)carbamato de fenilo. ^{1}H-RMN (CD_3OD) δ8,50 (d, J = 5,3 Hz, 1H), 8,12 (s, 1H), 7,98 (s, 1H), 7,84 (s, 1H), 7,77 (s, 1H), 7,76 (d, J = 8,1 Hz, 2H), 7,45 (d, J = 8,0 Hz, 2H), 7,29 (d, J = 6,3 Hz, 1H), 6,51 (s, 1H); EM $[M+H]^+$ = 481,0; LCMS TR = 2,70.

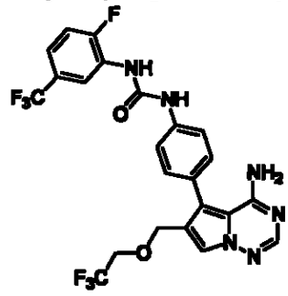
Ejemplo 157: **Preparación de *N*-(4-[4-amino-6-[(2-metoxietoxi)metil]-pirrolo[2,1-*f*][1,2,4]triazin-5-il]fenil)-*N*'-[2-fluoro-5-(trifluorometil)fenil]urea**



El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo el intermediario Z con el intermediario X y sustituyendo [2-fluoro-5-(trifluorometil)fenil]carbamato de fenilo con (4-*ter*-butilpiridin-2-il)carbamato de fenilo. ^{1}H-RMN (CD_3OD) δ8,62 (d, J = 8,0 Hz, 1H), 7,79 (s, 1H), 7,71 (s, 1H), 7,62 (d, J = 8,1, 2H), 7,44 (d, J = 8,2 Hz, 2H), 7,34 (d, J = 9,0 Hz, 2H), 4,45 (s, 2H), 3,59 a 3,48(m, 4H), 3,33 (s, 3H); EM $[M+H]^+$ = 519,2; LCMS TR = 3,13.

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Ejemplo 158: **Preparación de *N*-(4-[4-amino-6-[(2,2,2-trifluoroetoxi)-metil]pirrolo[2,1-f][1,2,4]triazin-5-il}fenil)-N'-[2-fluoro-5-(trifluorometil)fenil]-urea**



El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo el intermediario AA con el intermediario X y sustituyendo [2-fluoro-5-(trifluorometil)fenil]carbamato de fenilo con (4-*ter*-butilpiridin-2-il)carbamato de fenilo. ^{1}H-RMN (CD_3OD) δ8,53 (d, J = 6,7 Hz, 1H), 7,70 (s, 1H), 7,63 (s, 1H), 7,52 (d, J = 8,3, 2H), 7,33 (d, J = 8,3 Hz, 2H), 7,24 (d, J = 8,3 Hz, 2H), 4,47 (s, 2H), 4,00 (q, J = 7,9 Hz, 2H); EM $[M+H]^+$ = 543,3; LCMS TR = 3,10.

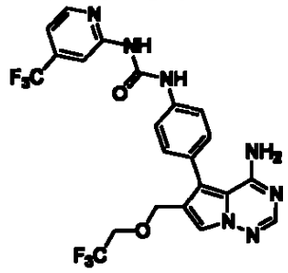
Ejemplo 159: **Preparación de *N*-(4-[4-amino-6-(1,3-oxazol-5-il)-pirrolo[2,1-f][1,2,4]triazin-5-il]fenil}-N'-[3-fluoro-5-(trifluorometil)fenil]urea**



El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo el intermediario AB con el intermediario X y sustituyendo [3-fluoro-5-(trifluorometil)fenil]carbamato de fenilo con (4-*ter*-butilpiridin-2-il)carbamato de fenilo. ^{1}H-RMN (CD_3OD) δ8,12 (s, 1H), 7,97 (s, 1H), 7,83 (s, 1H), 7,71 a 7,60 (m, 4H), 7,42 (d, J = 8,2 Hz, 2H), 7,05 (d, J = 8,1 Hz, 1H), 6,49 (s, 1H); EM $[M+H]^+$ = 498,2; LCMS TR = 2,90.

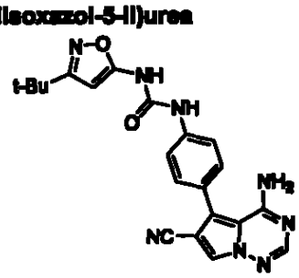
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Ejemplo 160: **Preparación de *N*-(4-[4-amino-8-[(2,2,2-trifluoroetoxi)-metil]pirrolo[2,1-*f*][1,2,4]triazin-5-il]fenil)-N'-[4-(trifluorometil)piridin-2-il]urea**



El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo el intermediario AA con el intermediario X y sustituyendo *[4-(trifluorometil)piridin-2-il]carbamato de fenilo* con *(4-ter-*butilpiridin-2-il)carbamato de fenilo. ^{1}H-RMN (DMSO-d_6) δ 9,90 (s, 1H), 9,75 (s, 1H), 8,53 (d, *J* = 4,7 Hz, 1H), 8,05 (s, 1H), 7,85 (s, 1H), 7,82 (s, 1H), 7,62 (d, *J* = 8,6 Hz, 2H), 7,39 a 7,32 (m, *J* = 8,0 Hz, 3H), 4,49 (s, 2H), 3,97 (q, *J* = 9,1 Hz, 2H); EM $[M+H]^+$ = 526,0; LCMS TR = 2,90.

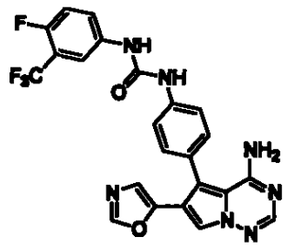
Ejemplo 161: **Preparación de *N*-[4-(4-amino-8-cianopirrolo[2,1-*f*][1,2,4]-triazin-5-il)fenil]-N'-(3-*ter*-butilisoxazol-5-il)urea**



El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo el intermediario P con el intermediario X y sustituyendo (3-*ter*-butilisoxazol-5-il)carbamato de fenilo con (4-*ter*-butilpiridin-2-il)carbamato de fenilo. ^{1}H-RMN (CD_3OD) δ8,17 (s, 1H), 7,90 (s, 1H), 7,68 (d, *J* = 7,8 Hz, 2H), 7,48 (d, *J* = 7,8 Hz, 2H), 6,13 (s, 1H), 1,31 (s, 9H); EM $[M+H]^+$ = 417,1; LCMS TR = 2,87.

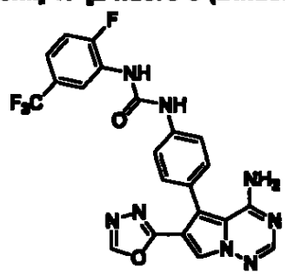
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Ejemplo 162: **Preparación de *N*-[4-[4-amino-8-(1,3-oxazol-5-il)pirrolo-[2,1-f][1,2,4]triazin-5-il]fenil]-N'-[4-fluoro-3-(trifluorometil)fenil]urea**



El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo el intermediario AB con el intermediario X y sustituyendo [4-fluoro-3-(trifluorometil)fenil]carbamato de fenilo con (4-*ter*-butilpiridin-2-il)carbamato de fenilo. ^{1}H-RMN (CD_3OD) δ8,12 (s, 1H), 7,97 (s, 1H), 7,92 (dd, *J* = 2,7, 6,2 Hz, 1H), 7,83 (s, 1H), 7,70 a 7,62 (m, 3H), 7,41 (d, *J* = 8,0 Hz, 2H), 7,28 (t, *J* = 9,5 Hz, 1H), 6,49 (s, 1H); EM $[M+H]^+$ = 498,2; LCMS TR = 3,14.

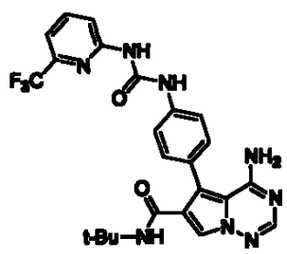
Ejemplo 163: **Preparación de *N*-[4-[4-amino-8-(1,3,4-oxadiazol-2-il)-pirrolo[2,1-*f*][1,2,4]triazin-5-il]fenil]-N'-[2-fluoro-5-(trifluorometil)fenil]urea**



El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo el intermediario AD con el intermediario X y sustituyendo [2-fluoro-5-(trifluorometil)fenil]carbamato de fenilo con (4-*ter*-butilpiridin-2-il)carbamato de fenilo. ^{1}H-RMN (CD_3OD) δ8,80 (s, 1H), 8,62 (d, *J* = 6,7 Hz, 1H), 8,28 (s, 1H), 7,89 (s, 1H), 7,64 (d, *J* = 8,2 Hz, 2H), 7,45 (d, *J* = 8,2 Hz, 2H), 7,34 (d, *J* = 8,9 Hz, 2H); EM $[M+H]^+$ = 499,2; LCMS TR = 2,82.

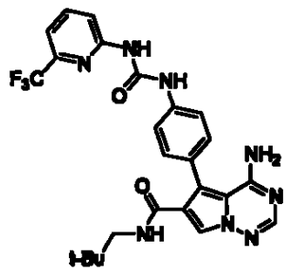
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Ejemplo 164: **Preparación de 4-amino-*N*-(*ter*-butil)-5-(4-[({[6-(trifluorometil)piridin-2-il]amino}carbonil)amino]fenil}pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida**



El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo el intermediario L con el intermediario X y sustituyendo [6-(trifluorometil)piridin-2-il]carbamato de fenilo con (4-*ter*-butilpiridin-2-il)carbamato de fenilo. ^{1}H-RMN (DMSO-d_6) δ9,88 (s, 1H), 9,73 (s, 1H), 8,05 a 7,99 (m, 1H), 8,04 (d, J = 8 Hz, h H), 7,88 (s, 1H), 7,55 (d, J = 8 Hz, 2H), 7,50 a 7,48 (m, 1H), 7,36 (d, J = 8 Hz, 2H), 6,66 (s, 1H), 5,00 (bs, 1H), 1,16 (s, 9H); EM $[M+H]^+$ = 513,1; LCMS TR = 2,84 min; TLC R_f = 0,64 (3:2 v/v CH_2Cl_2-THF).

Ejemplo 165: **Preparación de 4-amino-*N*-(2,2-dimetilpropil)-5-(4-[({[6-(trifluorometil)piridin-2-il]amino}carbonil)amino] fenil}pirrolo[2,1-*f*][1,2,4]-triazin-6-carboxamida**

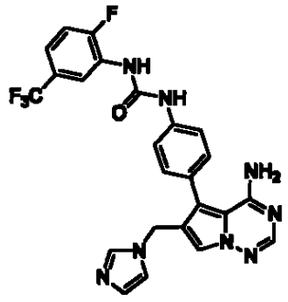


El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo el intermediario AE con el intermediario X y sustituyendo [6-(trifluorometil)piridin-2-il]carbamato de fenilo con (4-*ter*-butilpiridin-2-il)carbamato de fenilo. ^{1}H-RMN (DMSO-d_6) δ9,87 (s, 1H), 9,77 (s, 1H), 8,07 (s, 1H), 8,06 a 7,81 (m, 3 H), 7,89 (s, 1H), 7,54 (d, J = 8 Hz, 2H), 7,55 a 7,50 (m,

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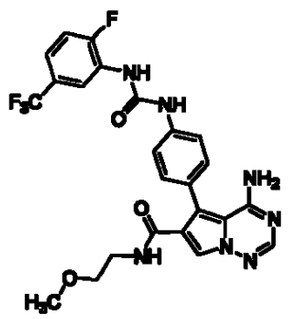
1H), 7,36 (d, *J* = 8 Hz, 2H), 7,28 a 7,20 (m, 1H), 4,95 (bs, 1H), 2,91 (d, *J* = 6 Hz, 2H), 0,72 (s, 9H); EM $[M+H]^+$ = 527,1; LCMS TR = 2,89 min; TLC R_f = 0,64 (3:2 v/v CH_2Cl_2-THF).

Ejemplo 166: Preparación de 1-[4-(4-amino-6-imidazol-1-ilmetil-pirrolo-[2,1-f][1,2,4]triazin-5-il)-fenil]-3-(2-fluoro-5-trifluorometil-fenil)-urea



El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo el intermediario AE con el intermediario X y sustituyendo [2-fluoro-5-(trifluorometil)fenil]carbamato de fenilo con (4-*ter*-butilpiridin-2-il)carbamato de fenilo: ^{1}H-RMN (CD_3OD) δ8,61 (d, *J* = 7,5 Hz, 1H), 7,80 (s, 1H), 7,72 (s, 1H), 7,61 (d, *J* = 8,6 Hz, 2H), 7,46 (s, 1H), 7,34 (d, *J* = 8,6 Hz, 2H), 7,24 (d, *J* = 8,4 Hz, 2H), 6,93 (d, *J* = 5,1 Hz, 2H), 5,17 (s, 2H); EM $[M+H]^+$ = 511,3; LCMS TR = 2,63 min.

Ejemplo 167: Preparación de 4-amino-5-[4-[({[2-fluoro-5-(trifluorometil)-fenil]amino}carbonil)amino]fenil]-*N*-(2-metoxietil)pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida

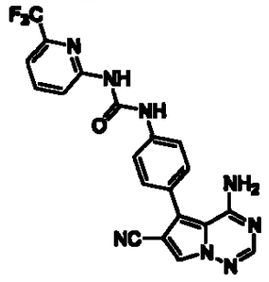


El procedimiento utilizado para la preparación del Ejemplo 69 se utilizó para preparar el compuesto del título sustituyendo 2-metoxietanamina con

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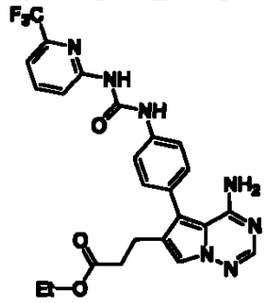
ciclopropanamina. ^{1}H-RMN (CD_3OD) δ8,62 (d, J = 7,5 Hz, 1H), 8,03 (s, 1H), 7,84 (s, 1H), 7,69 (d, J = 9,0 Hz, 2H), 7,45 (d, J = 9,0, 2H), 7,35 (d, J = 8,6 Hz, 2H), 3,39 a 3,34 (m, 4H), 3,24 (s, 3H); EM $[M+H]^+$ = 532,1; LCMS TR = 3,05 min.

Ejemplo 168: **Preparación de N-[4-(4-amino-8-cianopirrolo[2,1-f][1,2,4]-triazin-5-il)fenil]-N'-[6-(trifluorometil)piridin-2-il]urea**



El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo el intermediario P con el intermediario X y sustituyendo [6-(trifluorometil)piridin-2-il]carbamato de fenilo con (4-ter-butilpiridin-2-il)carbamato de fenilo. ^{1}H-RMN (DMSO-d_6) δ 9,89 (s, 1H), 9,75 (s, 1H), 8,51 (s, 1H), 8,03 a 7,99 (m, 3H), 7,63 (d, J = 8,4, 2H), 7,51 a 7,44 (m, 3H); EM $[M+H]^+$ = 439; LCMS TR = 2,62 min.

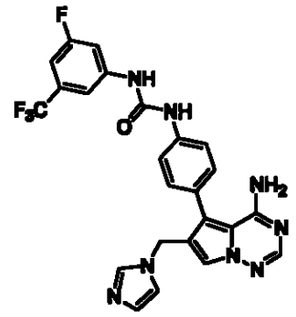
Ejemplo 169: **Preparación de 3-(4-amino-5-{4-[({[6-(trifluorometil)piridin-2-il]amino}carbonil)amino]fenil}pirrolo[2,1-f][1,2,4]triazin-8-il)propanoato de etilo**



El procedimiento utilizado para la preparación de intermediario I se utilizó para preparar el compuesto del título sustituyendo [6-(trifluorometil)piridin-2-il]carbamato de fenilo con [2-fluoro-5-(trifluorometil)fenil]carbamato de fenilo. ^{1}H-RMN (DMSO-d_6) δ 9,88 (s 1H), 9,73 (s, 1H), 8,05 a 7,98 (m, 3H), 7,79 (s, 1H), 7,61 a 7,57 (m, 3H),

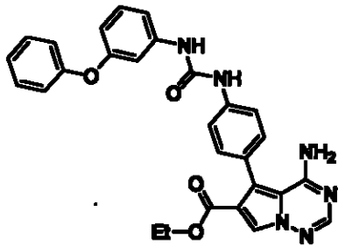
7,51 a 7,49 (m, 1H), 7,33 (d, *J* = 8,7, 2H), 4,03 a 3,97 (m, 2H), 2,74 a 2,70 (m, 2H), 2,55 a 2,51 (m, 2H), 1,15 a 1,11 (m, 3H); EM $[M+H]^+$ = 514; LCMS TR = 2,65 min.

Ejemplo 170: **Preparación de N-(4-[4-amino-6-(1H-imidazol-1-ilmetil)-pirrolo[2,1-*f*][1,2,4]triazin-5-il]fenil)-N'-[3-fluoro-5-(trifluorometil)fenil]urea**



El procedimiento utilizado para la preparación del Ejemplo 166 se utilizó para preparar el compuesto del título sustituyendo [3-fluoro-5-(trifluorometil)fenil]carbamato de fenilo con [2-fluoro-5-(trifluorometil)fenil]carbamato de fenilo. ^{1}H-RMN (CD_3OD) δ8,55 a 8,58 (m, 1H), 7,98 (s, 1H), 7,97 (s, 1H), 7,85 a 7,80 (m, 2H), 7,63 (d, J = 9 Hz, 2H), 7,41 a 7,43 (m, 1H), 7,2 a 7,4 (m, 1H), 7,25 (d, J = 9 Hz, 2H), 7,00 tp 7,1 (m, 1H), 5,46 (s, 2H), 4,89 (bs, 4H); EM $[M+H]^+$ = 511,0; LCMS TR = 2,29 min.

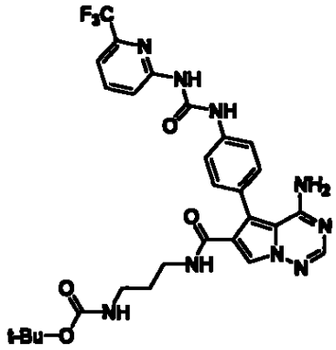
Ejemplo 171: **Preparación de 4-amino-5-[4-({[(3-fenoxifenil)amino]-carbonil}amino)fenil]pirrolo[2,1-*f*][1,2,4]triazin-6-carboxilato de etilo**



El procedimiento utilizado para la preparación del Ejemplo 1 se utilizó para preparar el compuesto del título sustituyendo 3-fenoxifenil isocianato con 1-fluoro-2-isocianato-4-(trifluorometil)benceno. ^{1}H-RMN (DMSO-d_6) δ8,60 (s, 1H), 8,82 (s, 1H), 8,11 (s, 1H), 7,91 (s, 1H), 7,50 a 7,48 (m, 2H), 7,41 a 7,37 (m, 2H), 7,29 a 7,25 (m,

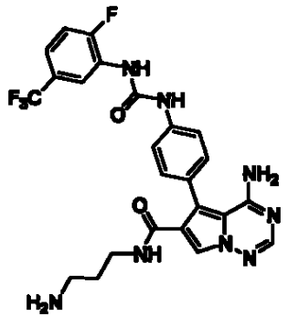
4H), 7,15 a 7,11 (m, 2H), 7,04 a 7,01 (m, 2H), 4,10 a 4,04 (m, 2H), 1,12 a 1,08 (m, 3H); EM $[M+H]^+$ = 509,1; LCMS TR = 3,48 min.

Ejemplo 172: **Preparación de (3-{[(4-amino-5-{4-[({[6-(trifluorometil)-piridin-2-il]amino}carbonil)amino] fenil}pirrolo[2,1-f][1,2,4] triazin-6-il)-carbonil]amino}propil)carbamato de ter-butilo**



El procedimiento utilizado para la preparación del Ejemplo 55 se utilizó para preparar el compuesto del título sustituyendo (3-aminopropil)carbamato de ter-butilo con N,N-dimetilpropano-1,3-diamina y [6-(trifluorometil)piridin-2-il]carbamato de fenilo con [2-fluoro-5-(trifluorometil)fenil]carbamato de fenilo. ^{1}H-RMN (DMSO-d_6) 59,88 (s, 1H), 9,72 (s, 1H), 8,06 a 7,97 (m, 3H), 7,89 (s, 1H), 7,78 a 7,75 (m, 1H), 7,53 a 7,48 (m, 3H), 7,33 a 7,31 (m, 2H), 6,75 a 6,72 (m, 1H), 3,11 a 3,06 (m, 2H), 2,91 a 2,86 (m, 2H), 1,52 a 1,48 (m, 2H), 1,35 (s, 9H); EM $[M+H]^+$ = 614,2; LCMS TR = 2,55 min.

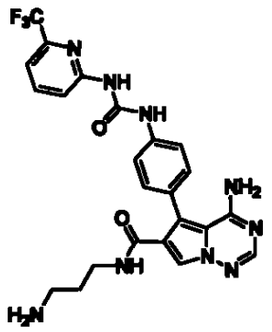
Ejemplo 173: **Preparación de 4-amino-N-(3-aminopropil)-5-{4-[({[2-fluoro-5-(trifluorometil)fenil]amino}carbonil) amino]fenil}pirrolo[2,1-f][1,2,4]-triazin-6-carboxamida**



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A una solución de DMF (5 ml) se agregó el intermediario G (100 mg, 0,21 mmol) y BOP (93 mg, 0,21 mmol) seguido de NMM (23 µl, 0,21 mmol), y (3-aminopropil)carbamato de ter-butilo (37 mg, 0,21 mmol). La reacción se dejó agitar bajo N_2 a temperatura ambiente durante 2h. La solución luego se diluyó con EtOAc (20 ml) y $NaHCO_3$ ac (20 ml), se transfirió a un embudo de separación, y se separó. La capa acuosa se retro extrajo con EtOAc (2 x 20 ml). Las capas orgánicas se combinaron, se secaron ($MgSO_4$), se filtraron, y se concentraron al vacío. El material bruto se purificó por cromatografía flash (9:1 v/v CH_2Cl_2/MeOH). El producto aislado, (3-{[(4-amino-5-{4-[({[2-fluoro-5-(trifluorometil)fenil]amino}-carbonil)amino]fenil}pirrolo[2,1-f][1,2,4]triazin-6-il)carbonil]amino}propil)carbamato de ter-butilo, se trató con CH_2Cl_2 (5 ml) y TFA (5 ml) y se dejó agitar bajo N_2 a temperatura ambiente durante 17h. La mezcla de reacción luego se concentró al vacío y se purificó por HPLC preparativa (10-90% de ACN/H_2O con 0,1% TFA). Las fracciones purificadas resultantes se diluyeron en EtOAc (20 ml) y $NaHCO_3$ ac (20 ml) y se separaron. La capa orgánica se lavó con H_2O, se aisló, se secó ($MgSO_4$), se filtró, y se concentró hasta sequedad produciendo 29 mg del compuesto anterior en forma de un sólido color blanco (0,055 mmol, rendimiento 26%). ^{1}H-RMN (DMSO-d_6) δ 9,59 a 9,55 (br s, 1H), 8,58 a 8,56 (d, J = 9,7 Hz, 1H), 8,05 (s, 1H), 7,89 (s, 1H), 7,76 a 7,74 (m, 1H), 7,57 a 7,55 (d, J = 8,5 Hz, 2H), 7,50 a 7,45 (m, 1H), 7,39 a 7,35 (m, 1H), 7,32 a 7,29 (d, J = 8,8 Hz, 2H), 3,19 a 3,14 (m, 2H), 2,57 a 2,54 (m, 2H), 1,57 a 1,50 (m, 2H); EM $[M+H]^+$ = 531,3; LCMS TR = 2,52 min.

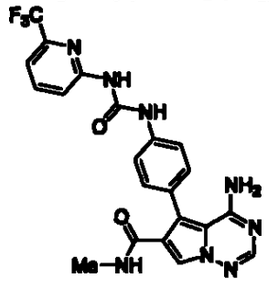
Ejemplo 174: Preparación de 4-amino-N-(3-aminopropil)-5-(4-[({[6-(trifluorometil)piridin-2-il]amino}carbonil)amino]fenil} pirrolo[2,1-f][1,2,4]-triazin-6-carboxamida



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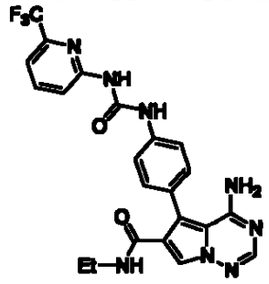
El procedimiento utilizado para la preparación del Ejemplo 173 se utilizó para preparar el compuesto del título sustituyendo el Ejemplo 250 con el intermediario G. ^{1}H-RMN (CD_3OD) δ 7,99 (s, 1H), 7,98 a 7,94 (m, 1H), 7,84 (s, 1H), 7,68 a 7,65 (m, 2H), 7,52 (d, *J* = 8,5, 1H), 7,47 a 7,43 (m, 3H), 3,35 (m, 2H), 2,83 a 2,80 (m, 2H), 1,82 a 1,75 (m, 2H); EM $[M+H]^+$ = 514,1; LCMS TR = 1,85 min.

Ejemplo 175: **Preparación de 4-amino-N-metil-5-{4-[({[6-(trifluorometil)-piridin-2-il]amino}carbonil)amino]fenil} pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida**



Una solución del intermediario AH (40mg, 1eq) y HATU (50mg, 1,5eq) en 1ml de DMF anhidro se agitó a temperatura ambiente durante 0,5 h. Luego la mezcla anterior se agregó a 0,2ml de solución de DMF anhidro de la amina (1,5eq). Se agregó trietilamina (26,5mg, 3eq) a la reacción y la reacción se agitó a temperatura ambiente durante toda la noche. La mezcla de reacción se purificó sin elaboración sobre LC-MS Prep utilizando gradiente Agua y Acetonitrilo con 0,1% de TFA como modificador. EM $[M+H]^+$ = 471,14; LCMS TR = 2,97 min.

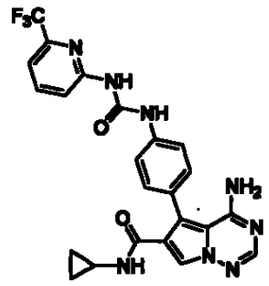
Ejemplo 176: **Preparación de 4-amino-N-etil-5-{4-[({[6-(trifluorometil)-piridin-2-il]amino}carbonil)amino]fenil} pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida**



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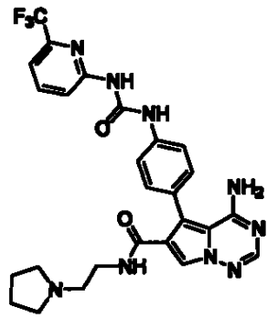
El procedimiento utilizado para la preparación del Ejemplo 175 se utilizó para preparar el compuesto del título sustituyendo etilamina con metilamina. EM $[M+H]^+$ = 485,16; LCMS TR = 2,91 min.

Ejemplo 177: **Preparación de 4-amino-N-ciclopropil-5-{4-[({[6-(trifluorometil)piridin-2-il]amino}carbonil)amino]fenil} pirrolo[2,1-f][1,2,4]-triazin-6-carboxamida**



El procedimiento utilizado para la preparación del Ejemplo 175 se utilizó para preparar el compuesto del título sustituyendo ciclopropilamina con metilamina. EM $[M+H]^+$ = 497,16; LCMS TR = 2,94 min.

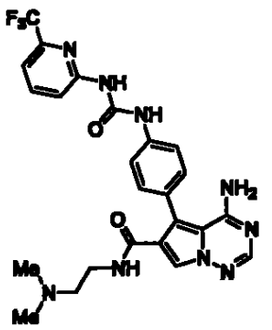
Ejemplo 178: **Preparación de 4-amino-N-(2-pirrolidin-1-iletil)-5-{4-[({[6-(trifluorometil)piridin-2-il]amino}carbonil)amino] fenil}pirrolo[2,1-f][1,2,4]-triazin-6-carboxamida**



El procedimiento utilizado para la preparación del Ejemplo 175 se utilizó para preparar el compuesto del título sustituyendo N-(2-aminoetil)-pirrolidina con metilamina. EM $[M+H]^+$ = 554,22; LCMS TR = 2,6 min.

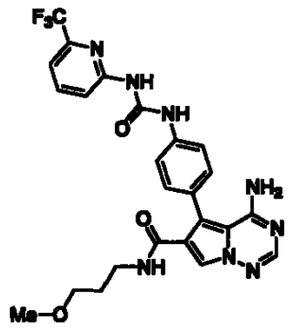
567

Ejemplo 179: **Preparación de 4-amino-N-[2-(dimetilamino)etil]-5-{4-[({[6-(trifluorometil)piridin-2-il]amino}carbonil) amino]fenil}pirrolo[2,1-f][1,2,4]-triazin-6-carboxamida**



El procedimiento utilizado para la preparación del Ejemplo 175 se utilizó para preparar el compuesto del título sustituyendo N,N-dimetiletilendiamina con metilamina. EM $[M+H]^+$ = 528,2; LCMS TR = 2,6 min.

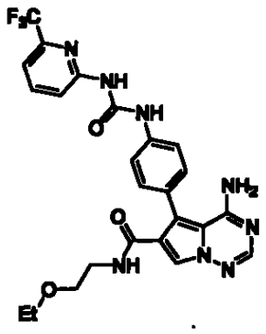
Ejemplo 180: **Preparación de 4-amino-N-(3-metoxipropil)-5-{4-[({[6-(trifluorometil)piridin-2-il]amino}carbonil) amino]fenil}pirrolo[2,1-f][1,2,4]-triazin-6-carboxamida**



El procedimiento utilizado para la preparación del Ejemplo 175 se utilizó para preparar el compuesto del título sustituyendo 3-metoxipropilamina con metilamina. EM $[M+H]^+$ = 528,18; LCMS TR = 2,9 min.

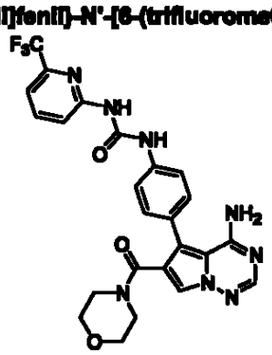
Ejemplo 181: **Preparación de 4-amino-N-(2-etoxietil)-5-{4-[({[6-(trifluorometil)piridin-2-il]amino}carbonil) amino]fenil}pirrolo[2,1-f][1,2,4]-triazin-6-carboxamida**

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El procedimiento utilizado para la preparación del Ejemplo 175 se utilizó para preparar el compuesto del título sustituyendo 2-etoxietilamina con metilamina. EM $[M+H]^+$ = 529,18; LCMS TR = 2,96 min.

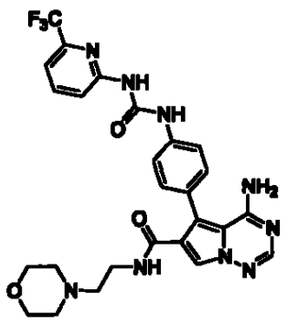
Ejemplo 182: Preparación de N-{4-[4-amino-6-(morfolin-4-ilcarbonil)-pirrolo[2,1-f][1,2,4]triazin-5-il]fenil}-N'-[6-(trifluorometil)piridin-2-il]urea



El procedimiento utilizado para la preparación del Ejemplo 175 se utilizó para preparar el compuesto del título sustituyendo morfolina con metilamina. EM $[M+H]^+$ = 527,17; LCMS TR = 2,84 min.

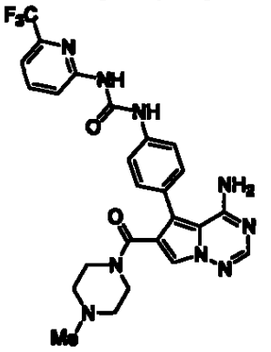
Ejemplo 183: Preparación de 4-amino-N-(2-morfolin-4-iletil)-5-(4-{[({[6-(trifluorometil)piridin-2-il]amino}carbonil)amino]fenil}pirrolo[2,1-f][1,2,4]-triazin-6-carboxamida

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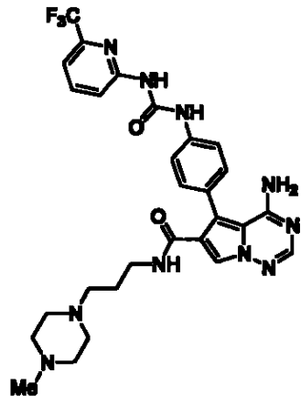
El procedimiento utilizado para la preparación del Ejemplo 175 se utilizó para preparar el compuesto del título sustituyendo 4-(2-aminoetil)morfolina con metilamina. EM $[M+H]^+$ = 570,21; LCMS TR = 2,58 min.

Ejemplo 184: Preparación de N-(4-(4-amino-6-[(4-metilpiperazin-1-il)-carbonil]pirrolo[2,1-f][1,2,4]triazin-5-il)fenil)-N'-[6-(trifluorometil)piridin-2-il]urea



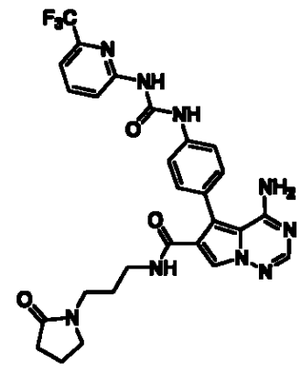
El procedimiento utilizado para la preparación del Ejemplo 175 se utilizó para preparar el compuesto del título sustituyendo 1-metilpiperazina con metilamina. EM $[M+H]^+$ = 540,2; LCMS TR = 2,55 min.

Ejemplo 185: Preparación de 4-amino-N-[3-(4-metilpiperazin-1-il)propil]-5-{4-[(([6-(trifluorometil)piridin-2-il]amino}carbonil)amino]fenil}pirrolo[2,1-f]-[1,2,4]triazin-6-carboxamida



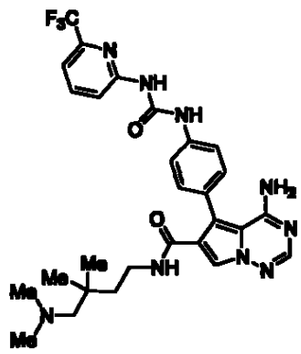
El procedimiento utilizado para la preparación del Ejemplo 175 se utilizó para preparar el compuesto del título sustituyendo 1-(3-aminopropil)-4- metilpiperazina con metilamina. EM $[M+H]^+$ = 597,26; LCMS TR = 2,5 min.

Ejemplo 186: Preparación de 4-amino-N-[3-(2-oxopirrolidin-1-il)propil]-5-{4-[({[6-(trifluorometil)piridin-2-il]amino}carbonil)amino]fenil}pirrolo[2,1-f]-[1,2,4]triazin-6-carboxamida



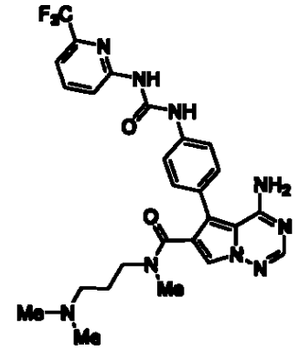
El procedimiento utilizado para la preparación del Ejemplo 175 se utilizó para preparar el compuesto del título sustituyendo 1-(3-aminopropil)-2- pirrolidinona con metilamina. EM $[M+H]^+$ = 582,21; LCMS TR = 2,81 min.

