# Industria y Comercio

SUPERINTENDENCIA

Delegatura de Propiedad Industrial

División de Nuevas Creaciones

SOLICITUD

# PATENTE DE INVENCIÓN

21 **EXPEDIENTE No.** 04-76760

54 **TÍTULO** PIRIDINONAS SUSTITUIDAS

51 **CLASIFICACIÓN INTERNACIONAL** A61K 31/4412

71 **SOLICITANTE** PHARMACIA CORPORATION

**DOMICILIO** 700 Chesterfield Parkway west, Chesterfield MISSOURI 63017-1732 EUA

74 **APODERADO** Carlos R Olarte.

22 **BOGOTÁ, D. C.,** 06/08/2004

(FORMA P 10)

04/103

# OLARTE RAISBECK

Industria y Comercio
SUPERINTENDENCIA

SUPERINDUSTRIA Y COMERCIO
Radicacion 04076760 00000000 Folios 1595
Fecha (AMD) 2004-08-06 17 00 00
Tramite 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia 2020 DIVISION DE NUEVAS CREACIONES

**PETITORIO - FORMULARIO UNICO DE SOLICITUD**
**PATENTE PCT**
**ENTRADA EN FASE NACIONAL**

**SOLICITUD DE**

(1) [X] Patente de Invencion [ ] Patente de Modelo de Utilidad

[ ] Capitulo I [X] Capitulo II

**(2) SOLICITANTE (71)**

**Nombre** PHARMACIA CORPORATION
**Direccion** 700 Chesterfield Parkway West, Chesterfield, Missouri 63017-1732 E U A
**Nacionalidad o Domicilio** ESTADOUNIDENSE
**Lugar de Constitucion** Delaware, E U A
**Teléfono** _____ **Fax** _____
**E-mail** _____

**IDENTIFICACI N**
**C C** [ ] **NIT** [ ]
**C E** [ ] **Otro** [ ]
**Cual** _____
**Numero** _____

**REPRESENTANTE O APODERADO**

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**Telefono** 601-7700 **Fax** 601-7799
**E-mail** office@olarteraisbeck com

**IDENTIFICACION**
**C C** [X] **NIT** [ ]
**C E** [ ] **Otro** [ ]
**Cual** _____
**Numero** 79 782 747 Bta
**TP** 74 295

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**Nombre** VER PAGINA ADJUNTA
**Direccion.** VER PACINA ADJUNTA.
**Nacionalidad o Domicilio** VER PAGINA ADJUNTA

(5) **PCT (86)**

Solicitud Internacional No PCT/US03/04634 Fecha Febrero 14, 2003

Publicacion Internacional No WO 03/068230 Fecha Agosto 21 2003

(6) **Titulo (54)** **PIRIDINONAS SUSTITUIDAS**

**Clasificación Internacional (51)** A61K31/4412

| **Prioridad** SI [X] NO [ ] | (33) Pais de Origen | (32) Fecha | (31) Numero de Solicitud |
|---|---|---|---|
| | US | Febrero 14, 2002 | 60/357,029 |
| | US | Diciembre 30, 2002 | 60/436,915 |
| | | | |
| | | | |

(9) **Comprobante de pago No** 60,559 **Fecha** Agosto 3, 2004

## (0) ANEXOS

- [x] Comprobante de pago de la tasa de presentacion de la solicitud
- [ ] Documento que acredita la existencia y representacion legal cuando el solicitante sea persona juridica
- [x] Poderes, si fuere el caso Ver expediente No
- [ ] Documento de cesion del inventor al solicitante o a su causante
- [ ] Declaraciones
- [x] Copia de la solicitud internacional (Resumen, descripcion, reivindicaciones, dibujos)
- [x] Traduccion de la solicitud internacional al castellano (Resumen, descripcion, reivindicaciones, dibujos)
- [x] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA)
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA
- [ ] De ser el caso, copia del contrato de acceso
- [ ] De ser el caso, documento que acredite la licencia o autorizacion de uso de conocimientos tradicionales de las comunidades indigenas
- [ ] De ser el caso, certificado de deposito del material biológico
- [ ] Arte final 12 x 12
- [ ] De ser el caso, informacion sobre otras solicitudes de patente o titulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional
- [x] Otros Busqueda Internacional

## (1) FIGURA CARACTERISTICA

## (2) Solicito la concesion de la patente,

NOMBRE CARLOS R. OLARTE FIRMA

C C 79 782 747 Bta T P 74 295

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

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SUPERINDUSTRIA Y COMERCIO

Radicacion 04076760 00000000 Folios 1595
Fecha (AMD) 2004-08-06 17 00 00
Tramite 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia 2020 DIVISION DE NUEVAS CREACIONES

N T 0000176000-2

RECIBO OFICIAL DE CAJA 04 - 00 559
FECHA AGOSTO 3 DE 2004

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

| DEPOSITANTE | TIPO PAGO | BANCO | CUENTA | No PAGO | FECHA PAGO | Vr PAGO |
|---|---|---|---|---|---|---|
| EDEFRONIK TORRES | CONSIGNACION | BANCO POPULAR | 050-00110-6 | 23200408 | 02/08/2004 | 1 607 000 00 |

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

| CANT | ESTADISTICO | CONCEPTO | TOTAL CONCEPTO |
|---|---|---|---|
| 1 | 50005-01-01 SOLICITUDES | 1 TRAMITES DE SOL DE PATENTE DE IN | 422 000 00 |
| | | TOTAL $ | 422 000 00 |

SON CUATROCIENTOS VEINTIDOS MIL PESOS

RESPONSABLE _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No _____

**TRADUCCION OFICIAL No 04-210**

Efectuada el día 17 de mayo de 2004, de un documento escrito en Inglés, al cual para su identificacion se le estampa el sello de Sergio Andres Rueda Iglesias, Traductor e Intérprete Oficial por Resolución No 0138 del 11 de febrero de 2002 expedida por el Ministerio de Justicia de la Republica de Colombia

---

Traducción Oficial de las autenticaciones notariales y subsiguientes correspondientes a un Poder otorgado por **Pharmacia Corporation** a **Carlos R Olarte**, y/o **James Ian Raisbeck** y/o **Ana Maria Frieri**, documento este que viene en español y se explica por si solo

(Fdo ) Grover F Fuller Jr, Abogado Autorizado

La firma y cargo de Grover F Fuller Jr fueron debidamente certificados por el Notario Publico Petrina Thompson el 4/30/05, quien estampo su firma y sello notarial al respaldo

## *APOSTILLA*

**(Convencion de La Haya del 5 de octubre de 1961)**

1 Pais Distrito de Columbia - Estados Unidos de América

El presente documento publico

2 Fue firmado por Petrina Thompson

3 Que actuó en su calidad de Notario Publico del Distrito de Columbia

4 Lleva el sello del Distrito de Columbia

CONO NOTARIO ... DE ESTE CIRCULO HACE CONSTAR QUE ESTA FOTO ... CONCUERDA CON EL ORIGINAL QUE HE TENIDO A LA VISTA

04 JUN 2004

BOGOTA, D.C. COLOMBIA

SERGIO ANDRES RUEDA IGLESIAS
NOTARIA UNICA (E)

TRADUCTOR E INTERPRETE OFICIAL
ESPAÑOL INGLES / INGLES ESPAÑOL
RESOLUCION No 0138 DE FEBRERO 11 2002
MINISTERIO DE JUSTICIA Y DEL DERECHO

Se certificó

En Washington, D C

El 30 de abril de 2004

Por parte del Secretario del Distrito de Columbia

Bajo el Numero **125758**

Aparece Sello del Distrito de Columbia

Firmado por Sherryl H Newman, Secretario Distrito de Columbia

Es traducción fiel y completa efectuada por

Sergio Andres Rueda Iglesias
C C 80 424 773 de Bogotá

**SERGIO ANDRES RUEDA IGLESIAS**
C C 80 424 773
TRADUCTOR E INTERPRETE OFICIAL
ESPAÑOL INGLES / INGLES ESPAÑOL
RESOLUCION No 0138 DE FEBRERO 11 2002
MINISTERIO DE JUSTICIA Y DEL DERECHO

COMO NOTARIO DEL CIRCULO HAGO CONSTAR QUE LA FOTOCOPIA QUE ANTECEDE ES FIEL AL ORIGINAL QUE HE TENIDO A LA VISTA
04 JUN 2004
BOGOTA D C COLOMBIA
ZULMA NAVARRO DE BAUTISTA
NOTARIA ONCE (11)

8

# APOSTILLE

*(Convention de La Haye du 5 octobre 1961)*

1 *District of Columbia*
*United States of America* PETRINA THOMPSON

2 This public document has been signed by ~~NOTARY PUBLIC IN AND FOR THE DISTRICT OF COLUMBIA~~

3 acting in the capacity of PETRINA THOMPSON, NOTARY PUBLIC IN AND FOR THE DISTRICT OF COLUMBIA

4 bears the seal/stamp of

## CERTIFIED

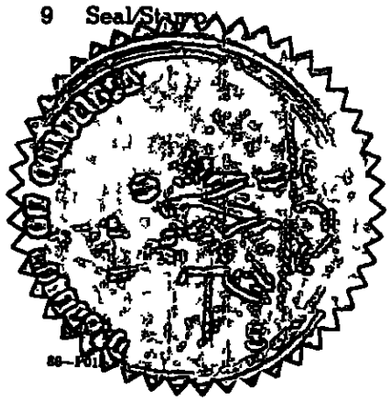
5 at Washington, D C

6 the 30 day of APRIL 2004

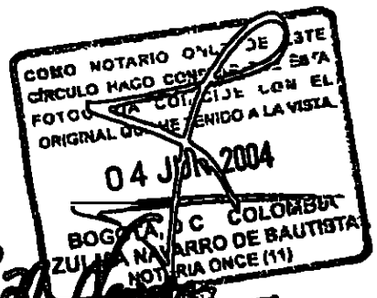
7 by *Secretary of the District of Columbia*

8 No 125758

9 Seal/Stamp



10 Signature




SHERRY H NEWMAN

OLARTERAISBECK

OLARTE RAISBECK & FRIERI, LTDA
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## Power of Attorney

The undersigned

domiciled in

by means of these presents hereby grants to **Carlos R. Olarte, James Ian Raisbeck and/or Ana María Frieri** full and sufficient Power of Attorney to file prosecute, obtain defend and enforce any and all of the company's **Patents, Utility Models, Industrial Designs and Obtainer's Certificates** in the Republic of Colombia, to which end it empowers them to take all steps necessary before any administrative or judicial authority of any class for the objects stated, to file petitions appeals, replies and oppositions, pay taxes and annuities request testimonies, receive documents and securities, abandon applications and collect refunds Sufficient power is hereby granted to receive notifications on behalf of the Company to confer powers on those who are to represent the company judicially and extrajudicially, to answer in court in the matter of all claims and demands that may be presented in connection with the objects stated, giving them likewise power to substitute these presents and revoke such substitutions

## Poder

El suscrito,

PHARMACIA CORPORATION

domiciliado en

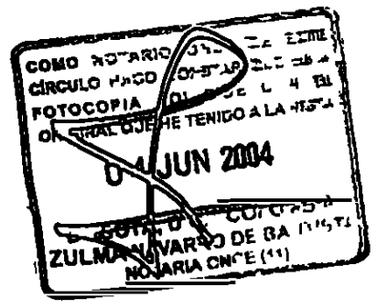
700 Chesterfield Parkway West, Chesterfield, St Louis, MO 63017-1732, Estados Unidos de America

por medio del presente otorga a **Carlos R. Olarte, James Ian Raisbeck y/o Ana Maria Frieri** poder especial amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de **Patentes, Modelos de Utilidad, Diseños Industriales y Certificados de Obtentor** de la compañia en la República de Colombia, a cuyo efecto los faculta para dar todos los pasos necesarios ante cualquier autoridad administrativa o judicial de cualquier jerarquía para cumplir con lo encomendado elevar solicitudes, apelaciones respuestas y oposiciones, pagar impuestos y anualidades solicitar testimonios recibir documentos y valores desistir y percibir Se concede poder bastante para recibir notificaciones a nombre de la compañia, otorgar poderes a quienes vayan a representar a la compañia judicial y extrajudicialmente, responder en juicio a todas las reclamaciones o demandas que por motivo de lo encomendado se presentaren, dandoles asimismo facultad para sustituir el presente y revocar dichas sustituciones

Signature/Firma

Date/Fecha 28 april 2004

City,Country/Ciudad,Pais United State of America



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## Notarial Certification

On this date

The undersigned Notary Public certifies

1 That

Grover F Fuller Jr

of legal age and domiciled in

150 East 42nd Street, New York, NY 10017, U S A

signed the foregoing document

2 That the grantor has executed the foregoing document as Authorized Attorney of Pharmacia Corporation

3 That Pharmacia Corporation, having its principal place of business located in St Louis, Missouri, U S A is duly incorporated, is currently in existence, and that the purposes for which the Power of Attorney is granted are within the scope of its corporate purposes

4 That the grantor has the authority to execute the Power of Attorney and that his/her representation is legal

5 The foundation for my certifications contained in points 2, 3 and 4 was the exhibition of the following authentic document(s) Corporate by laws and Minutes authorizing representation of Mr Grover Fuller

NOTARY PUBLIC (Signature) Grover F. Fuller Jr.

## Certificación Notarial

En esta fecha

el Notario Publico suscrito certifica

1 Que

mayor de edad y domiciliado

suscribió el documento que antecede

2 Que el otorgante ha suscrito el referido documento en su carácter de

de

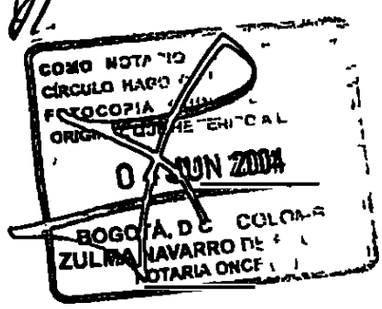
4 Que

con sede principal ubicada en

está legalmente constituida, que tiene existencia legal vigente y que los propósitos para los cuales se otorga el poder se encuentra dentro de los que comprenden su objeto social

4 Que el otorgante tiene la representación para suscribir el poder, y que ésta es legitima

5 El fundamento de mis certificaciones contenidas en los puntos 2, 3 y 4 fue la exhibicion de los (del) siguiente(s) documento(s) autentico(s) Artículos de constitución y minutas autorizando la representación del Sr Grover Fuller.



OLARTERAISBECK
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## INSTRUCTIONS FOR THE POWER OF ATTORNEY

### FILLING OUT THE FORM CORRECTLY

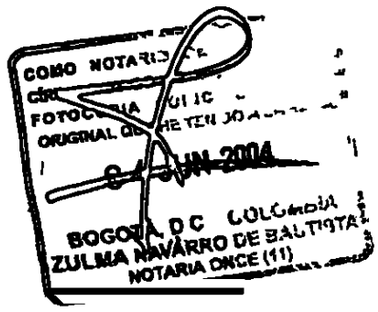
1 The document has TWO (2) pages that must be filled out, the Power of Attorney itself and the Notarial Certification that accompanies it
2 Please substitute all of the text highlighted in yellow (and only that text) with the appropriate information (or substitute it with a blank space if filled in by hand by the person signing the document)
3 We do NOT need copies of the documents you will list in point 5 of the Notarial Certification

### LEGALIZATION

The signature of the corporate official issuing the Power of Attorney should be authenticated by means of a Notarial Certification as the one enclosed herewith The Notary's signature should then be authenticated using one of the following two procedures

1 the Apostille, or
2 if an Apostille is not available or convenient, follow the normal chain of authentication leading to the legalization of the document by the Colombian Consul (the normal chain is that the Notary's signature is authenticated by the Country Clerk, sometimes the Consul legalizes the signature of the Clerk, other times the clerk's signature will first have to be legalized by the Secretary of the respective State)

Please do not hesitate to contact us by telephone or e-mail (filings@olarteraisbeck com) should you have any questions



I HEREBY CERTIFY THAT THIS
IS THE ORIGINAL DOCUMENT

SAMI SWANEK
4/30/04

Subscribed & Sworn
before me on 4/30/05
Petrina Thompson

PETRINA THOMPSON
Notary Public District of Columbia
Commission Expires September 30 2005



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

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International Bureau

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(81) Designated States (national) AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

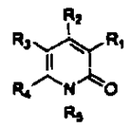
(84) Designated States (regional) ARIPO patent (GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW) Eurasian patent (AM AZ BY KG KZ MD RU TJ TM) European patent (AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT SE SI SK TR) OAPI patent (BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG)

Published
— with international search report

[Continued on next page]

WO 03/068230 A1

(54) Title SUBSTITUTED PYRIDINONES AS MODULATORS OF P38 MAP KINASE




(I)

(57) Abstract Disclosed are compounds of Formula (I) and pharmaceutically acceptable salts thereof wherein $R_1$, $R_2$, $R_3$, $R_4$ and $R_5$ are defined herein These compounds are useful for treating diseases and conditions caused or exacerbated by unregulated p38 MAP kinase and/or TNF activity Pharmaceutical compositions containing the compounds methods of preparing the compounds and methods of treatment using the compounds are also disclosed

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

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

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# SUBSTITUTED PYRIDINONES AS MODULATORS OF P38 MAP KINASE

## Cross Reference to Related Applications

This application claims priority from U S Provisional Application Serial Number 60/357,029, filed February 14, 2002, and U S Provisional Application Serial Number 60/436,915, filed December 30, 2002, the disclosure of each of which is incorporated herein by reference in its entirety

## Background of the invention

### Field of the invention

The instant invention relates to substituted pyridinones that are useful for treating diseases and conditions caused or exacerbated by unregulated p38 MAP kinase activity Pharmaceutical compositions containing the pyridinone compounds, methods of preparing the pyridone compounds and methods of treatment using the compounds are also disclosed

### Description of the Related Art

Numerous cell surface receptors use one or more of the mitogen-activated protein kinase (MAP kinase) cascades during signal transduction MAP kinases are a family of protein-directed serine/threonine kinases that are activated by dual phosphorylation One subgroup of the MAP kinases is p38 MAP kinase, which is activated by a variety of signals including proinflammatory cytokines such as tumor necrosis factor (TNF) and interleukin-1 (IL-1), as well as bacterial lipopolysaccharides and environmental stress such as osmotic shock and ultraviolet radiation (Ono, K and J Han, Cell Signal 12 1, 2000) Within the p38 kinase family, there are four distinct isozymes p38 alpha, p38 beta, p38 gamma, and p38 delta The p38 kinase family function downstream of an activating stimulus by phosphorylating and activating transcription factors (e g ATF2, CHOP and MEF2C) as well as

other kinases (e g MAPKAP-2 and MAPKAP-3) (Trends in Cell biology 7, 353-361, 1997,Mol Cell Biology 19, 21-30, 1999, EMBO J 20, 466-479, 2001) Upon activation, the p38 kinase cascade leads to the induction of gene expression of several factors involved in inflammation and immunity including TNF, interleukin-6, granulocyte-macrophage colony stimulating factor (GM-CSF), and HIV long terminal repeat (Paul et al , Cell Signal 9 403-410, 1997) The products of the p38 phosphorylation stimulate the production of inflammatory cytokines and other proteins, including TNF and IL-1, and cyclooxygenase-2, and also possibly modulate the effects of these cytokines on their target cells, and thus stimulate inflammation processes (Lee, J C et al, Nature, 372 376, 1994)

P38 MAP kinases have also been shown to promote apoptosis during ischemia in cardiac myocytes, which suggests that p38 MAP kinase inhibitors can be used to treat ischemic heart disease (J Biol Chem 274, 6272, 1999) They are also required for T-cell HIV-1 replication and may be useful targets for AIDS therapy P38 pathway inhibitors have been used to increase cancer cell sensitivity to cancer therapy also find use in the treatment of asthma (JPET 293, 281, 2000)

TNF is a cytokine and a potent proinflammatory mediator implicated in inflammatory conditions such as arthritis, asthma, septic shock, non-insulin dependent diabetes mellitus, multiple sclerosis, asthma, and inflammatory bowel disease Thus inhibitors of p38 MAP kinases (required for TNF production) may be useful for the treatment of inflammatory conditions resulting from excessive cytokine production such as arthritis (Boehm, J C and J L Adams, Exp Opin Ther Patents 10 25, 2000, and references cited therein) TNF has also been implicated in viral infections, such as HIV,

influenza virus, and herpes virus including herpes simplex virus type-1 (HSV-1), herpes simplex virus type-2 (HSV-2), cytomegalovirus (CMV), varicella-zoster virus (VZV), Epstein-Barr virus, human herpesvirus-6 (HHV-6), human herpesvirus-7 (HHV-7), human herpesvirus-8 (HHV-8), pseudorabies and rhinotracheitis, among others

Excessive or unregulated TNF production has also been shown to produce elevated levels of IL-1 Inhibition of TNF, therefore, should reduce levels of IL-1 (European Cytokine Netw 6, 225, 1995) and ameliorate disease states caused by unregulated IL-1 synthesis Such disease states include rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, bone resorption diseases, reperfusion injury, graft versus host reaction, alallograft rejections, fever and myalgias due to infection, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), AIDS related complex (ARC), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, and pyresis

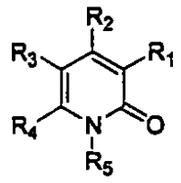
IL-1 has also been shown to mediate a variety of biological activities such as the activation of T-helper cells, induction of fever, stimulation of prostaglandin or collagenase production, neutrophil chemotaxis, and the suppression of plasma iron levels (*Rev Infect Disease*, 6, 51 (1984)) Elevated levels of IL-1 have also been implicated in mediating or exacerbating a number of disease states including rheumatoid arthritis, osteoarthritis, rheumatoid spondylitis, gouty arthritis, inflammatory bowel disease, adult respiratory distress syndrome (ARDS), psoriasis, Crohn's disease,

ulcerative colitis, anaphylaxis, muscle degeneration, cachexia, Reiter's syndrome, type I and type II diabetes, bone resorption diseases, ischemia reperfusion injury, arteriosclerosis, brain trauma, multiple sclerosis, sepsis, septic shock, and toxic shock syndrome Viruses sensitive to TNF inhibition, such as HIV-1, HIV-2, HIV-3, are also affected by IL-1 production In rheumatoid arthritis, both IL-1 and TNF induce collagenase synthesis and ultimately lead to tissue destruction within arthritic joints (*Lymphokine Cytokine Res* (11) 253-256, (1992) and *Clin Exp Immunol* 989 244-250, (1992))

IL-6 is another pro-inflammatory cytokine, which is associated with many conditions including inflammation Consequently, TNF, IL-1 and IL-6 affect a wide variety of cells and tissues and are important inflammatory mediators of a wide variety of disease states and conditions The inhibition of these cytokines by inhibition or modulation of p38 kinase is of benefit in controlling, reducing and alleviating many of these disease states and conditions Therefore, the present invention concerns finding small molecule inhibitors or modulators of p38 kinase and the p38 kinase pathway

## Summary of the Invention

In a broad aspect, the invention provides compounds of Formula I (Embodiment I)



(I)

and pharmaceutically acceptable salts thereof, wherein

$R_1$ is H, halogen, $NO_2$, alkyl, carboxaldehyde, hydroxyalkyl, dihydroxyalkyl, arylalkoxy, arylalkyl, alkenyl, alkynyl, arylalkynyl, -CN, aryl, alkanoyl, alkoxy, alkoxyalkyl, haloalkyl, haloalkoxy, carboxyl, or arylalkanoyl,

wherein the aryl portion of arylalkoxy, arylalkyl, and arylalkanoyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, nitro, CN, haloalkyl, haloalkoxy or $CO_2R$,

wherein the alkyl portion of the alkyl, hydroxyalkyl, dihydroxyalkyl, arylalkoxy, arylalkyl, alkanoyl, alkoxy, alkoxyalkyl and arylalkanoyl groups is unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkoxycarbonyl or $C_3$-$C_7$ cycloalkyl,