Ejemplo 187: Preparación de 4-amino-N-[4-(dimetilamino)-3,3-dimetilbutil]-5-{4-[({[6-(trifluorometil)piridin-2-il]amino}carbonil)amino]-fenil}pirrolo[2,1-f][1,2,4]triazin-6-carboxamida



El procedimiento utilizado para la preparación del Ejemplo 175 se utilizó para preparar el compuesto del título sustituyendo 2,2,N*1*,N*1*-tetrametil-butano-1,4-diamina con metilamina. EM $[M+H]^+$ = 570,25; LCMS TR = 2,65 min.

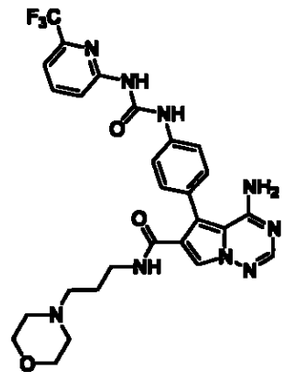
Ejemplo 188: Preparación de 4-amino-N-[3-(dimetilamino)propil]-N-metil-5-{4-[({[6-(trifluorometil)piridin-2-il]amino}carbonil)amino]fenil}-pirrolo[2,1-f][1,2,4]triazin-6-carboxamida



El procedimiento utilizado para la preparación del Ejemplo 175 se utilizó para preparar el compuesto del título sustituyendo N,N,N'-trimetil-1,3- propanodiamina con metilamina. EM $[M+H]^+$ = 556,23; LCMS TR = 2,57 min.

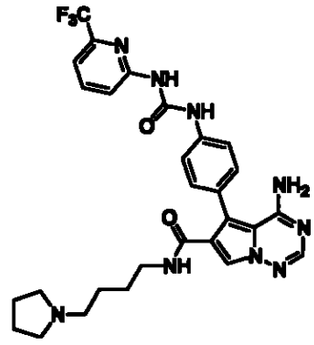
Ejemplo 189: Preparación de 4-amino-N-(3-morfolin-4-ilpropil)-5-{4-[({[6-(trifluorometil)piridin-2-il]amino}carbonil)amino]fenil}pirrolo[2,1-f][1,2,4]-triazin-6-carboxamida

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El procedimiento utilizado para la preparación del Ejemplo 175 se utilizó para preparar el compuesto del título sustituyendo 4-(3- aminopropil) morfolina con metilamina. EM $[M+H]^+$ = 584,23; LCMS TR = 2,6 min.

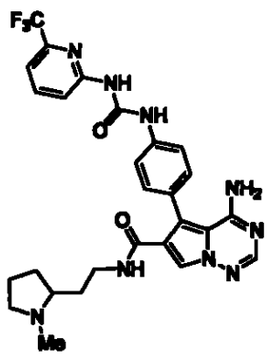
Ejemplo 190: **Preparación de 4-amino-N-(4-pirrolidin-1-ilbutil)-5-{4-[({[6-(trifluorometil)piridin-2-il]amino}carbonil) amino]fenil}pirrolo[2,1-f]-[1,2,4]triazin-6-carboxamida**



El procedimiento utilizado para la preparación del Ejemplo 175 se utilizó para preparar el compuesto del título sustituyendo 4-(1-pirrolidino)butilamina con metilamina. EM $[M+H]^+$ = 582,25; LCMS TR = 2,6 min.

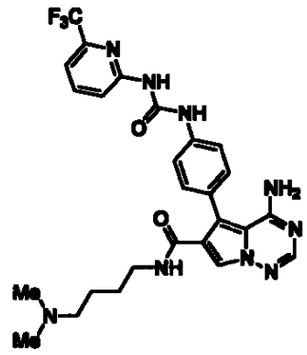
Ejemplo 191: **Preparación de 4-amino-N-[2-(1-metilpirrolidin-2-il)etil]-5-{4-[({[6-(trifluorometil)piridin-2-il]amino}carbonil)amino]fenil}pirrolo[2,1-f]-[1,2,4]triazin-6-carboxamida**

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El procedimiento utilizado para la preparación del Ejemplo 175 se utilizó para preparar el compuesto del título sustituyendo 2-(2-aminoetil)-1- metilpirrolidina con metilamina. EM $[M+H]^+$ = 568,23; LCMS TR = 2,6 min.

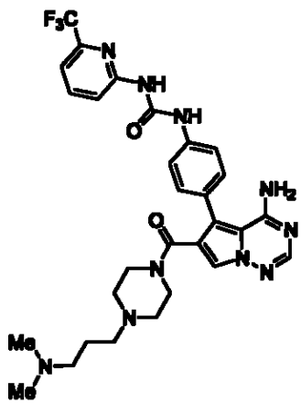
Ejemplo 192: Preparación de 4-amino-N-[4-(dimetilamino)butil]-5-{4-[({[6-(trifluorometil)piridin-2-il]amino}carbonil) amino]fenil}pirrolo[2,1-f]-[1,2,4]triazin-6-carboxamida



El procedimiento utilizado para la preparación del Ejemplo 175 se utilizó para preparar el compuesto del título sustituyendo 4-dimetilaminobutilamina con metilamina. EM $[M+H]^+$ = 556,23; LCMS TR = 2,6 min.

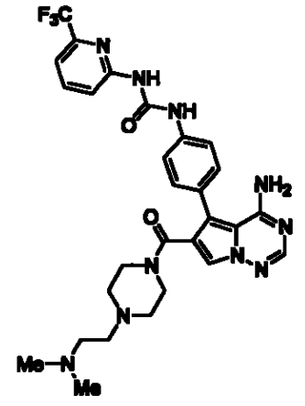
Ejemplo 193: Preparación de N-{4-[4-amino-6-({4-[3-(dimetilamino)-propil]piperazin-1-il}carbonil)pirrolo[2,1-f][1,2,4]triazin-5-il]fenil}-N'-[6-(trifluorometil)piridin-2-il]urea

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El procedimiento utilizado para la preparación del Ejemplo 175 se utilizó para preparar el compuesto del título sustituyendo 1-(3-dimetilaminopropil)-piperazina con metilamina. EM $[M+H]^+$ = 611,27; LCMS TR = 2,45 min.

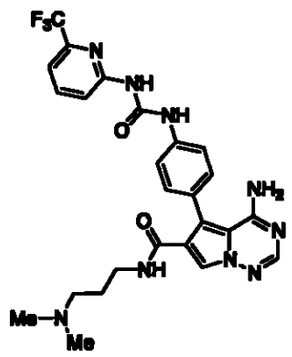
Ejemplo 194: **Preparación de N-(4-[4-amino-6-({4-[2-(dimetilamino)etil]-piperazin-1-il}carbonil)pirrolo[2,1-f][1,2,4]triazin-5-il]fenil}-N'-[6-(trifluoro-metil)piridin-2-il]urea**



El procedimiento utilizado para la preparación del Ejemplo 175 se utilizó para preparar el compuesto del título sustituyendo 1-(2-dimetilaminoetil)-piperazina con metilamina. EM $[M+H]^+$ = 597,26; LCMS TR = 2,52 min.

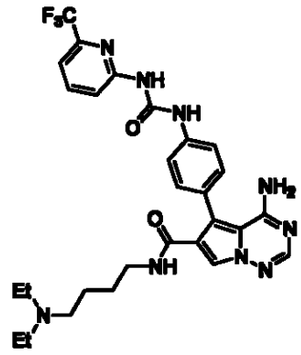
Ejemplo 195: **Preparación de 4-amino-N-[3-(dimetilamino)propil]-5-{4-[({[6-(trifluorometil)piridin-2-il]amino}carbonil)amino]fenil}pirrolo[2,1-f]-[1,2,4]triazin-6-carboxamida**

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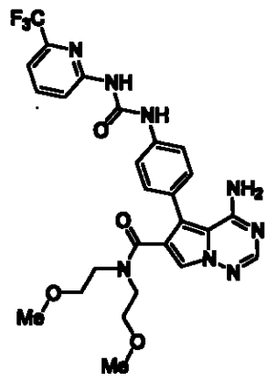
El procedimiento utilizado para la preparación del Ejemplo 175 se utilizó para preparar el compuesto del título sustituyendo 3- (dimetilamino)propilamina con metilamina. EM $[M+H]^+$ = 542,22; LCMS TR = 2,6 min.

Ejemplo 196: Preparación de 4-amino-N-[4-(dietilamino)butil]-5-(4-[({[6-(trifluorometil)piridin-2-il]amino}carbonil)amino]fenil)pirrolo[2,1-f]-[1,2,4]triazin-6-carboxamida



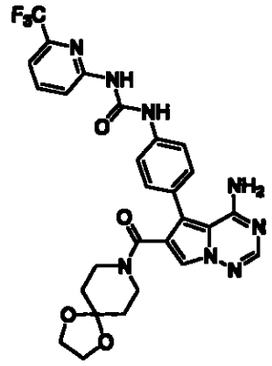
El procedimiento utilizado para la preparación del Ejemplo 175 se utilizó para preparar el compuesto del título sustituyendo 4-dietilaminobutilamina con metilamina. EM $[M+H]^+$ = 598,28; LCMS TR = 2,67 min.

Ejemplo 197: Preparación de 4-amino-N,N-bis(2-metoxietil)-5-(4-[({[6-(trifluorometil)piridin-2-il]amino}carbonil)amino]fenil)pirrolo[2,1-f][1,2,4]-triazin-6-carboxamida



El procedimiento utilizado para la preparación del Ejemplo 175 se utilizó para preparar el compuesto del título sustituyendo bis(2-metoxietil)amina con metilamina. EM $[M+H]^+$ = 573,21; LCMS TR = 2,93 min.

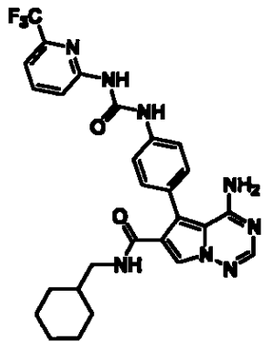
Ejemplo 198: Preparación de N-{4-[4-amino-8-(1,4-dioxa-8-azaspiro-[4,5]dec-8-ilcarbonil)pirrolo[2,1-f][1,2,4] triazin-5-il]fenil}-N'-[6-(trifluoro-metil)piridin-2-il]urea



El procedimiento utilizado para la preparación del Ejemplo 175 se utilizó para preparar el compuesto del título sustituyendo 1,4-dioxa-8- azaspiro[4,5]decano con metilamina. EM $[M+H]^+$ = 583,2; LCMS TR = 2,93 min.

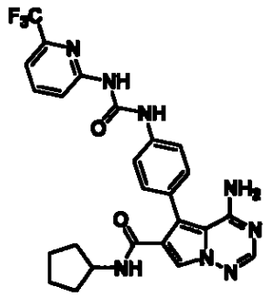
Ejemplo 199: Preparación de 4-amino-N-(ciclohexilmetil)-5-(4-[({[6-(trifluorometil)piridin-2-il]amino}carbonil)amino]fenil}pirrolo[2,1-f][1,2,4]-triazin-6-carboxamida

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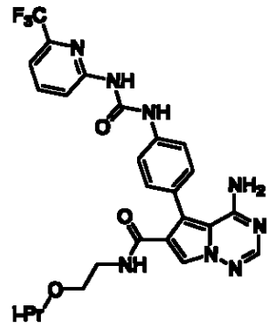
El procedimiento utilizado para la preparación del Ejemplo 175 se utilizó para preparar el compuesto del título sustituyendo ciclohexanometilamina con metilamina. EM $[M+H]^+$ = 553,22; LCMS TR = 3,31 min.

Ejemplo 200: Preparación de 4-amino-N-ciclopentil-5-{4-[({[6-(trifluorometil)piridin-2-il]amino}carbonil)amino]fenil}pirrolo[2,1-f][1,2,4]-triazin-6-carboxamida



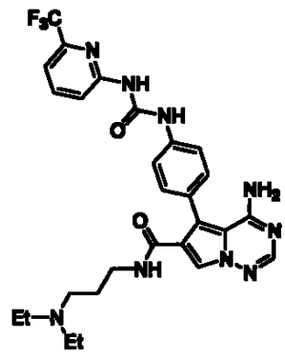
El procedimiento utilizado para la preparación del Ejemplo 175 se utilizó para preparar el compuesto del título sustituyendo ciclopentilamina con metilamina. EM $[M+H]^+$ = 525,19; LCMS TR = 3,1 min.

Ejemplo 201: Preparación de 4-amino-N-(2-isopropoxietil)-5-{4-[({[6-(trifluorometil)piridin-2-il]amino}carbonil)amino]fenil}pirrolo[2,1-f][1,2,4]-triazin-6-carboxamida



El procedimiento utilizado para la preparación del Ejemplo 175 se utilizó para preparar el compuesto del título sustituyendo éter 2-aminoetil isopropílico con metilamina. EM $[M+H]^+$ = 543,2; LCMS TR = 3,05 min.

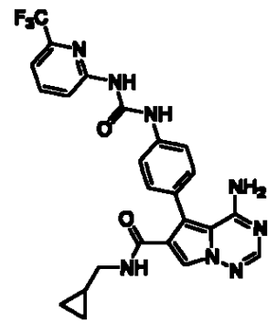
Ejemplo 202: Preparación de 4-amino-N-[3-(dietilamino)propil]-5-{4-[({[6-(trifluorometil)piridin-2-il]amino}carbonil) amino]fenil}pirrolo[2,1-f]-[1,2,4]triazin-6-carboxamida



El procedimiento utilizado para la preparación del Ejemplo 175 se utilizó para preparar el compuesto del título sustituyendo N,N-dietil-1,3-propanodiamina con metilamina. EM $[M+H]^+$ = 570,25; LCMS TR = 2,62 min.

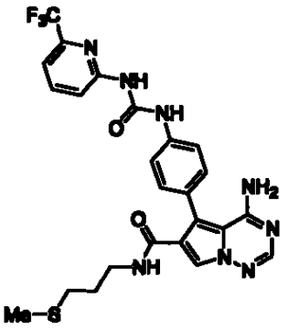
Ejemplo 203: Preparación de 4-amino-N-(ciclopropilmetil)-5-{4-[({[6-(trifluorometil)piridin-2-il]amino}carbonil)amino]fenil}pirrolo[2,1-f][1,2,4]-triazin-6-carboxamida

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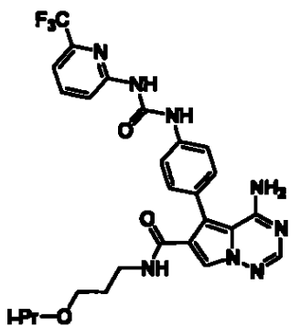
El procedimiento utilizado para la preparación del Ejemplo 175 se utilizó para preparar el compuesto del título sustituyendo ciclopropanometilamina con metilamina. EM $[M+H]^+$ = 511,17; LCMS TR = 3,04 min.

Ejemplo 204: Preparación de 4-amino-N-[3-(metiltio)propil]-5-(4-[({[6-(trifluorometil)piridin-2-il]amino}carbonil)amino]fenil}pirrolo[2,1-f][1,2,4]-triazin-6-carboxamida



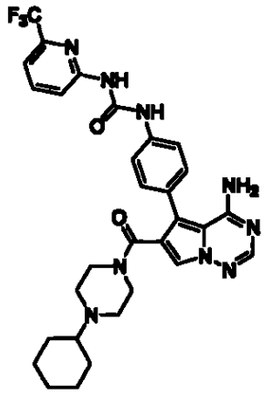
El procedimiento utilizado para la preparación del Ejemplo 175 se utilizó para preparar el compuesto del título sustituyendo 3-(metiltio)propilamina con metilamina. EM $[M+H]^+$ = 545,16; LCMS TR = 3,06 min.

Ejemplo 205: Preparación de 4-amino-N-(3-isopropoxipropil)-5-(4-[({[6-(trifluorometil)piridin-2-il]amino}carbonil)amino]fenil}pirrolo[2,1-f][1,2,4]-triazin-6-carboxamida



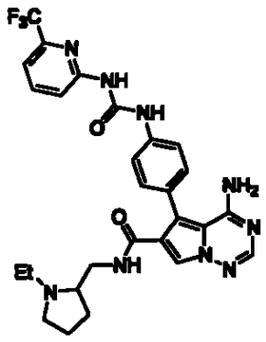
El procedimiento utilizado para la preparación del Ejemplo 175 se utilizó para preparar el compuesto del título sustituyendo 3-isopropoxipropilamina con metilamina. EM $[M+H]^+$ = 557,22; LCMS TR = 3,05 min.

Ejemplo 206: **Preparación de N-(4-{4-amino-6-[(4-ciclohexilpiperazin-1-il)carbonil]pirrolo[2,1-f][1,2,4]triazin-5-il}fenil)-N'-[6-(trifluorometil)piridin-2-il]urea**



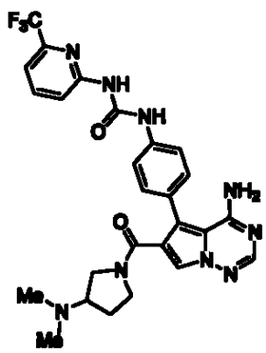
El procedimiento utilizado para la preparación del Ejemplo 175 se utilizó para preparar el compuesto del título sustituyendo 1-ciclohexilpiperazina con metilamina. EM $[M+H]^+$ = 608,26; LCMS TR = 2,63 min.

Ejemplo 207: **Preparación de 4-amino-N-[(1-etilpirrolidin-2-il)metil]-5-{4-[({[6-(trifluorometil)piridin-2-il]amino}carbonil)amino]fenil}pirrolo[2,1-f]-[1,2,4]triazin-6-carboxamida**



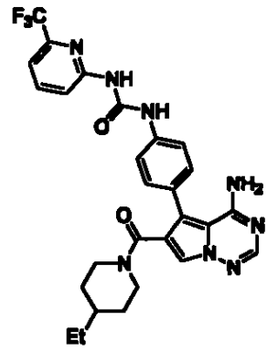
El procedimiento utilizado para la preparación del Ejemplo 175 se utilizó para preparar el compuesto del título sustituyendo 2-(aminometil)-1-etilpirrolidina con metilamina. EM $[M+H]^+$ = 568,23; LCMS TR = 2,64 min.

Ejemplo 208: Preparación de N-[4-(4-amino-6-{[3-(dimetilamino)-pirrolidin-1-il]carbonil}pirrolo[2,1-f][1,2,4]triazin-5-il)fenil]-N'-[6-(trifluoro-metil)piridin-2-il]urea



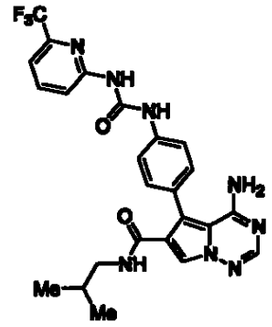
El procedimiento utilizado para la preparación del Ejemplo 175 se utilizó para preparar el compuesto del título sustituyendo 3- (dimetilamino)pirrolidina con metilamina. EM $[M+H]^+$ = 554,22; LCMS TR = 2,54 min.

Ejemplo 209: Preparación de N-(4-(4-amino-6-[(4-etilopiperidin-1-il)-carbonil]pirrolo[2,1-f][1,2,4]triazin-5-il)fenil)-N'-[6-(trifluorometil)piridin-2-il]-urea



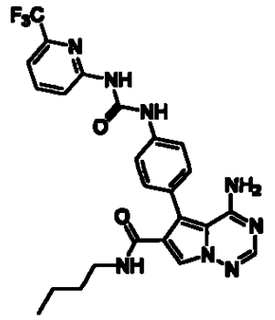
El procedimiento utilizado para la preparación del Ejemplo 175 se utilizó para preparar el compuesto del título sustituyendo 4-etilpiperidina con metilamina. EM $[M+H]^+$ = 553,22; LCMS TR = 3,25 min.

Ejemplo 210: Preparación de 4-amino-N-isobutil-5-{4-[({[6-(trifluorometil)piridin-2-il]amino}carbonil)amino]fenil}pirrolo[2,1-f][1,2,4]triazin-6-carboxamida



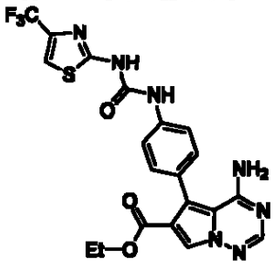
El procedimiento utilizado para la preparación del Ejemplo 175 se utilizó para preparar el compuesto del título sustituyendo isobutilamina con metilamina. EM $[M+H]^+$ = 513,19; LCMS TR = 3,11 min.

Ejemplo 211: Preparación de 4-amino-N-butil-5-{4-[({[6-(trifluorometil)-piridin-2-il]amino}carbonil)amino]fenil}pirrolo[2,1-f][1,2,4]triazin-6-carboxamida



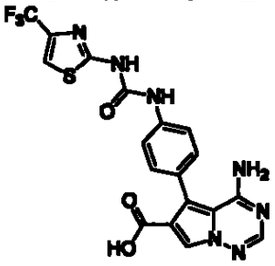
El procedimiento utilizado para la preparación del Ejemplo 175 se utilizó para preparar el compuesto del título sustituyendo N-butilamina con metilamina. EM $[M+H]^+$ = 513,19; LCMS TR = 3,14 min.

Ejemplo 212: **Preparación de 4-amino-5-{4-[({[4-(trifluorometil)-1,3-tiazol-2-il]amino}carbonil) amino]fenil}pirrolo[2,1-f][1,2,4]triazin-6-carboxilato de etilo**



El procedimiento utilizado para la preparación del Ejemplo 24 se utilizó para preparar el compuesto del título sustituyendo 4-(trifluorometil)-1,3-tiazol-2-amina con 2-isopropilanilina. ^{1}H-RMN (DMSO-d_6) δ11,0 (s, 1H), 9,15 (s, 1H), 8,13 (s, 1H), 7,93 (s, 1H), 7,87 (s, 1H), 7,57 a 7,55 (m, 2H), 7,35 a 3,33 (m, 2H), 1,12 a 1,09 (m, 3H); EM $[M+H]^+$ = 492; LCMS TR = 2,73 min.

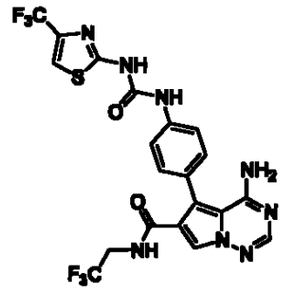
Ejemplo 213: **Preparación de ácido 4-amino-5-{4-[({[4-(trifluorometil)-1,3-tiazol-2-il]amino}carbonil)amino]fenil}pirrolo[2,1-f][1,2,4]triazin-6-carboxílico**



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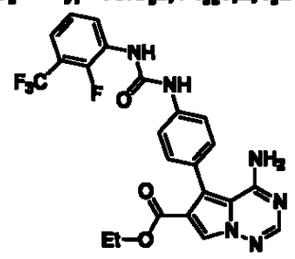
El procedimiento utilizado para el Paso 2 en la preparación del intermediario J se utilizó para preparar el compuesto del título sustituyendo [4-(trifluorometil)-1,3-tiazol-2-il]carbamato de fenilo con [2-cloro-5-(trifluorometil)fenil]carbamato de fenilo. ^{1}H-RMN (DMSO-d_6) δ12,3 a 12,2 (br s,1H), 11,2 a 11,1 (br s, 1H), 9,41 a 9,18 (br s, 1H), 8,30 (s, 1H), 8,29 a 8,1 (br s, 1H), 7,90 (s,1H), 7,82 (s, 1H), 7,65 a 7,58 (m, 2H), 7,55 a 7,30 (m, 2H), 5,27 a 4,71 (br s, 1H); EM $[M+H]^+$ = 464; LCMS TR = 2,28 min.

Ejemplo 214: **Preparación de 4-amino-N-(2,2,2-trifluoroetil)-5-{4-[({[4-(trifluorometil)-1,3-tiazol-2-il]amino}carbonil) amino]fenil}pirrolo[2,1-f][1,2,4]triazin-6-carboxamida**



El procedimiento utilizado para la preparación del Ejemplo 69 se utilizó para preparar el compuesto del título sustituyendo el Ejemplo 213 con el intermediario G y sustituyendo 2,2,2-trifluoroetanamina con ciclopropanamina. ^{1}H-RMN (DMSO-d_6) δ 11,0 (s, 1H), 9,13 (s, 1H), 8,55 a 8,52 (m, 1H), 8,19 (s, 1H), 7,91 (s, 1H), 7,85 (s, 1H), 7,55 a 7,52 (m, 2H), 7,32 a 7,30 (m, 2H), 3,97 a 3,93 (m, 2H); EM $[M+H]^+$ = 544,9; LCMS TR = 2,52 min.

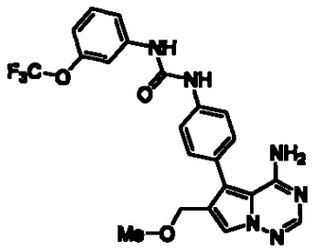
Ejemplo 215: **Preparación de 4-amino-5-{4-[({[2-fluoro-3-(trifluorometil)-fenil]amino}carbonil)amino]fenil}pirrolo[2,1-f][1,2,4]triazin-6-carboxilato de etilo**



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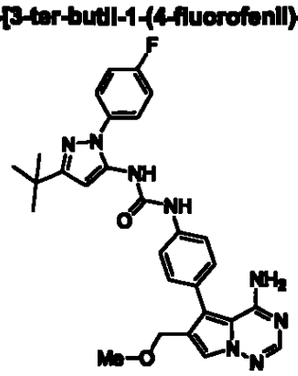
El procedimiento utilizado para la preparación del Ejemplo 24 se utilizó para preparar el compuesto del título sustituyendo 2-fluoro-3-(trifluorometil)fenilamina con 2-isopropilanilina. ^{1}H-RMN (DMSO-d_6) δ9,33 (s, 1H), 8,92 (s, 1H), 8,52 a 8,45 (m, 1H), 8,16 (s, 1H), 8,10 (ba, 1H), 7,96 (s, 1H), 7,57 (d, J = 9,0 Hz, 2H), 7,40 a 7,34 (m, 4H), 5,14 (ba, 1H), 4,10(q, J = 8,0 Hz, 2H), 1,12 (q, J = 7,8 Hz, 3H); EM $[M+H]^+$ = 503,2; LCMS TR = 3,14 min.

Ejemplo 216: Preparación de N-[4-[4-amino-6-(metoximetil)pirrolo[2,1-f][1,2,4]triazin-5-il]fenil]-N'-[3-(trifluorometoxi)fenil]urea



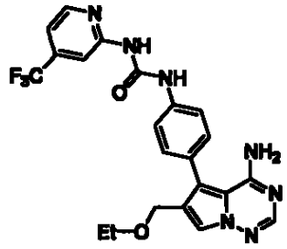
El procedimiento utilizado para la preparación del Ejemplo 24 se utilizó para preparar el compuesto del título sustituyendo 3-metoxianilina con 2-isopropilanilina y el intermediario U con el intermediario B. ^{1}H-RMN (DMSO-d_6) δ7,81 (s, 1H), 7,73 (s, 1H), 7,65 a 7,71 (m, 2H), 7,61 (d, J = 9 Hz, 2H), 7,40 ((d, J = 9Hz, 2H), 7,37 (m, 1H), 7,33 a 7,36 (m, 2H), 6,90 a 6,95 (m, 1H), 4,36 (s, 2H), 3,30 (s, 3H); EM $[M+H]^+$ = 473,1; LCMS TR = 2,69 min.

Ejemplo 217: Preparación de N-[4-[4-amino-6-(metoximetil)pirrolo[2,1-f][1,2,4]triazin-5-il]fenil]-N'-[3-ter-butil-1-(4-fluorofenil)-1H-pirazol-5-il]urea



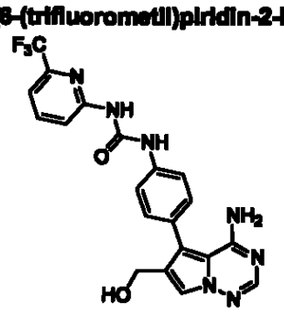
El procedimiento utilizado para la preparación del Ejemplo 24 se utilizó para preparar el compuesto del título sustituyendo 3-ter-butil-1-(4-fluorofenil)-1H-pirazol-5-amina con 2-isopropilanilina. ^{1}H-RMN (CD_3OD) δ7,78 (s, 1H), 7,68 (s, 1H), 7,52 a 7,58 (m, 2H), 7,52 (d, J = 9 Hz, 2H) 7,37 (d, J = 9Hz, 2H), 7,26 a 7,31 (m, 2H), 6,44 (s, 1H), 4,34 (s, 2H), 3,30 (s, 3H), 1,26 (s, 9H); EM $[M+H]^+$ = 529,2; LCMS TR = 3,04 min.

Ejemplo 218: Preparación de N-[4-[4-amino-6-(etoximetil)pirrolo[2,1-f][1,2,4]triazin-5-il]fenil]-N'-[4-(trifluorometil)piridin-2-il]urea



El procedimiento utilizado para la preparación del Ejemplo 246 se utilizó para preparar el compuesto del título sustituyendo [4-(trifluorometil)piridin-2-il]carbamato de fenilo con 1-fluoro-2-isocianato-4-(trifluorometil)benceno. ^{1}H-RMN (DMSO-d_6) δ 9,99 (s, 1H), 9,82 (s, 1H), 8,56 (d, J = 5 Hz, 1H), 8,10 (s, 1H), 7,87 (s, 1H), 7,77 (s, 1H), 7,65 (d, J = 9 Hz, 2H), 7,62 a 7,65 (m, 1H), 7,30 a 7,42 (m, 4 H), 4,32 (s, 2H), 3,40 (q, J = 7 Hz, 2H), 1,09 (t, J = 7 Hz, 3H); EM $[M+H]^+$ = 472,1; LCMS TR = 2,73 min.

Ejemplo 219: Preparación de N-[4-[4-amino-6-(hidroximetil)pirrolo[2,1-f][1,2,4]triazin-5-il]fenil]-N'-[6-(trifluorometil)piridin-2-il]urea

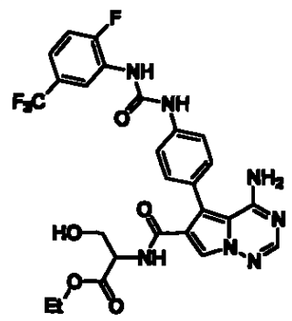


El procedimiento utilizado en el paso 1 de la preparación del Intermediario F se utilizó para preparar el compuesto del título sustituyendo el Ejemplo 144 con el

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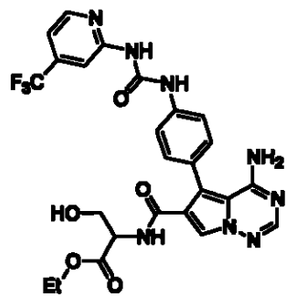
intermediario E. ^{1}H-RMN (DMSO-d_6) δ9,87 (s, 1H), 9,71 (s, 1H), 8,03 a 7,99 (m, 3H), 7,82 (s, 1H), 7,65 (s, 1H), 7,57 a 7,55 (m, 3H), 7,50 a 7,47 (m, 1H), 7,37 (d, J = 8,5 Hz, 2H), 4,97 a 4,94 (m, 1H), 4,36 (d, J = 5,2 Hz, 2H); EM $[M+H]^+$ = 444,0; LCMS TR = 2,24 min.

Ejemplo 220: **Preparación de N-[(4-amino-5-{4-[({[2-fluoro-5-(trifluorometil)fenil]amino}carbonil)amino]fenil}pirrolo[2,1-f][1,2,4]triazin-6-il)carbonil]serinato de etilo**



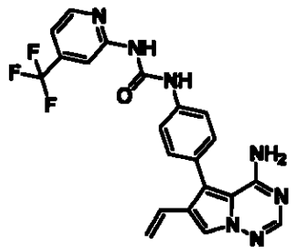
El procedimiento utilizado para la preparación del Ejemplo 143 se utilizó para preparar el compuesto del título sustituyendo clorhidrato de metil serinato con 2-amino-2-metilopropan-1-ol y el intermediario G con el intermediario J. ^{1}H-RMN (DMSO-d_6) δ 9,33 (s, 1H), 8,95 (d, J = 2,5 Hz, 1H), 8,62 a 8,60 (d, J = 8,8 Hz, 1H), 8,20 (s, 1H), 7,91 (s, 1H), 7,78 a 7,76 (d, J = 7,8 Hz, 1H), 7,55 a 7,53 (d, J = 8,7 Hz, 2H), 7,50 a 7,47 (m, 1H), 7,40 a 7,37 (m, 1H), 7,34 a 7,32 (d, J = 8,4 Hz, 2H), 4,98 a 4,95 (t, J = 5,9 Hz, 1H), 4,38 a 4,34 (m, 1H), 4,08 a 4,03 (q, J = 7,2 Hz, 2H), 3,70 a 3,61 (m, 2H), 1,18 a 1,15 (t, J = 7,1 Hz, 3H); EM $[M+H]^+$ = 590,0; LCMS TR = 2,69 min.

Ejemplo 221: **Preparación de N-[(4-amino-5-{4-[({[4-(trifluorometil)-piridin-2-il]amino}carbonil)amino]fenil} pirrolo[2,1-f][1,2,4]triazin-6-il)-carbonil]serinato de etilo**



El procedimiento utilizado para la preparación del Ejemplo 143 se utilizó para preparar el compuesto del título sustituyendo clorhidrato de metil serinato con 2-amino-2-metilopropan-1-ol y el Ejemplo 250 con el intermediario J. ^{1}H-RMN (DMSO-d_6) δ9,87 (s, 1H), 9,74 (s, 1H), 8,54 a 8,53 (d, J = 5,4 Hz, 1H), 8,20 (s, 1H), 8,06 (s, 1H), 7,91 (s, 1H), 7,79 a 7,77 (d, J = 7,6 Hz, 1H), 7,59 a 7,57 (d, J = 8,7 Hz, 2H), 7,37 a 7,33 (m, 3H), 4,98 a 4,95 (t, J = 5,8 Hz, 1H), 4,39 a 4,34 (m, 1H), 4,08 a 4,03 (q, J = 7,0 Hz, 2H), 3,72 a 3,61 (m, 2H), 1,18 a 1,14 (t, J = 7,1 Hz, 3H); EM $[M+H]^+$ = 573,0; LCMS TR = 2,55 min.