$R_2$ is H, OH, halogen, $-OSO_2-(C_1-C_6)$ alkyl, $-OSO_2$-aryl, arylalkoxy, aryloxy, arylthio, arylthioalkoxy, arylalkynyl, alkoxy, aryloxy($C_1$-$C_6$)alkyl, alkyl, alkynyl, $-OC(O)NH(CH_2)_n$aryl, $-OC(O)N(alkyl)(CH_2)_n$aryl, alkoxyalkoxy, dialkylamino, alkyl, alkoxy, aryl, arylalkyl, heteroaryl, heteroarylalkyl, arylalkenyl, heterocycloalkyl, heterocycloalkylalkyl, alkoxyalkoxy, $NR_8R_9$, dialkylamino, or $CO_2R$, wherein

n is 0, 1, 2, 3, 4, 5 or 6,

each of which groups is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, -($C_1$-$C_6$)alkyl-N(R)-$CO_2R_{30}$, haloalkyl, heteroaryl, heteroarylalkyl, -$NR_6R_7$, $R_6R_7N$-($C_1$-$C_6$ alkyl)-, -C(O)$NR_6R_7$, -($C_1$-$C_4$)alkyl-C(O)$NR_6R_7$, -($C_1$-$C_4$ alkyl)-NRC(O)$NR_{16}R_{17}$, haloalkoxy, alkyl, CN, hydroxyalkyl, dihydroxyalkyl, alkoxy, alkoxycarbonyl, phenyl, -$SO_2$-phenyl wherein the phenyl and -$SO_2$-phenyl groups are optionally substituted with 1, 2, or 3 groups that are independently halogen or $NO_2$, or -OC(O)$NR_6R_7$, wherein $R_{16}$ and $R_{17}$ are independently H or $C_1$-$C_6$ alkyl, or

$R_{16}$, $R_{17}$ and the nitrogen to which they are attached form a morpholinyl ring,

$R_6$ and $R_7$ are independently at each occurrence H, alkyl, hydroxyalkyl, dihydroxyalkyl, alkoxy, alkanoyl, arylalkyl, arylalkoxy, alkoxycarbonyl, -$SO_2$-alkyl, OH, alkoxy, alkoxyalkyl, arylalkoxycarbonyl, -($C_1$-$C_4$)alkyl-$CO_2$-alkyl, heteroarylalkyl, or arylalkanoyl, wherein each is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, OH, SH, heterocycloalkyl, heterocycloalkylalkyl, $C_3$-$C_7$ cycloalkyl, alkoxy, $NH_2$, NH(alkyl), N(alkyl)(alkyl), -O-alkanoyl, alkyl, haloalkyl, carboxaldehyde, or haloalkoxy, or

$R_6$, $R_7$, and the nitrogen to which they are attached form a morpholinyl, pyrrolidinyl, thiomorpholinyl, thiomorpholinyl S-oxide, thiomorpholinyl S,S-dioxide, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that

are independently $C_1$-$C_4$ alkyl, alkoxycarbonyl, $C_1$-$C_4$ alkoxy, hydroxyl, hydroxyalkyl, dihydroxyalkyl, or halogen,

R at each occurrence is independently hydrogen or $C_1$-$C_6$ alkyl optionally substituted with 1 or 2 groups that are independently OH, SH, halogen, amino, monoalkylamino dialkylamino or $C_3$-$C_6$ cycloalkyl

$R_{30}$ is $C_1$-$C_6$ alkyl optionally substituted with 1 or 2 groups that are independently OH, SH, halogen, amino, monoalkylamino, dialkylamino or $C_3$-$C_6$ cycloalkyl

each $R_8$ is independently hydrogen, alkyl, alkanoyl, arylalkyl and arylalkanoyl, wherein each of the above is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, alkoxy, alkoxycarbonyl, halogen, or haloalkyl,

each $R_9$ is hydrogen, alkyl, alkanoyl, arylalkyl, cycloalkyl cycloalkylalkyl, alkenyl, heteroaryl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, arylalkanoyl, -$SO_2$-phenyl, and aryl wherein each of the above is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, alkoxy, alkoxycarbonyl, halogen, or haloalkyl,

$R_3$ is H, halogen, alkoxycarbonyl, arylalkoxycarbonyl, aryloxycarbonyl, arylalkyl, -OC(O)NH$(CH_2)_n$aryl, arylalkoxy, -OC(O)N(alkyl)$(CH_2)_n$aryl, aryloxy, arylthio, thioalkoxy, arylthioalkoxy, alkenyl, -$NR_6R_7$, $NR_6R_7$-($C_1$-$C_6$)alkyl, or alkyl, wherein

the aryl portion of arylalkoxycarbonyl, aryloxycarbonyl, arylalkyl, -OC(O)NH$(CH_2)_n$aryl, arylalkoxy, -OC(O)N(alkyl)$(CH_2)_n$aryl, and arylthioalkoxy, is

unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently, halogen, alkoxy, alkyl, haloalkyl, or haloalkoxy,

wherein n is 0, 1, 2, 3, 4, 5, or 6, or

$R_4$ is hydrogen or $R_4$ is alkyl unsubstituted or substituted with one or two groups that are independently $CO_2R$, $-CO_2-(C_1-C_6)$alkyl, $-C(O)NR_6R_7$, $-C(O)R_6$, $-N(R_{30})C(O)NR_{16}R_{17}$, $-N(R_{30})C(O)-(C_1-C_6)$alkoxy, or $-NR_6R_7$, arylalkoxy, arylalkyl, heteroaryl, heteroarylalkyl, hydroxyalkyl, dihydroxyalkyl, haloalkyl, $R_6R_7N-(C_1-C_6$ alkyl)-, $-NR_6R_7$, alkoxy, carboxaldehyde, $-C(O)NR_6R_7$, $CO_2R$, alkoxyalkyl, or alkoxyalkoxy, wherein the heteroaryl or aryl portions of is the above are unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, hydroxy, alkoxy, alkyl, $-CO_2-(C_1-C_6)$alkyl, $-CONR_6R_7$, $-NR_6R_7$, $R_6R_7N-(C_1-C_6)$alkyl-, nitro, haloalkyl, or haloalkoxy, and

$R_5$ is H, aryl, arylalkyl, arylthioalkyl, alkyl optionally substituted with 1, 2, or 3 groups that are independently arylalkoxycarbonyl, $-NR_8R_9$, halogen, $-C(O)NR_8R_9$, alkoxycarbonyl, $C_3-C_7$ cycloalkyl, or alkanoyl, alkoxy, alkoxyalkyl optionally substituted with one trimethylsilyl group, amino, alkoxycarbonyl, hydroxyalkyl, dihydroxyalkyl, alkynyl, $-SO_2$-alkyl, alkoxy optionally substituted with one trimethylsilyl group, heterocycloalkylalkyl, cycloalkyl, cycloalkylalkyl, -alkyl-S-aryl, -alkyl-$SO_2$-aryl, heteroarylalkyl, heterocycloalkyl, heteroaryl, or alkenyl optionally substituted with alkoxycarbonyl, wherein

each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, halogen, alkoxy, hydroxyalkyl, dihydroxyalkyl, arylalkoxy, thioalkoxy, alkoxycarbonyl, arylalkoxycarbonyl, $CO_2R$, CN, OH, hydroxyalkyl,

dihydroxyalkyl, amidinooxime, $-NR_6R_7$, $-NR_8R_9$, $R_6R_7N-(C_1-C_6$ alkyl)-, carboxaldehyde, $SO_2$alkyl, $-SO_2H$, $-SO_2NR_6R_7$, alkanoyl wherein the alkyl portion is optionally substituted with OH, halogen or alkoxy, $-C(O)NR_6R_7$, $-(C_1-C_4$ alkyl)$-C(O)NR_6R_7$ amidino, haloalkyl, $-(C_1-C_4$ alkyl)$-NR_{15}C(O)NR_{16}R_{17}$, $-(C_1-C_4$ alkyl)$-NR_{15}C(O)R_{18}$, $-O-CH_2-O$, $-O-CH_2CH_2-O-$, or haloalkoxy, wherein

$R_{15}$ is H or $C_1-C_6$ alkyl, and

$R_{18}$ is $C_1-C_6$ alkyl optionally substituted with $-O-(C_2-C_6$ alkanoyl, $C_1-C_6$ hydroxyalkyl, $C_1-C_6$ dihydroxyalkyl, $C_1-C_6$ alkoxy, $C_1-C_6$ alkoxy $C_1-C_6$ alkyl, amino $C_1-C_6$ alkyl, mono or dialkylamino $C_1-C_6$ alkyl

The invention also includes the intermediates that are useful in making the compounds of the invention

These compounds bind and/or interact with p38 kinase and/or TNF Preferably, they inhibit the activity of p38 kinase and/or TNF They are therefore used in treating p38 map kinase or TNF mediated disorders Preferably they are used in treating p38 alpha or TNF mediated disorders

The instant invention also includes pharmaceutical compositions comprising at least one compound of formula I and at least one pharmaceutically acceptable carrier, solvent, adjuvant or excipient

The instant invention also includes methods of treating a TNF mediated disorder, a p38 kinase mediated disorder, inflammation and/or arthritis in a subject, the method comprising treating a subject having or susceptible to such disorder or condition with a therapeutically-effective amount of a compound of Formula I

## Detailed Description of the Invention

In a preferred aspect, the invention provides compounds of formula I wherein

when $R_2$ is benzyloxy, $R_3$ is H, $R_4$ is H, and $R_5$ is benzyl or methyl, $R_1$ is not hydrogen,

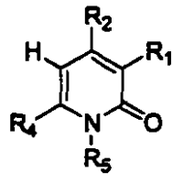
no more than two of $R_1$, $R_2$, $R_4$, and $R_5$ are simultaneously hydrogen,

$R_6$ and $R_7$ are not simultaneously OH,

when $R_2$ is OH, $R_4$ is methyl and $R_5$ is phenyl, $R_1$ is not acetyl, and

$R_4$ and $R_5$ are not simultaneously hydrogen

Embodiment 2 Compounds of the formula




and the pharmaceutically acceptable salts thereof, wherein

$R_1$ is H, halogen, alkyl, carboxaldehyde, hydroxyalkyl, dihydroxyalkyl, arylalkoxy, arylalkyl, alkenyl, alkynyl, arylalkynyl, CN, alkanoyl, alkoxy, alkoxyalkyl, haloalkyl, carboxyl, or arylalkanoyl,

wherein the aryl portion of arylalkoxy, arylalkyl, and arylalkanoyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, nitro, CN, haloalkyl, haloalkoxy or $CO_2R$,

wherein the alkyl portion of the alkyl, hydroxyalkyl, dihydroxyalkyl, arylalkoxy, arylalkyl, alkanoyl, alkoxy, alkoxyalkyl and arylalkanoyl groups is unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkoxycarbonyl, or cyclopropyl,

$R_2$ is H, OH, halogen, $-OSO_2-(C_1-C_3)$ alkyl, $-OSO_2$-aryl, arylalkoxy, aryloxy, arylthioalkoxy, arylalkynyl, alkoxy, phenyloxy$(C_1-C_6)$alkyl, $-OC(O)NH(CH_2)_n$aryl, $-OC(O)N$(alkyl)$(CH_2)_n$aryl, alkyl, alkynyl, alkoxyalkoxy, dialkylamino, heteroaryl, heterocycloalkyl, aryloxyalkyl, or $CO_2R$, wherein

each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, $-NR_6R_7$, haloalkyl, haloalkoxy, alkyl, heteroaryl, heteroarylalkyl, $-(C_1-C_4)$alkyl$-C(O)NR_6R_7$, $R_6R_7N-(C_1-C_6$ alkyl$)-$, $-C(O)NR_6R_7$, $-(C_1-C_4$ alkyl$)-NRC(O)NR_{16}R_{17}$, CN, hydroxyalkyl, dihydroxyalkyl, $-OC(O)NR_6R_7$, or $-(C_1-C_6)$alkyl$-N(R)-CO_2R_{30}$, wherein

$R_{16}$ and $R_{17}$ are independently H or $C_1-C_6$ alkyl, or

$R_{16}$, $R_{17}$ and the nitrogen to which they are attached form a morpholinyl ring,

$R_6$ and $R_7$ are independently at each occurrence H, alkyl, hydroxyalkyl, dihydroxyalkyl, alkoxy, alkoxyalkyl, alkanoyl, arylalkyl, arylalkoxy, arylalkoxycarbonyl, or arylalkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, alkoxy, alkyl, OH, SH, carboxaldehyde, haloalkyl, or haloalkoxy, or

$R_6$, $R_7$, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, thiomorpholinyl S-oxide, thiomorpholinyl S,S-dioxide, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently $C_1-C_4$ alkyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, dihydroxyalkyl, or halogen,

n is 0, 1, 2, 3, 4, 5 or 6,

R at each occurrence is independently H or $C_1$-$C_6$ alkyl optionally substituted with 1 or 2 groups that are independently OH, SH, halogen, amino, monoalkylamino, dialkylamino or $C_3$-$C_6$ cycloalkyl,

$R_{30}$ is $C_1$-$C_6$ alkyl optionally substituted with 1 or 2 groups that are independently OH, SH, halogen, amino, monoalkylamino, dialkylamino or $C_3$-$C_6$ cycloalkyl,

$R_4$ is H, alkyl optionally substituted with one or two groups that are independently $CO_2R$, $-CO_2$alkyl, $-C(O)NR_6R_7$, $-C(O)R_6$, $-N(R_{30})C(O)NR_{16}R_{17}$, $-N(R_{30})C(O)-(C_1-C_6)$alkoxy, or $-NR_6R_7$, arylalkoxy, heteroaryl, arylalkyl, hydroxyalkyl, dihydroxyalkyl, haloalkyl, $-NR_6R_7$, $-C(O)NR_6R_7$, alkoxy, alkoxyalkyl, or alkoxyalkoxy, wherein the heteroaryl or aryl portions of the above are unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, hydroxy, alkoxy, alkyl, $-CO_2-(C_1-C_6)$alkyl, $-CONR_6R_7$, $-NR_6R_7$, $R_6R_7N-(C_1-C_6)$alkyl-, nitro, haloalkyl, or haloalkoxy, and

$R_5$ is H, arylalkyl, alkyl optionally substituted with 1, 2, or 3 groups that are independently arylalkoxycarbonyl, $-NR_8R_9$, halogen, $-C(O)NR_8R_9$, alkoxycarbonyl, or alkanoyl, alkoxyalkyl optionally substituted with one trimethylsilyl group, alkoxycarbonyl, amino, hydroxyalkyl, dihydroxyalkyl, alkenyl optionally substituted with alkoxycarbonyl, alkynyl, $-SO_2$-alkyl, aryl, alkoxy optionally substituted with one trimethylsilyl group, heterocycloalkylalkyl, heteroarylalkyl, heterocycloalkyl, or heteroaryl, wherein each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl,

halogen, alkoxy, arylalkoxy, hydroxyalkyl, dihydroxyalkyl, thioalkoxy, -$SO_2$alkyl, alkoxycarbonyl, arylalkoxycarboryl, $CO_2R$, CN, On, amidinooxime, $NR_8R_9$, $R_6R_7N$-($C_1$-$C_6$ alkyl)-, -$C(O)NR_6R_7$, amidino, hydroxyalkyl, dihydroxyalkyl, carboxaldehyde, -$NR_6R_7$, haloalkyl, -($C_1$-$C_4$ alkyl)-$C(O)NR_6R_7$, -($C_1$-$C_4$ alkyl)-$CO_2R$, -($C_1$-$C_4$ alkyl)-$C_1$-$C_6$ alkoxycarbonyl, -($C_1$-$C_4$ alkyl)-CN, -($C_1$-$C_4$ alkyl)-$NR_{15}C(O)R_{18}$, -O-$CH_2$-O-, -O-$CH_2CH_2$-O-, phenyl or haloalkoxy,

$R_8$ is hydrogen, alkyl, alkanoyl, arylalkyl and arylalkanoyl,

$R_9$ is alkyl, alkanoyl, arylalkyl, heteroaryl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, and arylalkanoyl

Embodiment 3 Compounds according to embodiment 2 wherein

$R_1$ is H, halogen, alkyl optionally substituted with $C_1$-$C_4$ alkoxycarbonyl, carboxaldehyde, hydroxyalkyl, dihydroxyalkyl, phenyl($C_1$-$C_6$)alkoxy, phenyl($C_1$-$C_6$)alkyl, CN, alkanoyl, alkoxy, $C_2$-$C_4$ alkynyl, $C_2$-$C_6$ alkenyl optionally substituted with $C_1$-$C_4$ alkoxycarbonyl, alkoxyalkyl, haloalkyl, or phenyl($C_1$-$C_6$)alkanoyl,

wherein the phenyl groups are unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, nitro, CN, $CF_3$, $OCF_3$ or $CO_2R$,

wherein the alkyl groups are unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, methoxy, or ethoxy,

$R_2$ is OH, phenyl($C_1$-$C_6$)alkoxy, phenyloxy, phenyloxy($C_1$-$C_6$)alkyl, phenyl ($C_1$-$C_4$) thioalkoxy, $C_1$-$C_8$ alkoxy, alkoxyalkoxy, -O-

$SO_2$phenyl, alkynyl, phenyl $(C_2-C_4)$ alkynyl, alkyl, $-OC(O)NH(CH_2)_n$phenyl, $-OC(O)N(alkyl)(CH_2)_n$phenyl, dialkylamino, pyridyl, pyrimidyl, pyridazyl, pyrazolyl, imidazolyl, pyrrolyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, tetrazolyl, pyrazinyl, benzimidazolyl, triazinyl, tetrahydrofuryl, piperidinyl, hexahydropyrimidinyl, thiazolyl, thienyl, or $CO_2R$, wherein n is 0, 1, 2, 3, 4, 5 or 6,

each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, $NR_6R_7$, haloalkyl, haloalkoxy, hydroxyalkyl, dihydroxyalkyl, alkyl, phenyl, pyridyl, piperidinyl, piperazinyl, $-(C_1-C_6)alkyl-N(R)-CO_2R_{30}$, $R_6R_7N-(C_1-C_6$ alkyl)-, $-C(O)NR_6R_7$, $-(C_1-C_4)alkyl-C(O)NR_6R_7$, $-(C_1-C_4$ alkyl)$-NRC(O)NR_{16}R_{17}$, or $-OC(O)NR_6R_7$, wherein

$R_6$ and $R_7$ are independently at each occurrence H, alkyl, $(C_1-C_4)$ hydroxyalkyl, $(C_1-C_4)$ dihydroxyalkyl, $(C_1-C_4)$ alkoxy, $(C_1-C_4)$ alkoxy $(C_1-C_4)$ alkyl, $(C_1-C_4)$ alkanoyl, phenyl $(C_1-C_4)$ alkyl, phenyl $(C_1-C_4)$ alkoxy, phenyl $(C_1-C_4)$ alkoxycarbonyl, or phenyl $(C_1-C_4)$ alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, OH, SH, $C_3-C_6$ cycloalkyl, $(C_1-C_4)$ alkoxy, $(C_1-C_4)$ alkyl, $CF_3$, carboxaldehyde, $NH_2$, $NH(C_1-C_6)alkyl$, $N(C_1-C_6)alkyl$ $(C_1-C_6)alkyl$, $OCF_3$, or

$R_6$, $R_7$, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently $C_1-C_4$ alkyl, hydroxy, hydroxy $C_1-C_4$ alkyl, $C_1-C_4$

dihydroxyalkyl, $C_1$-$C_4$ alkoxycarbonyl, or halogen, and

$R_4$ is H, alkyl optionally substituted with one or two groups that are independently $CO_2R$, $-CO_2$alkyl, $-C(O)NR_6R_7$, $-C(O)R_6$, $-N(R_{30})C(O)NR_{16}R_{17}$, $-N(R_{30})C(O)-(C_1-C_6)$alkoxy, or $-NR_6R_7$, $-C(O)NR_6R_7$, phenyl$(C_1-C_6)$alkoxy, phenyl$(C_1-C_6)$alkyl, hydroxyalkyl, dihydroxyalkyl, haloalkyl, alkoxy, alkoxyalkyl, or alkoxyalkoxy, wherein

the phenyl groups are unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, hydroxy, alkoxy, alkyl, nitro, $CF_3$, $OCF_3$,

$R_5$ is phenyl$(C_1-C_6)$alkyl, $(C_1-C_6)$alkyl optionally substituted with 1, 2, 3, 4, or 5 groups that are independently phenyl $C_1$-$C_4$ alkoxycarbonyl, $-NR_8R_9$, halogen, $-C(O)NR_8R_9$, alkoxycarbonyl, or alkanoyl, phenyl, alkoxy, $C_2$-$C_6$ alkynyl, $C_2$-$C_6$ alkenyl optionally substituted with alkoxycarbonyl, indolyl, quinolinyl, isoquinolinyl, isoindolyl, dihydroindolyl, pyrazolyl, imidazolyl, dihydroisoindolyl, indolon-2-yl, indazolyl, benzimidazolyl, pyridyl, imidazolidine dione, pyrazolyl$(C_1-C_6$ alkyl), imidazolyl$(C_1-C_6$ alkyl), piperidinyl$(C_1-C_6)$alkyl, pyrrolidinyl$(C_1-C_6)$alkyl, imidazolidinyl$(C_1-C_6)$alkyl, tetrahydroisoquinolinyl$(C_1-C_6)$alkyl, 1H-indazolyl$(C_1-C_6)$alkyl, dihydroindolon-2-yl$(C_1-C_6$ alkyl), indolinyl$(C_1-C_6$ alkyl), dihydrobenzimidazolyl$(C_1-C_6$ alkyl), or dihydrobenzoimidazolonyl$(C_1-C_6$ alkyl), pyridyl $(C_1-C_6)$ alkyl, pyridazinyl $(C_1-C_6)$ alkyl, pyrimidinyl $(C_1-C_6)$ alkyl, pyrazinyl $(C_1-C_6)$ alkyl, tetrahydrofuryl$(C_1-C_6)$alkyl, naphthyl$(C_1-C_6)$alkyl, morpholinyl $(C_1-C_6)$ alkyl, tetrahydrofuryl $(C_1-C_6)$ alkyl, thienyl $(C_1-C_6)$ alkyl, piperazinyl $(C_1-C_6)$ alkyl, indolyl $(C_1-C_6)$ alkyl, quinolinyl$(C_1-C_6)$ alkyl, isoquinolinyl$(C_1-C_6)$ alkyl,

isoindolyl($C_1$-$C_6$) alkyl, dihydroindolyl($C_1$-$C_6$) alkyl, pyrazolyl($C_1$-$C_4$) alkyl, imidazolyl($C_1$-$C_4$) alkyl, dihydroisoindolyl($C_1$-$C_6$) alkyl, indoon-2-yl($C_1$-$C_6$) alkyl, indolon-2-yl($C_1$-$C_6$) alkyl, or morpholinyl $C_1$-$C_6$ alkyl, wherein

each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently $C_1$-$C_6$ alkyl, halogen, $C_1$-$C_6$ alkoxy, phenyl $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ thioalkoxy, $C_1$-$C_6$ alkoxycarbonyl, $CO_2R$, CN, -$SO_2$($C_1$-$C_6$)alkyl, amidinooxime, $NR_8R_9$, -$NR_6R_7$, $NR_6R_7$ $C_1$-$C_6$ alkyl, -C(O)$NR_6R_7$, -($C_1$-$C_4$)alkyl-C(O)$NR_6R_7$, amidino, $C_1$-$C_4$ haloalkyl, hydroxy $C_1$-$C_6$ alkyl, $C_1$-$C_6$ dihydroxyalkyl, or $C_1$-$C_4$ haloalkoxy, wherein

$R_8$ is hydrogen, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkanoyl, phenyl $C_1$-$C_6$ alkyl and phenyl $C_1$-$C_6$ alkanoyl, and

$R_9$ is aminoalkyl, mono $C_1$-$C_6$ alkylamino $C_1$-$C_6$ alkyl, di $C_1$-$C_6$ alkylamino $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkanoyl, phenyl $C_1$-$C_6$ alkyl, indazolyl, and phenyl $C_1$-$C_6$ alkanoyl

Embodiment 4 Compounds according to embodiment 3, wherein

$R_1$ is H, halogen, $C_1$-$C_4$ alkyl optionally substituted with $C_1$-$C_4$ alkoxycarbonyl, $C_2$-$C_4$ alkenyl optionally substituted with $C_1$-$C_4$ alkoxycarbonyl, $C_2$-$C_4$ alkynyl, or carboxaldehyde,