Ejemplo 222: Preparación de N-[4-(4-amino-6 vinilpirrolo[2,1-f][1,2,4]-triazin-5-il)fenil]-N'-[4-(trifluorometil)piridin-2-il]urea

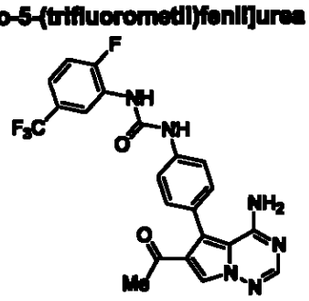


Se suspendió ter-butóxido de potasio (0,51g, 4,53 mmol) en 1,4-dioxano (40 ml) y se trató con bromuro de metil(trifenil)fosfonio (1,6 g, 4,53 mmol). La suspensión color amarillo resultante se agitó a temperatura ambiente durante 30 min. La mezcla luego se trató con el intermediario AG (1,0 g, 2,27 mmol). La mezcla se agitó durante 3 horas a temperatura ambiente. La mezcla luego se vertió en agua y se agitó durante 1 hora. La mezcla luego se filtró y se enjuagó con agua y metanol. El sólido restante se secó bajo presión reducida dando 0,62 g del producto en forma de un sólido color marrón claro (1,41 mmol, 62 % de rendimiento). ^{1}H-RMN (DMSO-d_6)

589

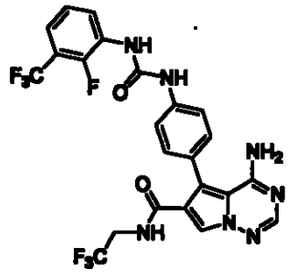
δ10,0(bs, 1H), 9,86 (bs, 1H), 8,53 (d, *J* = 5,1 Hz, 1H), 8,07 (s, 1H), 8,04 (s, 1H), 7,84 (s, 1H), 7,64 (d, *J* = 8,5 Hz, 2H), 7,35 (d, *J* = 5,2 Hz, H), 7,30 (d, *J* = 8,4 Hz, 2H), 6,39 (q, *J* = 11,0 Hz, 1H), 5,83 (dd, *J* = 1,6 Hz, 1H), 5,11 (dd, *J* = 1,6 Hz, 1H); EM $[M+H]^+$ = 440,0; LCMS TR = 2,89 min.

Ejemplo 223: **Preparación de N-[4-(8-acetil-4-aminopirrolo[2,1-f][1,2,4]-triazin-5-il)fenil]-N'-[2-fluoro-5-(trifluorometil)fenil]urea**



El procedimiento utilizado para la preparación del Ejemplo 233 se utilizó para preparar el compuesto del título sustituyendo el Ejemplo XXX con el Ejemplo 269. ^{1}H-RMN (DMSO-d_6) δ 9,32 (s, 1H), 8,95 (d, J = 2Hz, 1H), 8,61 (dd, J = 2, 5 Hz, 1H), 8,37 (s, 1H), 8,05 (bs, 1H), 7,92 (s, 1H), 7,54 (d, J = 9 Hz, 2H), 7,46 a 7,52 (m, 1H), 7,36 a 7,40 (m, 1H), 7,31, d, J = 9 Hz, 2H), 5,02 (bs, 1H), 2,30 (s, 3H); EM $[M+H]^+$ = 473,3; LCMS TR = 2,95 min.

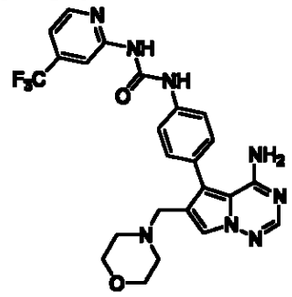
Ejemplo 224: **Preparación de 4-amino-5-{4-[({[2-fluoro-3-(trifluoro-metil)fenil]amino}carbonil)amino]fenil}-N-(2,2,2-trifluoroetil)pirrolo[2,1-f]-[1,2,4]triazin-6-carboxamida**



El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo el intermediario M con el intermediario X y fenil ester del ácido (2-fluoro-3-trifluorometil-fenil)-carbámico con (4-terbutilpiridin-

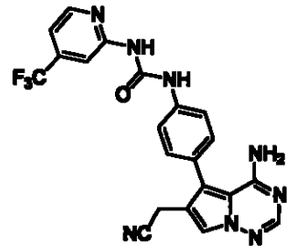
2-il)carbamato de fenilo. ^{1}H-RMN (DMSO-d_6) δ9,34 (s, 1H), 8,94 (s, 1H), 8,58 a 8,48 (m, 2H), 8,23 (s, 1H), 7,98 (ba, 1H), 7,96 (s, 1H), 7,58 (d, *J* = 7,5 Hz, 2H), 7,41 a 7,33 (m, 4H), 5,11 (ba, 1H), 4,10(m, 2H); EM $[M+H]^+$ = 556,1; LCMS TR = 3,00 min.

Ejemplo 225: **Preparación de N-[4-[4-amino-6-(morfolin-4-ilmetil)pirrolo-[2,1-*f*][1,2,4]triazin-5-il]fenil]-N'-[4-(trifluorometil)piridin-2-il]urea**

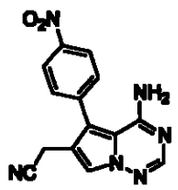


El procedimiento utilizado para la preparación del Ejemplo 30 se utilizó para preparar el compuesto del título sustituyendo el intermediario AG con el intermediario F. ^{1}H-RMN (CD_3OD) δ8,54 (s, 1H), 8,06 (s, 1H), 8,05 (s, 1H), 7,64 a 7,41 (m, 2H), 7,39 a 7,38 (m, 2H), 3,57 a 3,50 (m, 2H), 3,42 a 3,41 (m, 2H), 2,67 a 2,66 (m, 2H), 2,47 a 2,32 (m, 4H); EM $[M+H]^+$ = 513,0; LCMS TR = 1,92 min.

Ejemplo 226: **Preparación de N-[4-[4-amino-6-(cianometil)pirrolo[2,1-*f*][1,2,4]triazin-5-il]fenil]-N'-[4-(trifluorometil)piridin-2-il]urea**



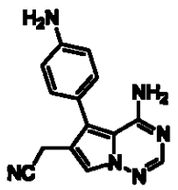
Paso 1: **Preparación de [4-amino-5-(4-nitrofenil)pirrolo[2,1-*f*][1,2,4]triazin-6-il]acetonitrilo**



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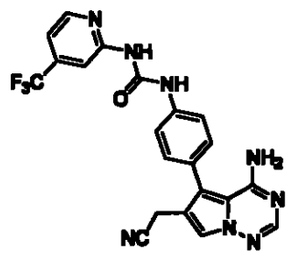
El procedimiento utilizado para la preparación del intermediario U Paso 1 se utilizó para preparar el compuesto del título sustituyendo DMF con metanol y cianuro de sodio con hidruro de sodio. EM $[M+H]^+$ = 295,4; LCMS TR = 2,11 min.

Paso 2: Preparación de 4-amino-5-(4-aminofenil)pirrolo[2,1-f][1,2,4]triazin-6-il]acetonitrilo



Una solución de 4-amino-5-(4-aminofenil)pirrolo[2,1-f][1,2,4]triazin-6-il]acetonitrilo (250 mg, 0,85 mmol) y cloruro de estaño (II) (1,61 g, 8,5 mmol) en 75 ml EtOH se calentó a 80° C durante 1h. La reacción luego se diluyó con EtOAc y se diluyó con $NaHCO_3$ sat. Después de 15 minutos de vigorosa agitación la mezcla se filtró a través de un taco de celite, lavando bien con EtOAc. La capa orgánica luego se separó, se secó (Na_2SO_4) y se evaporó hasta sequedad. La trituración con Et_2O dio 210 mg del compuesto del título (93% de rendimiento). EM $[M+H]^+$ = 265; LCMS TR = 2,63 min.

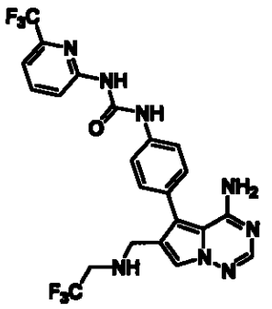
Paso 3: Preparación de [Preparación de N-[4-[4-amino-6-(cianometil)pirrolo [2,1-f][1,2,4]triazin-5-il]fenil]-N'-[4-(trifluorometil)piridin-2-il]urea



El procedimiento utilizado para la preparación del Ejemplo 101 se utilizó para preparar el compuesto del título sustituyendo 4-amino-5-(4-aminofenil)pirrolo[2,1-f][1,2,4]triazin-6-il]acetonitrilo con el intermediario U. ^{1}H-RMN (DMSO-d_6) δ 8,54 (d, J = 5 Hz, 1H), 8,07 (s, 1H), 7,87 (s, 1H), 7,77 (s, 1H), 7,66 (d, J = 9 Hz, 2H), 7,36 (d,

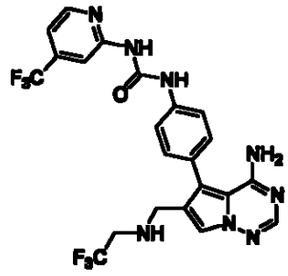
J = 9 Hz, 2H), 7,34 a 7,36 (m, 1H), 3,81 (s, 2H); EM $[M+H]^+$ = 453,1; LCMS TR = 2,67 min.

Ejemplo 227: Preparación de N-[4-(4-amino-6-{[(2,2,2-trifluoroetil)-amino]metilo}pirrolo[2,1-*f*][1,2,4]triazin-5-il)fenil]-N'-[6-(trifluorometil)piridin-2-il]urea



El procedimiento utilizado para la preparación del Ejemplo 30 se utilizó para preparar el compuesto del título sustituyendo 2,2,2-trifluoroetanamina con morfolina y N-[4-(4-amino-6-formilpirrolo[2,1-*f*][1,2,4]triazin-5-il)fenil]-N'-[6-(trifluorometil)piridin-2-il]urea con el intermediario F. ^{1}H-RMN (DMSO-d_6) δ9,88 (s, 1H), 9,75 (s, 1H), 8,02 a 7,99 (m, 2H), 7,82 (s, 1H), 7,69 (s, 1H), 7,57 a 7,48 (m, 4H), 7,38 a 3,36 (m, 2H), 3,67 a 3,66 (s, 2H), 3,28 a 3,14 (m, 2H), 2,66 a 2,56 (m, 2H); EM $[M+H]^+$ = 525,0; LCMS TR = 2,10 min.

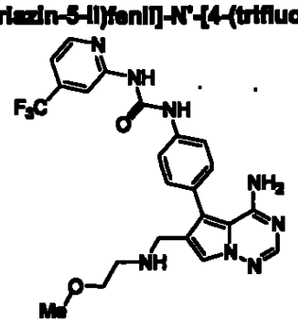
Ejemplo 228: Preparación de N-[4-(4-amino-6-{[(2,2,2-trifluoroetil)-amino]metilo}pirrolo[2,1-*f*][1,2,4]triazin-5-il)fenil]-N'-[4-(trifluorometil)piridin-2-il]urea



El procedimiento utilizado para la preparación del Ejemplo 30 se utilizó para preparar el compuesto del título sustituyendo 2,2,2-trifluoroetanamina con morfolina y

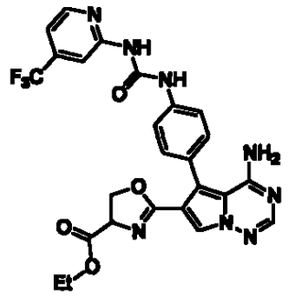
el intermediario AG con el intermediario F. ^{1}H-RMN (CD_3OD) δ8,51 (d, *J* = 5,3 Hz, 1H), 7,77 (s, 1H), 7,48 (br s, 1H), 7,70 a 7,68 (m, 3H), 7,44 a 7,42 (m, 2H), 7,29 a 7,27 (m, 2H), 3,81 (s, 2H), 3,18 a 3,11 (m, 2H); EM $[M+H]^+$ = 525,1; LCMS TR = 2,19 min.

Ejemplo 229: Preparación de N-[4-(4-amino-6-{[(2-metoxietil)amino]metil}pirrolo[2,1-f][1,2,4]triazin-5-il)fenil]-N'-[4-(trifluorometil)piridin-2-il]urea



El procedimiento utilizado para la preparación del Ejemplo 30 se utilizó para preparar el compuesto del título sustituyendo 2-metoxietanamina con morfolina y el intermediario AG con el intermediario F. ^{1}H-RMN (CD_3OD) δ8,51 (d, *J* = 5,3 Hz, 1H), 7,80 (s, 1H), 7,78 (s, 1H), 7,75 a 7,72 (m, 3H), 7,43 a 7,41 (m, 2H), 7,28 (d, *J* = 5,6 Hz, 1H), 3,97 (s, 2H), 3,48 a 3,45 (m, 2H), 2,89 a 2,86 (m, 2H); EM $[M+H]^+$ = 501,0; LCMS TR = 1,99 min.

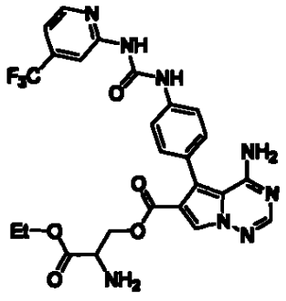
Ejemplo 230: Preparación de 2-(4-amino-5-{4-[({[4-(trifluorometil)piridin-2-il]amino}carbonil)amino]fenil}pirrolo[2,1-f][1,2,4]triazin-6-il)-4,5-dihidro-1,3-oxazol-4-carboxilato de etilo



A una solución de THF (2 ml) se agregó N-[(4-amino-5-{4-[({[4-(trifluorometil)piridin-2-il]amino}carbonil)amino]fenil}pirrolo[2,1-f][1,2,4]triazin-6-

il)carbonil]aerinato de etilo (Ejemplo 221) (50 mg, 0,09 mmol) la cual se enfrió a -78 °C. Se agregó DAST (13 µl, 0,10 mmol) y la reacción procedió durante 1h mientras se agitaba bajo N_2. Luego se agregó K_2CO_3 anhidro y la solución se dejó entibiar a ta durante los siguientes 30min. La mezcla de reacción se transfirió a un embudo de separación, se diluyó con EtOAc (20 ml), se lavó con $NaHCO_3$ ac saturado (20 ml) y H_2O (20 ml). La fase orgánica se recolectó, se secó (MgSO4), y se evaporó al vacío. El material bruto se purificó por HPLC preparativa (10-90% de ACN/H_2O con 0,1% de TFA). Las fracciones se dejaron durante toda la noche dando por resultado la formación de un nuevo producto. Los dos productos se separaron por cromatografía de columna 5:4:1 v/v/v DCM/EtOAc/MeOH dando por resultado el aislamiento de 9 mg del compuesto del título (0,016 mmol, 18%). ^{1}H-RMN (DMSO-d_6) δ 9,91 (a, 1H), 9,78 (a, 1H), 8,54 a 8,53 (d, J = 5,0 Hz, 1H), 8,08 (a, 1H), 8,05 (a, 1H), 7,91 (a, 1H), 7,58 a 7,56 (d, J = 8,6 Hz, 2H), 7,37 a 7,36 (d, J = 5,1 Hz, 1H), 7,34 a 7,32 (d, J = 8,6 Hz, 2H), 4,75 a 4,71 (m, 1H), 4,38 a 4,29 (m, 2H), 4,13 a 4,08 (q, J = 7,1 Hz, 2H), 1,21 a 1,18 (t, J = 7,0 Hz, 3H); EM $[M+H]^+$ = 555,1; LCMS TR = 2,84 min.

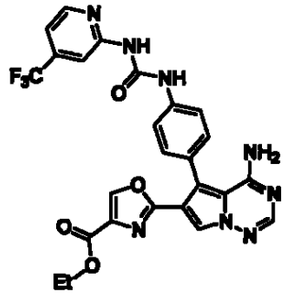
Ejemplo 231: **Preparación de 2-amino-3-etoxi-3-oxopropil 4-amino-5-{4-[({[4-(trifluorometil)piridin-2-il]amino}carbonil)amino]fenil}pirrolo[2,1-f]-[1,2,4]triazin-6-carboxilato**



A una solución de THF (2 ml) se agregó N-[(4-amino-5-[4-[({[4-(trifluorometil)piridin-2-il]amino}carbonil)amino]fenil}pirrolo[2,1-f][1,2,4]triazin-6-il)carbonil]aerinato de etilo (Ejemplo 221) (50 mg, 0,09 mmol) la cual se enfrió a -78 °C. DAST (13 µl, 0,10 mmol) se agregó y la reacción procedió durante 1h mientras se agitaba bajo N_2. Luego se agregó K_2CO_3 anhidro y la solución se dejó entibiar a ta durante los siguientes 30min. La mezcla de reacción se transfirió a un embudo de

separación, se diluyó con EtOAc (20 ml), se lavó con $NaHCO_3$ ac saturado (20 ml) y H_2O (20 ml). La fase orgánica se recolectó, se secó (MgSO4), y se evaporó al vacío. El material bruto se purificó por HPLC preparativa (10-90% de ACN/H_2O con 0,1% de TFA). Las fracciones se dejaron durante toda la noche dando por resultado la formación parcial de un nuevo producto. Los dos productos se separaron por cromatografía de columna 5:4:1 v/v/v DCM/EtOAc/MeOH dando por resultado el aislamiento de 4 mg del compuesto del título (0,0075 mmol, 9%). ^{1}H-RMN (DMSO-d_6) δ9,92 (s, 1H), 9,78 (s, 1H), 8,54 a 8,53 (d, *J* = 5,4 Hz, 1H), 8,15 (s, 1H), 8,07 (s, 1H), 7,93 (s, 1H), 7,60 a 7,58 (d, *J* = 8,8 Hz, 2H), 7,37 a 7,35 (d, *J* = 8,4 Hz, 1H), 7,33 a 7,31 (d, *J* = 8,8 Hz, 2H), 4,25 a 4,21(m, 1H), 4,12 a 4,08 (m, 1H), 4,07 a 4,02 (q, *J* = 7,0 Hz, 2H), 3,55 a 3,52 (t, *J* = 4,9 Hz, 1H), 1,15 a 1,11 (t, *J* = 7,2 Hz, 3H); EM $[M+H]^+$ = 573,1; **LCMS TR = 2,38 min.**

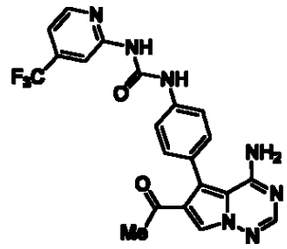
Ejemplo 232: Preparación de 2-(4-amino-5-{4-[({[4-(trifluorometil)piridin-2-il]amino}carbonil)amino]fenil} pirrolo[2,1-f][1,2,4]triazin-6-il)-1,3-oxazol-4-carboxilato de etilo



A una solución de THF (16 ml) se agregó N-[(4-amino-5-{4-[({[4-(trifluorometil)piridin-2-il]amino}carbonil)amino]fenil}pirrolo[2,1-f][1,2,4]triazin-6-il)carbonil]serinato de etilo (Ejemplo 221) (437 mg, 0,76 mmol) la cual se enfrió a -78 °C. Se agregó DAST (0,14 ml, 1,07 mmol) y la reacción procedió durante 1h mientras se agitaba bajo N_2. Se agregó DAST adicional (0,14 ml, 1,07 mmol) y la solución se agitó durante 30min. El baño de enfriamiento en acetona/hielo seco se reemplazó con un baño de agua/hielo y se agregaron DBU (0,41 ml, 2,75 mmol) y $BrCCl_3$ (0,27 ml, 2,75 mmol) y la solución se dejó entibiar a ta durante 17h. Se agregaron DBU adicional (0,41 ml, 2,75 mmol) y $BrCCl_3$ (0,27 ml, 2,75 mmol) y la

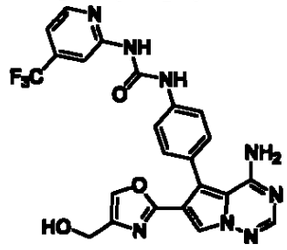
solución se dejó agitar durante 6h. La mezcla de reacción se transfirió a un embudo de separación, se diluyó con EtOAc (50 ml), se lavó con $NaHCO_3$ ac saturado (50 ml) y H_2O (50 ml). La fracción acuosa se retro extrajo con DCM (3 x 30 ml). Las capas orgánicas combinadas se secaron (MgSO4), se evaporaron al vacío y se cromatografiaron flash 5:4:1 v/v/v DCM/EtOAc/MeOH dando por resultado el aislamiento de 33 mg del compuesto del título (0,060 mmol, rendimiento 8%). ^{1}H-RMN (DMSO-d_6) δ9,93 (s, 1H), 9,77 (s, 1H), 8,70 (s, 1H), 8,55 a 8,54 (d, J = 5,0 Hz, 1H), 8,30 (s, 1H), 8,06 (s, 1H), 7,95 (s, 1H), 7,64 a 7,61 (d, J = 8,8 Hz, 2H), 7,42 a 7,40 (d, J = 8,8 Hz, 2H), 7,38 a 7,36 (d, J = 6,2 Hz, 1H), 4,28 a 4,23 (q, J = 7,6 Hz, 2H), 1,28 a 1,25 (t, J = 7,1 Hz, 3H); EM $[M+H]^+$ = 553,1; LCMS TR = 3,04 min.

Ejemplo 233: Preparación de N-[4-(6-acetil-4-aminopirrolo[2,1-*f*]-[1,2,4]triazin-5-il)fenil]-N'-[4-(trifluorometil)piridin-2-il]urea



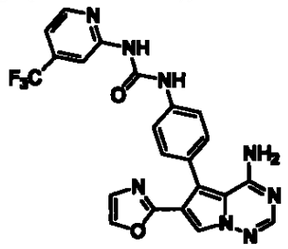
El procedimiento utilizado para la preparación del Intermediario F paso 2 se utilizó para preparar el compuesto del título sustituyendo el Ejemplo 269 con *N*-(4-[4-amino-6-(hidroximetil)pirrolo[2,1-*f*][1,2,4]triazin-5-il]fenil]-N'-[2-fluoro-5-(trifluorometil)fenil]urea. ^{1}H-RMN (CD_3OD) δ 8,51 (d, J = 5 Hz, 1H), 8,15 (s, 1H), 7,97 (s, 1H), 7,69 (s, 1H), 7,77 (d, J = 9 Hz, 2H), 7,38 (d, J = 9 Hz, 2H), 7,26 (d, J = 5Hz, 1H), 2,29 (s, 3H); EM $[M+H]^+$ = 456,0; LCMS TR = 2,71 min.

Ejemplo 234: Preparación de N-(4-[4-amino-6-[4-(hidroximetil)-1,3-oxazol-2-il]pirrolo[2,1-*f*][1,2,4]triazin-5-il]fenil)-N'-[4-(trifluorometil)piridin-2-il]urea

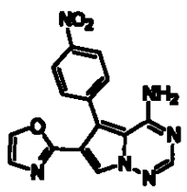


El procedimiento utilizado para la preparación del Ejemplo 241 se utilizó para preparar el compuesto del título sustituyendo el Ejemplo 232 con el Ejemplo 237. ^{1}H-RMN (DMSO-d_6) δ9,91 (s, 1H), 9,76 (s, 1H), 8,53 (d, J = 5,4 Hz, 1H), 8,17 (s, 1H), 8,05 (s, 1H), 7,92 (s, 1H), 7,75 (s, 1H), 7,62 (s, 1H), 7,61 (d, J = 8,6 Hz, 2H), 7,40 a 7,36 (m, 3H), 5,14 a 5,11 (m, 1H), 4,31 (d, J = 5,7 Hz, 2H); EM $[M+H]^+$ = 511,0; LCMS TR = 2,33 min.

Ejemplo 235: Preparación de N-{4-[4-amino-6-(1,3-oxazol-2-il)pirrolo-[2,1-f][1,2,4]triazin-5-il]fenil}-N'-[4-(trifluorometil)piridin-2-il]urea



Paso 1: Preparación de 5-(4-nitro-fenil)-6-oxazol-2-il-pirrolo[2,1-f]-[1,2,4]triazin-4-ilamina

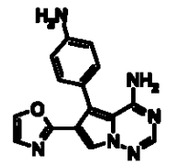


El procedimiento utilizado para la preparación del primer paso del intermediario M se utilizó para preparar (2,2-dimetoxi-etil)-amida del ácido 4-amino-5-(4-nitro-fenil)-pirrolo[2,1-f][1,2,4]triazin-6-carboxílico sustituyendo 2,2-dimetoxi-etilamina con sal clorhidrato de 2,2,2-trifluoro-etilamina. A una solución de ácido metansulfónico (1,5ml) se agregó P_2O_5 (225,0 mg, 1,58 mmol) seguido de la adición de (2,2-dimetoxi-etil)-amida del ácido 4-amino-5-(4-nitro-fenil)-pirrolo[2,1-f][1,2,4]triazin-6-carboxílico (150 mg, 0,388 mmol). La mezcla color marrón oscuro se calentó a 100 °C y se dejó agitar durante 18 hrs. La mezcla luego se vertió en hielo (15 g), se agitó durante quince minutos y se agregó suficiente solución de carbonato de sodio acuoso saturado para neutralizar la reacción. Un precipitado color blanco se

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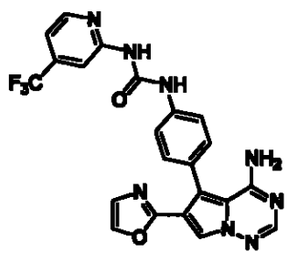
filtró y se recolectó (35 mg, 27%). ^{1}H-RMN (DMSO-d_6) δ 8,33 (s, 1H), 8,31 (m, 2H), 8,03 (d, J = 10 Hz, 2H), 7,73 (d, J = 10 Hz, 2H), 7,28 (s, 1H). EM $[M+H]^+$ = 323,2; LCMS TR = 2,51 min.

Paso 2: Preparación de 5-(4-Amino-fenil)-6-oxazol-2-il-pirrolo[2,1-f]-[1,2,4]triazin-4-ilamina.



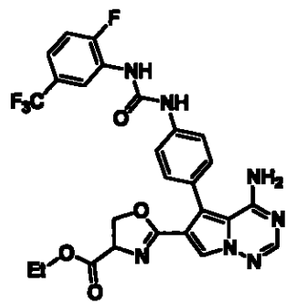
El procedimiento utilizado para la preparación del intermediario B se utilizó para preparar el compuesto del título sustituyendo 5-(4-Nitro-fenil)-6-oxazol-2-il-pirrolo[2,1-f][1,2,4]triazin-4-ilamina con 4-amino-5-(4-aminofenil)pirrol[2,1-f][1,2,4]triazin-6-carboxilato. $[M+H]^+$ = 293,3; LCMS TR = 0,38 min.

Paso 3: Preparación de N-{4-[4-amino-6-(1,3-oxazol-2-il)pirrolo[2,1-f]-[1,2,4]triazin-5-il]fenil}-N'-[4-(trifluorometil)piridin-2-il]urea



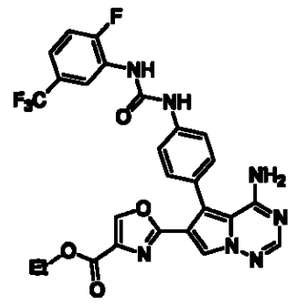
El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo 5-(4-amino-fenil)-6-oxazol-2-il-pirrolo[2,1-f][1,2,4]triazin-4-ilamina con el intermediario X y [4-(trifluorometil)piridin-2-il]carbamato de fenilo con (4-*ter*butilpiridin-2-il)carbamato de fenilo. ^{1}H-RMN (DMSO-d_6) δ9,94 (s, 1H), 9,79 (s, 1H), 8,55 (d, J = 6,2 Hz, 1H), 8,23 (s, 1H), 8,07 (s, 1H), 8,00 (s, 1H), 7,94 (s, 1H), 7,61 (d, J = 7,9 Hz, 2H), 7,40 (d, J = 7,9 Hz, 2H), 7,36(s, 1H), 7,18 (s,1H); EM $[M+H]^+$ = 481,1; LCMS TR = 3,11 min.

Ejemplo 236: Preparación de 2-(4-amino-5-{4-[({[2-fluoro-5-(trifluorometil)fenil]amino}carbonil)amino]fenil}pirrolo[2,1-f][1,2,4]triazin-6-il)-4,5-dihidro-1,3-oxazol-4-carboxilato de etilo



El procedimiento utilizado para la preparación del Ejemplo 230 se utilizó para preparar el compuesto del título sustituyendo N-[(4-amino-5-{4-[({[2-fluoro-5-(trifluorometil)fenil]amino}carbonil)amino]fenil}pirrolo[2,1-f][1,2,4]triazin-6-il)carbonil]serinato de etilo (Ejemplo 220) con 2-(4-amino-5-{4-[({[4-(trifluorometil)piridin-2-il]amino}carbonil)amino]fenil}pirrolo[2,1-f][1,2,4]triazin-6-il)-4,5-dihidro-1,3-oxazol-4-carboxilato de etilo (Ejemplo 221). ^{1}H-RMN (DMSO-d_6) δ9,31 (s, 1H), 8,96 a 8,95 (d, J = 2,9 Hz, 1H), 8,63 a 8,61 (d, J = 7,2 Hz, 1H), 8,08 (s, 1H), 7,91 (s, 1H), 7,54 a 7,52 (d, J = 8,6 Hz, 2H), 7,50 a 7,48 (d, J = 10,9 Hz, 1H), 7,41 a 7,38 (m, 1H), 7,33 a 7,31 (d, J = 8,6 Hz, 2H), 4,76 a 4,71(m, 1H), 4,38 a 4,29 (m, 2H), 4,13 a 4,08 (q, J = 6,5 Hz, 2H), 1,21 a 1,18 (t, J = 7,2 Hz, 3H); EM $[M+H]^+$ = 572,2; LCMS TR = 2,94 min.

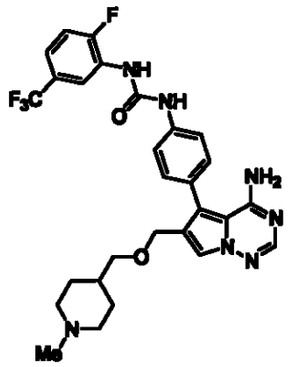
Ejemplo 237: Preparación de 2-(4-amino-5-{4-[({[2-fluoro-5-(trifluorometil)fenil]amino}carbonil)amino]fenil}pirrolo[2,1-f][1,2,4]triazin-6-il)-1,3-oxazol-4-carboxilato de etilo



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A una solución de THF (2 ml) y DCM (2 ml) enfriada en un baño de agua/hielo se agregó 2-(4-amino-5-{4-[({[2-fluoro-5-(trifluorometil)fenil]amino}-carbonil)amino]fenil}pirrolo[2,1-f][1,2,4]triazin-6-il)-4,5-dihidro-1,3-oxazol-4-carboxilato de etilo (Ejemplo 236) seguido de DBU (24 µl, 0,16 mmol) y $BrCCl_3$ (16 µl, 0,16 mmol). La solución se dejó agitar bajo N_2 durante 1h y luego la solución se dejó entibiar a ta mientras se agitaba durante 17h. La mezcla de reacción se evaporó al vacío y luego se purificó por cromatografía flash 50:45:5 v/v/v DCM/EtOAc/MeOH dando por resultado el aislamiento de 16 mg del compuesto del título en forma de un sólido color blanco (0,028 mmol, rendimiento 65%). ^{1}H-RMN (DMSO-d_6) δ9,35 (s, 1H), 8,96 (d, *J* = 2,8 Hz, 1H), 8,69 (s, 1H), 8,62 a 8,60 (d, *J* = 9,3 Hz, 1H), 8,29 (s, 1H), 7,94 (s, 1H), 7,58 a 7,56 (d, *J* = 8,4 Hz, 2H), 7,52 a 7,47 (m, 1H), 7,40 a 7,37 (m, 3H), 4,27 a 4,23 (q, *J* = 6,3 Hz, 2H), 1,28 a 1,24 (t, *J* = 7,1 Hz, 3H); EM $[M+H]^+$ = 570,1; LCMS TR = 3,16 min.

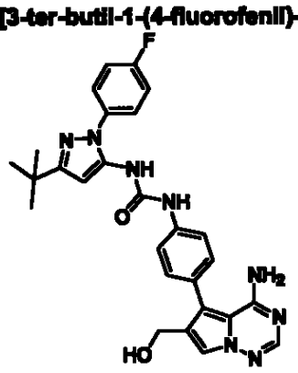
Ejemplo 238: Preparación de N-[4-(4-amino-6-{[(1-metilpiperidin-4-il)-metoxi]metil}pirrolo[2,1-f][1,2,4]triazin-5-il)fenil]-N'-[2-fluoro-5-(trifluoro-metil)fenil]urea



El procedimiento utilizado para la preparación del Ejemplo 271 se utilizó para preparar el compuesto del título sustituyendo (1-metilpiperidin-4-il)metanol con metanol y el producto del Intermediario F (Paso 1) con el Ejemplo 262. ^{1}H-RMN (DMSO-d_6) δ8,58 a 8,57 (m, 1H), 8,05 a 7,93 (m, 2H), 1,68 a 7,64 (m, 2H), 7,51 a 7,46 (m, 1H), 7,38 a 7,36 (m, 2H), 4,46 (s, 2H), 4,02 a 4,00 (m, 1H), 3,27 a 3,09 (m,

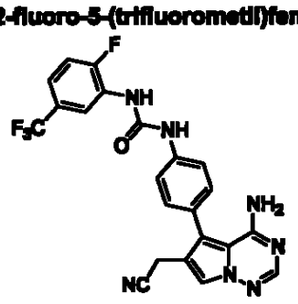
4H), 2,66 (s, 3H), 1,62 a 1,55 (m, 2H), 1,25 a 1,15 (m, 2H); EM $[M+H]^+$ = 572,1; LCMS TR = 2,06 min.

Ejemplo 239: **Preparación de N-{4-[4-amino-6-(hidroximetil)pirrolo[2,1-f][1,2,4]triazin-5-il]fenil}-N'-[3-ter-butil-1-(4-fluorofenil)-1H-pirazol-5-il]urea**



El procedimiento utilizado para la preparación del Intermediario F paso 1 se utilizó para preparar el compuesto del título sustituyendo el Ejemplo 25 con el Intermediario E. ^{1}H-RMN (DMSO-d_6) δ 9,11 (s, 1H), 8,42 (s, 1H), 7,81 (s, 1H), 7,64 (s, 1H), 7,48 a 7,58 (m, 5 H), 7,28 a 7,48 (m, 5H), 6,36 (s, 1H), 4,94 (t, J = 5 Hz, 1H), 4,34 (d, J = 5 Hz, 2H), 1,26 (s, 9H); EM $[M+H]^+$ = 515,2; LCMS TR = 2,48 min.

Ejemplo 240: **Preparación de N-{4-[4-amino-6-(clanometil)pirrolo[2,1-f]-[1,2,4]triazin-5-il]fenil}-N'-[2-fluoro-5-(trifluorometil)fenil]urea**

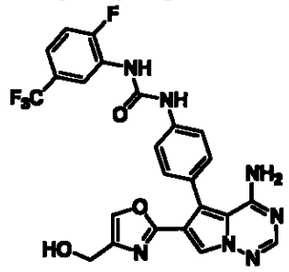


El procedimiento utilizado para la preparación del Ejemplo 226 se utilizó para preparar el compuesto del título sustituyendo [2-fluoro-5-(trifluorometil)fenil]carbamato de fenilo con [2-fluoro-5-(trifluorometil)fenil]carbamato de fenilo. ^{1}H-RMN (DMSO-d_6) δ9,41 (s, 1H), 9,01 (d, J = 3 Hz, 1H), 8,62 (d, J = 3, 8 Hz, 1H), 7,81 (s, 1H), 7,77 (s, 1H), 7,61 (d, J = 9 Hz, 2H), 7,47 a 7,54 (m, 1H), 7,38 a

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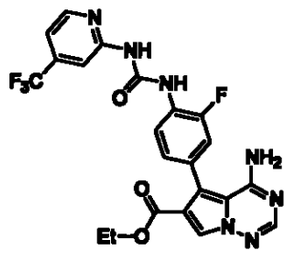
7,42 (m, 1H), 7,35 (d, J = 9 Hz, 2H), 5,35 (dd, J = 2, 6 Hz), 3,82 (s, 2H); EM $[M+H]^+$ = 470,1; LCMS TR = 2,80 min.

Ejemplo 241: **Preparación de N-(4-(4-amino-6-[4-(hidroximetil)-1,3-oxazol-2-il]pirrolo[2,1-f][1,2,4]triazin-5-il)fenil)-N'-[2-fluoro-5-(trifluorometil)-fenil]urea**



El procedimiento utilizado para la preparación del Intermediario F Paso 1 se utilizó para preparar el compuesto del título sustituyendo 2-(4-amino-5-{4-[({[2-fluoro-5-(trifluorometil)fenil]amino}carbonil)amino]fenil}pirrolo [2,1-f][1,2,4]triazin-6-il)-1,3-oxazol-4-carboxilato de etilo (Ejemplo 232) con el Intermediario E. ^{1}H-RMN (DMSO-d_6) δ 9,35 (s, 1H), 8,97 a 8,96 (d, *J* = 3,4 Hz, 1H), 8,63 a 8,61 (d, *J* = 7,4 Hz, 1H), 8,17 (s, 1H), 7,93 (s, 1H), 7,75 (s, 1H), 7,58 a 7,56 (d, *J* = 8,7 Hz, 2H), 7,53 a 7,48 (m, 1H), 7,41 a 7,36 (m, 3H), 5,16 a 5,13 (t, *J* = 5,6 Hz, 1H), 4,32 a 4,31 (d, *J* = 5,5 Hz, 2H); EM $[M+H]^+$ = 528,1; LCMS TR = 2,68 min.

Ejemplo 242: **Preparación de 4-amino-5-{3-fluoro-4-[({[4-(trifluorometil)-piridin-2-il]amino}carbonil)amino]fenil} pirrolo[2,1-f][1,2,4]triazin-6-carboxilato de etilo**

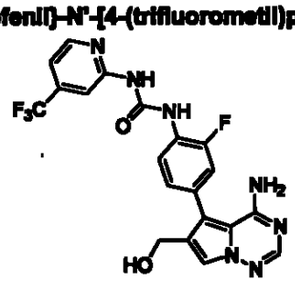


El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo el Intermediario AJ con el Intermediario X y sustituyendo [4-(trifluorometil)piridin-2-il]carbamato con fenilo (4-*ter*-butilpiridin-2-il)carbamato de fenilo. ^{1}H-RMN (DMSO-d_6) δ 10,14 (s, 1H), 10,11 a 10,04 (br s, 1H),

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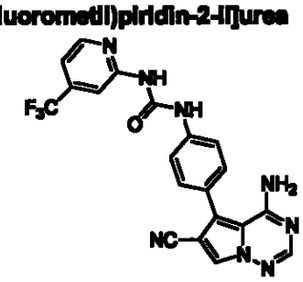
8,54 a 8,53 (d, *J* = 5,3 Hz, 1H), 8,28 a 8,23 (t, *J* = 8,4 Hz, 1H), 8,14 (s, 1H), 8,01 (s, 1H), 7,94 (s, 1H), 7,39 a 7,33 (m, 2H), 7,18 a 7,16 (d, *J* = 10,0 Hz, 1H), 4,12 a 4,06 (q, *J* = 8,3 Hz, 2H), 1,14 a 1,10 (t, *J* = 7,1 Hz, 3H); EM $[M+H]^+$ = 504,1; LCMS TR = 3,12 min.

Ejemplo 243: **Preparación de N-[4-[4-amino-6-(hidroximetil)pirrolo[2,1-f][1,2,4]triazin-5-il]-2-fluorofenil]-N'-[4-(trifluorometil)piridin-2-il]urea**



El procedimiento utilizado para la preparación del Intermediario F Paso 1 se utilizó para preparar el compuesto del título sustituyendo 4-amino-5-[3-fluoro-4-[([[4-(trifluorometil)piridin-2-il]amino}carbonil)amino]fenil}pirrolo [2,1-f][1,2,4]triazin-6-carboxilato de etilo (Ejemplo 242) con el intermediario E. ^{1}H-RMN (DMSO-d_6) δ10,13 (s, 1H), 10,07 a 10,02 (br s, 1H), 8,54 a 8,53 (d, *J* = 5,3 Hz, 1H), 8,29 a 8,24 (t, *J* = 8,5 Hz, 1H), 8,03 (s, 1H), 7,84 (s, 1H), 7,67 (s, 1H), 7,39 (s, 1H), 7,38 a 7,35 (d, *J* = 8,7 Hz, 1H), 7,21 a 7,19 (d, *J* = 9,7 Hz, 1H), 5,02 a 5,00 (t, *J* = 5,1 Hz, 1H), 4,39 a 4,37 (d, *J* = 5,2 Hz, 2H); EM $[M+H]^+$ = 482,0; LCMS TR = 2,44 min.

Ejemplo 244: **Preparación de N-[4-(4-amino-6-cianopirrolo[2,1-f][1,2,4]-triazin-5-il)fenil]-N'-[4-(trifluorometil)piridin-2-il]urea**

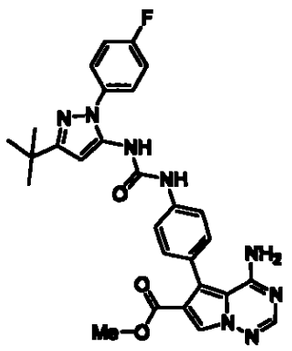


El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo el intermediario P con el intermediario X y sustituyendo [2-fluoro-5-(trifluorometil)fenil]carbamato de fenilo con (4-*ter*-

604

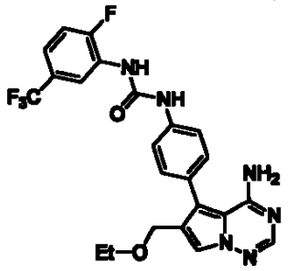
butilpiridin-2-il)carbamato de fenilo. ^{1}H-RMN (DMSO-d_6) δ9,96 (s, 1H), 9,78 (s, 1H), 8,55 (d, J = 5 Hz, 1H), 8,52 (s, 1H), 8,07 (s, 1H), 7,99 (s, 1H), 7,69 (d, J = 9 Hz, 2H), 7,45 (d, J = 9 Hz, 2H), 7,36 (d, J = 5 Hz, 1H); EM $[M+H]^+$ = 439,1; LCMS TR = 3,01 min.

Ejemplo 245: **Preparación de 4-amino-5-{4-[({[3-ter-butil-1-(4-fluoro-fenil)-1H-pirazol-5-il]amino}carbonil)amino] fenil}pirrolo[2,1-f][1,2,4]triazin-6-carboxilato de metilo**



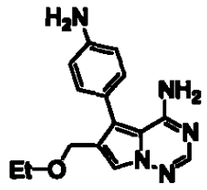
El procedimiento utilizado para la preparación del Ejemplo 25 se utilizó para preparar el compuesto del título sustituyendo 4-amino-5-(4-aminofenil)pirrolo[2,1f][1,2,4] triazin-6-carboxilato de metilo con el intermediario B. ^{1}H-RMN (DMSO-d_6) δ9,14 (s, 1H), 8,43 (s, 1H), 8,13 (s, 1H), 7,92 (s, 1H), 7,25 a 7,60 (m, 8H), 6,36 (s, 1H), 7,32 a 7,40 (m, 4H), 7,17 a 7,25 (m, 1H), 7,14 (bs, 1H), 6,34 (s, 1H), 3,81 (s, 1H); EM $[M+Na]^+$ = 565,2; LCMS TR = 3,13 min.

Ejemplo 246: **Preparación de N-{4-[4-amino-6-(etoximetil)pirrolo[2,1-f][1,2,4]triazin-5-il]fenil}-N'-[2-fluoro-5-(trifluorometil)fenil]urea**



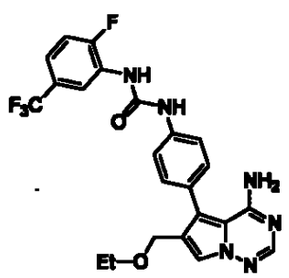
605

Paso 1: Preparación de 6-(etoximetil)-5-(4-nitrofenil)pirrolo[2,1-f][1,2,4]-triazin-4-amina



El método utilizado en la preparación del intermediario U se utilizó para preparar el compuesto del título sustituyendo etanol con metanol. EM $[M+H]^+$ = 284,1; LCMS TR = 0,35 min.

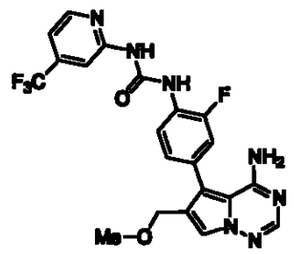
Paso 2: Preparación de N-{4-[4-amino-6-(etoximetil)pirrolo[2,1-f][1,2,4]-triazin-5-il]fenil}-N'-[2-fluoro-5-(trifluorometil)fenil urea



El procedimiento utilizado para la preparación del Ejemplo 1 se utilizó para preparar el compuesto del título sustituyendo 6-(etoximetil)-5-(4-aminofenil)pirrolo[2,1-f][1,2,4]triazin-4-amina en lugar del intermediario B. ^{1}H-RMN (DCM-d_2) δ 12,19 (s, 1H), 8,51 (d, *J* = 7,5 Hz, 1H), 8,01 (s, 1H), 7,74 (s, 1H), 7,4-7,3 (bs, 1H), 7,29-7,14 (m, 5H), 6,8 (s, 1H), 4,34 (s, 2H), 3,40 (q, *J* = 7,0 Hz, 2H), 0,80 (m, 3H); EM $[M+H]^+$ = 489,2; LCMS TR = 3,92 min.

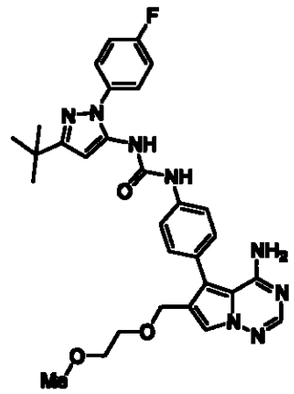
Ejemplo 247: Preparación de N-{4-[4-amino-6-(metoximetil)pirrolo[2,1-f][1,2,4]triazin-5-il]-2-fluorofenil}-N'-[4-(trifluorometil)piridin-2-il]urea

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El procedimiento utilizado para la preparación del Ejemplo 271 se utilizó para preparar el compuesto del título sustituyendo N-{4-[4-amino-6-(hidroximetil)pirrolo[2,1-*f*][1,2,4]triazin-5-il]-2-fluorofenil}-N'-[4-(trifluorometil)piridin-2-il]urea (Ejemplo 243) con N-{4-[4-amino-6-(hidroximetil)pirrolo[2,1-*f*][1,2,4]triazin-5-il]fenil}-N'-(4-metilpiridin-2-il)urea (Ejemplo 262). ^{1}H-RMN (DMSO-d_6) δ10,14 (s, 1H), 10,09 a 10,04 (br s, 1H), 8,54 a 8,53 (d, *J* = 5,5 Hz, 1H), 8,30 a 8,26 (t, *J* = 8,5 Hz, 1H); 8,00 (s, 1H), 7,86 (s, 1H), 7,76 (s, 1H), 7,39 a 7,38 (d, *J* = 5,2 Hz, 1H), 7,35 a 7,32 (d, *J* = 12,0 Hz, 1H), 7,21 a 7,18 (d, *J* = 10,2 Hz, 1H), 4,26 (s, 2H), 3,22 (s, 3H); EM [M+H]$^+$ = 476,1; LCMS TR = 2,77 min.

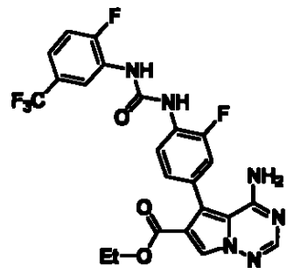
Ejemplo 248: Preparación de N-(4-[4-amino-6-[(2-metoxietoxi)metil]-pirrolo[2,1-*f*][1,2,4]triazin-5-il]fenil)-N'-[3-*ter*-butil-1-(4-fluorofenil)-1H-pirazol-5-il]urea



El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo el Intermediario Z con el Intermediario X y sustituyendo (3-*ter*-butil-1-(4-fluorofenil)-1*H*-pirazol-5-)-carbamato de fenilo con (4-*ter*-butilpiridin-2-il)carbamato de fenilo. ^{1}H-RMN (DMSO-d_6) δ9,13 (s, 1H), 8,43 (s,

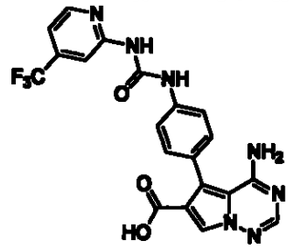
1H), 7,83 (s, 1H), 7,73 (s, 1H), 7,58-7,49 (m, 4H), 7,38 (d, *J* = 9,4 Hz 2H), 7,31 (d, *J* = 9,4 Hz, 2H), 6,37 (s, 1H), 4,30(s, 2H), 3,46-3,43 (m, 2H), 3,40-3,37 (m, 2H), 3,20 (s, 3H), 1,26 (s, 9H); EM $[M+H]^+$ = 573,1; LCMS TR = 2,71 min.

Ejemplo 249: Preparación de 4-amino-5-{3-fluoro-4-[({[2-fluoro-5-(trifluorometil)fenil]amino}carbonil)amino]fenil}pirrolo[2,1-*f*][1,2,4]triazin-6-carboxilato de etilo



El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo el intermediario AJ con el intermediario X y [2-fluoro-5-(trifluorometil)fenil]carbamato de fenilo con (4-ter-butilpiridin-2-il)carbamato de fenilo. ^{1}H-RMN (DMSO-d_6) δ9,42 (s, 1H), 9,28 (s, 1H), 8,65 a 8,63 (m, 1H), 8,27 a 8,22 (m, 1H), 8,13 (s, 1H), 7,93 (s, 1H), 4,11 a 4,06 (m, 2H), 1,14 a 1,10 (m, 3H); EM $[M+H]^+$ = 521,3; LCMS TR = 2,98 min.

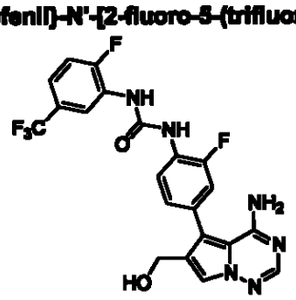
Ejemplo 250: Preparación de ácido 4-amino-5-{4-[({[4-(trifluorometil)-piridin-2-il]amino}carbonil)amino] fenil}pirrolo[2,1-*f*][1,2,4]triazin-6-carboxílico



El procedimiento utilizado para la preparación del intermediario G se utilizó para preparar el compuesto del título sustituyendo el Ejemplo 51 con el intermediario E. ^{1}H-RMN (DMSO-d_6) δ12,3 (s, 1H), 9,87 (s, 1H), 9,75 (s, 1H), 8,53 (d, *J* = 5,3 Hz, 2H), 8,07 a 8,06 (m, 3H), 7,86 (s, 1H), 7,58 a 7,56 (m, 2H), 7,36 a 7,33 (m, 3H); EM $[M+H]^+$ = 458,0; LCMS TR = 2,28 min.

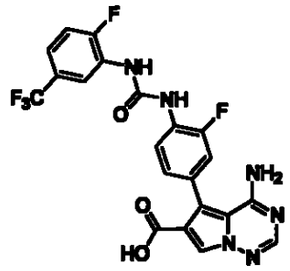
608

Ejemplo 251: **Preparación de N-{4-[4-amino-6-(hidroximetil)pirrolo[2,1-f][1,2,4]triazin-5-il]-2-fluorofenil}-N'-[2-fluoro-5-(trifluorometil)fenil]urea**



El procedimiento utilizado para la preparación del intermediario AF se utilizó para preparar el compuesto del título sustituyendo el Ejemplo 249 con el Ejemplo 51. ^{1}H-RMN (DMSO-d_6) δ 9,41 (s, 1H), 9,40 (s, 1H), 9,26 a 8,63 (m, 1H), 8,28 a 8,24 (m, 1H), 7,83 (s, 1H), 7,66 (s, 1H), 7,53 a 7,48 (m, 1H), 7,41 a 7,33 (m, 2H), 7,18 (d, J = 8,2 Hz, 1H), 5,01 a 4,98 (m, 1H), 4,37 (d, J = 5,0 Hz, 2H); EM $[M+H]^+$ = 479,1; LCMS TR = 2,49 min.

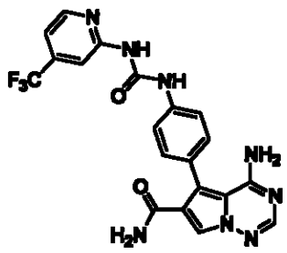
Ejemplo 252: **Preparación de ácido 4-amino-5-{3-fluoro-4-[({[2-fluoro-5-(trifluorometil)fenil]amino}carbonil)amino] fenil}pirrolo[2,1-f][1,2,4]triazin-6-carboxílico**



El procedimiento utilizado para la preparación del intermediario G se utilizó para preparar el compuesto del título sustituyendo el Ejemplo 249 con el intermediario E. ^{1}H-RMN (DMSO-d_6) δ 12,3 (s, 1H), 9,43 (s, 1H), 9,27 (s, 1H), 8,65 a 8,63 (m, 1H), 8,25 a 8,20 (m, 1H), 8,07 (s, 1H), 8,02 (s, 1H); EM $[M+H]^+$ = 433,1; LCMS TR = 2,58 min.

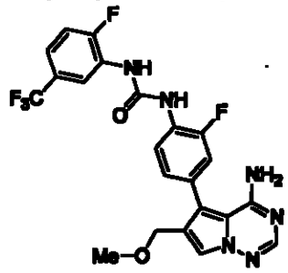
Ejemplo 253: **Preparación de 4-amino-5-{4-[({[4-(trifluorometil) piridin-2-il]amino}carbonil)amino]fenil}pirrolo[2,1-f][1,2,4]triazin-6-carboxamida**

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El procedimiento utilizado para la preparación del Ejemplo 104 se utilizó para preparar el compuesto del título sustituyendo [4-(trifluorometil)piridin-2-il]carbamato de fenilo con [3-fluoro-5-(trifluorometil)fenil]carbamato de fenilo. ^{1}H-RMN (CD_3OD) δ8,52 (d, J = 5 Hz, 1H), 8,06 (s, 1H), 7,84 (s, 1H), 7,71 (s, 1H), 7,70 (d, J = 9 Hz, 2H), 7,46 (d, J = 9 Hz, 2H), 7,28 (d, J = 5 Hz, 1H); EM $[M+H]^+$ = 457,0; LCMS TR = 2,36 min.

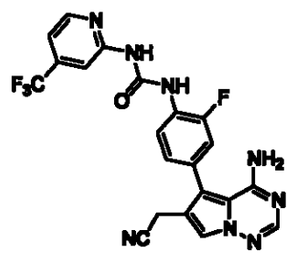
Ejemplo 254: **Preparación de N-{4-[4-amino-6-(metoximetil)pirrolo[2,1-f][1,2,4]triazin-5-il]-2-fluorofenil}-N'-[2-fluoro-5-(trifluorometil)fenil]urea**



El procedimiento utilizado para la preparación del Ejemplo 271 se utilizó para preparar el compuesto del título sustituyendo el Ejemplo 251 con el Ejemplo 262. ^{1}H-RMN (CD_3OD) δ 8,65 (d, *J* = 8,0 Hz, 1H), 8,31 a 8,27 (m, 1H), 7,80 (s, 1H), 7,70 (s, 1H), 7,35 a 7,23 (m, 4H), 4,37 (s, 2H), 3,33 (s, 3H); EM $[M+H]^+$ = 493,1; LCMS TR = 2,84 min.

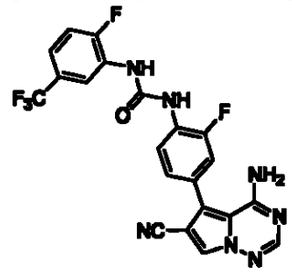
Ejemplo 255: **Preparación de N-{4-[4-amino-6-(cianometil)pirrolo[2,1-f]-[1,2,4]triazin-5-il]-2-fluorofenil}-N'-[4-(trifluorometil)piridin-2-il]urea**

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El procedimiento utilizado para la preparación del Ejemplo 271 se utilizó para preparar el compuesto del título sustituyendo N-[4-[4-amino-6-(hidroximetil)pirrolo[2,1-f][1,2,4]triazin-5-il]-2-fluorofenil]-N'-[4-(trifluorometil) piridin-2-il]urea (Ejemplo 243) con N-[4-[4-amino-6-(hidroximetil)pirrolo[2,1-f][1,2,4]triazin-5-il]fenil]-N'-(4-metilpiridin-2-il)urea (Ejemplo 262) y cianuro de sodio con MeOH. ^{1}H-RMN (Acetona-d_6) δ10,99 (a, 1H), 9,39 (a, 1H), 8,59 a 8,58 (d, *J* = 5,1 Hz, 1H), 8,51 a 8,47 (t, *J* = 8,5 Hz, 1H), 7,84 (a, 1H), 7,82 a 7,81 (d, *J* = 6,4 Hz, 1H), 7,75 (a, 1H), 7,38 a 7,35 (m, 2H), 7,30 a 7,28 (d, *J* = 8,4 Hz, 1H), 3,86 (a, 2H); EM $[M+H]^+$ = 471,0; LCMS TR = 2,75 min.

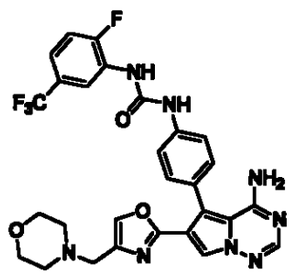
Ejemplo 256: Preparación de N-[4-(4-amino-6-cianopirrolo[2,1-*f*][1,2,4]-triazin-5-il)-2-fluorofenil]-N'-[2-fluoro-5-(trifluorometil)fenil]urea



El procedimiento utilizado para la preparación del intermediario O se utilizó para preparar el compuesto del título sustituyendo el intermediario AN con el intermediario H. ^{1}H-RMN (CD_3OD) δ8,66 a 8,64 (m, 1H), 8,41 a 8,37 (m, 1H), 8,20 (a, 1H), 7,92 (a, 1H), 7,40 a 7,31 (m, 4H); EM $[M+H]^+$ = 474,1; LCMS TR = 2,92 min.

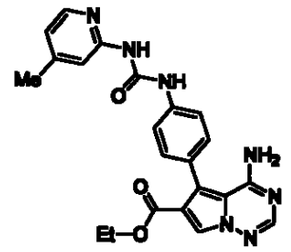
Ejemplo 257: Preparación de N-(4-[4-amino-6-[4-(morfolin-4-ilmetil)-1,3-oxazol-2-il]pirrolo[2,1-*f*][1,2,4]triazin-5-il]fenil)-N'-[2-fluoro-5-(trifluorometil)-fenil]urea

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El procedimiento utilizado para la preparación del Ejemplo 66 se utilizó para preparar el compuesto del título sustituyendo el intermediario AM con el intermediario I. ^{1}H-RMN (CD_3OD) δ8,62 a 8,60 (d, *J* = 7,6 Hz, 1H), 8,15 (s, 1H), 7,85 (s, 1H), 7,65 (s, 1H), 7,61 a 7,59 (d, *J* = 8,7 Hz, 2H), 7,42 a 7,40 (d, *J* = 8,5 Hz, 2H), 7,35 a 7,33 (m, 2H), 3,69 a 3,66 (t, *J* = 4,7 Hz, 4H), 3,46 (s, 2H), 2,53 a 2,50 (t, *J* = 4,6 Hz, 4H); EM $[M+H]^+$ = 597,1; LCMS TR = 2,44 min.

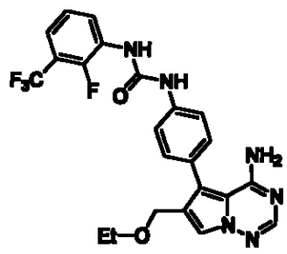
Ejemplo 258: Preparación de 4-amino-5-[4-({[(4-metilpiridin-2-il)amino]-carbonil}amino)fenil]pirrolo[2,1-*f*][1,2,4]triazin-6-carboxilato de etilo



El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo el intermediario B con el intermediario X y sustituyendo (4-metilpiridin-2-il)imidodicarbonato de difenilo con (4-*ter*-butilpiridin-2-il)carbamato de fenilo. ^{1}H-RMN (DMSO-d_6) □10,83 (s, 1H), 9,45 (s, 1H), 8,15 a 8,13 (d, *J* = 5,3 Hz, 1H), 8,13 (s, 1H), 7,93 (s, 1H), 7,62 a 7,60 (d, *J* = 8,3 Hz, 2H), 7,34 a 7,32 (d, *J* = 8,3 Hz, 2H), 7,26 (s, 1H), 6,87 a 6,86 (d, *J* = 5,3 Hz, 1H), 4,11 a 4,06 (q, *J* = 7,1 Hz, 2H), 2,30 (s, 3H) 1,13 a 1,10 (t, *J* = 7,1 Hz, 3H); EM $[M+H]^+$ = 432,1; LCMS TR = 2,30 min.

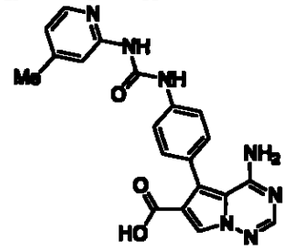
Ejemplo 259: Preparación de N-(4-[4-amino-6-(etoximetil)pirrolo [2,1-*f*][1,2,4]triazin-5-il]fenil}-N'-[2-fluoro-3-(trifluorometil)fenil]urea

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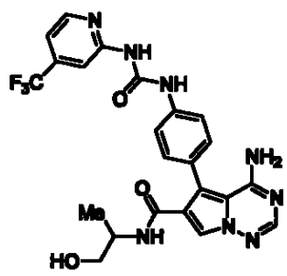
El procedimiento utilizado para la preparación del Ejemplo 1 se utilizó para preparar el compuesto del título sustituyendo 6-(etoximetil)-5-(4-nitrofenil)pirrolo[2,1-f][1,2,4]triazin-4-amina con el intermediario B y sustituyendo 2-fluoro-1-isocianato-3-(trifluorometil)benceno con 1-fluoro-2-isocianato-4-(trifluorometil)benceno. ^{1}H-RMN (DMSOD6) δ9,28 (s, 1H), 8,89 (s, 1H), 8,48-8,42 (m, 1H), 7,83 (s, 1H), 7,73 (s, 1H), 7,59 (s, 1H), 7,56 (s, 1H), 7,36-7,32 (m, 4H), 4,28(s, 2H), 3,37 (q, *J*= 5,2 Hz, 2H), 1,06 (t, *J*= 7 Hz, 3H); EM $[M+H]^+$ = 489,1; LCMS TR = 2,87.

Ejemplo 260: **Preparación de ácido 4-amino-5-[4-({[(4-metilpiridin-2-il)-amino]carbonil}amino)fenil]pirrolo[2,1-*f*][1,2,4]triazin-6-carboxílico**



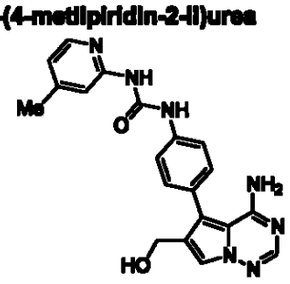
El procedimiento utilizado para la preparación del intermediario G se utilizó para preparar el compuesto del título sustituyendo 4-amino-5-[4-({[(4-metilpiridin-2-il)amino]carbonil}amino)fenil]pirrolo[2,1-*f*][1,2,4]triazin-6-carboxilato de etilo (Ejemplo 258) con el intermediario E. ^{1}H-RMN (DMSO-d_6) δ 12,28 (s, 1H) 10,82 (s, 1H), 9,46 (s, 1H), 8,14 a 8,13 (d, *J* = 5,4 Hz, 1H), 8,07 (s, 1H), 7,91 (s, 1H), 7,60 a 7,58 (d, *J* = 8,6 Hz, 2H), 7,34 a 7,31 (d, *J* = 8,6 Hz, 2H), 7,27 (s, 1H), 6,86 a 6,85 (d, *J* = 5,9 Hz, 1H), 2,30 (s, 3H); EM $[M+H]^+$ = 404,2; LCMS TR = 0,38 min.

Ejemplo 261: **Preparación de 4-amino-N-(2-hidroxi-1-metiletil)-5-[4-[({[4-(trifluorometil)piridin-2-il]amino}carbonil)amino] fenil}pirrolo[2,1-*f*][1,2,4]-triazin-6-carboxamida**



El procedimiento utilizado para la preparación del Ejemplo 143 se utilizó para preparar el compuesto del título sustituyendo 1-aminopropan-2-ol con 2-amino-2-metilopropan-1-ol y el Ejemplo 250 con el intermediario J. ^{1}H-RMN (DMSO-d_6) δ9,87 (s, 1H), 9,74 (s, 1H), 8,54 a 8,53 (d, *J* = 5,0 Hz, 1H), 8,11 (s, 1H), 8,06 (s, 1H), 7,89 (s, 1H), 7,59 a 7,57 (d, *J* = 8,6 Hz, 2H), 7,37 a 7,31 (m, 4H), 4,65 a 4,62 (t, *J* = 5,8 Hz, 1H), 3,85 a 3,79 (m, 1H), 3,23 a 3,16 (m, 2H), 1,01 a 1,00 (d, *J* = 6,7 Hz, 3H); EM [M+H]$^+$ = 515,0; LCMS TR = 2,41 min.

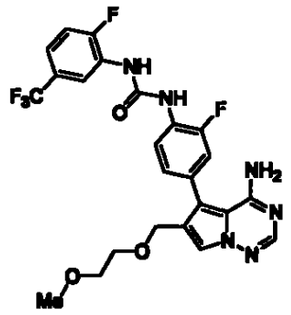
Ejemplo 262: **Preparación de N-[4-[4-amino-6-(hidroximetil)pirrolo [2,1-f][1,2,4]triazin-5-il]fenil]-N'-(4-metilpiridin-2-il)urea**



El procedimiento utilizado para la preparación del intermediario F Paso 1 se utilizó para preparar el compuesto del título sustituyendo 4-amino-5-[4-({[(4-metilpiridin-2-il)amino]carbonil}amino)fenil]pirrolo[2,1-f][1,2,4]triazin-6-carboxilato de etilo (Ejemplo 258) con el intermediario E. ^{1}H-RMN (DMSO-d_6) δ10,84 (s, 1H), 9,45 (s, 1H), 8,14 a 8,13 (d, *J* = 5,6 Hz, 1H), 7,82 (s, 1H), 7,65 (s, 1H), 7,64 a 7,62 (d, *J* = 8,5 Hz, 2H), 7,37 a 7,35 (d, *J* = 8,5 Hz, 2H), 7,27 (s, 1H), 6,86 a 6,85 (d, *J* = 5,1 Hz, 1H), 4,97 a 4,95 (t, *J* = 5,3 Hz, 1H), 4,38 a 4,37 (d, *J* = 5,4 Hz, 2H), 2,30 (s, 3H); EM [M+H]$^+$ = 390,0; LCMS TR = 1,51 min.

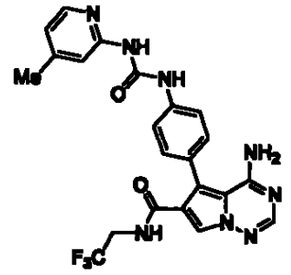
614

Ejemplo 263: Preparación de N-(4-[4-amino-6-[(2-metoxietoxi)metil]-pirrolo[2,1-f][1,2,4]triazin-5-il]-2-fluorofenil)-N'-[2-fluoro-5-(trifluorometil)-fenil]urea



El procedimiento utilizado para la preparación del Ejemplo 271 se utilizó para preparar el compuesto del título sustituyendo 3-metoxipropan-1-ol con metanol y el Ejemplo 251 con el Ejemplo 262. ^{1}H-RMN (CD_3OD) δ8,64 (d, *J* = 6,9 Hz, 1H), 8,31 a 8,26 (m, 1H), 7,79 (s, 1H), 7,71 (s, 1H), 7,37 a 7,33 (m, 3H), 7,25 (d, *J* = 8,4 Hz, 1H), 4,49 (s, 2H), 3,54 a 3,52 (m, 2H), 3,33 (s, 3H); EM $[M+H]^+$ = 537,1; LCMS TR = 2,82 min.

Ejemplo 264: Preparación de 4-amino-5-[4-({[(4-metilpiridin-2-il)amino]-carbonil}amino)fenil]-N-(2,2,2-trifluoroetil)pirrolo[2,1-f][1,2,4]triazin-6-carboxamida

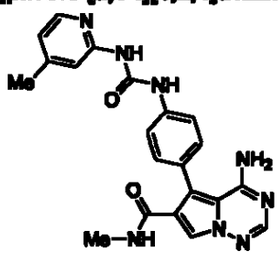


El procedimiento utilizado para la preparación del Ejemplo 143 se utilizó para preparar el compuesto del título sustituyendo 2,2,2-trifluoroetanamina con 2-amino-2-metilpropan-1-ol y ácido 4-amino-5-[4-({[(4-metilpiridin-2-il)amino]-carbonil}amino)fenil]pirrolo[2,1-f][1,2,4]triazin-6-carboxílico (Ejemplo 260) con el intermediario J. ^{1}H-RMN (DMSO-d_6) δ10,80 (s, 1H), 9,44 (s, 1H), 8,52 a 8,49 (t, *J* =

615

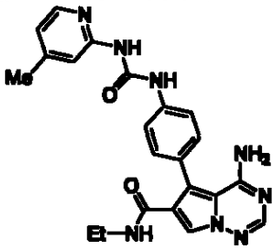
6,2 Hz, 1H), 8,18 (s, 1H), 8,14 a 8,13 (d, *J* = 5,3 Hz, 1H), 7,91 (s, 1H), 7,59 a 7,57 (d, *J* = 8,6 Hz, 2H), 7,31 a 7,28 (d, *J* = 8,6 Hz, 2H), 7,28 (s, 1H), 6,86 a 6,85 (d, *J* = 5,2 Hz, 1H), 3,97 a 3,93 (m, 2H), 2,30 (s, 3H); EM $[M+H]^+$ = 485,1; LCMS TR = 2,06 min.