$R_2$ is benzyloxy, OH, phenyloxy, phenyloxy($C_1$-$C_6$)alkyl, phenyl ($C_1$-$C_4$) thioalkoxy, or pyridyl, wherein each of the above is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, -($C_1$-$C_6$)alkyl-N(R)-$CO_2R_{30}$, $NR_6R_7$, -($C_1$-$C_4$)alkyl-C(O)$NR_6R_7$, ($C_1$-$C_4$) haloalkyl, -C(O)$NR_6R_7$, -($C_1$-$C_4$ alkyl)-NRC(O)$NR_{16}R_{17}$, ($C_1$-$C_4$) haloalkoxy, hydroxyalkyl, $C_1$-$C_6$ dihydroxyalkyl, ($C_1$-$C_6$) alkyl, pyridyl, or $R_6R_7N$-($C_1$-$C_6$ alkyl)-

Embodiment 4a Compounds according to embodiment 4, wherein $R_1$ is H

Embodiment 4b Compounds according to embodiment 4, wherein $R_1$ is halogen

Embodiment 4c Compounds according to embodiment 4, wherein $R_1$ is $C_1$-$C_4$ alkyl optionally substituted with $C_1$-$C_4$ alkoxycarbonyl

Embodiment 5 Compounds according to embodiment 4, wherein $R_5$ is indolyl, pyridyl, pyridazinyl, pyrimidinyl, indazolyl, tetrahydroquinolyl, tetrahydroisoquinolyl, pyrazolyl, imidazolyl, furanyl, quinolinyl, isoquinolinyl, isoindolyl, dihydroindolyl, dihydroisoindolyl, indolon-2-yl, or pyrazinyl, each of which is unsubstituted or substituted with 1, 2, 3, 4 or 5 groups that are independently $C_1$-$C_4$ alkyl, halogen, $CF_3$, $OCF_3$, $-CO_2CH_3$, $C_1$-$C_4$ hydroxyalkyl, dihydroxyalkyl, $C_1$-$C_4$ alkoxy, $-CO_2(C_1$-$C_5$ alkyl), benzyloxy, $-NR_6R_7$, $-(C_1$-$C_4)$alkyl-$C(O)NR_6R_7$, $-NR_8R_9$, $NR_6R_7$-($C_1$-$C_4$ alkyl), $-C(O)NR_6R_7$, or amidinooxime, wherein

$R_6$ and $R_7$ are independently at each occurrence H, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ dihydroxyalkyl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkoxy $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkanoyl, phenyl $C_1$-$C_4$ alkyl, phenyl $C_1$-$C_4$ alkoxy, or phenyl $C_1$-$C_4$ alkanoyl, wherein each is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, OH, SH, $C_3$-$C_6$ cycloalkyl, aryl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkyl, OH, $CF_3$, or $OCF_3$, or

$R_6$, $R_7$, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently $C_1$-$C_4$

alkyl, hydroxy, hydroxy $C_1$-$C_4$ alkyl, $C_1$-$C_4$ dihydroxyalkyl, or halogen

Embodiment 6 Compounds according to embodiment 5, wherein

$R_5$ is indolyl, pyridyl, pyrimidinyl, pyrazolyl, furanyl, indazolyl, dihydroindolyl, dihydroisoindolyl, indolon-2-yl, or pyrazinyl, each of which is unsubstituted or substituted with 1, 2, 3, or 4 groups that are independently $C_1$-$C_4$ alkyl, halogen, $CF_3$, $OCF_3$, $-CO_2CH_3$, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ dihydroxyalkyl, $C_1$-$C_4$ alkoxy, $-CO_2(C_1$-$C_5$ alkyl), benzyloxy, $-C(O)NR_6R_7$, $-NR_8R_9$, $-(C_1$-$C_4)$alkyl-$C(O)NR_6R_7$, $-NR_6R_7$, $NR_6R_7$-$(C_1$-$C_4$ alkyl)-, and amidinooxime

Embodiment 7 Compounds according to embodiment 6, wherein

$R_5$ is indolyl, pyridyl, pyrimidinyl, dihydroindolyl, dihydroisoindolyl, pyrazolyl, or pyrazinyl, each of which is unsubstituted or substituted with 1, 2, 3, or 4 groups that are independently $C_1$-$C_4$ alkyl, halogen, $CF_3$, $OCF_3$, $-CO_2CH_3$, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ dihydroxyalkyl, $C_1$-$C_4$ alkoxy, $-CO_2(C_1$-$C_5$ alkyl), benzyloxy, $-C(O)NR_6R_7$, $NR_8R_9$, $-(C_1$-$C_4)$alkyl-$C(O)NR_6R_7$, $-NR_6R_7$, $NR_6R_7$-$(C_1$-$C_4$ alkyl)-, or amidinooxime, wherein

$R_6$ and $R_7$ are independently at each occurrence H, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ dihydroxyalkyl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkanoyl, $C_1$-$C_4$ alkoxy $C_1$-$C_4$ alkyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently halogen, OH, SH, $C_3$-$C_6$ cycloalkyl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkyl, OH, $CF_3$, or $OCF_3$

Embodiment 8 Compounds according to embodiment 7, wherein

$R_5$ is indolyl, pyridyl, pyrimidinyl, dihydroindolyl, dihydroisoindolyl, pyrazolyl, or pyrazinyl, each of which is unsubstituted or substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkyl, halogen, $CF_3$, $OCF_3$, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ dihydroxyalkyl, $C_1$-$C_4$ alkoxy, $-C(O)NR_6R_7$, $-(C_1$-$C_4)$alkyl-$C(O)NR_6R_7$, $NR_8R_9$, $-NR_6R_7$, or $NR_6R_7$-$(C_1$-$C_4$ alkyl)-, wherein

$R_6$ and $R_7$ are independently at each occurrence H, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ dihydroxyalkyl, $C_1$-$C_4$ alkanoyl, or $C_1$-$C_4$ alkoxy, each of which is optionally substituted with 1, 2, or 3 groups that are independently halogen, OH, SH, $C_3$-$C_6$ cycloalkyl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkyl, OH, $CF_3$, or $OCF_3$

Embodiment 9 Compounds according to embodiment 4, wherein

$R_5$ is phenyl, phenyl$(C_1$-$C_6)$alkyl, or $(C_1$-$C_6)$alkyl, wherein

each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, halogen, alkoxy, benzyloxy, hydroxyalkyl, dihydroxyalkyl, thioalkoxy, $-CO_2(C_1$-$C_5$ alkyl), $CO_2R$, CN, amidinooxime, $-NR_8R_9$, $-NR_6R_7$, $R_6R_7N$-$(C_1$-$C_6$ alkyl)-, $-C(O)NR_6R_7$, $-(C$-$C_4)$alkyl-$C(O)NR_6R_7$, amidino, $CF_3$, or $OCF_3$,

$R_8$ is hydrogen, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkanoyl, phenyl $C_1$-$C_6$ alkyl and phenyl $C_1$-$C_6$ alkanoyl, and

$R_9$ is aminoalkyl, mono $C_1$-$C_6$ alkylamino $C_1$-$C_6$ alkyl, di $C_1$-$C_6$ alkylamino $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkanoyl, phenyl $C_1$-$C_4$ alkyl, indazolyl, and phenyl $C_1$-$C_4$ alkanoyl

Embodiment 10 Compounds according to embodiment 4, wherein

$R_5$ is phenyl, phenyl($C_1$-$C_6$)alkyl, which is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, halogen, alkoxy, benzyloxy, thioalkoxy, -$CO_2$($C_1$-$C_5$ alkyl), $CO_2R$, CN, amidinooxime, -$NR_8R_9$, -$NR_6R_7$, $R_6R_7N$-($C_1$-$C_6$ alkyl)-, $R_6R_7NC(O)$-($C_1$-$C_4$ alkyl)-, $R_6R_7NC(O)$-($C_5$-$C_6$ alkyl)-, -$C(O)NR_6R_7$, amidino, $CF_3$, or $OCF_3$, wherein

$R_6$ and $R_7$ are independently at each occurrence H, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ dihydroxyalkyl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkoxy $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkanoyl, phenyl $C_1$-$C_4$ alkyl, phenyl $C_1$-$C_4$ alkoxy, or phenyl $C_1$-$C_4$ alkanoyl, wherein each is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, OH, SH, $C_3$-$C_6$ cycloalkyl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkyl, $CF_3$, or $OCF_3$, or

$R_6$, $R_7$, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently $C_1$-$C_4$ alkyl, hydroxy, hydroxy $C_1$-$C_4$ alkyl, $C_1$-$C_4$ dihydroxyalkyl, or halogen,

$R_8$ is hydrogen, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkanoyl, phenyl $C_1$-$C_6$ alkyl and phenyl $C_1$-$C_6$ alkanoyl, and

$R_9$ is aminoalkyl, mono $C_1$-$C_6$ alkylamino $C_1$-$C_6$ alkyl, di $C_1$-$C_6$ alkylamino $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkanoyl, phenyl $C_1$-$C_4$ alkyl, indazolyl, and phenyl $C_1$-$C_4$ alkanoyl

Embodiment 11 Compounds according to embodiment 10, wherein

$R_5$ is phenyl, benzyl or phenethyl, wherein each is optionally substituted with 1, 2, 3, 4, or 5 groups that are

independently $C_1$-$C_6$ alkyl, $-NR_6R_7$, $-C(O)NR_6R_7$ $-(C_1$-$C_4$ alkyl)$-C(O)NR_6R_7$, $-NR_8R_9$ halogen, $C_1$-$C_6$ alkoxy, $CO_2R$, $-(C_1$-$C_4$ alkyl)$-CO_2R$, $C_1$-$C_6$ thioalkoxy, amidinooxime, $C_1$-$C_6$ alkoxycarbonyl, $-(C_1$-$C_4$ alkyl)$-C_1$-$C_6$ alkoxycarbonyl, $C_1$-$C_6$ hydroxyalkyl, $C_2$-$C_6$ dihydroxyalkyl, $-(C_1$-$C_4$ alkyl)$-CN$, CN, phenyl $C_1$-$C_6$ alkoxy, OH, $C_1$-$C_4$ haloalkyl, $C_1$-$C_4$ haloalkoxy, $R_6R_7N-(C_1$-$C_6$ alkyl)-, $-(C_1$-$C_4$ alkyl)$-NR_5C(O)R_{18}$, amidinooxime, $-SO_2(C_1$-$C_6$ alkyl), $-O-CH_2-O-$, $-O-CH_2CH_2-O-$, phenyl $C_1$-$C_4$ alkoxy, or phenyl, wherein

$R_6$ and $R_7$ are independently at each occurrence H, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ dihydroxyalkyl, $C_1$-$C_4$ alkanoyl, or $C_1$-$C_4$ alkoxy, each of which is optionally substituted with 1, 2, or 3 groups that are independently halogen, OH, SH, $C_3$-$C_6$ cycloalkyl, $C_1$-$C_4$ alkoxy, $C_1$ $C_4$ alkyl, OH, $CF_3$, or $OCF_3$

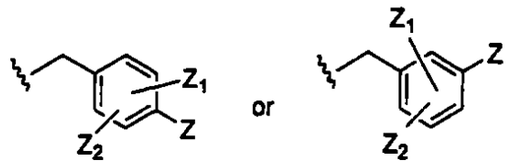
Embodiment 12 Compounds according to embodiment 11, wherein

$R_5$ is phenyl, benzyl or phenethyl, each of which is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently CN, halogen, $C_1$-$C_4$ alkoxy, $CF_3$, $OCF_3$, $C_1$-$C_4$ alkyl, $-NR_8R_9$, $-NR_6R_7$, $R_6R_7N-(C_1$-$C_6$ alkyl)-, or $-C(O)NR_6R_7$, wherein

$R_6$ and $R_7$ are independently at each occurrence H, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ dihydroxyalkyl, $C_1$-$C_4$ alkanoyl, or $C_1$-$C_4$ alkoxy, each of which is optionally substituted with 1, 2, or 3 groups that are independently halogen, OH, SH, $C_3$-$C_6$ cycloalkyl, $C_1$-$C_4$ alkoxy, $C_1$ $C_4$ alkyl, OH, $CF_3$, or $OCF_3$

Embodiment 13 Compounds according to embodiment 4, wherein

the $R_5$ group is of the formula



wherein

$Z_1$ and $Z_2$ are independently H, halogen, $C_1$-$C_4$ alkyl, or $CO_2R$, and

Z is $-C(O)NR_6R_7$ $-(C_1-C_4)alkyl-C(O)NR_6R_7$, $-(C_1-C_4$ alkyl)-$NR_{15}C(O)R_{18}$, $-NR_6R_7$, $R_6R_7N-(C_1-C_6$ alkyl)-, $-NR_8R_9$, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ dihydroxyalkyl, $C_1$-$C_6$ alkyl, $CO_2R$, or halogen, wherein