Ejemplo 265: **Preparación de 4-amino-N-metil-5-[4-({[(4-metilpiridin-2-il)-amino]carbonil}amino)fenil]pirrolo [2,1-*f*][1,2,4]triazin-6-carboxamida**



El procedimiento utilizado para la preparación del Ejemplo 143 se utilizó para preparar el compuesto del título sustituyendo metanamina con 2-amino-2-metilopropan-1-ol y ácido 4-amino-5-[4-({[(4-metilpiridin-2-il)amino]carbonil}-amino)fenil]pirrolo[2,1-*f*][1,2,4]triazin-6-carboxílico (Ejemplo 260) con el intermediario J. ^{1}H-RMN (DMSO-d_6) δ10,80 (s, 1H), 9,45 (s, 1H), 8,14 a 8,13 (d, *J* = 5,4 Hz, 1H), 8,05 (s, 1H), 7,89 (s, 1H), 7,82 a 7,80 (m, 1H), 7,59 a 7,57 (d, *J* = 8,6 Hz, 2H), 7,31 a 7,29 (d, *J* = 8,4 Hz, 2H), 7,28 (s, 1H), 6,86 a 6,85 (d, *J* = 5,1 Hz, 1H), 2,64 a 2,63 (d, *J* = 4,7 Hz, 3H), 2,30 (s, 3H); EM $[M+H]^+$ = 417,0; LCMS TR = 1,54 min.

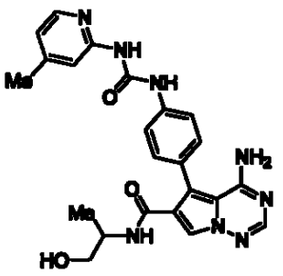
Ejemplo 266: **Preparación de 4-amino-N-etilo-5-[4-({[(4-metilpiridin-2-il)-amino]carbonil}amino)fenil]pirrolo[2,1-*f*][1,2,4] triazin-6-carboxamida**



El procedimiento utilizado para la preparación del Ejemplo 143 se utilizó para preparar el compuesto del título sustituyendo etanamina con 2-amino-2-metilopropan-1-ol y ácido 4-amino-5-[4-({[(4-metilpiridin-2-il)amino]carbonil}-

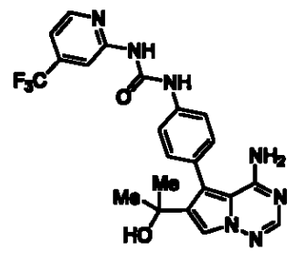
amino)fenil]pirrolo[2,1-f][1,2,4]triazin-6-carboxílico (Ejemplo 260) con el intermediario J. ^{1}H-RMN (DMSO-d_6) δ 10,80 (s, 1H), 9,45 (s, 1H), 8,14 a 8,13 (d, *J* = 5,1 Hz, 1H), 8,06 (s, 1H), 7,89 (s, 1H), 7,76 a 7,73 (t, *J* = 5,9 Hz, 1H), 7,59 a 7,57 (d, *J* = 8,6 Hz, 2H), 7,32 a 7,30 (d, *J* = 8,6 Hz, 2H), 7,28 (s, 1H), 6,86 a 6,85 (d, *J* = 6,9 Hz, 1H), 3,16 a 3,09 (m, 2H), 2,30 (s, 3H) 1,03 a 1,00 (t, *J* = 7,1 Hz, 3H); EM $[M+H]^+$ = 431,1; LCMS TR = 1,80 min.

Ejemplo 267: Preparación de 4-amino-N-(2-hidroxi-1-metiletil)-5-[4-({[(4-metilpiridin-2-il)amino]carbonil}amino)fenil] pirrolo[2,1-f][1,2,4]triazin-6-carboxamida



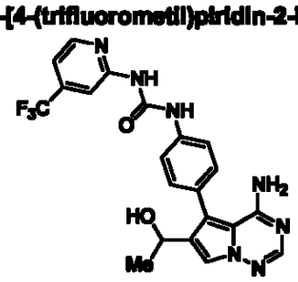
El procedimiento utilizado para la preparación del Ejemplo 143 se utilizó para preparar el compuesto del título sustituyendo 2-aminopropan-1-ol con 2-amino-2-metilopropan-1-ol y ácido 4-amino-5-[4-({[(4-metilpiridin-2-il)amino]carbonil}amino)fenil]pirrolo[2,1-f][1,2,4]triazin-6-carboxílico (Ejemplo 260) con el intermediario J. ^{1}H-RMN (DMSO-d_6) δ 10,82 (s, 1H), 9,45 (s, 1H), 8,14 a 8,13 (d, *J* = 5,2 Hz, 1H), 8,10 (s, 1H), 7,89 (s, 1H), 7,61 a 7,59 (d, *J* = 8,8 Hz, 2H), 7,33 a 7,31 (d, *J* = 8,6 Hz, 2H), 7,30 a 7,28 (m, 2H), 6,87 a 6,85 (d, *J* = 5,8 Hz, 1H), 4,65 a 4,62 (t, *J* = 5,7 Hz, 1H), 3,84 a 3,78 (m, 1H). 3,22 a 3,16 (m, 2H), 2,30 (s, 3H), 1,01 a 0,99 (d, *J* = 6,7 Hz, 3H)); EM $[M+H]^+$ = 461,1; LCMS TR = 1,62 min.

Ejemplo 268: Preparación de N-[4-[4-amino-6-(1-hidroxi-1-metiletil)pirrolo[2,1-f][1,2,4]triazin-5-il]fenil]-N'-[4-(trifluorometil)piridin-2-il]urea

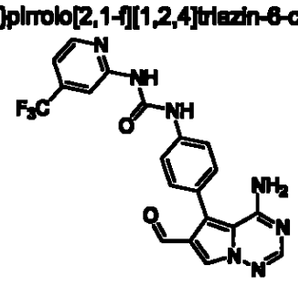


Una solución del Ejemplo 51 (78 mg, 0,155 mmol) en 5 ml de THF se trató con bromuro de metilmagnesio (0,78 ml, 2,3 mmol, 3N en Et_2O) y se calentó a 60°C durante 4h. La reacción se templó con MeOH y se diluyó con EtOAc y se lavó con NH_4Cl sat. La capa orgánica se secó con sulfato de sodio y se evaporó hasta sequedad. El residuo se trituró con Et_2O para dar 64 mg del producto del título (87% de rendimiento). ^{1}H-RMN (DMSO-d_6) δ9,98 (s, 1H), 9,79 (s, 1H), 8,52 (d, J = 5 Hz, 1H), 8,70 (s, 1H), 7,77 (s, 1H), 7,58 (d, J = 9 Hz, 2H), 7,56 (s, 1H), 7,33 (d, J = 9 Hz, 2H), 7,30 a 7,35 (m, 1 H), 7,11 (bs, 2 H), 4,91 (s, 1 H), 1,24 (s, 6H); EM $[M+H]^+$ = 472,1; LCMS TR = 2,48 min.

Ejemplo 269: **Preparación de N-{4-[4-amino-6-(1-hidroxietil)pirrolo[2,1-f][1,2,4]triazin-5-il]fenil}-N'-[4-(trifluorometil)piridin-2-il]urea**

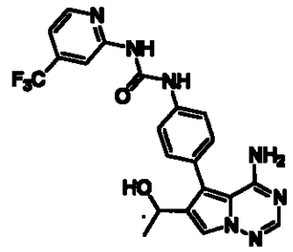


Paso 1: **Preparación de ácido 4-amino-5-{4-[({[4-(trifluorometil)piridin-2-il]amino}carbonil)amino]fenil}pirrolo[2,1-f][1,2,4]triazin-6-carboxílico;**



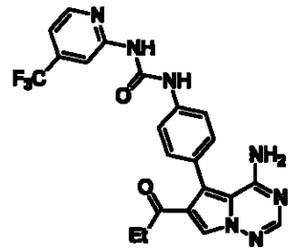
El procedimiento utilizado para la preparación del intermediario F se utilizó para preparar el compuesto del título sustituyendo el Ejemplo 51 con el intermediario E. ^{1}H-RMN (DMSO-d_6) δ9,97 (s, 1H), 9,78 (s, 1H), 9,75 (s, 1H), 8,54 (d, J = 5Hz, 1H), 8,27 (s, 1H), 8,07 (s, 1H), 7,96 (s, 1H), 7,67 (d, J = 9 Hz, 2H), 7,75 (d, J = 9 Hz, 2H), 7,36 (d, J = 5 Hz, 1H), 5,33 a 5,37 (m, 1H); EM $[M+H]^+$ = 422,0; LCMS TR = 2,77 min.

Paso 2: Preparación de N-{4-[4-amino-6-(1-hidroxietil)pirrolo[2,1f]-[1,2,4]triazin-5-il]fenil}-N'-[4-(trifluorometil)piridin-2-il]urea



Una solución de ácido 4-amino-5-{4-[({[4-(trifluorometil)piridin-2-il] amino} carbonil)amino]fenil}pirrolo[2,1-f][1,2,4]triazin-6-carboxílico (60 mg, 0,136 mmol) en 5 ml THF se trató con bromuro de metilmagnesio (0,68 ml, 2,1 mmol, 3 M en Et_2O) gota a gota durante 2 min. La reacción se dejó agitar durante 15 min, luego se templó con MeOH, se diluyó con EtOAc y se lavó con NH_4Cl ac. La capa orgánica se secó con sulfato de sodio y se evaporó hasta sequedad. El residuo se trituró con Et_2O para dar 50,1 mg del compuesto del título (82% de rendimiento). ^{1}H-RMN (DMSO-d_6) δ10,05 (s, 1H), 9,82 (s, 1H), 8,52 (d, J = 5 Hz, 1H), 8,09 (s, 1H), 7,81 (s, 1H), 7,64 (s, 1H), 7,61 (d, J = 9 Hz, 2H), 7,34 (d, J = 9 Hz, 2H), 4,96 (d, J = 5 Hz, 1 H), 4,63 (dq, J = 5, 6 Hz, 1 H), 1,24 (d, J = 6 Hz, 3 H); EM $[M+H]^+$ = 458,0; LCMS TR = 2,41 min.

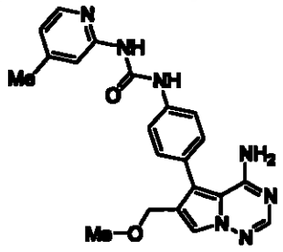
Ejemplo 270: Preparación de N-[4-(4-amino-6-propionilpirrolo[2,1-f]-[1,2,4]triazin-5-il)fenil]-N'-[4-(trifluorometil)piridin-2-il]urea



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El procedimiento utilizado para la preparación del Ejemplo 233 se utilizó para preparar el compuesto del título sustituyendo el Ejemplo 274 con el Ejemplo 269. ^{1}H-RMN (DMSO-d_6) δ9,98 (s, 1H), 9,85 (s,1H), 8,53 (d, J = 5 Hz, 1H), 8,37 (s, 1H), 8,07 (s, 1H), 8,00 a 8,10 (bs, 1H), 7,59 (d, J = 9 Hz, 2H), 7,30 a 7,39 (m, 3H), 2,71 (d, J = 7 Hz, 2H), 0,92 (t, J = 7 Hz, 3H); EM [M+Na]$^+$ = 492,0; LCMS TR = 2,87 min.

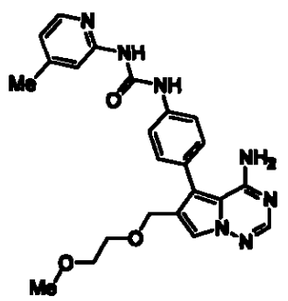
Ejemplo 271: **Preparación de N-(4-[4-amino-6-(metoximetil)pirrolo[2,1-f][1,2,4]triazin-5-il]fenil)-N'-(4-metilpiridin-2-il)urea**



A una solución de DCM (5 ml) se agregó N-(4-[4-amino-6-(hidroximetil)pirrolo[2,1-f][1,2,4]triazin-5-il]fenil)-N'-(4-metilpiridin-2-il)urea (Ejemplo 262) (40 mg, 0,10 mmol) seguido de cloruro de tionilo 2M en DCM (0,51 ml, 1,03 mmol). La solución se agitó a temperatura ambiente durante 1h y luego se evaporó al vacío. Se agregaron THF (5 ml) y MeOH (5 ml) a la reacción bruta seguido de trietilamina (43 µl, 0,31 mmol). La solución se calentó a 50 °C durante 3 días y luego se evaporó al vacío y se purificó por MPLC (Isco) 0-5% de MeOH/DCM. Las fracciones purificadas resultantes se combinaron y se evaporaron produciendo 25 mg del compuesto del título (0,061 mmol, rendimiento 60%). ^{1}H-RMN (DMSO-d_6) δ10,86 (s, 1H), 9,46 (s, 1H), 8,14 a 8,13 (d, *J* = 6,3 Hz, 1H), 7,84 (s, 1H), 7,75 (s, 1H), 7,65 a 7,63 (d, *J* = 8,7 Hz, 2H), 7,36 a 7,34 (d, *J* = 8,6 Hz, 2H), 7,27 (s, 1H), 6,87 a 6,86 (d, *J* = 5,0 Hz, 1H), 4,27 (s, 2H), 3,20 (s, 3H), 2,30 (s, 3H); EM [M+H]$^+$ = 404,0; LCMS TR = 1,99 min.

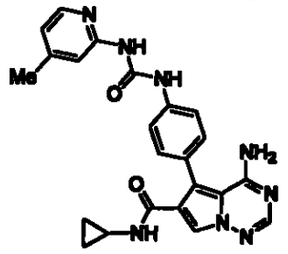
Ejemplo 272: **Preparación de N-(4-[4-amino-6-[(2-metoxietoxi)metil]-pirrolo[2,1-f][1,2,4]triazin-5-il]fenil)-N'-(4-metilpiridin-2-il)urea**

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El procedimiento utilizado para la preparación del Ejemplo 271 se utilizó para preparar el compuesto del título sustituyendo 2-metoxietanol con MeOH. ^{1}H-RMN (DMSO-d_6) δ10,85 (s, 1H), 9,46 (s, 1H), 8,14 a 8,13 (d, *J* = 5,4 Hz, 1H), 7,84 (s, 1H), 7,75 (s, 1H), 7,65 a 7,62 (d, *J* = 8,6 Hz, 2H), 7,38 a 7,36 (d, *J* = 8,1 Hz, 2H), 7,26 (s, 1H), 6,87 a 6,85 (d, *J* = 5,9 Hz, 1H), 4,33 (s, 2H), 3,49 a 3,46 (m, 2H), 3,43 a 3,40 (m, 2H), 3,22 (s, 2H), 2,30 (s, 3H); EM $[M+H]^+$ = 448,0; LCMS TR = 2,00 min.

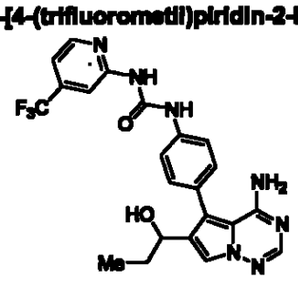
Ejemplo 273: **Preparación de 4-amino-N-ciclopropil-5-[4-({[(4-metil-piridin-2-il)amino]carbonil}amino)fenil]pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida**



El procedimiento utilizado para la preparación del Ejemplo 143 se utilizó para preparar el compuesto del título sustituyendo ciclopropanamina con 2-amino-2-metilopropan-1-ol y ácido 4-amino-5-[4-({[(4-metilpiridin-2-il)amino]carbonil}-amino)fenil]pirrolo[2,1-f][1,2,4]triazin-6-carboxílico (Ejemplo 260) con el Intermediario J. ^{1}H-RMN (DMSO-d_6) δ10,79 (s, 1H), 9,45 (s, 1H), 8,15 a 8,13 (d, *J* = 5,6 Hz, 1H), 8,05 (s, 1H), 7,89 (s, 1H), 7,83 a 7,82 (d, *J* = 3,6 Hz, 1H), 7,59 a 7,57 (d, *J* = 8,7 Hz, 2H), 7,31 a 7,29 (m, 3H), 6,86 a 6,85 (d, *J* = 5,1 Hz, 1H), 2,68 a 2,63 (m, 1H), 2,30 (s, 3H). 0,63 a 0,58 (m, 2H), 0,44 a 0,40 (m, 2H); EM $[M+H]^+$ = 465,1; LCMS TR = 1,86 min.

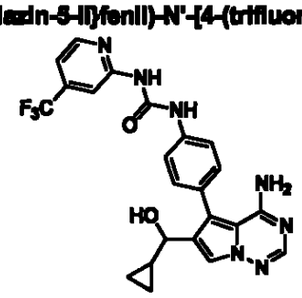
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Ejemplo 274: **Preparación de N-(4-[4-amino-6-(1-hidroxipropil)pirrolo-[2,1-f][1,2,4]triazin-5-il]fenil)-N'-[4-(trifluorometil)piridin-2-il]urea**



El procedimiento utilizado para la preparación del Ejemplo 269 se utilizó para preparar el compuesto del título sustituyendo bromuro de etilmagnesio con bromuro de metilmagnesio. ^{1}H-RMN (DMSO-d_6) δ9,95 (s, 1H), 9,77 (s, 1H), 8,53 (d, J = 5 Hz, 1H), 8,04 (s, 1H), ,1 a 8,2 (bs, 1H), 8,05 a 8,10 (m, 1H), 7,65 (d, J = 9 Hz, 2H), 7,39 (d, J = 9 Hz, 2H), 7,32 a 7,40 (m, 1H); EM $[M+H]^+$ = 472,0; LCMS TR = 2,59 min.

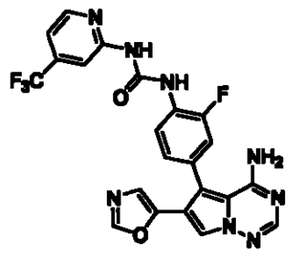
Ejemplo 275: **Preparación de N-(4-[4-amino-6-[ciclopropil(hidroxi)-metil]pirrolo[2,1-f][1,2,4]triazin-5-il]fenil)-N'-[4-(trifluorometil)piridin-2-il]urea**



El procedimiento utilizado para la preparación del Ejemplo 269 se utilizó para preparar el compuesto del título sustituyendo bromuro de ciclopropilmagnesio con bromuro de metilmagnesio. ^{1}H-RMN (DMSO-d_6) δ9,95 (s, 1H), 9,83 (s, 1H), 8,61 (d, J = 5 Hz, 1H), 8,14 (s, 1H), 7,91 (s, 1H), 7,78 (s, 1H), 7,69 (d, J = 9 Hz, 2H), 7,40 a 46 (m, 3H), 5,00 (d, J = 5 Hz, 1H), 4,00-4,02 (m, 1H), 0,25 a 0,48 (m, 3H), 0,00 a 0,08 (m, 2H); EM $[M+H]^+$ = 484,0; LCMS TR = 2,60 min.

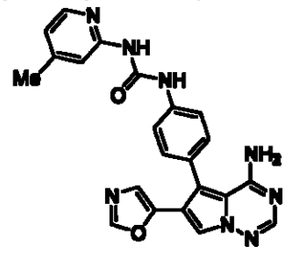
Ejemplo 276: **Preparación de N-(4-[4-amino-6-(1,3-oxazol-5-il)pirrolo-[2,1-f][1,2,4]triazin-5-il]-2-fluorofenil)-N'-[4-(trifluorometil)piridin-2-il]urea**

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A una solución de THF (10 ml) y MeOH (10 ml) enfriada en una baño de agua/hielo se agregó metóxido de sodio 0,5 M en MeOH (0,96 ml, 0,48 mmol) seguido de TosMIC (93 mg, 0,48 mmol). La solución se dejó agitar durante 5min y luego se agregó el Intermediario AL (73 mg, 0,16 mmol). La solución se calentó a 60°C durante 17h. La mezcla de reacción se dejó enfriar y se transfirió a un embudo de separación, se diluyó con EtOAc (20 ml), se lavó con $NaHCO_3$ ac saturado (20 ml) y H_2O (20 ml). La capa acuosa se retro extrajo con EtOAc (2 x 20 ml). Las capas orgánicas combinadas se secaron ($MgSO_4$), se filtraron, se evaporaron al vacío y se purificaron por cromatografía flash 5:4:1 v/v/v de DCM/EtOAc/MeOH, las fracciones purificadas resultantes se combinaron y se evaporaron dando 26 mg del compuesto del título en forma de un sólido color blanco (0,052 mmol, rendimiento 33%). ^{1}H-RMN (DMSO-d_6) δ10,18 (s, 1H), 10,16 a 10,12 (br s, 1H), 8,55 a 8,54 (d, J = 5,4 Hz, 1H), 8,35 a 8,31 (t, J = 8,3 Hz, 1H), 8,30 (s, 1H), 8,10 (s, 1H), 8,01 (s, 1H), 7,91 (s, 1H), 7,39 a 7,36 (m, 2H), 7,23 a 7,21 (d, J = 10,4 Hz, 1H), 6,63 (s, 1H); EM $[M+H]^+$ = 499,0; LCMS TR = 2,85 min.

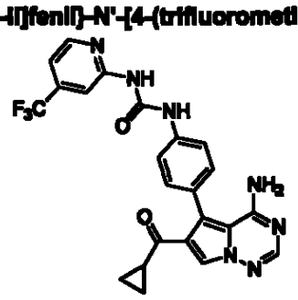
Ejemplo 277: **Preparación de N-(4-[4-amino-8-(1,3-oxazol-5-il)pirrolo-[2,1-f][1,2,4]triazin-5-il]fenil)-N'-(4-metilpiridin-2-il)urea**



El procedimiento utilizado para la preparación del Ejemplo 276 se utilizó para preparar el compuesto del título sustituyendo el Intermediario AK con el Intermediario

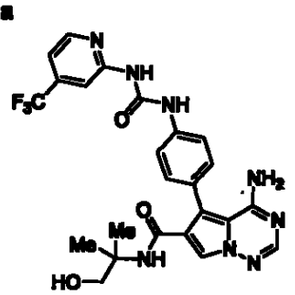
5. ^{1}H-RMN (DMSO-d_6) δ10,92 (s, 1H), 9,50 (s, 1H), 8,29 (s, 1H), 8,15 a 8,14 (d, *J* = 4,9 Hz, 1H), 8,09 (s, 1H), 7,90 (s, 1H), 7,69 a 7,67 (d, *J* = 8,4 Hz, 2H), 7,38 a 7,36 (d, *J* = 8,5 Hz, 2H), 7,27 (s, 1H), 6,87 a 6,86 (d, *J* = 5,8 Hz, 1H), 6,57 (s, 1H), 2,30 (s, 3H); EM $[M+H]^+$ = 427,1; LCMS TR = 2,09 min.

Ejemplo 278: **Preparación de N-{4-[4-amino-6-(ciclopropilcarbonil)-pirrolo[2,1-*f*][1,2,4]triazin-5-il]fenil}-N'-[4-(trifluorometil)piridin-2-il]urea**



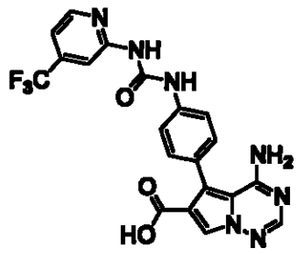
El procedimiento utilizado para la preparación del Ejemplo 233 se utilizó para preparar el compuesto del título sustituyendo el Ejemplo 275 con el Ejemplo 269. ^{1}H-RMN (DMSO-d_6) δ9,87 (s, 1H), 9,74 (s, 1H), 8,53 (d, J = 5 Hz, 1H), 8,51 (s, 1H), 8,05 (s, 1H), 8,00 a 8,05 (bs, 1H), 7,57 (d, J = 9 Hx, 2H), 7,30 a 7,40 (m, 3H), 2,40 (m, 1H), 0,76 a 0,9 (m, 4H); EM $[M+H]^+$ = 482,0; LCMS TR = 2,96 min.

Ejemplo 279: **Preparación de 4-amino-N-(2-hidroxi-1,1-dimetiletil)-5-{4-[({[4-(trifluorometil)piridin-2-il]amino}carbonil)amino]fenil}pirrolo[2,1-*f*]-[1,2,4]triazin-6-carboxamida**



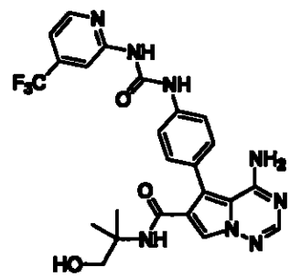
Paso 1: **Preparación de ácido 4-amino-5-{4-[({[4-(trifluorometil)-piridin-2-il]amino}carbonil)amino]fenil}pirrolo[2,1-*f*][1,2,4]triazin-6-carboxílico**

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El procedimiento utilizado para la preparación del intermediario G se utilizó para preparar el compuesto del título sustituyendo el Ejemplo 51 con el intermediario E. ^{1}H-RMN (DMSO-d_6) δ12,28 (bs, 1H), 9,87 (s, 1H) 9,75 (s, 1H), 8,53 (d, J = 5 Hz, 1H), 8,07 (s, 1H), 8,06 (s, 1H), 7,91 (s, 1H), 7,57 (d, J = 9 Hz, 2H), 7,34 a 7,37 (m, 1H), 7,34 (d, J = 9 Hz, 2H); EM $[M+H]^+$ = 458,1; LCMS TR = 2,53 min.

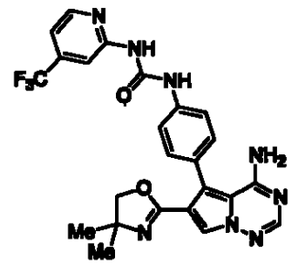
Paso 2: Preparación de 4-amino-N-(2-hidroxi-1,1-dimetiletil)-5-{4-[({[4-(trifluorometil)piridin-2-il]amino}carbonil)amino]fenil}pirrolo[2,1-f][1,2,4]-triazin-6-carboxamida



El procedimiento utilizado para la preparación del Ejemplo 143 se utilizó para preparar el compuesto del título sustituyendo el ácido 4-amino-5-{4-[({[4-(trifluorometil)piridin-2-il]amino}carbonil)amino]fenil}pirrolo[2,1-f][1,2,4]triazin-6-carboxílico con el intermediario J. ^{1}H-RMN (DMSO-d_6) δ 9,92 (s, 1H), 9,77 (s, 1H), 8,54 (d, J= 5,0Hz, 1H), 8,06 (s, 1H), 8,03 (s, 1H), 7,89 (s, 1H), 7,62 (d, J= 8,8Hz, 2H), 7,36 (d, J= 8,8Hz, 4H), 6,53(s, 1H), 4,75 (t, J= 6,2 Hz, 2H), 3,27 (d, J= 5,9 Hz, 2H), 1,09(s, 6H); EM $[M+H]^+$ = 529,0; LCMS TR = 2,59 min.

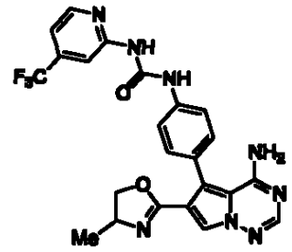
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Ejemplo 280: Preparación de N-{4-[4-amino-6-(4,4-dimetil-4,5-dihidro-1,3-oxazol-2-il)pirrolo[2,1-f][1,2,4]triazin-5-il]fenil}-N'-[4-(trifluorometil)piridin-2-il]urea



Una solución del Ejemplo 279 (25 mg, 0,047 mmol) en 2 ml CH_2Cl_2 se trató con cloruro de tionilo (0,95 mmol, 11,2 mg) y se dejó agitar durante 15 min. La reacción se diluyó con acetato de etilo y se lavó con bicarbonato de sodio. La capa orgánica se secó (Na_2SO_4), se filtró y se concentró hasta sequedad. El residuo se trituró con Et_2O/hexanos para dar 19,4 mg del compuesto anterior en forma de un sólido color amarillo (rendimiento 81%). ^{1}H-RMN (DMSO-d_6) δ10,40 (s, 1H), 9,96 (s, 1H), 8,91 (s, 1H), 8,54 (d, *J*= 6,2Hz, 1H), 8,13 (s, 1H), 8,07 (s, 1H), 7,64 (d, *J*= 8,8Hz, 2H), 7,44 (d, *J*= 8,8Hz, 4H), 7,35 (d, *J*= 5,3Hz, 1H), 5,67 (bs, 1H), 4,54 (s, 2H), 1,47 (s, 6H); EM $[M+H]^+$ = 511,0; LCMS TR = 2,44 min.

Ejemplo 281: Preparación de N-{4-[4-amino-6-(4-metil-4,5-dihidro-1,3-oxazol-2-il)pirrolo[2,1-f][1,2,4]triazin-5-il]fenil}-N'-[4-(trifluorometil)piridin-2-il]urea

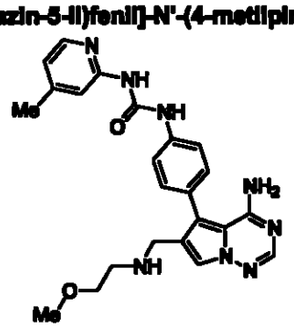


El procedimiento utilizado para la preparación del Ejemplo 230 se utilizó para preparar el compuesto del título sustituyendo 4-amino-N-(2-hidroxi-1-metiletil)-5-(4-[({[4-(trifluorometil)piridin-2-il]amino}carbonil) amino]fenil)pirrolo[2,1-f][1,2,4]triazin-6-carboxamida (Ejemplo 281) con 2-(4-amino-5-[4-[({[4-(trifluorometil)piridin-2-

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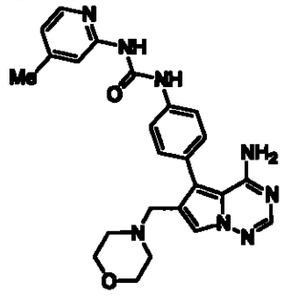
il]amino}carbonil)amino]fenil}pirrolo [2,1-f][1,2,4]triazin-6-il)-4,5-dihidro-1,3-oxazol-4-carboxilato de etilo (Ejemplo 221). ^{1}H-RMN (DMSO-d_6) δ9,69 (s, 1H), 9,77 (s, 1H), 8,54 a 8,53 (d, J = 5,3 Hz, 1H), 8,05 (s, 1H), 8,01 (s, 1H), 7,90 (s, 1H), 7,58 a 7,56 (d, J = 8,7 Hz, 2H), 7,37 a 7,36 (m, 1H), 7,35 a 7,33 (d, J = 8,6 Hz, 2H), 4,28 a 4,24 (t, J = 8,6 Hz, 2H), 4,15 a 4,06 (m, 1H), 3,71 a 3,67 (t, J = 7,9 Hz, 2H, 1,13 a 1,11 (d, J = 6,6 Hz, 3H); EM $[M+H]^+$ = 497,0; LCMS TR = 2,43 min.

Ejemplo 282: **Preparación de N-[4-(4-amino-6-[[(2-metoxietil)amino]-metil}pirrolo[2,1-f][1,2,4]triazin-5-il)fenil]-N'-(4-metilpiridin-2-il)urea**



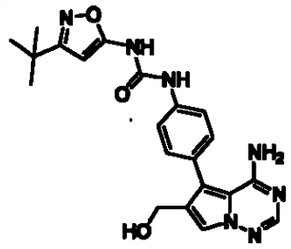
El procedimiento utilizado para la preparación del Ejemplo 66 se utilizó para preparar el compuesto del título sustituyendo el intermediario AK con el intermediario I y 2-metoxietanamina con morfolina. ^{1}H-RMN (CD_3OD) δ8,15 a 8,14 (d, J = 5,3 Hz, 1H), 7,81 (s, 1H), 7,80 (s, 1H), 7,74 a 7,72 (d, J = 8,7 Hz, 2H), 7,42 a 7,40 (d, J = 8,6 Hz, 2H), 7,00 (s, 1H), 6,90 a 6,89 (d, J = 5,3 Hz, 1H), 4,04 (s, 2H), 3,49 a 3,46 (t, J = 5,1 Hz, 2H), 2,95 a 2,92 (t, J = 5,1 Hz, 2H), 2,37 (s, 3H), 1,93 (s, 3H); EM $[M+H]^+$ = 446,9; LCMS TR = 1,25 min.

Ejemplo 283: **Preparación de N-{4-[4-amino-6-(morfolin-4-ilmetil)-pirrolo[2,1-f][1,2,4]triazin-5-il]fenil}-N'-(4-metilpiridin-2-il)urea**



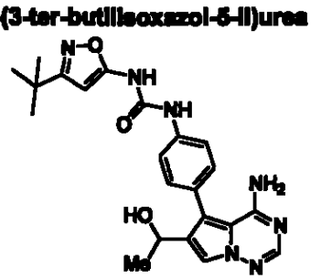
El procedimiento utilizado para la preparación del Ejemplo 66 se utilizó para preparar el compuesto del título sustituyendo el intermediario AK con el intermediario I. ^{1}H-RMN (DMSO-d_6) δ10,90 a 10,87 (br s, 1H), 9,48 (s, 1H), 8,14 a 8,13 (d, J = 5,1 Hz, 1H), 7,82 (s, 1H), 7,64 (s, 1H), 7,64 a 7,62 (d, J = 8,5 Hz, 2H), 7,40 a 7,38 (d, J = 8,5 Hz, 2H), 7,26 (s, 1H), 6,87 a 6,85 (d, J = 5,6 Hz, 1H), 3,55 a 3,50 (m, 4H), 3,34 a 3,33 (br s, 2H), 2,32 a 2,28 (m, 4H), 2,30 (s, 3H); EM $[M+H]^+$ = 459,0; LCMS TR = 1,16 min.

Ejemplo 284: Preparación de N-[4-[4-amino-6-(hidroximetil)pirrolo[2,1-f][1,2,4]triazin-5-il]fenil]-N'-(3-ter-butilisoxazol-5-il)urea



El procedimiento utilizado para la preparación del intermediario F se utilizó para preparar el compuesto del título sustituyendo el Ejemplo 52 con el intermediario E. ^{1}H-RMN (DMSO-d_6) δ10,13 (s, 1H), 8,96 (s, 1H), 7,82 (s, 1H), 7,65 (s, 1H), 7,56 (d, J = 9 Hz, 2H), 7,35 (d, J = 9 Hz, 2H), 6,05 (s, 1H), 4,94 (t, J = 5 Hz, 1 H), 4,35 (d, J = 5 Hz, 2H), 1,24 (s, 9H); EM $[M+H]^+$ = 422,1; LCMS TR = 2,26 min.

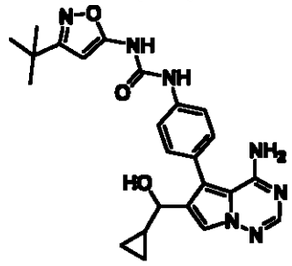
Ejemplo 285: Preparación de N-[4-[4-amino-6-(1-hidroxietil)pirrolo[2,1-f][1,2,4]triazin-5-il]fenil]-N'-(3-ter-butilisoxazol-5-il)urea



El procedimiento utilizado para la preparación del Ejemplo 269 se utilizó para preparar el compuesto del título sustituyendo el Ejemplo 52 con el Ejemplo 51. ^{1}H-RMN (DMSO-d_6) δ 10,19 (s, 1H), 9,07 (s, 1H), 8,81 (s, 1H), 7,64 (s, 1H), 7,56 (d, J =

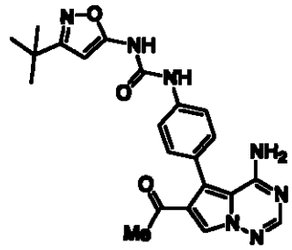
8 Hz, 2H), 7,30 a 7,40 (m, 2H), 6,05 (s, 1H), 4,95 (m, 1), 4,60 a 4,64 (m, 1H), 1,36 (m, 2H), 1,23 (s, 9H); EM $[M+H]^+$ = 436,1; LCMS TR =2,41 min.

Ejemplo 286: Preparación de N-(4-(4-amino-6-[ciclopropil(hidroxi)-metil]pirrolo[2,1-f][1,2,4]triazin-5-il)fenil)-N'-(3-ter-butilisoxazol-5-il)urea



El procedimiento utilizado para la preparación del Ejemplo 269 se utilizó para preparar el compuesto del título sustituyendo el Ejemplo 52 con el Ejemplo 51 y sustituyendo bromuro de ciclopropilmagnesio con bromuro de metilmagnesio. ^{1}H-RMN (DMSO-d_6) δ10,24 (s, 1H), 9,07 (s, 1H), 8,81 (s, 1H), 7,64 (s, 1H), 7,56 (d, J = 8 Hz, 2H), 7,30 a 7,40 (m, 2H), 6,05 (s, 1H) 4,98 (d, J = 5Hz, 1H), 3,97 a 4,01 (m, 1H), 1,28 (s, 9H), 0,25 a 0,48 (m, 3H), 0,00 a 0,08 (m, 2H); EM $[M+H]^+$ = 434,1; LCMS TR =2,63 min.

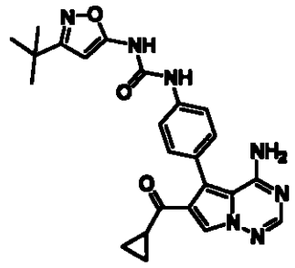
Ejemplo 287: Preparación de N-[4-(6-acetil-4-aminopirrolo[2,1-f][1,2,4]-triazin-5-il)fenil]-N'-(3-ter-butilisoxazol-5-il)urea



El procedimiento utilizado para la preparación del Ejemplo 233 se utilizó para preparar el compuesto del título sustituyendo el Ejemplo 285 con el Ejemplo 269 . ^{1}H-RMN (DMSO-d_6) δ10,15 (s, 1H), 8,98 (s, 1H), 8,37 (s, 1H), (8,01 (bs, 1H), 7,92 (s, 1H), 7,53 (d, J = 9 Hz, 2H), 7,30 (d, J = 9 Hz, 2H), 6,05 (s, 1H), 2,27 (s, 3H); EM $[M+H]^+$ = 434,1; LCMS TR = 2,63 min.

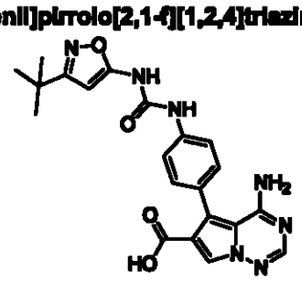
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Ejemplo 288: **Preparación de N-[4-[4-amino-6-(ciclopropilcarbonil)-pirrolo[2,1-f][1,2,4]triazin-5-il]fenil]-N'-(3-ter-butilisoxazol-5-il)urea**



El procedimiento utilizado para la preparación del Ejemplo 233 se utilizó para preparar el compuesto del título sustituyendo el Ejemplo 286 con el Ejemplo 289. ^{1}H-RMN (DMSO-d_6) δ δ10,15 (s, 1H), 8,98 (s, 1H), 8,37 (s, 1H), (8,01 (bs, 1H), 7,92 (s, 1H), 7,53 (d, J = 9 Hz, 2H), 7,30 (d, J = 9 Hz, 2H), 6,05 (s, 1H); EM $[M+H]^+$ = 460,1; LCMS TR = 2,81 min.

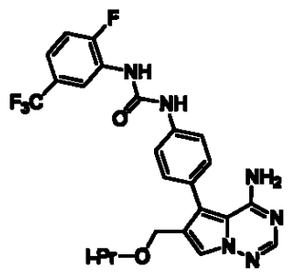
Ejemplo 289: **Preparación de ácido 4-amino-5-[4-({[(3-ter-butilisoxazol-5-il)amino]carbonil}amino)fenil]pirrolo[2,1-f][1,2,4]triazin-6-carboxílico**



El procedimiento utilizado para la preparación del Intermediario G se utilizó para preparar el compuesto del título sustituyendo el Ejemplo 52 con el Intermediario E. ^{1}H-RMN (DMSO-d_6) δ10,18 (s, 1H), 9,04 (s, 1H), 8,07 (s, 1H), 7,19 (s, 1H), 7,52 (d, *J*= 8,2 Hz, 1H), 7,31 (d, *J*= 8,2Hz, 2H), 6,05 (s, 1H), 5,73 (s, 1H), 1,24 (s, 9H); EM $[M+H]^+$ = 436,1; LCMS TR = 2,43 min.

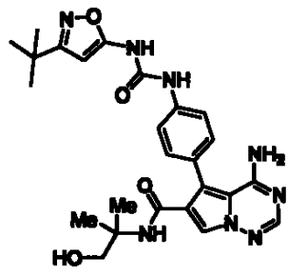
Ejemplo 290: **Preparación de N-[4-[4-amino-6-(isopropoximetil)pirrolo-[2,1-f][1,2,4]triazin-5-il]fenil]-N'-[2-fluoro-5-(trifluorometil)fenil]urea**

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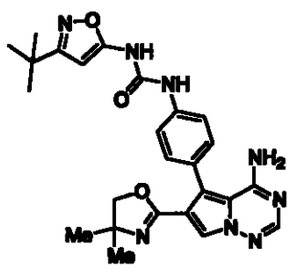
El procedimiento utilizado para la preparación del Ejemplo 246 se utilizó para preparar el compuesto del título sustituyendo alcohol isopropílico con etanol. ^{1}H-RMN (DMSO-d_6) δ 12,25 (s, 1H), 8,48 (d, *J*= 6,8Hz, 1H), 8,27 (s, 1H), 8,04 (s, 1H), 7,61-7,51 (m, 3H), 7,18 (d, *J*= 8,2Hz, 2H), 6,70 (d, *J*= 8,2Hz, 2H), 4,33 (s, 2H), 3,55 (m, 1H), 1,04 (d, *J*= 6,2Hz, 6H); EM $[M+H]^+$ = 503,1; LCMS TR = 3,70 min.

Ejemplo 291: **Preparación de 4-amino-5-[4-({[(3-ter-butilisoxazol-5-il)amino]carbonil}amino)fenil]-N-(2-hidroxi-1,1-dimetiletil)pirrolo[2,1-f]-[1,2,4]triazin-6-carboxamida**



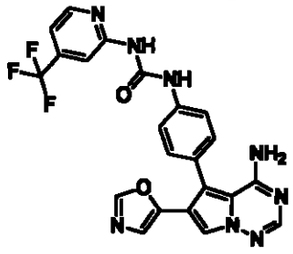
El procedimiento utilizado para la preparación del Ejemplo 143 se utilizó para preparar el compuesto del título sustituyendo el Ejemplo 289 con el intermediario J. ^{1}H-RMN (DMSO-d_6) δ10,14 (s, 1H), 9,00 (s, 1H), 8,03 (s, 1H), 7,89 (s, 1H), 7,56 (d, *J*= 8,8Hz, 2H), 7,34 (d, *J*= 8,8Hz, 4H), 6,51(s, 1H), 6,06 (s, 1H), 5,74 (s, 1H), 4,75 (t, *J*= 3,8 Hz, 1H), 3,27 (bs, 2) 1,24(s, 9H), 1,09 (s, 6H) ; EM $[M+H]^+$ = 507,1; LCMS TR = 2,46 min.

Ejemplo 292: **Preparación de N-(4-[4-amino-8-(4,4-dimetil-4,5-dihidro-1,3-oxazol-2-il)pirrolo[2,1-f][1,2,4]triazin-5-il]fenil)-N'-(3-ter-butilisoxazol-5-il)urea**



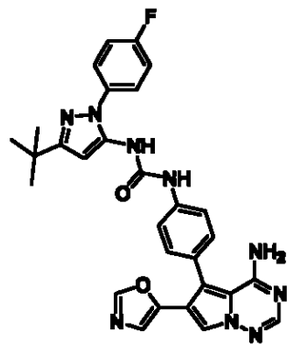
El procedimiento utilizado para la preparación del Ejemplo 280 se utilizó para preparar el compuesto del título sustituyendo el Ejemplo 291 con el Ejemplo 279. ^{1}H-RMN (DMSO-d_6) δ10,19 (s, 1H), 9,43 (s, 1H), 8,61 (s, 1H), 8,41 (bs, 1H), 8,01 (s, 1H), 7,56 (d, *J*= 8,8Hz, 2H), 7,40 (d, *J*= 8,8Hz, 2H), 6,12(s, 1H), 5,41 (bs, 1H), 4,45 (s, 2H), 1,41 (s, 6H), 1,24(s, 9H); EM $[M+H]^+$ = 469,1; LCMS TR = 2,36 min.

Ejemplo 293: Preparación de N-{4-[4-amino-6-(1,3-oxazol-5-il)pirrolo-[2,1-f][1,2,4]triazin-5-il]fenil}-N'-(4-ter-butilpiridin-2-il)urea



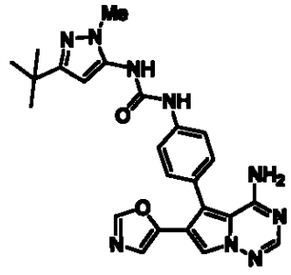
El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo el intermediario AB con el intermediario X. ^{1}H-RMN (DMSO-d_6) δ10,96 a 10,93 (br s, 1H), 9,48 (s, 1H), 8,30 (s, 1H), 8,20 a 8,18 (d, *J* = 6,1 Hz, 1H), 8,09 (s, 1H), 7,90 (s, 1H), 7,70 a 7,68 (d, *J* = 8,6 Hz, 2H), 7,50 (s, 1H), 7,38 a 7,36 (d, *J* = 8,5 Hz, 2H), 7,08 a 7,06 (d, *J* = 5,4 Hz, 1H), 6,57 (s, 1H), 1,28 (s, 9H); EM $[M+H]^+$ = 469,1; LCMS TR = 2,44 min.

Ejemplo 294: Preparación de N-{4-[4-amino-6-(1,3-oxazol-5-il)pirrolo-[2,1-f][1,2,4]triazin-5-il]fenil}-N'-[3-ter-butil-1-(4-fluorofenil)-1H-pirazol-5-il]urea



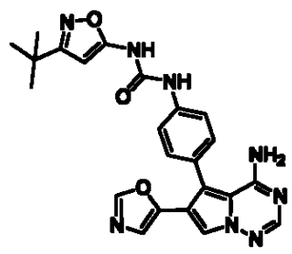
El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo el intermediario AB con el intermediario X y sustituyendo [3-ter-butil-1-(4-fluorofenil)-1H-pirazol-5-il]carbamato de fenilo con (4-*ter*-butilpiridin-2-il)carbamato de fenilo. ^{1}H-RMN (DMSO-d_6) δ 9,19 (s, 1H), 8,45 (s, 1H), 8,28 (s, 1H), 8,07 (s, 1H), 7,89 (s, 1H), 7,58 a 7,54 (m, 4H), 7,39 a 7,31 (m, 4H), 6,53 (s, 1H), 6,36 (s, 1H), 1,28 (s, 9H); EM $[M+H]^+$ = 552,1; LCMS TR = 2,88 min.

Ejemplo 295: Preparación de N-(4-[4-amino-8-(1,3-oxazol-5-il)pirrolo-[2,1-f][1,2,4]triazin-5-il]fenil}-N'-(3-ter-butil-1-metil-1H-pirazol-5-il)urea



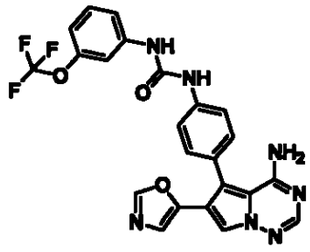
El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo el intermediario AB con el intermediario X y sustituyendo (3-ter-butil-1-metil-1H-pirazol-5-il)carbamato de fenilo con (4-*ter*-butilpiridin-2-il)carbamato de fenilo. ^{1}H-RMN (DMSO-d_6) δ9,10 (s, 1H), 8,54 (s, 1H), 8,29 (s, 1H), 8,08 (s, 1H), 7,90 (s, 1H), 7,62 a 7,59 (d, *J* = 8,6 Hz, 2H), 7,35 a 7,33 (d, *J* = 8,6 Hz, 2H), 6,54 (s, 1H), 6,05 (s, 1H), 3,61 (s, 3H), 1,22 (s, 9H); EM $[M+H]^+$ = 472,2; LCMS TR = 2,43 min.

Ejemplo 296: Preparación de N-(4-[4-amino-8-(1,3-oxazol-5-il)pirrolo-[2,1-f][1,2,4]triazin-5-il]fenil}-N'-(3-ter-butilisoxazol-5-il)urea



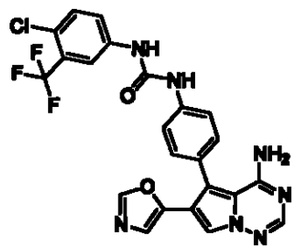
El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo el intermediario AB con el intermediario X y sustituyendo (3-*ter*-butilisoxazol-5-il)carbamato de fenilo con (4-*ter*-butilpiridin-2-il)carbamato de fenilo. ^{1}H-RMN (DMSO-d_6) δ10,21 (s, 1H), 9,07 (s, 1H), 8,29 (s, 1H), 8,09 (s, 1H), 7,90 (s, 1H), 7,62 a 7,60 (d, *J* = 8,6 Hz, 2H), 7,38 a 7,35 (d, *J* = 8,5 Hz, 2H), 6,55 (s, 1H), 6,07 (s, 1H), 1,26 (s, 9H); EM $[M+H]^+$ = 459,1; LCMS TR = 2,65 min.

Ejemplo 297: **Preparación de N-[4-[4-amino-6-(1,3-oxazol-5-il)pirrolo-[2,1-f][1,2,4]triazin-5-il]fenil]-N'-[3-(trifluorometoxi)fenil]urea**



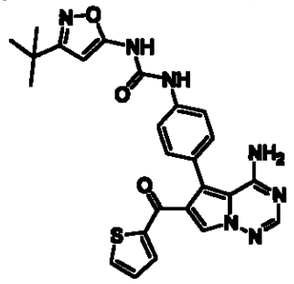
El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo el intermediario AB con el intermediario X y sustituyendo [3-(trifluorometoxi)fenil]carbamato de fenilo con (4-*ter*-butilpiridin-2-il)carbamato de fenilo. ^{1}H-RMN (DMSO-d_6) δ9,11 (s, 1H), 9,02 (s, 1H), 8,30 (s, 1H), 8,08 (s, 1H), 7,90 (s, 1H), 7,71 (s, 1H), 7,62 a 7,60 (d, *J* = 8,4 Hz, 2H), 7,42 a 7,38 (t, *J* = 8,1 Hz, 1H), 7,36 a 7,34 (d, *J* = 8,7 Hz, 2H), 7,32 a 7,29 (d, *J* = 9,1 Hz, 1H), 6,96 a 6,93 (d, *J* = 10,6, 1H), 6,55 (s, 1H); EM $[M+H]^+$ = 496,1; LCMS TR = 2,69 min.

Ejemplo 298: **Preparación de N-[4-[4-amino-6-(1,3-oxazol-5-il)pirrolo-[2,1-f][1,2,4]triazin-5-il]fenil]-N'-[4-cloro-3-(trifluorometil)fenil]urea**



El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo el intermediario AB con el intermediario X y sustituyendo [4-cloro-3-(trifluorometil)fenil]carbamato de fenilo con (4-*ter*-butilpiridin-2-il)carbamato de fenilo. ^{1}H-RMN (DMSO-d_6) δ9,26 (s, 1H), 9,08 (s, 1H), 8,30 (s, 1H), 8,12 (s, 1H), 8,09 (s, 1H), 7,90 (s, 1H), 7,64 a 7,61 (m, 4H), 7,37 a 7,35 (d, *J* = 8,5 Hz, 2H), 6,55 (s, 1H); EM [M+H]$^+$ = 514,1; LCMS TR = 3,02 min.

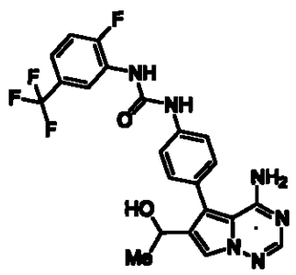
Ejemplo 299: Preparación de N-{4-[4-amino-6-(2-tienilcarbonil)-pirrolo[2,1-f][1,2,4]triazin-5-il]fenil}-N'-(3-ter-butilisoxazol-5-il)urea



El procedimiento utilizado para la preparación del Ejemplo 287 se utilizó para preparar el compuesto del título sustituyendo 2-bromuro de tienilmagnesio con bromuro de metilmagnesio. ^{1}H-RMN (DMSO-d_6) 8,26 (s, 1H), 7,98 (dd, J = 1, 4 Hz, 1H), 7,96 (s, 1H), 7,75 (dd, J = 1, 3 Hz), 7,53 (d, J = 6 Hz, 2H), 7,30 (d, J = 6 Hz, 2H), 7,19 (dd, J = 3, 4 Hz, 1H), 6,05 (s, 1H) 1,25 (s, 9H); EM [M+H]$^+$ = 502,1; LCMS TR = 2,98 min.

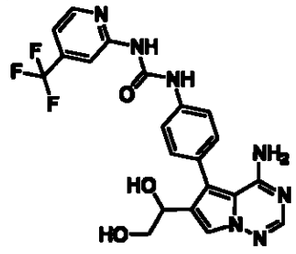
Ejemplo 300: Preparación de N-{4-[4-amino-6-(1-hidroxietil)pirrolo[2,1-f][1,2,4]triazin-5-il]fenil}-N'-[2-fluoro-5-(trifluorometil)fenil]urea

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El procedimiento utilizado para la preparación del Ejemplo 269 se utilizó para preparar el compuesto del título sustituyendo el Ejemplo 1 con el Ejemplo 51. ^{1}H-RMN (DMSO-d_6) δ9,41 (s, 1H), 9,01 (d, J = 3 Hz, 1H), 8,62 (d, J = 3, 8 Hz, 1H), 7,81 (s, 1H), 7,77 (s, 1H), 7,61 (d, J = 9 Hz, 2H), 7,47 a 7,54 (m, 1H), 7,38 a 7,42 (m, 1H), 7,35 (d, J = 9 Hz, 2H); EM $[M+H]^+$ = 475,1; LCMS TR =2,59 min.

Ejemplo 301: Preparación de N-[4-[4-amino-6-(1,2-dihidroxietil)pirrolo-[2,1-f][1,2,4]triazin-5-il]fenil]-N'-[4-(trifluorometil)piridin-2-il]urea

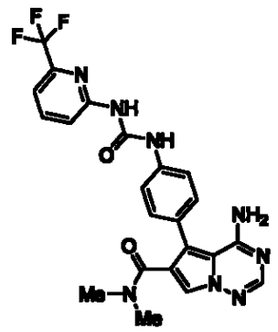


Se disolvió metanosulfonamida (65 mg, 0,683 mmol) en una solución 1:1 de terbutanol:agua (5 ml) y se trató con una mezcla de AD β (1,0 g). La mezcla luego se trató con el Ejemplo 222 (0,3 g, 0,683 mmol) y la reacción se agitó a temperatura ambiente durante toda la noche. Al cabo de la terminación, la solución se trató con sulfito de sodio sólido (1,5 g) y se agitó durante 1 hora. La reacción luego se transfirió a un embudo de separación y el producto bruto se extrajo con EtOAc. La capa orgánica se lavó con agua y solución de NaCl saturada. La solución luego se secó sobre $MgSO_4$, se filtró y se concentró bajo presión reducida. No fue necesaria la purificación para el compuesto del título aislado como 0,3 g de un sólido color tostado (0,634 mmol, 93 % de rendimiento). ^{1}H-RMN (DMSO-d_6) δ9,88 (bs, 1H), 9,76 (bs, 1H), 8,53 (d, *J* = 5,7 Hz, 1H), 8,06 (s, 1H), 7,82 (s, 1H), 7,63 (s, 1H), 7,61 (d, *J* = 8,8

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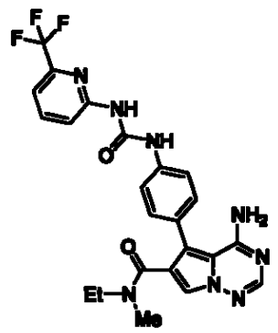
Hz, 2H), 7,37-7,35 (m, 3H), 5,03 (d, *J* = 4,6 Hz, 2H), 4,65 (t, *J* = 5,8 Hz, 1H), 4,47-4,43 (m, 1H), 3,45-3,38 (m, 2H); EM $[M+H]^+$ = 474,0; **LCMS TR** = 2,13 min.

Ejemplo 302: Preparación de 4-amino-N,N-dimetil-5-{4-[({[6-(trifluorometil)piridin-2-il]amino}carbonil) amino]fenil}pirrolo[2,1-f][1,2,4]triazin-6-carboxamida



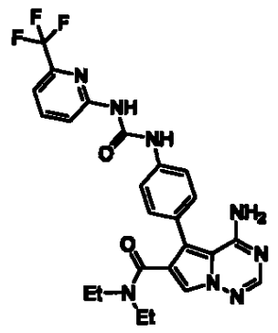
El procedimiento utilizado para la preparación del Ejemplo 69 se utilizó para preparar el compuesto del título sustituyendo el intermediario AH con el intermediario G y dimetilamina con ciclopropilamina. La reacción se agitó durante 16 h y se purificó por HPLC (20-85% de acetonitrilo en agua). ^{1}H RMN (DMSO-d_6) δ 9,87 (s, 1H), 9,68 (s, 1H), 8,05 a 7,96 (m, 2H), 7,89 (s, 1 H), 7,85 (s, 1 H), 7,57 a 7,52 (m, 2H), 7,49 (dd, *J* = 6,6, 1,6 Hz, 1 H), 7,32 a 7,27 (m, 2H), 2,81 (s, 3H), 2,64 (s, 3H); EM $[M+H]^+$ = 485,0; **LCMS TR** = 2,43 min.

Ejemplo 303: Preparación de 4-amino-N-etil-N-metil-5-{4-[({[6-(trifluorometil)piridin-2-il]amino}carbonil)amino]fenil}pirrolo[2,1-f][1,2,4]-triazin-6-carboxamida



El procedimiento utilizado para la preparación del Ejemplo 69 se utilizó para preparar el compuesto del título sustituyendo el intermediario AH con el intermediario G y N-etil-N-metilamina con ciclopropilamina. La reacción se agitó durante 16 h y se purificó por HPLC (20-85% de acetonitrilo en agua). ^{1}H RMN (DMSO-d_6) δ9,86 (s, 1H), 9,68 (s, 1H), 8,05 a 7,96 (m, 2H), 7,89 (s, 1H), 7,85 (s, 1H), 7,58 a 7,46 (m, 3H), 7,30 (d, *J* = 8,1 Hz, 2H), 3,31 y 3,06 (cuartetos diastereoméricos, 2H), 2,79 y 2,58 (singuletes diastereoméricos, 3H), 0,93 y 0,81 (tripletes diastereoméricos, 3H); EM $[M+H]^+$ = 499,1; LCMS TR = 2,55 min.

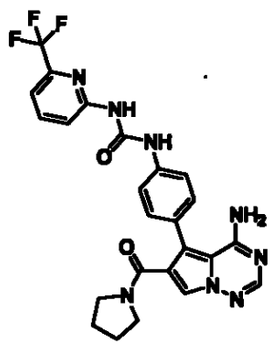
Ejemplo 304: **Preparación de 4-amino-N,N-dietil-5-[4-[({[6-(trifluorometil)piridin-2-il]amino}carbonil)amino]fenil}pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida**



El procedimiento utilizado para la preparación del Ejemplo 69 se utilizó para preparar el compuesto del título sustituyendo el intermediario AH con el intermediario G y dietilamina con ciclopropilamina. La reacción se agitó durante 16 h y se purificó por HPLC (20-85% de acetonitrilo en agua). ^{1}H RMN (DMSO-d_6) δ9,85 (s, 1H), 9,67 (s, 1H), 8,05 a 7,96 (m, 2H), 7,89 (s, 1H), 7,85 (s, 1H), 7,55 a 7,46 (m, 3H), 7,33 a 7,28 (m, 2H), 3,32 y 3,02 (cuartetos diastereoméricos, 2H), 0,94 y 0,82 (tripletes diastereoméricos, 3H); EM $[M+H]^+$ = 513,1; LCMS TR = 2,64 min.

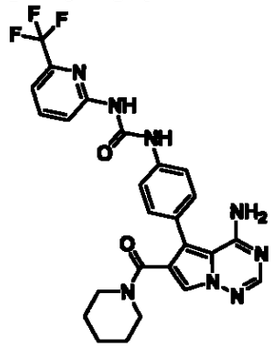
Ejemplo 305: **Preparación de N-{4-[4-amino-6-(pirrolidin-1-ilcarbonil)pirrolo[2,1-*f*][1,2,4]triazin-5-il]fenil}-N'-[6-(trifluorometil)piridin-2-il]urea**

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El procedimiento utilizado para la preparación del Ejemplo 69 se utilizó para preparar el compuesto del título sustituyendo el intermediario AH con el intermediario G y pirrolidina con ciclopropilamina. La reacción se agitó durante 16 h y se purificó por HPLC (20-85% de acetonitrilo en agua). ^{1}H RMN (DMSO-d_6) δ9,86 (s, 1H), 9,67 (s, 1H), 8,04 a 7,98 (m, 2H), 7,91 (s, 1H), 7,89 (s, 1H), 7,56 a 7,46 (m, 3H), 7,34 a 7,29 (m, 2H), 3,32 (t, *J* = 6,4 Hz, 2H), 3,11 (t, *J* = 6,4 Hz, 2H), 1,77 a 1,60 (m, 4H); EM $[M+H]^+$ = 511,1; LCMS TR = 2,53 min.

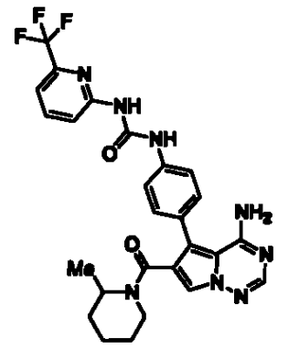
Ejemplo 306: Preparación de N-(4-[4-amino-6-(piperidin-1-ilcarbonil)-pirrolo[2,1-f][1,2,4]triazin-5-il]fenil}-N'-[6-(trifluorometil)piridin-2-il]urea



El procedimiento utilizado para la preparación del Ejemplo 69 se utilizó para preparar el compuesto del título sustituyendo el intermediario AH con el intermediario G y piperidina con ciclopropilamina. La reacción se agitó durante 16 h y se purificó por HPLC (20-85% de acetonitrilo en agua). ^{1}H RMN (DMSO-d_6) δ9,86 (s, 1H), 9,68 (s, 1H), 8,04 a 7,98 (m, 2H), 7,89 (s, 1H), 7,83 (s, 1H), 7,58 a 7,47 (m, 3H), 7,33 a

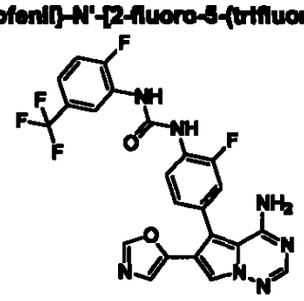
7,28 (m, 2H), 3,43 (br s, 2 H), 3,04 (br s, 2H), 1,43 a 1,31 (m, 4H), 0,98 (br s, 2H); EM $[M+H]^+$ = 525,1; **LCMS TR** = 2,73 min.

Ejemplo 307: **Preparación de N-(4-(4-amino-8-[(2-metilpiperidin-1-il)carbonil]pirrolo[2,1-f][1,2,4]triazin-5-il)fenil)-N'-[6-(trifluorometil)piridin-2-il]urea**



El procedimiento utilizado para la preparación del Ejemplo 69 se utilizó para preparar el compuesto del título sustituyendo el intermediario AH con el intermediario G y piperidina con ciclopropilamina. La reacción se agitó durante 16 h y se purificó por HPLC (20-85% de acetonitrilo en agua). ^{1}H RMN (DMSO-d_6) δ9,85 (s, 1H), 9,68 (s, 1H), 8,05 a 7,97 (m, 2H), 7,89 (s, 1H), 7,83 (s, 1H), 7,58 a 7,47 (m, 3H), 7,33 a 7,27 (m, 2H), 2,69 a 2,60 (m, 1H), 2,50 (br s, 2H), 1,50 a 1,31 (m, 4H), 0,99 a 0,90 (m, 5H); EM $[M+H]^+$ = 539,1; **LCMS TR** = 2,81 min.

Ejemplo 308: **Preparación de N-(4-[4-amino-8-(1,3-oxazol-5-il)pirrolo-[2,1-f][1,2,4]triazin-5-il]-2-fluorofenil)-N'-[2-fluoro-5-(trifluorometil)fenil]urea**

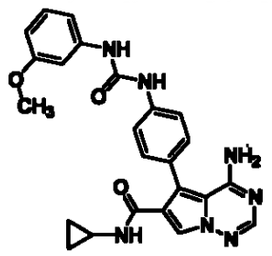


El procedimiento utilizado para la preparación del Ejemplo 276 se utilizó para preparar el compuesto del título sustituyendo el intermediario AL con el intermediario

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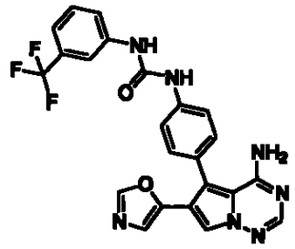
7. ^{1}H-RMN (DMSO-d_6) δ9,48 (s, 1H), 9,32 (s, 1H), 8,65 a 8,64 (d, *J* = 7,4 Hz, 1H), 8,35 a 8,30 (t, *J* = 8,5 Hz, 1H), 8,30 (s, 1H), 8,09 (s, 1H), 7,90 (s, 1H), 7,53 a 7,48 (m, 1H), 7,42 a 7,39 (m, 1H), 7,37 a 7,34 (d, *J* = 12,0 Hz, 1H), 7,21 a 7,19 (d, *J* = 8,4 Hz, 1H), 6,62 (s, 1H); EM $[M+H]^+$ = 516,1; LCMS TR = 3,01 min.

Ejemplo 309: **Preparación de 4-amino-N-ciclopropil-5-[4-({[(3-metoxifenil)amino]carbonil}amino)fenil]pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida**



El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo el intermediario W con el intermediario X y (3-metoxifenil)carbamato de fenilo con (4-*ter*-butilpiridin-2-il)carbamato de fenilo. La reacción se calentó a reflujo durante toda la noche en THF. ^{1}H RMN (DMSO-d_6) δ 8,81 (s, 1H), 8,75 (s, 1H), 8,04 (s, 1H), 7,92 (br s, 1H), 7,88 (s, 1H), 7,88 (d, *J* = 4,3 Hz, 1H), 7,54 a 7,48 (m, 2H), 7,31 a 7,23 (m, 2H), 7,21 a 7,12 (m, 2H), 6,98 a 6,90 (m, 1H), 6,55 (ddd, *J* = 8,1, 2,7, 0,7 Hz, 1H), 4,66 (br s, 1H), 3,73 (s, 3H), 2,70 a 2,62 (m, 1H), 0,64 a 0,58 (m, 2H), 0,44 a 0,38 (m, 2H); MS $[M+H]^+$ = 458,1; LCMS TR = 2,38 min.

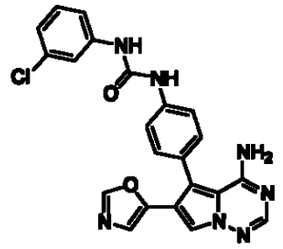
Ejemplo 310: **Preparación de N-(4-[4-amino-6-(1,3-oxazol-5-il)pirrolo-[2,1-*f*][1,2,4]triazin-5-il]fenil}-N'-[3-(trifluorometil)fenil]urea**



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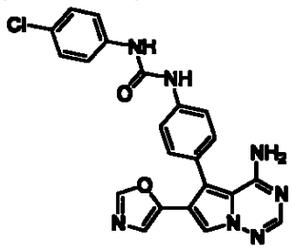
El procedimiento utilizado para la preparación del Ejemplo 3 se utilizó para preparar el compuesto del título sustituyendo el intermediario AO con el intermediario C y 3-(trifluorometil)anilina con 4-fluoro-3-(trifluorometil)anilina. ^{1}H-RMN (DMSO-d_6) δ9,23 a 9,16 (br s, 2H), 8,28 (s, 1H), 8,07 (s, 1H), 7,89 (s, 1H), 7,72 (s, 1H), 7,63 a 7,61 (d, J = 8,6 Hz, 2H), 7,34 a 7,28 (m, 4H), 7,01 a 6,99 (d, J = 7,1 Hz, 1H), 6,55 (s, 1H); EM $[M+H]^+$ = 480,0; LCMS TR = 2,84 min.

Ejemplo 311: **Preparación de N-{4-[4-amino-6-(1,3-oxazol-5-il)pirrolo-[2,1-f][1,2,4]triazin-5-il]fenil}-N'-(3-clorofenil)urea**



El procedimiento utilizado para la preparación del Ejemplo 3 se utilizó para preparar el compuesto del título sustituyendo el intermediario AO con el intermediario C y 3-cloroanilina con 4-fluoro-3-(trifluorometil)anilina. ^{1}H-RMN (DMSO-d_6) δ8,29 (s, 1H), 8,08 (s, 1H), 8,04 (s, 1H), 7,90 (s, 1H), 7,68 a 7,66 (m, 3H), 7,51 a 7,47 (t, J = 8,1 Hz, 1H), 7,34 a 7,32 (d, J = 8,6 Hz, 2H), 7,30 a 7,28 (d, J = 8,4 Hz, 1H), 6,56 (s, 1H); EM $[M+H]^+$ = 446,1; LCMS TR = 2,72 min.