$R_6$ and $R_7$ at each occurrence are independently H, OH, $C_1$-$C_6$ alkyl, amino $C_1$-$C_4$ alkyl, $NH(C_1-C_6$ alkyl)alkyl, $N(C_1-C_6$ alkyl)$(C_1-C_6$ alkyl) $C_1$-$C_6$ alkyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ dihydroxyalkyl, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, or $-SO_2(C_1-C_6$ alkyl) each of which is optionally substituted with 1, 2, or 3 groups that are independently halogen, OH, SH, $C_3$-$C_6$ cycloalkyl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkyl, OH, $CF_3$, or $OCF_3$,

or

$R_6$, $R_7$, and the nitrogen to which they are attached form a piperidinyl, pyrrolidinyl, piperazinyl, or a morpholinyl, thiomorpholinyl, ring optionally substituted with 1 or 2 groups that are independently alkyl, hydroxy, hydroxy $C_1$-$C_4$ alkyl, $C_1$-$C_4$ dihydroxyalkyl, or halogen, and

$R_{18}$ is $C_1$-$C_6$ alkyl optionally substituted with $-O-(C_2-C_6$ alkanoyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_4$ dihydroxyalkyl, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, amino $C_1$-$C_6$ alkyl, mono or dialkylamino $C_1$-$C_6$ alkyl

Embodiment 14 Compounds according to embodiment 4, wherein

$R_5$ is pyrazolyl($C_1$-$C_6$ alkyl), imidazolyl($C_1$-$C_6$ alkyl), thienyl($C_1$-$C_6$ alkyl), furanyl($C_1$-$C_6$ alkyl), piperidinyl($C_1$-$C_6$)alkyl, pyrrolidinyl($C_1$-$C_6$)alkyl, imidazolidinyl($C_1$-$C_6$)alkyl piperazinyl($C_1$-$C_6$)alkyl, pyridyl($C_1$-$C_6$)alkyl, pyrimidyl($C_1$-$C_6$)alkyl, pyridazyl($C_1$-$C_6$)alkyl, pyrazinyl($C_1$-$C_6$)alkyl, isoquinolinyl($C_1$-$C_6$)alkyl, tetrahydroisoquinolinyl($C_1$-$C_6$)alkyl, indolyl($C_1$-$C_6$)alkyl, 1H-indazolyl($C_1$-$C_6$)alkyl, dihydroindolyl($C_1$-$C_6$ alkyl), dihydroindolon-2-yl($C_1$-$C_6$ alkyl), indolinyl($C_1$-$C_6$ alkyl), dihydroisoindolyl($C_1$-$C_6$ alkyl), dihydrobenzimdazolyl($C_1$-$C_6$ alkyl), or dihydrobenzoimidazolonyl($C_1$-$C_6$ alkyl), wherein each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently ($C_1$-$C_6$)alkyl, halogen, ($C_1$-$C_6$)alkoxy, ($C_1$-$C_6$)hydroxyalkyl, $C_1$-$C_6$ dihydroxyalkyl, phenyl($C_1$-$C_6$)alkoxy, ($C_1$-$C_6$)thioalkoxy, ($C_1$-$C_6$)alkoxycarbonyl, phenyl($C_1$-$C_6$)alkoxycarbonyl, OH, $CO_2R$, CN, amidinooxime, $-NR_8R_9$, $-NR_6R_7$, $R_6R_7N$-($C_1$-$C_6$ alkyl)-, $-C(O)NR_6R_7$, -($C_1$-$C_4$ alkyl)-$C(O)NR_6R_7$ amidino, piperazinyl, morpholinyl, $-SO_2$ ($C_1$-$C_6$) alkyl, $-SO_2NH_2$, $-SO_2NH(C_1$-$C_6)$alkyl, $-SO_2N(C_1$-$C_6)$alkyl ($C_1$-$C_6$)alkyl, ($C_1$-$C_4$)haloalkyl, -($C_1$-$C_4$ alkyl)-$NR_{15}C(O)NR_{16}R_{17}$, -($C_1$-$C_4$ alkyl)-$NR_{15}C(O)R_{18}$, $-O-CH_2-O$, $-O-CH_2CH_2-O$-, or ($C_1$-$C_4$)haloalkoxy, wherein $R_6$ and $R_7$ are independently at each occurrence H, ($C_1$-$C_6$)alkyl, ($C_1$-$C_6$)alkoxy, ($C_1$-$C_6$)alkoxy($C_1$-$C_6$)alkyl, ($C_1$-$C_6$)alkoxycarbonyl, ($C_1$-$C_6$)hydroxyalkyl, $C_1$-$C_6$ dihydroxyalkyl, -($C_1$-$C_4$)alkyl-$CO_2$-($C_1$-$C_6$)alkyl, ($C_1$-$C_6$)alkanoyl, phenyl($C_1$-$C_6$)alkyl, phenyl($C_1$-$C_6$)alkoxy, or phenyl($C_1$-$C_6$)alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, ($C_1$-$C_4$)alkoxy, OH, SH, $C_3$-$C_6$ cycloalkyl, $NH_2$, NH($C_1$-

$C_6$ alkyl), N($C_1$-$C_6$ alkyl)($C_1$-$C_6$ alkyl), ($C_1$-$C_4$)alkyl, $CF_3$ or $OCF_3$, or

$R_6$, $R_7$, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently $C_1$-$C_4$ alkyl, hydroxy, hydroxy $C_1$-$C_4$ alkyl, $C_1$-$C_4$ dihydroxyalkyl, or halogen, and

$R_{18}$ is $C_1$-$C_6$ alkyl optionally substituted with -O-($C_2$-$C_6$ alkanoyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ dihydroxyalkyl, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, amino $C_1$-$C_6$ alkyl, mono or dialkylamino $C_1$-$C_6$ alkyl

In this embodiment, it is preferred that $R_6$ and $R_7$ are not simultaneously OH, and

$R_6$ and $R_7$ are not simultaneously -$SO_2$($C_1$-$C_6$ alkyl)

Embodiment 15 Compounds according to embodiment 14, wherein

$R_5$ is pyrazolyl($C_1$-$C_6$ alkyl), imidazolyl($C_1$-$C_6$ alkyl), benzimidazolyl($C_1$-$C_6$ alkyl), thienyl($C_1$-$C_6$ alkyl), pyrimidyl($C_1$-$C_6$)alkyl, indolyl($C_1$-$C_6$ alkyl), dihydroindolyl($C_1$-$C_6$ alkyl), dihydroisoindolyl($C_1$-$C_6$ alkyl), dihydroindolon-2-yl($C_1$-$C_6$ alkyl), pyridinyl($C_1$-$C_6$ alkyl), piperazinyl($C_1$-$C_6$ alkyl), or pyrazinyl($C_1$-$C_6$ alkyl) each of which is optionally substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkyl, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ dihydroxyalkyl, halogen, -C(O)$NR_6R_7$, -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$ $C_1$-$C_6$ alkoxycarbonyl, -$NR_6R_7$, $R_6R_7N$-($C_1$-$C_6$ alkyl)-, haloalkyl, $C_1$-$C_6$ alkanoyl,

$R_6$ and $R_7$ at each occurrence are independently H, $C_1$-$C_6$ alkyl optionally substituted with 1, 2, or 3 groups

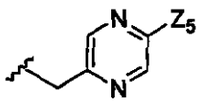
that are independently $C_1$-$C_4$ alkoxycarbonyl halogen, $C_3$-$C_6$ cycloalkyl, OH, SH, or $C_1$-$C_4$ alkoxy,

or

$R_6$, $R_7$, and the nitrogen to which they are attached form a piperidinyl, pyrrolidinyl, piperazinyl, or a morpholinyl ring optionally substituted with 1 or 2 groups that are independently alkyl, hydroxy, hydroxy $C_1$-$C_4$ alkyl, $C_1$-$C_4$ dihydroxyalkyl, or halogen

Embodiment 16 Compounds according to embodiment 15, wherein

$R_5$ is of the formula



wherein

$Z_5$ is $C_1$-$C_4$ alkyl, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ dihydroxyalkyl, halogen, $-C(O)NR_6R_7$, $-(C_1$-$C_4$ alkyl$)-C(O)NR_6R_7$ $C_1$-$C_6$ alkoxycarbonyl, $R_6R_7N-(C_1$-$C_6$ alkyl$)-$, $-NR_6R_7$, $CF_3$, or $C_1$-$C_6$ alkanoyl, wherein

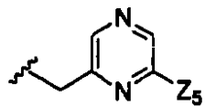
$R_6$ and $R_7$ at each occurrence are independently H, $C_1$-$C_6$ alkyl optionally substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkoxycarbonyl, halogen, $C_3$-$C_6$ cycloalkyl, OH, SH, or $C_1$-$C_4$ alkoxy,

or

$R_6$, $R_7$, and the nitrogen to which they are attached form a piperidinyl, pyrrolidinyl, piperazinyl, or a morpholinyl ring optionally substituted with 1 or 2 groups that are independently alkyl, hydroxy, hydroxy $C_1$-$C_4$ alkyl, $C_1$-$C_4$ dihydroxyalkyl, or halogen

Embodiment 17 Compounds according to embodiment 15, wherein

$R_5$ is of the formula



wherein

$Z_5$ is $C_1$-$C_4$ alkyl, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ dihydroxyalkyl, halogen, -C(O)$NR_6R_7$, -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$ $C_1$-$C_6$ alkoxycarbonyl, $R_6R_7N$-($C_1$-$C_6$ alkyl)-, -$NR_6R_7$, $CF_3$, or $C_1$-$C_6$ alkanoyl, wherein

$R_6$ and $R_7$ at each occurrence are independently H, $C_1$-$C_6$ alkyl optionally substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkoxycarbonyl, halogen, $C_3$-$C_6$ cycloalkyl, OH, SH, or $C_1$-$C_4$ alkoxy,

or

$R_6$, $R_7$, and the nitrogen to which they are attached form a piperidinyl, pyrrolidinyl, piperazinyl, or a morpholinyl ring optionally substituted with 1 or 2 groups that are independently alkyl, hydroxy, hydroxy $C_1$-$C_4$ alkyl, $C_1$-$C_4$ dihydroxyalkyl, or halogen

Embodiment 18 Compounds according to either embodiment 16 or 17, wherein

$Z_5$ is $C_1$-$C_4$ alkyl, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ dihydroxyalkyl, halogen, $C_1$-$C_6$ alkoxycarbonyl, $CF_3$, or $C_1$-$C_6$ alkanoyl

Embodiment 19 Compounds according to either embodiment 16 or 17, wherein

$Z_5$ is $C_1$-$C_4$ alkyl, -C(O)$NR_6R_7$, -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$, $R_6R_7N$-($C_1$-$C_6$ alkyl)-, or -$NR_6R_7$, $CF_3$, or $C_1$-$C_4$ alkanoyl, wherein

$R_6$ and $R_7$ at each occurrence are independently H, $C_1$-$C_6$ alkyl optionally substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkoxycarbonyl, halogen, $C_3$-$C_6$ cycloalkyl, OH, SH, or $C_1$-$C_4$ alkoxy,

or

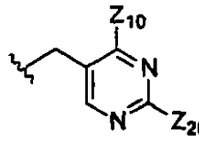
$R_6$, $R_7$, and the nitrogen to which they are attached form a piperidinyl, pyrrolidinyl, piperazinyl, or a morpholinyl ring optionally substituted with 1 or 2 groups that are independently alkyl, hydroxy, hydroxy $C_1$-$C_4$ alkyl, $C_1$-$C_4$ dihydroxyalkyl, or halogen

Embodiment 20 Compounds according to embodiment 19, wherein

$Z_5$ is $-C(O)NR_6R_7$, $-(C_1$-$C_4$ alkyl$)-C(O)NR_6R_7$, $R_6R_7N-(C_1$-$C_6$ alkyl$)-$, or $-NR_6R_7$, wherein