Ejemplo 312: **Preparación de N-{4-[4-amino-6-(1,3-oxazol-5-il)pirrolo-[2,1-f][1,2,4]triazin-5-il]fenil}-N'-(4-clorofenil)urea**

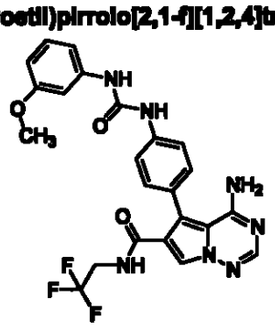


El procedimiento utilizado para la preparación del Ejemplo 3 se utilizó para preparar el compuesto del título sustituyendo el intermediario AO con el intermediario C y 4-cloroanilina con 4-fluoro-3-(trifluorometil)anilina. ^{1}H-RMN (DMSO-d_6) δ8,93 (s,

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1H), 8,90 (s, 1H), 8,29 (s, 1H), 8,08 (s, 1H), 7,90 (s, 1H), 7,61 a 7,59 (d, *J* = 8,6 Hz, 2H), 7,50 a 7,48 (d, *J* = 9,1 Hz, 2H), 7,35 a 7,32 (m, 4H), 6,55 (s, 1H); EM $[M+H]^+$ = 446,1; LCMS TR = 2,65 min.

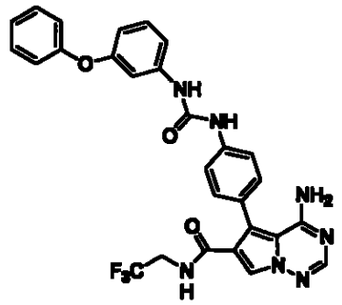
Ejemplo 313: Preparación de 4-amino-5-[4-({[(3-metoxifenil)amino]carbonil}-amino)fenil]-N-(2,2,2-trifluoroetil)pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida



El procedimiento utilizado para la preparación del Ejemplo 73 se utilizó para preparar el compuesto del título sustituyendo el intermediario M con el intermediario X y (3-metoxifenil)carbamato de fenilo con (4-*ter*-butilpiridin-2-il)carbamato de fenilo. La reacción se calentó a reflujo durante toda la noche en THF. ^{1}H RMN (DMSO-d_6) δ8,79 (s, 1H), 8,72 (s, 1H), 8,48 (dd, *J* = 6,4, 6,4 Hz, 1H), 8,17 (s, 1H), 8,00 (br s, 1H), 7,91 (s, 1H), 7,52 a 7,47 (m, 2H), 7,30 a 7,23 (m, 2H), 7,21 a 7,12 (m, 2H), 6,96 a 6,90 (m 1H), 6,54 (ddd, *J* = 8,2, 2,6, 0,8 Hz, 1H), 5,08 (br s, 1H), 4,02 a 3,90 (m, 2H), 3,73 (s, 3H); EM $[M+H]^+$ = 500,2; LCMS TR = 2,61 min.

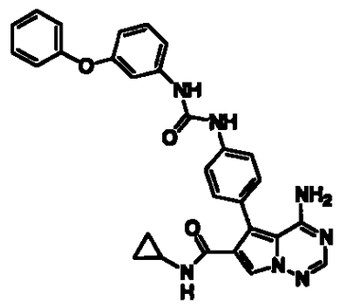
Los siguientes ejemplos se pueden sintetizar de acuerdo con los procedimientos de síntesis delineados anteriormente:

4-amino-5-[4-({[(3-fenoxifenil)amino]carbonil}amino)fenil]-N-(2,2,2-trifluoroetil)pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida

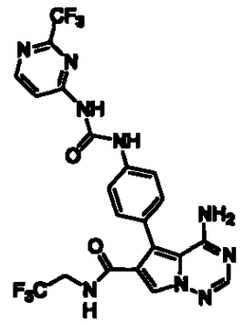


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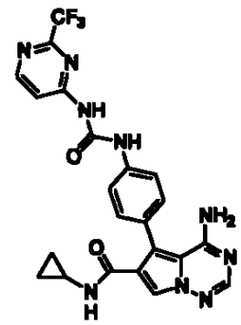
4-amino-N-ciclopropil-5-{4-[({[(3-fenoxifenil)amino]carbonil}amino)fenil]-pirrolo[2,1-f][1,2,4]triazin-6-carboxamida



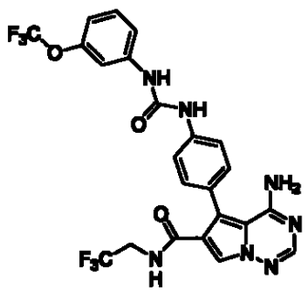
4-amino-N-(2,2,2-trifluoroetil)-5-{4-[({[2-(trifluorometil)pirimidin-4-il]-amino}carbonil)amino]fenil}pirrolo[2,1-f][1,2,4]triazin-6-carboxamida



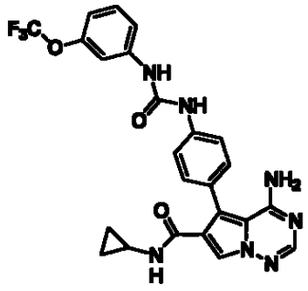
4-amino-N-ciclopropil-5-{4-[({[2-(trifluorometil)pirimidin-4-il]amino}-carbonil)amino]fenil}pirrolo[2,1-f][1,2,4]triazin-6-carboxamida



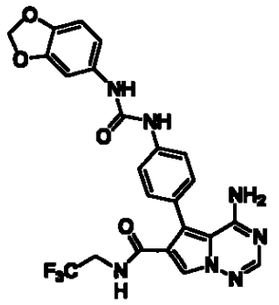
4-amino-N-(2,2,2-trifluoroetil)-5-{4-[({[3-(trifluorometoxi)fenil]-amino}carbonil)amino]fenil}pirrolo[2,1-f][1,2,4]triazin-6-carboxamida



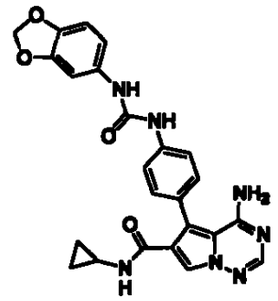
4-amino-N-ciclopropil-5-(4-[({[3-(trifluorometoxi)-fenil]amino}carbonil)amino]fenil}pirrolo[2,1-f][1,2,4]triazin-6-carboxamida



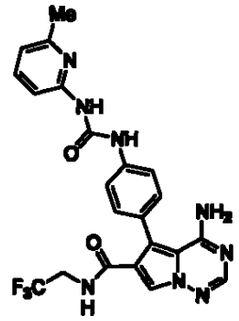
4-amino-5-(4-{[(1,3-benzodioxol-5-ilamino)carbonil]amino}fenil)-N-(2,2,2-trifluoroetil)pirrolo[2,1-f][1,2,4]triazin-6-carboxamida



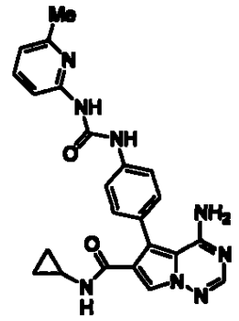
4-amino-5-(4-{[(1,3-benzodioxol-5-ilamino)carbonil]amino}fenil)-N-ciclopropilpirrolo[2,1-f][1,2,4]triazin-6-carboxamida



4-amino-5-[4-({[(6-metilpiridin-2-il)amino]carbonil}amino)fenil]-N-(2,2,2-trifluoroetil)pirrolo[2,1-f][1,2,4]triazin-6-carboxamida

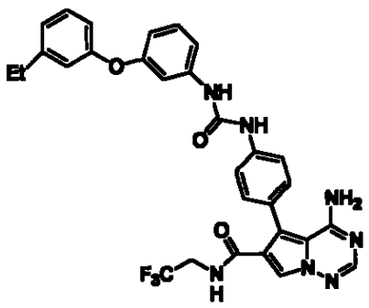


4-amino-N-ciclopropil-5-[4-({[(6-metilpiridin-2-il)amino]carbonil}amino)fenil]pirrolo[2,1-f][1,2,4]triazin-6-carboxamida

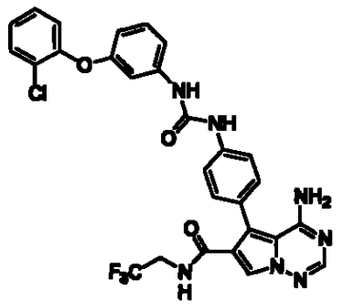


4-amino-5-{4-[({[3-(3-etilfenoxi)fenil]amino}carbonil)amino]fenil}-N-(2,2,2-trifluoroetil)pirrolo[2,1-f][1,2,4]triazin-6-carboxamida

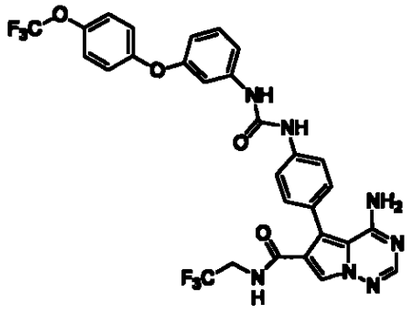
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4-amino-5-{4-[({[3-(2-clorofenoxi)fenil]amino}carbonil)amino]fenil}-N-(2,2,2-trifluoroetil)pirrolo[2,1-f][1,2,4]triazin-6-carboxamida

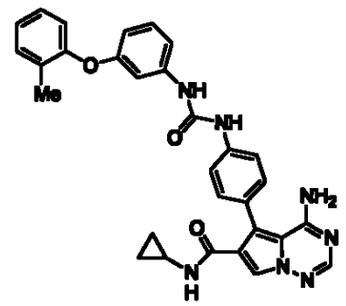


4-amino-N-(2,2,2-trifluoroetil)-5-(4-{[({3-[4-(trifluorometoxi)fenoxi]fenil}-amino)carbonil]amino}fenil)pirrolo[2,1-f][1,2,4]triazin-6-carboxamida

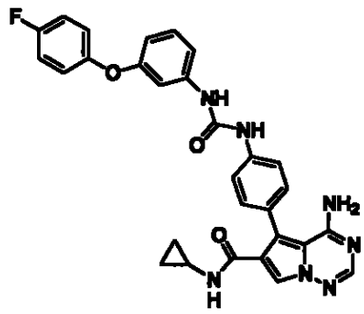


4-amino-N-ciclopropil-5-{4-[({[3-(2-metilfenoxi)fenil]-amino}carbonil)amino]fenil}pirrolo[2,1-f][1,2,4]triazin-6-carboxamida

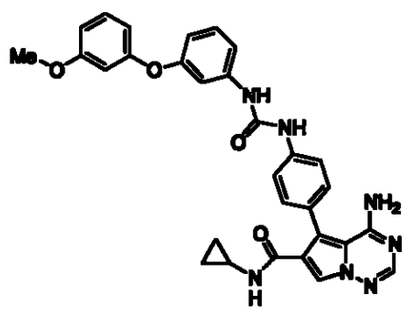
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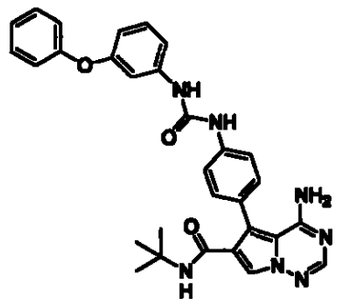
4-amino-N-ciclopropil-5-{4-[({[3-(4-fluorofenoxi)fenil]-amino}carbonil)amino]fenil}pirrolo[2,1-f][1,2,4]triazin-6-carboxamida



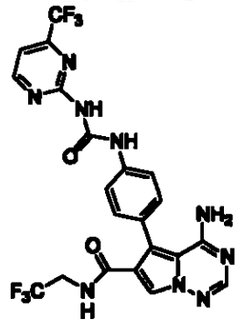
4-amino-N-ciclopropil-5-{4-[({[3-(3-metoxifenoxi)-fenil]amino}carbonil)amino]fenil}pirrolo[2,1-f][1,2,4]triazin-6-carboxamida



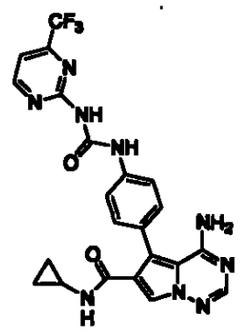
4-amino-N-(ter-butil)-5-[4-({[(3-fenoxifenil)amino]-carbonil}amino)fenil]pirrolo[2,1-f][1,2,4]triazin-6-carboxamida



4-amino-N-(2,2,2-trifluoroetil)-5-(4-[({[4-(trifluorometil)pirimidin-2-il]-amino}carbonil)amino]fenil}pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida

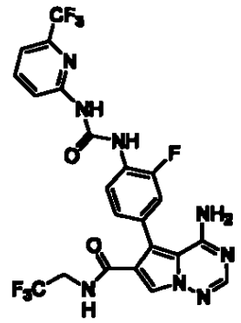


4-amino-N-ciclopropil-5-{4-[({[4-(trifluorometil)pirimidin-2-il]amino}-carbonil)amino]fenil}pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida

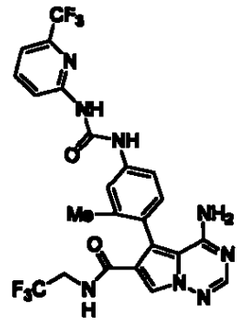


4-amino-5-{3-fluoro-4-[({[6-(trifluorometil)piridin-2-il]amino}carbonil)-amino]fenil}-N-(2,2,2-trifluoroetil)pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida

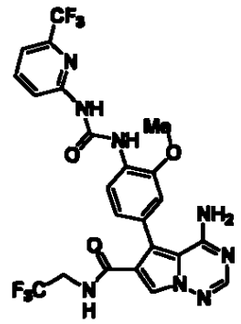
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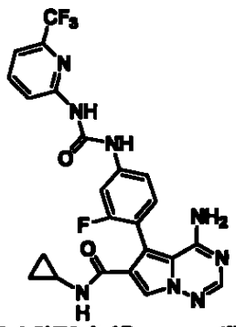
4-amino-5-[2-metil-4-[({[6-(trifluorometil)piridin-2-il]amino}carbonil)amino]-fenil]-N-(2,2,2-trifluoroetil)pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida



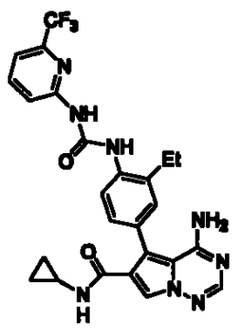
4-amino-5-[3-metoxi-4-[({[6-(trifluorometil)piridin-2-il]amino}carbonil)amino]-fenil]-N-(2,2,2-trifluoroetil)pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida



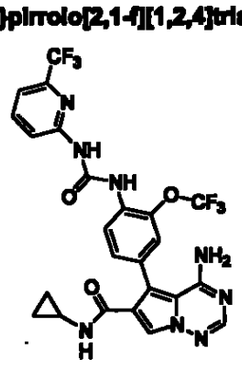
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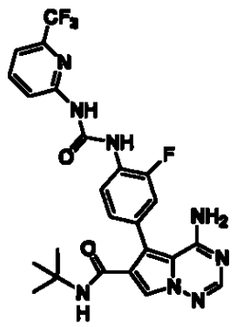
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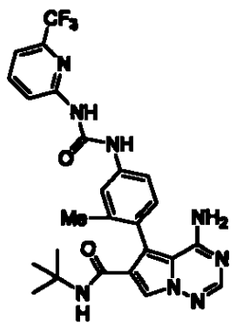
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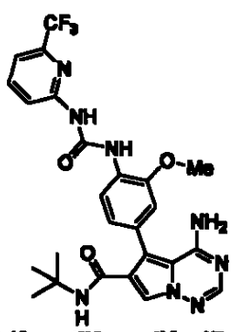
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4-amino-N-(ter-butil)-5-{2-metil-4-[({[6-(trifluorometil)piridin-2-il]amino}-carbonil)amino]fenil}pirrolo[2,1-*f*][1,2,4]triazin-6-carboxamida

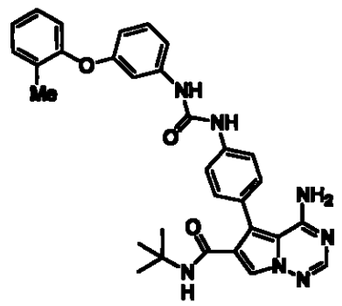


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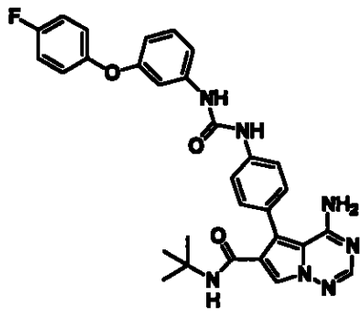


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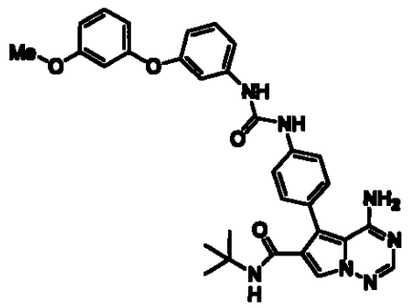
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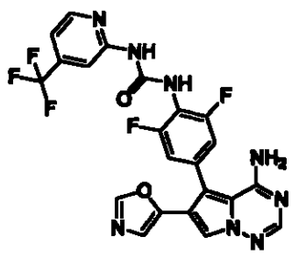
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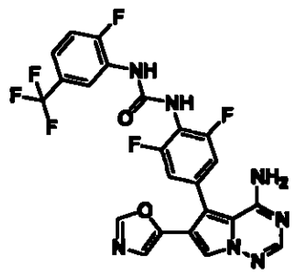
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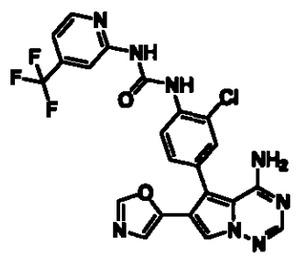
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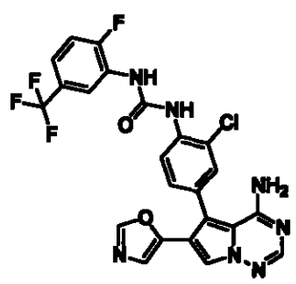
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N-{4-[4-amino-8-(1,3-oxazol-5-il)pirrolo[2,1-f][1,2,4]triazin-5-il]-2-clorofenil}-N'-[4-(trifluorometil)piridin-2-il]urea

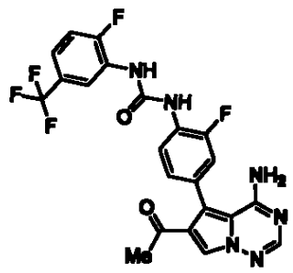


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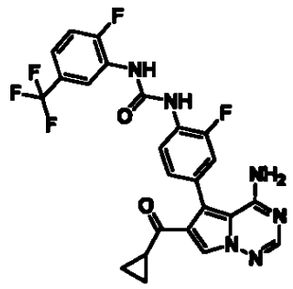


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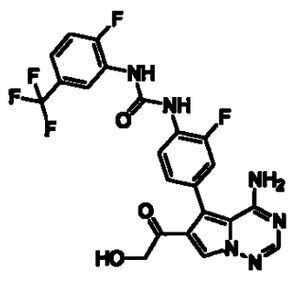
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N-{4-[4-amino-6-(ciclopropilcarbonil)pirrolo[2,1-f][1,2,4]triazin-5-il]-2-fluorofenil}-N'-[2-fluoro-5-(trifluorometil)fenil]urea

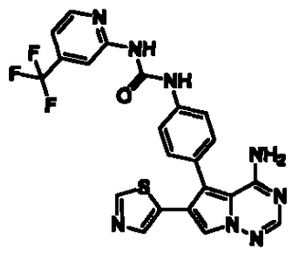


N-[4-(4-amino-6-glicoloilpirrolo[2,1-f][1,2,4]triazin-5-il)-2-fluorofenil]-N'-[2-fluoro-5-(trifluorometil)fenil]urea

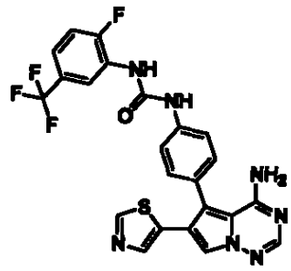


N-(4-[4-amino-6-(1,3-tiazol-5-il)pirrolo[2,1-f][1,2,4]triazin-5-il]fenil}-N'-[4-(trifluorometil)piridin-2-il]urea

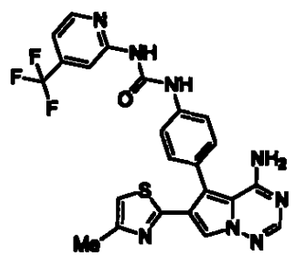
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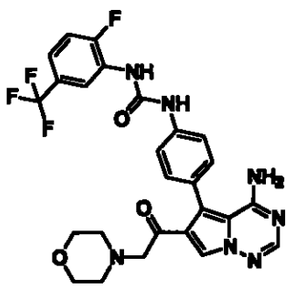
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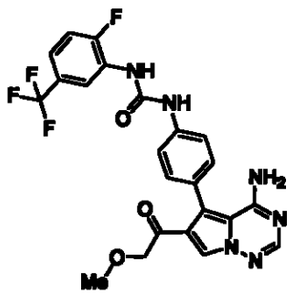
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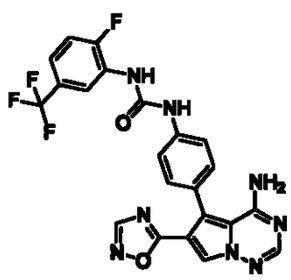
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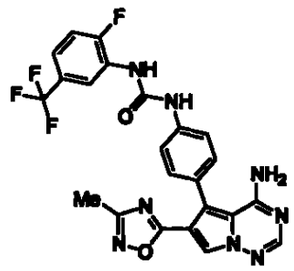
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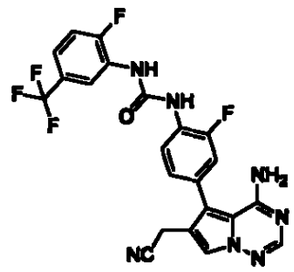
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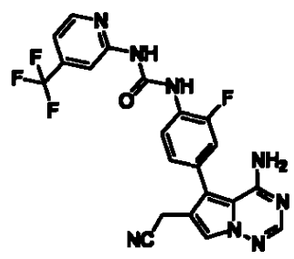
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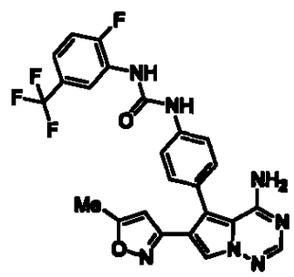
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N-{4-[4-amino-6-(cianometil)pirrolo[2,1-f][1,2,4]triazin-5-il]-2-fluorofenil}-N'-[4-(trifluorometil)piridin-2-il]urea

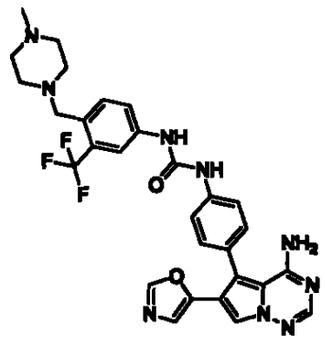


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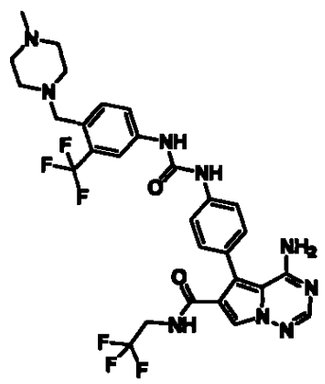


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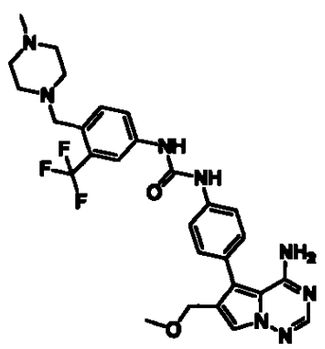
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N-{4-[4-amino-6-(metoximetil)pirrolo[2,1-f][1,2,4]triazin-5-il]fenil}-N'-[4-[(4-metilpiperazin-1-il)metil]-3-(trifluorometil)fenil]urea

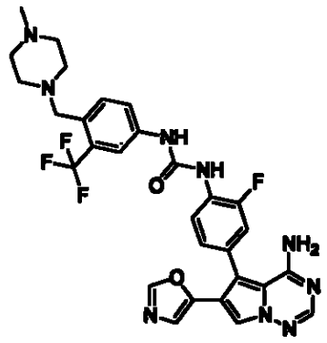


4-amino-5-{4-[({[4-[(4-metilpiperazin-1-il)metil]-3-(trifluorometil)fenil]amino}carbonil)amino]fenil}-N-(2,2,2-trifluoroetil)pirrolo[2,1-f][1,2,4]triazin-6-carboxamida

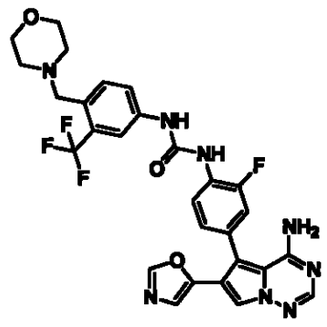


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N-{4-[4-amino-6-(metoximetil)pirrolo[2,1-f][1,2,4]triazin-5-il]fenil}-N'-[4-[(4-metilpiperazin-1-il)metil]-3-(trifluorometil)fenil]urea



N-{4-[4-amino-6-(1,3-oxazol-5-il)pirrolo[2,1-f][1,2,4]triazin-5-il]-2-fluorofenil}-N'-[4-[(4-metilpiperazin-1-il)metil]-3-(trifluorometil)fenil]urea



N-{4-[4-amino-6-(1,3-oxazol-5-il)pirrolo[2,1-f][1,2,4]triazin-5-il]-2-fluorofenil}-N'-[4-(morfolin-4-ilmetil)-3-(trifluorometil)fenil]urea

B. Evaluación de la actividad fisiológica

El efecto *in vitro* de los compuestos de acuerdo con la invención se puede demostrar en los siguientes ensayos:

Ensayo de p-ERK estimulado por el factor de crecimiento en HUVECs

Células HUVECs endoteliales de crecimiento exponencial (células endoteliales de la vena umbilical humana), cat# CC-2517, Cambrex, Walkersville, MD) se sembraron veinticinco mil células/pocillo en placas de 96 pocillos en medio de EBM-2MV con factores de crecimiento (cat# CC-3202, Cambrex) y se desarrollaron a 37°C en 5% de CO_2. Al cabo de 16 horas de plantación, las células se cambiaron a un medio libre de suero (RPMI 1640 conteniendo 0,1% de BSA (albúmina de suero

bovino) y se agregaron compuestos a diferentes concentraciones durante 2 horas, después de lo cual las células se estimularon durante 10 min con 50 ng/ml de, ya sea VEGF (factor de crecimiento endotelial vascular, Protein Sciences, Meriden, CT) o bFGF factor de crecimiento fibroblástico básico cat# PHG0026, Biosource International, Camarillo, CA). El resto del ensayo se llevó a cabo según indicaciones del fabricante para el ensayo ERK1/2 Bioplex (cat#171-304004, Bio-Rad, Hercules, CA). Después de eliminar el medio de cultivo por aspiración, las células se enjuagaron rápidamente con 100 µl de buffer A de lavado celular para detener la reacción del tratamiento. Ochenta microlitros de buffer de lisis celular luego se agregaron inmediatamente a cada pocillo de la placa de 96 pocillos la cual se colocó sobre hielo. Las células en cada recipiente se lisaron pipeteando arriba y abajo cinco veces con una pipeta multicanal. Luego la placa se agitó sobre un agitador de placa de microtítulo a 300 rpm durante 20 min a 4°C. El desperdicio celular se peleteó por centrifugación a 4500 g durante 15 min a 4°C y se recolectó el sobrenadante. Cuarenta y cinco microlitros del sobrenadante se diluyeron con un volumen igual de buffer B de ensayo de fosfoproteína Bio-Plex. Las perlas acopladas y recubiertas de color se agregaron a una placa de filtro de 96 pocillo, y se agregaron los lisados preparados. Las perlas y la mezcla de lisado se incubaron a temperatura ambiente durante 15-18 horas. Al día siguiente, la placa se filtró al vacío y luego se lavó 3x. Se agregaron veinticinco microlitros de solución de anticuerpo de detección a cada pocillo y la placa luego se incubó durante 30 minutos a temperatura ambiente. La placa luego se filtró al vacío y se lavó según se describió previamente. Se agregaron cincuenta microlitros de solución de estreptavidin-PE a cada pocillo, la placa se incubó durante 10 minutos a temperatura ambiente y luego se filtró al vacío y se lavó según se describió anteriormente. Se agregaron ciento veinticinco microlitros de buffer de resuspensión a cada pocillo y los datos se adquirieron sobre el instrumento Luminex 100 (Bio-Rad). Los compuestos de los Ejemplos 1, 8, 9, 12, 23, 27, 30, 32, 49, 59 y 70 mostraron una inhibición superior al 50% @ 100 nM en el ERK-estimulado por VEGF en el ensayo de HUVEC. Los compuestos de los Ejemplos 11, 22, 24, 28, 29, 37, 39, 41, 47, 66, 75, 85, 93, 99, 100, 131, 143, 146 y 168 mostraron una inhibición superior al 50% @ 1 µM pero inferior al 50% @ 100 nM en el ERK-

estimulado por VEGF en el ensayo de HUVEC. Los compuestos de los Ejemplos 14, 18, 62, 96, 98, 104 y 140 mostraron una inhibición superior al 50% @ 10 μM pero inferior a 50% @ 100 nM y 1 μM en el ERK-estimulado por VEGF en el ensayo de HUVEC.

Proliferación de HUVEC estimulada por el factor de crecimiento de BRDU

Células endoteliales de vena umbilical humana de crecimiento exponencial (HUVEC; Cat# CC-2519A, Cambrex, Walkersville, MD) se sembraron a dos mil células/pocillo en placas de 96 pocillos recubiertas con Collagen IV (Cat# 35-4429, Becton Dickinson, Bedford, MA) en medios de ensayo conteniendo RPMI-1640 (Cat# 11875-093, Gibco, Carlsbad, CA), 0,5% de suero con franjas de carbón (Cat# SH30068,03, HyClone, Logan, Utah), y 1% de suplemento N-2 (Cat# 17502-048, Gibco, Carlsbad, CA). Cuatro horas después de la incubación de las placas a 37°C en 5% de CO_2, las células se trataron con diferentes concentraciones de compuesto (se diluyeron en medios de ensayo con una concentración final de DMSO = 0,1%) y luego se estimularon inmediatamente con 80 ng/ml de factor de crecimiento endotelial vascular (VEGF, Cat# 100-20, PeproTech, Rocky Hill, NJ) o 1,5 ng/ml de factor de crecimiento fibroblasto básico (bFGF, Cat# 100-18B, PeproTech, Rocky Hill, NJ). Las células tratadas se incubaron durante 3 días a 37°C en 5% de CO_2. Se midió la síntesis de ADN mediante la incorporación de bromodeoxiuridina (BrdU) en ADN recientemente sintetizado utilizando el sistema Amersham Cell Proliferation BioTrack ELISA (Cat# RPN250, Amersham, Piscataway, NJ). La solución de BrdU diluida (20 μl de reserva de BrdU diluida 1:20 veces en medios de ensayo) se agregó a cada pocillo y se procedió a la incubación durante 6 horas a 37°C en 5% de CO_2. Se eliminó el medio y las células se fijaron de acuerdo con las especificaciones del kit de ensayo Amersham durante 30 minutos a temperatura ambiente. Después de eliminar el agente de fijación, se agregó el buffer de bloqueo (suministrado por Amersham kit; 200 μl/pocillo) y las placas se almacenaron a 4°C durante toda la noche. El buffer de bloque se aspiró y se agregó el anticuerpo anti-BrdU marcado con peroxidasa (suministrado por Amersham kit; 100 μl/pocillo) y se incubó durante 3 horas a temperatura ambiente. Las placas se lavaron tres veces con buffer de lavado (suministrado por Amersham kit; 300 μl/pocillo/lavado). Inmediatamente a

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continuación de los lavados, se dispensaron 100 µl del sustrato de TMB en cada pocillo y las placas se incubaron nuevamente durante 30 , 30 minutos a temperatura ambiente. La reacción se terminó con la adición de 25 µl de H_2SO_4 1M. Las placas se leyeron inmediatamente a 450 nm utilizando un lector de placa de espectrofotómetro SpectraMAX 250 (Molecular Devices, Sunnyvale, CA). El software utilizado fue el SoftMAX pro v,2,4,1.

Los compuestos de los Ejemplos 70, 101, 218 y 226 muestran un IC_{50} inferior a 10 nM en el ensayo de proliferación de HUVEC estimulado por VEGFR. Los compuestos de los Ejemplos 103, 151, 155, 157, 159, 162, 223, 233, 234, 239 y 243 muestran un IC_{50} superior a 10 nM pero inferior a 100 nM en el ensayo de proliferación de HUVEC estimulado por VEGFR. Los compuestos de los Ejemplos 30, 99, 102, 152, 240 y 247 muestran un IC_{50} superior a 100 nM pero inferior a 500 nM en el ensayo de proliferación de HUVEC estimulado por VEGFR. Los compuestos de los Ejemplos 100 y 163 muestran un IC_{50} superior a 500 nM pero inferior a 2 µM en el ensayo de proliferación de HUVEC estimulado por VEGFR.

Los compuestos de los Ejemplos 70, 99, 101, 103, 151 y 223 muestran un IC_{50} inferior a 100 nM en el ensayo de proliferación de HUVEC estimulado por VEGFR. Los compuestos de los Ejemplos 30, 102, 152, 155, 157, 159, 162, 218, 226, 233, 234, 239, 243 y 247 muestran un IC_{50} superior a 100 nM pero inferior a 500 nM en el ensayo de proliferación de HUVEC estimulado por VEGFR. El compuesto del Ejemplo 240 muestra una IC_{50} superior a 500 nM pero inferior a 1 µM en el ensayo de proliferación de HUVEC estimulado por VEGFR.

Proliferación de Células Tumorales

Células tumorales humanas (por ejemplo, células HCT116 o MDA-MB-231), se sembraron en una placa Costar de 96 pocillos a $3,0x10^3$ células/pocillo y se desarrollaron en 150 µl de medios completos de RPMI (Invitrogen Corporation, Grand Island, NY) conteniendo 10% suero fetal bovino (Hyclone, Logan, Utah) a 37°C durante 16 h en un incubador con 5% de CO_2. A cada pocillo, se agregaron 50 µl de medio de crecimiento adicional conteniendo 40 µM a concentraciones de 18 nM del compuesto con 0,4% de DMSO. Las células se desarrollaron durante otras 72 h a 37°C con 5% de CO_2. Se agregaron 20 µl del reactivo Alamar Blue (Trek Diagnostic

Systems, Inc., Cleveland, Ohio) a cada pocillo y se incubaron durante 3 h a 37 °C. Las placas se leyeron en un SpectraMax Gemini (Molecular Devices, CA) con excitación de 544 nm y una emisión de longitud de onda de 590 nm. Los valores IC_{50} se determinaron por análisis de regresión lineal de concentración de fármaco log versus la inhibición porcentual.

Los compuestos de los Ejemplos 25, 70, 93, 155, 235 y 237 muestran un IC_{50} inferior a 500 nM en el ensayo de proliferación de HCT116. Los compuestos de los Ejemplos 59, 69, 71, 76, 156, 159, 161, 162, 223, 239, 241, 256 y 257 muestran un IC_{50} superior a 500 nM pero inferior a 1,5 μM en el ensayo de proliferación de HCT116. Los compuestos de los Ejemplos 30, 73, 74, 82, 99, 100, 102, 149, 157, 163, 217, 225, 226, 232, 233, 234, 240, 242, 243, 247, 248, 254 y 255 muestran un IC_{50} superior a 1,5 μM pero inferior a 5 μM en el ensayo de proliferación de HCT116. Los compuestos de los Ejemplos 84, 94, 103, 153 y 218 muestran un IC_{50} superior a 5 μM pero inferior a 10 μM en el ensayo de proliferación de HCT116.

Los compuestos de los Ejemplos 25, 70, 71, 155 y 156 muestran un IC_{50} inferior a 500 nM en el ensayo de proliferación de MDA-MB-231. Los compuestos de los Ejemplos 59, 82, 93, 99, 149, 159, 217, 223, 235, 239, 248, 251, 255, 256 y 257 muestran un IC_{50} superior a 500 nM pero inferior a 1,5 μM en el ensayo de proliferación de MDA-MB-231. Los compuestos de los Ejemplos 69, 73, 74, 76, 94, 100, 157, 161, 162, 163, 225, 226, 232, 233, 234, 237, 240, 241, 242, 243, 247 y 254 muestran un IC_{50} superior a 1,5 μM pero inferior a 5 μM en el ensayo de proliferación de MDA-MB-231. Los compuestos de los Ejemplos 102, 103, 153 y 218 muestran un IC_{50} superior a 5 μM pero inferior a 10 μM en el ensayo de proliferación de MDA-MB-231.

<u>p-Histona3</u>

Se ensayaron compuestos para la inhibición de la fosforilación de histona 3 en carcinoma de colon (HCT116). Brevemente, 20.000 células/pocillo se sembraron en placas de 96 pocillo de pared negra, de poli-d-lisina en RPMI + 10% de FBS y se incubaron a 37°C en 5% de CO_2 durante la noche. Al día siguiente, las células se trataron con compuestos durante 24 horas a 37°C. Siguiendo el tratamiento del compuesto; las placas se centrifugaron a 1000 rpm durante 2 minutos y se lavaron

dos veces con 100 µl de TBS estéril frío. Luego las células se fijaron con 3,7% de formaldehído frío en TBS (4°C durante 1 hora) y luego se permeabilizaron con 0,1% de Triton-X-100 en TBS (temperatura ambiente durante 30 minutos). Luego las placas se lavaron con 0,25% de BSA-TBS y se bloquearon con solución de BSA durante 1 hora a temperatura ambiente mientras se agitaba. El sobrenadante se eliminó y se reemplazó con anticuerpo primario diluido (anti-fosfo-histona 3, serina 10, señalización de células) a 1:250 en 0,25% de BSA-TBS y se incubó durante toda la noche a 4°C. Las placas se lavaron y se trataron con anticuerpo secundario diluido (anti-conejo marcado con Eu) a 1:10000 en 0,25% de BSA-TBS (temperatura ambiente durante 1 hora). La solución de anticuerpo se eliminó de cada pocillo y se lavó ocho veces. El buffer de lavado se reemplazó con 50 µl de solución de mejoramiento pre-entibiada y se mezció sobre el agitador orbital durante 10 minutos. Se detectó fluorescencia con un Detector de Fluorescencia Victor V. Los datos se expresaron como porcentaje de inhibición: % de inhibición = 100 –((Señal con antecedente de inhibidor)/(Señal sin antecedente de inhibidor)) x 100. Los compuestos de los Ejemplos 88, 92, 139, 164, 165, 171, 176 y 177 muestran un IC_{50} inferior a 500 nM en el ensayo de p-histona3. Los compuestos de los Ejemplos 7, 13, 59, 167 y 204 muestran un IC_{50} superior a 500 nM pero inferior a 1 µM en el ensayo de p-histona3.

El efecto *in vivo* de los compuestos de acuerdo con la invención se puede demostrar en los experimentos de xenoinjerto tumoral, tal como se describe en Wilhelm, S. *et al. Cancer Res.* 2004, *64*, 7099-09.

C. <u>Ejemplos operativos relacionados con composiciones farmacéuticas</u>

Los compuestos de acuerdo con la invención se pueden convertir en preparaciones farmacéuticas de la siguiente forma:

<u>Comprimido:</u>

<u>Composición:</u> 100 mg del compuesto del Ejemplo 1, 50 mg de lactosa (monohidrato), 50 mg de almidón de maíz (natural), 10 mg de polivinilpirrolidona (PVP 25) (de BASF, Ludwigshafen, Alemania) y 2 mg de estearato de magnesio.

Peso del comprimido 212 mg, diámetro 8 mm, radio de curvatura 12 mm.

Preparación:

La mezcla del componente activo, lactosa y almidón se granula con una solución al 5% (m/m) del PVP en agua. Después de secar, los gránulos se mezclaron con estearato de magnesio durante 5 min. Esta mezcla se moldeó utilizando la prensa de comprimido habitual (formato de comprimido, ver anterior). La fuerza de moldeado aplicada es típicamente 15 kN..

Suspensión para administración oral:

Composición: 1000 mg del compuesto del Ejemplo 1, 1000 mg de etanol (96%), 400 mg de Rhodigel (goma xantano de FMC, Pensilvania, EE.UU) y 99 g de agua.

Se suministró una dosis simple de 100 mg del compuesto de acuerdo con la invención mediante 10 ml de suspensión oral.

Preparación:

El Rhodigel se suspendió en etanol y se agregó el componente activo a la suspensión. Se agregó agua con agitación. La agitación continuó durante casi 6 horas hasta que se completó la dilatación del Rhodigel.

Solución para administración intravenosa 1:

Composición: 100-200 mg del compuesto del Ejemplo 1, 15 g polietilenglicol 400 y 250 g de agua opcionalmente con hasta 15 % de Cremophor EL, y opcionalmente hasta 15% de alcohol etílico, y opcionalmente hasta 2 equivalentes de un ácido adecuado para uso farmacéutico tal como ácido cítrico o ácido clorhídrico.

Preparación:

El compuesto del Ejemplo 1 y el polietilenglicol 400 se disolvieron en agua con agitación. La solución se filtró estéril (tamaño de poro 0,22 µm) y se colocó en botellas de infusión esterilizadas calientes bajo condiciones asépticas. Las botellas de infusión se sellarán con sellos de goma.

Solución para administración intravenosa 2:

Composición: 100-200 mg del compuesto del Ejemplo 1, solución salina, opcionalmente con hasta 15 % en peso de Cremophor EL, y opcionalmente hasta 15% en peso de alcohol etílico, y opcionalmente hasta 2 equivalentes de un ácido adecuado para uso farmacéutico tal como ácido cítrico o ácido clorhídrico.

Preparación:

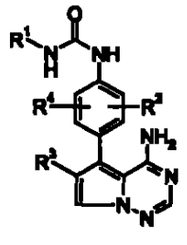
El compuesto del Ejemplo 1 se disolvió en solución salina con agitación. Opcionalmente se agregaron Cremophor EL, alcohol etílico o ácido. La solución se filtró estéril (tamaño de poro 0,22 µm) y se colocaron en botellas de infusión esterilizadas calientes bajo condiciones asépticas. Las botellas de infusión se sellarán con sellos de goma.

Debe ser evidente para los expertos en la técnica que podrán efectuarse cambios y modificaciones a esta invención sin apartarse del espíritu o alcance de la invención según se establece en la presente.

REIVINDICACIONES

Habiendo así especialmente descrito y determinado la naturaleza de la presente invención y la manera cómo la misma ha de ser llevada a la práctica, se declara reivindicar como de propiedad y derecho exclusivo:

1. Un compuesto de fórmula (I)



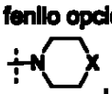
(I),

en la cual

. R^1 se selecciona del grupo integrado por arilo, bencilo, y heteroarilo,

donde arilo y heteroarilo pueden estar opcionalmente sustituidos con 0, 1, 2, 3 o 4 sustituyentes seleccionados independientemente del grupo integrado por

- alquilo (C_1-C_4), donde alquilo (C_1-C_4) puede estar sustituido con 0, 1, 2 o 3 halógenos, 0 o 1 heterocicilo, o 0 o 1 alcoxi (C_1-C_3), donde

  alcoxi (C_1-C_3) puede estar opcionalmente sustituido con alquilamino (C_1-C_3),
- alcoxi (C_1-C_3), donde alcoxi (C_1-C_3) puede estar opcionalmente sustituido con alquilamino (C_1-C_3),
- halógeno,
- trifluorometilo,
- trifluorometoxi,
- cicloalquilo (C_3-C_6),
- fenilo opcionalmente sustituido con 1 o 2 halógenos,
-  , donde X es CH_2, O, S o NR^{1-1}, y donde R^{1-1} es hidrógeno o alquilo (C_1-C_3),
- nitro,
- ciano,

- alquiltio (C_1-C_3),
- trifluorometiltio,
- alquil (C_1-C_3)-carbonilo,
- alcoxi (C_1-C_6)-carbonilo, y
- fenoxi, donde fenoxi puede estar opcionalmente sustituido con 0, 1 o 2 sustituyentes seleccionados independientemente del grupo integrado por alquilo (C_1-C_6), alcoxi (C_1-C_6), trifluorometoxi y halógeno,

y

donde bencilo puede estar sustituido con 0, 1, 2 o 3 grupos seleccionados de halógeno, alquilo (C_1-C_3) y alcoxi (C_1-C_3);

R^2 se selecciona del grupo integrado por hidrógeno, halógeno, alquilo (C_1-C_4) y alcoxi (C_1-C_4);

R^3 se selecciona del grupo integrado por

- carboxilo,
- formilo,
- alquil (C_1-C_6)-carbonilo opcionalmente sustituido con 0, 1, 2, o 3 grupos seleccionados de flúor, cloro, hidroxi, alcoxi (C_1-C_6), y heterociclo,
- cicloalquil (C_3-C_6)-carbonilo,
- alcoxi (C_1-C_6)-carbonilo opcionalmente sustituido con 0, 1, 2, o 3 grupos seleccionados de amino y alcoxi (C_1-C_6)-carbonilo,
- aminocarbonilo,
- alquilamino (C_1-C_6)-carbonilo, donde alquilamino (C_1-C_6)-carbonilo puede estar opcionalmente sustituido con 0, 1, 2 o 3 sustituyentes seleccionados independientemente del grupo integrado por cicloalquilo (C_3-C_6), halógeno, amino, alquilamino (C_1-C_6), hidroxi, alcoxi (C_1-C_6), alcoxi (C_1-C_6)-carbonilo, alquiltio (C_1-C_6), alcoxi (C_1-C_6)-carbonilamino, y metilsulfonilo, y donde alquilamino (C_1-C_6)-carbonilo puede estar opcionalmente sustituido con o 0 o 1 heterocicilo, donde heterocicilo puede estar

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opcionalmente sustituido con 0 o 1 alquilo (C_1-C_6), y donde alquilamino (C_1-C_6)-carbonilo puede estar opcionalmente sustituido con 0 o 1 fenilo, donde fenilo puede estar opcionalmente sustituido con 0 o 1 halógeno, alquilo (C_1-C_6), o alcoxi (C_1-C_6),

- heterociclilcarbonilo opcionalmente sustituido con 0 o 1 amino, alquilamino (C_1-C_6), cicloalquilo, o alquilo (C_1-C_6), donde alquilo (C_1-C_6) puede estar opcionalmente sustituido con 0 o 1 amino o alquilamino (C_1-C_6),

- alquilo (C_1-C_6) opcionalmente sustituido con 0, 1, 2 o 3 sustituyentes seleccionados independientemente del grupo integrado por

a) hidroxilo,

b) amino,

c) alquilamino (C_1-C_6), donde alquilamino (C_1-C_6) puede estar sustituido con 0, 1, 2, 3 o 4 sustituyentes seleccionados independientemente del grupo integrado por halógeno, amino, alquilamino, metoxi, metiltio y metilsulfonilo,

d) arilamino, donde arilamino puede estar sustituido con 0, 1 o 2 sustituyentes seleccionados independientemente del grupo integrado por alquilo (C_1-C_6), alcoxi (C_1-C_6), y trifluorometilo,

e) heterocicilo, donde heterocicilo puede estar sustituido con 0, 1 o 2 alquilo (C_1-C_6), donde alquilo (C_1-C_6) puede estar sustituido con 0, 1 o 2 hidroxi, metoxi o piridilo,

f) imidazolilo,

g) piridilamino,

h) alcoxi (C_1-C_3) opcionalmente sustituido con fluoro hasta el nivel de perfluoro, o con heterociclo, donde heterociclo puede estar opcionalmente sustituido con 0 o 1 alquilo (C_1-C_6),

I) alcoxi (C_1-C_3)-alcoxi (C_2-C_3), y

J) alcoxi (C_1-C_6)-carbonilo,

k) cicloalquilo (C_3-C_6),

l) ciano,

• alcoxi (C_1-C_6) opcionalmente sustituido con 1, 2 o 3 sustituyentes seleccionados independientemente del grupo integrado por amino, alquilamino (C_1-C_6), y heterocicilo, donde heterocicilo puede estar sustituido con 0, 1, 2 o 3 alquilo (C_1-C_6),

• cicloalquilamino (C_3-C_6)-carbonilo opcionalmente sustituido con alquilo (C_1-C_3),

• ciano,

• heteroarilo, donde heteroarilo puede estar sustituido con 0, 1, 2, o 3 grupos seleccionados independientemente del grupo integrado por

k) alquilo (C_1-C_6), donde alquilo (C_1-C_6) puede estar sustituido con 0, 1, 2, o 3 halógeno, 0 o 1 heterocicilo, 0 o 1 alquilamino, o 0 o 1 hidroxi o metoxi,

l) halógeno,

m) amino,

n) alquilamino,

o) alcoxi (C_1-C_6)-carbonilo, y

p) cicloalquilo (C_3-C_6),

• heteroarilcarbonilo, el cual puede estar sustituido con 0, 1, 2, o 3 grupos seleccionados independientemente del grupo integrado por alquilo (C_1-C_6), cicloalquilo (C_3-C_6) y halógeno,

• heterocicilo, donde heterocicilo puede estar sustituido con 0, 1, 2, o 3 grupos seleccionados independientemente del grupo integrado por alquilo (C_1-C_6) y alcoxi (C_1-C_6)-carbonilo; y

R^4 se selecciona del grupo integrado por hidrógeno, alquilo (C_1-C_6), alcoxi (C_1-C_6) y halógeno;

o su sal aceptable para uso farmacéutico.

2. El compuesto de la reivindicación 1, donde

R^1 se selecciona del grupo integrado por fenilo y heteroarilo monocíclico que tiene 5 o 6 átomos de anillo,

donde fenilo y heteroarilo pueden estar opcionalmente sustituidos con 0, 1, 2, 3 o 4 sustituyentes seleccionados independientemente del grupo integrado por

- alquilo (C_1-C_4), donde alquilo (C_1-C_4) puede estar sustituido con 0, 1, 2 o 3 halógenos, 0 o 1 pirrolidinilo, 0 o 1 morfolinilo, o 0 o 1 alcoxi (C_1-C_3) donde alcoxi (C_1-C_3) puede estar opcionalmente sustituido con alquilamino (C_1-C_3),
- alcoxi (C_1-C_3), donde alcoxi (C_1-C_3) puede estar opcionalmente sustituido con alquilamino (C_1-C_3),
- halógeno,
- trifluorometilo,
- trifluorometoxi,
- cicloalquilo (C_3-C_6),
- fenilo opcionalmente sustituido con 1 o 2 halógenos,
- trifluorometilitio;

R^2 se selecciona del grupo integrado por hidrógeno, halógeno, alquilo (C_1-C_4) y alcoxi (C_1-C_4);

R^3 se selecciona del grupo integrado por

- carboxilo,
- formilo,
- alquil (C_1-C_6)-carbonilo opcionalmente sustituido con 0, 1, 2, o 3 grupos seleccionados de flúor, cloro, hidroxi, alcoxi (C_1-C_6), y heterociclo monocíclico que tiene 5 o 6 átomos de anillo,
- cicloalquil (C_3-C_6)-carbonilo,
- alcoxi (C_1-C_6)-carbonilo opcionalmente sustituido con 0, 1, 2, o 3 grupos seleccionados de amino, y alcoxi (C_1-C_6)-carbonilo,
- aminocarbonilo,
- alquilamino (C_1-C_6)-carbonilo, donde alquilamino (C_1-C_6)-carbonilo puede estar opcionalmente sustituido con 0, 1, 2 o 3 sustituyentes seleccionados independientemente del grupo integrado por cicloalquilo (C_3-C_6), halógeno, amino, alquilamino (C_1-C_6), hidroxi,

alcoxi (C_1-C_6), alcoxi (C_1-C_6)-carbonilo, alquiltio (C_1-C_6), alcoxi (C_1-C_6)-carbonilamino, y metilsulfonilo, y donde alquilamino-C_1-C_6)-carbonilo puede estar opcionalmente sustituido con 0 o 1 hidroxilo o 0 o 1 heterocicilo monocíclico que tiene 5 o 6 átomos de anillo, donde heterocicilo puede estar opcionalmente sustituido con 0 o 1 alquilo (C_1-C_6), y donde alquilamino (C_1-C_6)-carbonilo puede estar opcionalmente sustituido con 0 o 1 fenilo, donde fenilo puede estar opcionalmente sustituido con 0 o 1 halógeno o alquilo (C_1-C_6),

- heterocicilicarbonilo monocíclico que tiene 5 o 6 átomos de anillo, opcionalmente sustituido con 0 o 1 amino, alquilamino (C_1-C_6), cicloalquilo (C_3-C_6), o alquilo (C_1-C_6), donde alquilo (C_1-C_6) puede estar opcionalmente sustituido con 0 o 1 amino o alquilamino (C_1-C_6),
- alquilo (C_1-C_6) opcionalmente sustituido con 0, 1, 2 o 3 sustituyentes seleccionados independientemente del grupo integrado por

  a) hidroxilo,

  b) amino,

  c) alquilamino (C_1-C_6), donde alquilamino (C_1-C_6) puede estar sustituido con 0, 1, 2, 3 o 4 sustituyentes seleccionados independientemente del grupo integrado por halógeno, amino, alquilamino, metoxi, metilo y metilsulfonilo,

  e) heterocicilo monocíclico que tiene 5 o 6 átomos de anillo, donde heterocicilo puede estar sustituido con 0, 1 o 2 alquilo (C_1-C_6), donde alquilo (C_1-C_6) puede estar sustituido con 0, 1 o 2 hidroxi, metoxi o piridilo,

  f) imidazolilo,

  h) alcoxi (C_1-C_3) opcionalmente sustituido con fluoro hasta el nivel de perfluoro, o con heterocicio monocíclico que tiene 5 o 6 átomos de anillo, donde heterocicio puede estar opcionalmente sustituido con 0 o 1 alquilo (C_1-C_6),

  i) alcoxi (C_1-C_3)-alcoxi (C_2-C_3), y

j) alcoxi (C_1-C_6)-carbonilo,

k) cicloalquilo (C_3-C_6),

l) ciano,

- cicloalquilamino (C_3-C_6)-carbonilo opcionalmente sustituido con alquilo (C_1-C_3),
- ciano,
- heteroarilo, donde heteroarilo puede estar sustituido con 0, 1, 2, o 3 grupos seleccionados independientemente del grupo integrado por

a) alquilo (C_1-C_6), donde alquilo (C_1-C_6) puede estar sustituido con 0, 1, 2, o 3 halógeno, 0 o 1 heterocicilo monocíclico que tiene 5 o 6 átomos de anillo, 0 o 1 alquilamino, o 0 o 1 hidroxi o metoxi,

b) halógeno,

e) alcoxi (C_1-C_6)-carbonilo, y

f) cicloalquilo (C_3-C_6),

- heteroarilcarbonilo monocíclico que tiene 5 o 6 átomos de anillo,
- heterocicilio monocíclico que tiene 5 o 6 átomos de anillo, donde heterocicilio puede estar sustituido con 0, 1, 2, o 3 grupos seleccionados independientemente del grupo integrado por alquilo (C_1-C_6) y alcoxi (C_1-C_6)-carbonilo; y

R^4 se selecciona del grupo integrado por hidrógeno y halógeno;

o su sal aceptable para uso farmacéutico.

3. El compuesto de la reivindicación 1, donde

R^1 se selecciona del grupo integrado por fenilo, pirazolilo, oxazolilo, isoxazolilo, tiazolilo, piridinilo y pirimidinilo,

donde fenilo, pirazolilo, oxazolilo, isoxazolilo, tiazolilo, piridinilo, y pirimidinilo pueden estar opcionalmente sustituidos con 0, 1, 2, 3 o 4 sustituyentes seleccionados independientemente del grupo integrado por

- alquilo (C_1-C_4), donde alquilo (C_1-C_4) puede estar sustituido con 0, 1, 2 o 3 halógenos,

- alcoxi (C_1-C_3), donde alcoxi (C_1-C_3) pueden estar opcionalmente sustituidos con alquilamino (C_1-C_3),
- halógeno,
- trifluorometilo,
- trifluorometoxi,
- ciclopropilo,
- fenilo opcionalmente sustituido con 1 o 2 halógenos;

R^2 se selecciona del grupo integrado por hidrógeno, fluoro y cloro;

R^3 se selecciona del grupo integrado por

- alquil (C_1-C_6)-carbonilo opcionalmente sustituido con 0, 1, 2, o 3 grupos seleccionados de flúor, cloro, hidroxi, alcoxi (C_1-C_6), *piperazinilo, morfolinilo, pirrolidinilo y piperidinilo,*
- ciclopropilcarbonilo,
- aminocarbonilo,
- alquilamino (C_1-C_6)-carbonilo, donde alquilamino (C_1-C_6)-carbonilo puede estar opcionalmente sustituido con 0, 1, 2 o 3 sustituyentes seleccionados independientemente del grupo integrado por cicloalquilo (C_3-C_6), halógeno, amino, alquilamino (C_1-C_6), hidroxi, alcoxi (C_1-C_6), alcoxi (C_1-C_6)-carbonilo, alquiltio (C_1-C_6), alcoxi (C_1-C_6)-carbonilamino, y metilsulfonilo, y donde alquilamino (C_1-C_6)-carbonilo puede estar opcionalmente sustituido con 0 o 1 hidroxilo, piperazinilo, morfolinilo, pirrolidinilo o piperidinilo, donde piperazinilo, morfolinilo, pirrolidinilo o piperidinilo puede estar opcionalmente sustituido con 0 o 1 alquilo (C_1-C_6), y donde alquilamino (C_1-C_6)-carbonilo puede estar opcionalmente sustituido con 0 o 1 fenilo, donde fenilo puede estar opcionalmente sustituido con 0 o 1 halógeno o alquilo (C_1-C_6),
- heterociclilcarbonilo seleccionado de piperazinilcarbonilo, morfolinilcarbonilo, pirrolidinilcarbonilo o piperidinilcarbonilo, opcionalmente sustituido con 0 o 1 amino, alquilamino (C_1-C_6),

cicloalquilo (C_3-C_8), o alquilo (C_1-C_8), donde alquilo (C_1-C_8) puede estar opcionalmente sustituido con 0 o 1 amino o alquilamino (C_1-C_8),

- alquilo (C_1-C_8) opcionalmente sustituido con 0, 1, 2 o 3 sustituyentes seleccionados independientemente del grupo integrado por

  a) hidroxilo,

  c) alquilamino (C_1-C_8), donde alquilamino (C_1-C_8) puede estar sustituido con 0, 1, 2, 3 o 4 sustituyentes seleccionados independientemente del grupo integrado por halógeno, alquilamino y metoxi,

  e) piperazinilo, morfolinilo, pirrolidinilo o piperidinilo, donde piperazinilo, morfolinilo, pirrolidinilo o piperidinilo puede estar sustituido con 0, 1 o 2 alquilo (C_1-C_8), donde alquilo (C_1-C_8) puede estar sustituido con 0, 1 o 2 hidroxi o metoxi,

  f) imidazolilo,

  h) alcoxi (C_1-C_3) opcionalmente sustituido con fluoro hasta el nivel de perfluoro, o con heterociclo monocíclico que tiene 5 o 6 átomos de anillo, donde heterociclo puede estar opcionalmente sustituido con 0 o 1 alquilo (C_1-C_8),

  i) alcoxi (C_1-C_2)-alcoxi (C_2-C_3), y

  j) alcoxi (C_1-C_8)-carbonilo,

  k) cicloalquilo (C_3-C_8),

  l) ciano,

- cicloalquilamino (C_3-C_8)-carbonilo opcionalmente sustituido con alquilo (C_1-C_3),
- ciano,
- pirazolilo, oxazolilo, isoxazolilo, tiazolilo, isotiazolilo, piridinilo, imidazolilo o pirimidinilo, donde pirazolilo, oxazolilo, isoxazolilo, tiazolilo, isotiazolilo, piridinilo, imidazolilo o pirimidinilo puede

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estar sustituido con 0, 1, 2, o 3 grupos seleccionados independientemente del grupo integrado por

a) alquilo (C_1-C_6), donde alquilo (C_1-C_6) puede estar sustituido con 0, 1, 2, o 3 halógenos, 0 o 1 alquilamino, o 0 o 1 metoxi,

b) halógeno, y

f) cicloalquilo (C_3-C_8),

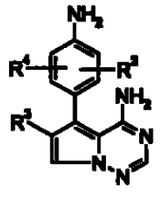
- pirazolilcarbonilo, oxazolilcarbonilo, isoxazolilcarbonilo, tiazolilcarbonilo, piridinilcarbonilo o pirimidinilcarbonilo; y

R^4 se selecciona del grupo integrado por hidrógeno y fluoro;

o su sal aceptable para uso farmacéutico.

4. *Un proceso para preparar un compuesto de la reivindicación 1, donde*

un compuesto de fórmula (II)



(II)

en la cual R^2, R^3 y R^4 tienen el significado indicado en la reivindicación 1,

se hace reaccionar con un compuesto con grupo isocianato de fórmula (III)

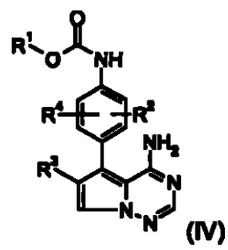
R^1-NCO (III)

o con un carbamato de fórmula (VI)

R^1-NH-C(O)-OPh (VI),

donde R^1 tiene el significado indicado en la reivindicación 1; o

un compuesto de fórmula (IV)



(IV)

en la cual R^1, R^2, R^3 y R^4 tienen el significado indicado en la reivindicación 1, se hace reaccionar con una amina de fórmula (V)

R^1-NH_2 (V),

donde R^1 tiene el significado indicado en la reivindicación 1.

5. Un compuesto de la reivindicación 1 para el tratamiento o prevención de trastornos.
6. Una composición farmacéutica que comprende un compuesto de la reivindicación 1.
7. La composición farmacéutica de la reivindicación 6 en combinación con al menos un excipiente o vehículo seguro y aceptable para uso farmacéutico.
8. Un proceso para preparar la composición farmacéutica de la reivindicación 7, que comprende combinar al menos un compuesto de la reivindicación 1 con al menos un excipiente o vehículo seguro y aceptable para uso farmacéutico, mezclando la combinación y llevando la combinación a una forma de administración adecuada.
9. Un uso del compuesto de la reivindicación 1 para fabricar una composición farmacéutica para el tratamiento de trastornos proliferativos.
10. Una composición farmacéutica de la reivindicación 6 o 7 para el tratamiento o prevención de trastornos proliferativos.
11. Un método para tratar una enfermedad o afección en un mamífero, que comprende la administración a un mamífero que lo necesita de una cantidad terapéuticamente eficaz de un compuesto de fórmula (I).
12. El método de la reivindicación 11, donde la enfermedad o afección es el cáncer.
13. El método de la reivindicación 11, donde dicha cantidad terapéuticamente eficaz de un compuesto de fórmula (I) muestra un efecto sobre la angiogénesis.

p.: BAYER PHARMACEUTICALS CORPORATION

Resumen

La presente invención se refiere a nuevos compuestos con estructura de pirrolotriazina, a composiciones farmacéuticas que contienen tales compuestos y al uso de esos compuestos y composiciones para la prevención y/o tratamiento de trastornos hiper-proliferativos y enfermedades asociadas con la angiogénesis.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/019472

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D487/04 C07D519/00 A61K31/53

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)
IPC 7 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, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00/71129 A (BRISTOL-MYERS SQUIBB COMPANY) 30 November 2000 (2000-11-30) page 1, line 10 - line 14 claim 1	1

☐ Further documents are listed in the continuation of box C.

☒ 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
19 September 2005	26/09/2005

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	Fanni, S

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/019472

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.: 11-13
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 11-13 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US2005/019472

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0071129 A	30-11-2000	AU 770377 B2	19-02-2004
		AU 4852400 A	12-12-2000
		BR 0010482 A	23-04-2002
		CA 2373990 A1	30-11-2000
		CN 1351498 A	29-05-2002
		CZ 20014169 A3	16-10-2002
		EP 1183033 A1	06-03-2002
		HU 0301005 A2	28-07-2003
		JP 2003500359 T	07-01-2003
		MX PA01011832 A	21-06-2002
		NO 20015650 A	20-11-2001
		NZ 516292 A	30-01-2004
		PL 351720 A1	02-06-2003
		TR 200103352 T2	21-03-2005

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
EXTRACTO PARA PUBLICACIÓN
SOLICITUD DE PATENTE DE INVENCIÓN PCTd3

(21) N° de solicitud:

22) Fecha de solicitud:

(30) Prioridad (31) *No. Prioridad* (32) *Fecha* (33) *País*
60/576,852 03/06/04 US
60/626,531 09/11/04 US

(51) Int Cl: C07D 487/004

(71)Solicitante(s) BAYER PHARMACEUTICALS CORPORATION

(72) Inventor(es) JULIE A. DIXON
Y OTROS

(74) Apoderado: EMILIO FERRERO

(85) Fecha límite inicio fase nacional: *03/01/2007*
(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: *03/06/2005*
No. de solicitud PCT/US2005/019472

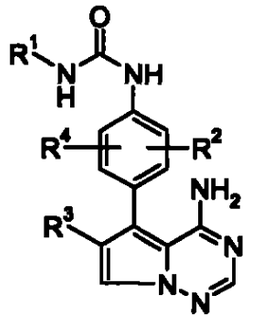
(87) Publicación internacional
Fecha: *22/12/2005*
N° publicación: *WO 2005/121147 A1*

(54) Título: **DERIVADOS DE PIRROLOTRIAZINA ÚTILES PARA TRATAR TRASTORNOS HIPER-PROLIFERATIVOS Y ENFERMEDADES ASOCIADAS CON ANGIOGÉNESIS**

REIVINDICACIONES

Habiendo así especialmente descrito y determinado la naturaleza de la presente invención y la manera cómo la misma ha de ser llevada a la práctica, se declara reivindicar como de propiedad y derecho exclusivo:

1. Un compuesto de fórmula (I)



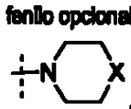
(I),

en la cual

R^1 se selecciona del grupo integrado por arilo, bencilo, y heteroarilo,
donde arilo y heteroarilo pueden estar opcionalmente sustituidos con 0, 1, 2, 3 o 4 sustituyentes seleccionados independientemente del grupo integrado por

- alquilo (C_1-C_4), donde alquilo (C_1-C_4) puede estar sustituido con 0, 1, 2 o 3 halógenos, 0 o 1 heterociclilo, o 0 o 1 alcoxi (C_1-C_3), donde

alcoxi (C_1-C_3) puede estar opcionalmente sustituido con alquilamino (C_1-C_3),

- alcoxi (C_1-C_3), donde alcoxi (C_1-C_3) puede estar opcionalmente sustituido con alquilamino (C_1-C_3),
- halógeno,
- trifluorometilo,
- trifluorometoxi,
- cicloalquilo (C_3-C_6),
- fenilo opcionalmente sustituido con 1 o 2 halógenos,
-  , donde X es CH_2, O, S o NR^{1-1}, y donde R^{1-1} es hidrógeno o alquilo (C_1-C_6),
- nitro,
- ciano,
- alquiltio (C_1-C_3),
- trifluorometiltio,

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-121701- -00000-0000
Fec: 2006-12-01 17:57:59 Dep: 2020 NUECREACIONES
Tra: 11 PATENTES
Act: 379 FASENACIONALI
Act: 411 PRESENTACION Folio: 684

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 06 - 86,289
FECHA : NOVIEMBRE 8 DE 2006

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAG	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	54739450	07/11/2006	47,091,000.00

***** 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._____

COLO 14125 841 0135

689

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-121701- -00000-0000
Fec: 2006-12-01 17:57:32 Dep: 2020 NUECREACIONES
Tra: 11 PATENTEIYII
Cla: 379 FASENACIONALII
Act: 411 PRESENTACION Folios: 684

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 [ ] 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 [ ]

Fdo B
Firma Responsable

Fecha Dic 01/06.

Carrera 13 No. 27-00 Piso 5, 7 y 10
Conmutador: 3 82 08 40
Fax: 350 52 20
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

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REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
FERRERO EMILIO
Apoderado(a) y/o Representante de
BAYER PHARMACEUTICALS CORPORATION

REFERENCIA	Radicación No.	6 121701
	Solicitud internacional	PCT/US2005/019472
	Fecha inicio fase nacional	03/01/2007
	Trámite	11
	Evento	379
	Actuación	430
	Oficio No.	0 0 0 1889

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. Si fuere el caso, el solicitante debe adjuntar la traducción de los anexos del reporte de examen preliminar internacional (Art. 36.2.b) del tratado PCT.

2. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

ALIX CARMENZA ESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 09 FEB. 2007
lerazo