$R_6$ and $R_7$ at each occurrence are independently H, $C_1$-$C_6$ alkyl optionally substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkoxycarbonyl, halogen, cyclopropyl, OH, SH, or $C_1$-$C_4$ alkoxy

Embodiment 21 Compounds according to embodiment 15, wherein

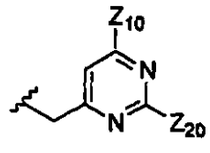
$R_5$ is of the formula  , wherein

$Z_{10}$ is H or methyl, and

$Z_{20}$ is hydroxy$(C_1$-$C_4)$alkyl, $C_1$-$C_4$ dihydroxyalkyl, OH, halogen, haloalkyl, $(C_1$-$C_4)$alkyl, $OCF_3$, $-NR_6R_7$, $R_6R_7N-(C_1$-$C_6$ alkyl$)-$, $-(C_1$-$C_4$ alkyl$)-C(O)NR_6R_7$, or $-C(O)NR_6R_7$, wherein

$R_6$ and $R_7$ at each occurrence are independently H, $C_1$-$C_6$ alkyl optionally substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkoxycarbonyl, halogen, $C_3$-$C_6$ cycloalkyl, OH, SH, or $C_1$-$C_4$ alkoxy

Embodiment 22 Compounds according to embodiment 15, wherein

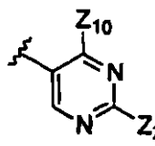
$R_5$ is of the formula  , wherein

$Z_{10}$ is H or methyl, and

$Z_{20}$ is hydroxy($C_1$-$C_4$)alkyl, $C_1$-$C_4$ dihydroxyalkyl, OH, halogen, $CF_3$, ($C_1$-$C_4$)alkyl, $OCF_3$, $-NR_6R_7$, $R_6R_7N$-($C_1$-$C_6$ alkyl)-, -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$, or -C(O)$NR_6R_7$, wherein

$R_6$ and $R_7$ at each occurrence are independently H, $C_1$-$C_6$ alkyl optionally substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkoxycarbonyl, halogen, $C_3$-$C_6$ cycloalkyl, OH, SH, or $C_1$-$C_4$ alkoxy

Embodiment 23 Compounds according to embodiment 15, wherein

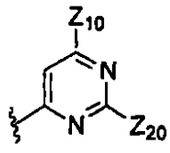
$R_5$ is of the formula  , wherein

$Z_{10}$ is H or methyl, and

$Z_{20}$ is hydroxy($C_1$-$C_4$)alkyl, $C_1$-$C_4$ dihydroxyalkyl, OH, halogen, haloalkyl, ($C_1$-$C_4$)alkyl, $OCF_3$, $-NR_6R_7$, $R_6R_7N$-($C_1$-$C_6$ alkyl)-, -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$, or -C(O)$NR_6R_7$, wherein

$R_6$ and $R_7$ at each occurrence are independently H, $C_1$-$C_6$ alkyl optionally substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkoxycarbonyl, halogen, $C_3$-$C_6$ cycloalkyl, OH, SH, or $C_1$-$C_4$ alkoxy

Embodiment 24 Compounds according to embodiment 15, wherein

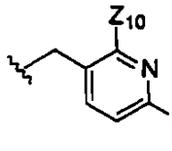
$R_5$ is of the formula  , wherein

$Z_{10}$ is H or methyl, and

$Z_{20}$ is hydroxy($C_1$-$C_4$)alkyl, $C_1$-$C_4$ dihydroxyalkyl, OH, halogen, $CF_3$, ($C_1$-$C_4$)alkyl, $OCF_3$, -$NR_6R_7$, $R_6R_7N$-($C_1$-$C_6$ alkyl)-, -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$, or -C(O)$NR_6R_7$, wherein

$R_6$ and $R_7$ at each occurrence are independently H, $C_1$-$C_6$ alkyl optionally substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkoxycarboryl, halogen, $C_3$-$C_6$ cycloalkyl, OH, SH, or $C_1$-$C_4$ alkoxy

Embodiment 25 Compounds according to embodiment 15, wherein

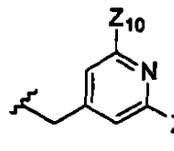
$R_5$ is of the formula  , wherein

$Z_{10}$ is H or methyl, and

$Z_{20}$ is hydroxy($C_1$-$C_4$)alkyl, $C_1$-$C_4$ dihydroxyalkyl, OH, halogen, haloalkyl, ($C_1$-$C_4$)alkyl, $OCF_3$, -$NR_6R_7$, $R_6R_7N$-($C_1$-$C_6$ alkyl)-, -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$, or -C(O)$NR_6R_7$, wherein

$R_6$ and $R_7$ at each occurrence are independently H, $C_1$-$C_6$ alkyl optionally substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkoxycarbonyl, halogen, $C_3$-$C_6$ cycloalkyl, OH, SH, or $C_1$-$C_4$ alkoxy

Embodiment 26 Compounds according to embodiment 15, wherein

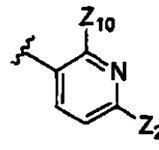
$R_5$ is of the formula  , wherein

$Z_{10}$ is H or methyl, and

$Z_{20}$ is hydroxy($C_1$-$C_4$)alkyl, $C_1$-$C_4$ dihydroxyalkyl, OH, halogen, $CF_3$, ($C_1$-$C_4$)alkyl, $OCF_3$, -$NR_6R_7$, $R_6R_7N$-($C_1$-$C_6$ alkyl)-, -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$, or -C(O)$NR_6R_7$, wherein

$R_6$ and $R_7$ at each occurrence are independently H, $C_1$-$C_6$ alkyl optionally substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkoxycarbonyl, halogen, $C_3$-$C_6$ cycloalkyl, OH, SH, or $C_1$-$C_4$ alkoxy

Embodiment 27 Compounds according to embodiment 15, wherein

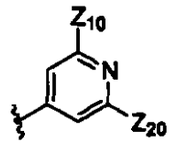
$R_5$ is of the formula  , wherein

$Z_{10}$ is H or methyl, and

$Z_{20}$ is hydroxy($C_1$-$C_4$)alkyl, $C_1$-$C_4$ dihydroxyalkyl, OH, halogen, haloalkyl, ($C_1$-$C_4$)alkyl, $OCF_3$, -$NR_6R_7$, $R_6R_7N$-($C_1$-$C_6$ alkyl)-, -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$, or -C(O)$NR_6R_7$, wherein

$R_6$ and $R_7$ at each occurrence are independently H, $C_1$-$C_6$ alkyl optionally substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkoxycarbonyl, halogen, $C_3$-$C_6$ cycloalkyl, OH, SH, or $C_1$-$C_4$ alkoxy

Embodiment 28 Compounds according to embodiment 15, wherein

$R_5$ is of the formula  , wherein

$Z_{10}$ is H or methyl, and

$Z_{20}$ is hydroxy($C_1$-$C_4$)alkyl, $C_1$-$C_4$ dihydroxyalkyl, OH, halogen, $CF_3$, ($C_1$-$C_4$)alkyl, $OCF_3$, -$NR_6R_7$, $R_6R_7N$-($C_1$-$C_6$ alkyl)-, -($C_1$-$C_4$ alkyl)-$C(O)NR_6R_7$, or -$C(O)NR_6R_7$, wherein $R_6$ and $R_7$ at each occurrence are independently H, $C_1$-$C_6$ alkyl optionally substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkoxycarbonyl, halogen, $C_3$-$C_6$ cycloalkyl, OH, SH, or $C_1$-$C_4$ alkoxy

Embodiment 29 Compounds according to embodiment 4, wherein

$R_5$ is phenyl, which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently $C_1$-$C_4$ alkyl, -$C(O)NR_6R_7$, -($C_1$-$C_4$ alkyl)-$C(O)NR_6R_7$ -$NR_6R_7$, $NR_6R_7$($C_1$-$C_6$ alkyl), $C_1$-$C_6$ hydroxyalkyl, dihydroxyalkyl, halogen, $C_1$-$C_4$ alkoxy, $CO_2R$, OH, $C_1$-$C_6$ alkoxycarbonyl, $CF_3$, -($C_1$-$C_4$ alkyl)-$NR_{15}C(O)NR_{16}R_{17}$, -($C_1$-$C_4$ alkyl)-$NR_{15}C(O)R_{18}$, wherein

$R_{15}$ is H or $C_1$-$C_6$ alkyl,

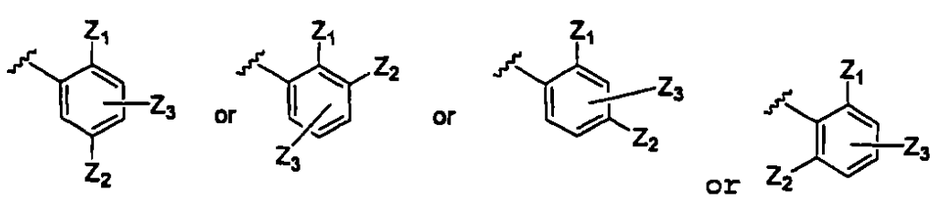
$R_{16}$ and $R_{17}$ are independently H or $C_1$-$C_6$ alkyl, or

$R_{16}$, $R_{17}$, and the nitrogen to which they are attached form a morpholinyl ring, and

$R_{18}$ is $C_1$-$C_6$ alkyl optionally substituted with -O-($C_2$-$C_6$ alkanoyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ dihydroxyalkyl, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, amino $C_1$-$C_6$ alkyl, mono or dialkylamino $C_1$-$C_6$ alkyl

Embodiment 30 Compounds according to embodiment 29, wherein

$R_5$ is of the formula



$Z_1$ is H, halogen, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ haloalkyl, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ dihydroxyalkyl, or $C_1$-$C_4$ alkoxy, and

$Z_2$ is $C_1$-$C_4$ alkyl, $-C(O)NR_6R_7$, $-(C_1$-$C_4$ alkyl$)-C(O)NR_6R_7$ $-NR_6R_7$, $NR_6R_7(C_1$-$C_6$ alkyl), $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ dihydroxyalkyl, halogen, $C_1$-$C_4$ alkoxy, $CO_2R$, OH, $C_1$-$C_6$ alkoxycarbonyl, or $C_1$-$C_4$ haloalkyl,

$Z_3$ is H, $C_1$-$C_4$ alkyl, $-C(O)NR_6R_7$, $-(C_1$-$C_4$ alkyl$)-C(O)NR_6R_7$ $-NR_6R_7$, $NR_6R_7(C_1$-$C_6$ alkyl), $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ dihydroxyalkyl, halogen, $C_1$-$C_4$ alkoxy, $CO_2R$, OH, $C_1$-$C_6$ alkoxycarbonyl, or $C_1$-$C_4$ haloalkyl,

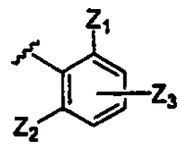
and wherein

$R_6$ and $R_7$ at each occurrence are independently H, OH, $C_1$-$C_6$ alkyl, amino $C_1$-$C_4$ alkyl, $NH(C_1$-$C_6$ alkyl)alkyl, $N(C_1$-$C_6$ alkyl)$(C_1$-$C_6$ alkyl) $C_1$-$C_6$ alkyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ dihydroxyalkyl, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, $-SO_2(C_1$-$C_6$ alkyl), $-SO_2NH_2$, $-SO_2NH(C_1$-$C_6$ alkyl), $-SO_2N(C_1$-$C_6$ alkyl$)(C_1$-$C_6$ alkyl), or $C_1$-$C_6$ alkanoyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently halogen, OH, SH, $C_3$-$C_6$ cycloalkyl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkyl, OH, $CF_3$, or $OCF_3$

In this embodiment, it is preferred that at least one of $Z_1$, $Z_2$, and $Z_3$ is not hydrogen

Embodiment 31 Compounds according to embodiment 30, wherein

$R_5$ is of the formula




wherein

$Z_1$ is H, halogen, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ haloalkyl, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ dihydroxyalkyl, or $C_1$-$C_4$ alkoxy, and

$Z_2$ is $C_1$-$C_4$ alkyl, -C(O)$NR_6R_7$, -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$ -$NR_6R_7$, $NR_6R_7$($C_1$-$C_6$ alkyl), $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ dihydroxyalkyl, halogen, $C_1$-$C_4$ alkoxy, $CO_2R$, OH, $C_1$-$C_6$ alkoxycarbonyl, or $C_1$-$C_4$ haloalkyl,

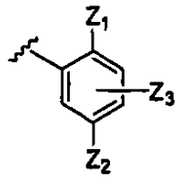
$Z_3$ is H, $C_1$-$C_4$ alkyl, -C(O)$NR_6R_7$, -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$ -$NR_6R_7$, $NR_6R_7$($C_1$-$C_6$ alkyl), $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ dihydroxyalkyl, halogen, $C_1$-$C_4$ alkoxy, $CO_2R$, OH, $C_1$-$C_6$ alkoxycarbonyl, or $C_1$-$C_4$ haloalkyl, and wherein

$R_6$ and $R_7$ at each occurrence are independently H, OH, $C_1$-$C_6$ alkyl, amino $C_1$-$C_4$ alkyl, NH($C_1$-$C_6$ alkyl)alkyl, N($C_1$-$C_6$ alkyl)($C_1$-$C_6$ alkyl) $C_1$-$C_6$ alkyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ dihydroxyalkyl, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, -$SO_2$($C_1$-$C_6$ alkyl), -$SO_2NH_2$, -$SO_2$NH($C_1$-$C_6$ alkyl) -$SO_2$N($C_1$-$C_6$ alkyl)($C_1$-$C_6$ alkyl), or $C_1$-$C_6$ alkanoyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently halogen, OH, SH, $C_3$-$C_6$ cycloalkyl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkyl, OH, $CF_3$, or $OCF_3$

In this embodiment, it is preferred that at least one of $Z_1$, $Z_2$, and $Z_3$ is not hydrogen

Embodiment 32 Compounds according to embodiment 30, wherein

$R_5$ is of the formula




wherein

$Z_1$ is H, halogen, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ haloalkyl, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ dihydroxyalkyl, or $C_1$-$C_4$ alkoxy, and

$Z_2$ is $C_1$-$C_4$ alkyl, -C(O)$NR_6R_7$, -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$ -$NR_6R_7$, $NR_6R_7$($C_1$-$C_6$ alkyl), $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$

dihydroxyalkyl, halogen, $C_1$-$C_4$ alkoxy, $CO_2R$, OH, $C_1$-$C_6$ alkoxycarbonyl, or $C_1$-$C_4$ naloalkyl,

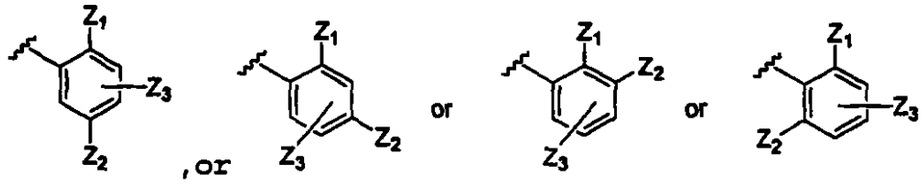
$Z_3$ is H, $C_1$-$C_4$ alkyl, $-C(O)NR_6R_7$, $-(C_1$-$C_4$ alkyl$)-C(O)NR_6R_7$ $-NR_6R_7$, $NR_6R_7(C_1$-$C_6$ alkyl), $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ dihydroxyalkyl, halogen, $C_1$-$C_4$ alkoxy, $CO_2R$, OH, $C_1$-$C_6$ alkoxycarbonyl, or $C_1$-$C_4$ haloalkyl, and wherein

$R_6$ and $R_7$ at each occurrence are independently H, OH, $C_1$-$C_6$ alkyl, amino $C_1$-$C_4$ alkyl, $NH(C_1$-$C_6$ alkyl)alkyl, $N(C_1$-$C_6$ alkyl)$(C_1$-$C_6$ alkyl) $C_1$-$C_6$ alkyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ dihydroxyalkyl, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, $-SO_2(C_1$-$C_6$ alkyl), $-SO_2NH_2$, $-SO_2NH(C_1$-$C_6$ alkyl), $-SO_2N(C_1$-$C_6$ alkyl$)(C_1$-$C_6$ alkyl), or $C_1$-$C_6$ alkanoyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently halogen, OH, SH, $C_3$-$C_6$ cycloalkyl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkyl, OH, $CF_3$, or $OCF_3$

In this embodiment, it is preferred that at least one of $Z_1$, $Z_2$, and $Z_3$ is not hydrogen

Embodiment 33 Compounds according to embodiment 29, wherein

$R_5$ is either



wherein

$Z_1$ is H, halogen, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ haloalkyl, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ dihydroxyalkyl, or $C_1$-$C_4$ alkoxy, and

$Z_2$ is $C_1$-$C_4$ alkyl, $-C(O)NR_6R_7$, $-(C_1$-$C_4$ alkyl$)-C(O)NR_6R_7$ $-NR_6R_7$, $NR_6R_7(C_1$-$C_6$ alkyl), $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ dihydroxyalkyl, halogen, $C_1$-$C_4$ alkoxy, $CO_2R$, $C_1$-$C_6$

alkoxycarbonyl, -($C_1$-$C_4$ alkyl)-$NR_{15}C(O)NR_{16}R_{17}$, or -($C_1$-$C_4$ alkyl)-$NR_{15}C(O)R_{18}$,

$Z_3$ is H, $C_1$-$C_4$ alkyl, $-C(O)NR_6R_7$, -($C_1$-$C_4$ alkyl)-$C(O)NR_6R_7$ $-NR_6R_7$, $NR_6R_7$($C_1$-$C_6$ alkyl), $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ dihydroxyalkyl, halogen, $C_1$-$C_4$ alkoxy, $CO_2R$, $C_1$-$C_6$ alkoxycarbonyl, -($C_1$-$C_4$ alkyl)-$NR_{15}C(O)NR_{16}R_{17}$, or -($C_1$-$C_4$ alkyl)-$NR_{15}C(O)R_{18}$,

$R_6$, $R_7$, and the nitrogen to which they are attached form a piperidinyl, pyrrolidinyl, piperazinyl, or a morpholinyl ring optionally substituted with 1 or 2 groups that are independently alkyl, hydroxy, hydroxy $C_1$-$C_4$ alkyl, $C_1$-$C_4$ dihydroxyalkyl, or halogen,

$R_{15}$ is H or $C_1$-$C_6$ alkyl,

$R_{16}$ and $R_{17}$ are independently H or $C_1$-$C_6$ alkyl, or

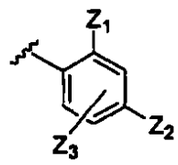
$R_{16}$, $R_{17}$, and the nitrogen to which they are attached form a morpholinyl ring, and

$R_{18}$ is $C_1$-$C_6$ alkyl optionally substituted with -O-($C_2$-$C_6$ alkanoyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ dihydroxyalkyl, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, amino $C_1$-$C_6$ alkyl, mono or dialkylamino $C_1$-$C_6$ alkyl

In this embodiment, it is preferred that at least one of $Z_1$, $Z_2$, and $Z_3$ is not hydrogen

Embodiment 34 Compounds according to embodiment 33, wherein

$R_5$ is of the formula




$Z_1$ is H, halogen, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ haloalkyl, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ dihydroxyalkyl, or $C_1$-$C_4$ alkoxy, and

$Z_2$ is $C_1$-$C_4$ alkyl, -C(O)$NR_6R_7$, -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$ -$NR_6R_7$, $NR_6R_7$($C_1$-$C_6$ alkyl), $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ dihydroxyalkyl, halogen, $C_1$-$C_4$ alkoxy, $CO_2R$, $C_1$-$C_6$ alkoxycarbonyl, -($C_1$-$C_4$ alkyl)-$NR_{15}$C(O)$NR_{16}R_{17}$, or -($C_1$-$C_4$ alkyl)-$NR_{15}$C(O)$R_{18}$,

$Z_3$ is H, $C_1$-$C_4$ alkyl, -C(O)$NR_6R_7$, -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$ -$NR_6R_7$, $NR_6R_7$($C_1$-$C_6$ alkyl), $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ dihydroxyalkyl, halogen, $C_1$-$C_4$ alkoxy, $CO_2R$, $C_1$-$C_6$ alkoxycarbonyl, -($C_1$-$C_4$ alkyl)-$NR_{15}$C(O)$NR_{16}R_{17}$, or -($C_1$-$C_4$ alkyl)-$NR_{15}$C(O)$R_{18}$,

$R_6$, $R_7$, and the nitrogen to which they are attached form a piperidinyl, pyrrolidinyl, piperazinyl, or a morpholinyl ring optionally substituted with 1 or 2 groups that are independently alkyl, hydroxy, hydroxy $C_1$-$C_4$ alkyl, $C_1$-$C_4$ dihydroxyalkyl, or halogen,

$R_{15}$ is H or $C_1$-$C_6$ alkyl,

$R_{16}$ and $R_{17}$ are independently H or $C_1$-$C_6$ alkyl, or

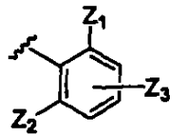
$R_{16}$, $R_{17}$, and the nitrogen to which they are attached form a morpholinyl ring, and

$R_{18}$ is $C_1$-$C_6$ alkyl optionally substituted with -O-($C_2$-$C_6$ alkanoyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ dihydroxyalkyl, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, amino $C_1$-$C_6$ alkyl, mono or dialkylamino $C_1$-$C_6$ alkyl

In this embodiment, it is preferred that at least one of $Z_1$, $Z_2$, and $Z_3$ is not hydrogen

Embodiment 35 Compounds according to embodiment 33, wherein

$R_5$ is of the formula




wherein

$Z_1$ is H, halogen, $C_1$-$C_4$ alkyl $C_1$-$C_4$ haloalkyl, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ dihydroxyalkyl, or $C_1$-$C_4$ alkoxy, and

$Z_2$ is $C_1$-$C_4$ alkyl, $-C(O)NR_6R_7$, $-(C_1$-$C_4$ alkyl$)$-$C(O)NR_6R_7$ $-NR_6R_7$, $NR_6R_7(C_1$-$C_6$ alkyl$)$, $C_1$-$C_6$ hydroxyalkyl, $C_2$-$C_6$ dihydroxyalkyl, halogen, $C_1$-$C_4$ alkoxy, $CO_2R$, $C_1$-$C_6$ alkoxycarbonyl, $-(C_1$-$C_4$ alkyl$)$-$NR_{15}C(O)NR_{16}R_{17}$, or $-(C_1$-$C_4$ alkyl$)$-$NR_{15}C(O)R_{18}$,

$Z_3$ is H, $C_1$-$C_4$ alkyl, $-C(O)NR_6R_7$, $-(C_1$-$C_4$ alkyl$)$-$C(O)NR_6R_7$ $-NR_6R_7$, $NR_6R_7(C_1$-$C_6$ alkyl$)$, $C_1$-$C_6$ hydroxyalkyl, $C_2$-$C_6$ dihydroxyalkyl, halogen, $C_1$-$C_4$ alkoxy, $CO_2R$, $C_1$-$C_6$ alkoxycarbonyl, $-(C_1$-$C_4$ alkyl$)$-$NR_{15}C(O)NR_{16}R_{17}$, or $-(C_1$-$C_4$ alkyl$)$-$NR_{15}C(O)R_{18}$,

$R_6$, $R_7$, and the nitrogen to which they are attached form a piperidinyl, pyrrolidinyl, piperazinyl, or a morpholinyl ring, each of which is optionally substituted with 1 or 2 groups that are independently alkyl, hydroxy, hydroxy $C_1$-$C_4$ alkyl, $C_1$-$C_4$ dihydroxyalkyl, or halogen,

$R_{15}$ is H or $C_1$-$C_6$ alkyl,

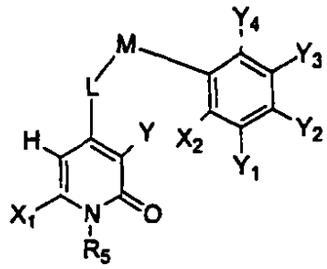
$R_{16}$ and $R_{17}$ are independently H or $C_1$-$C_6$ alkyl, or

$R_{16}$, $R_{17}$, and the nitrogen to which they are attached form a morpholinyl ring, and

$R_{18}$ is $C_1$-$C_6$ alkyl optionally substituted with $-O-(C_2$-$C_6$ alkanoyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ dihydroxyalkyl, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, amino $C_1$-$C_6$ alkyl, mono or dialkylamino $C_1$-$C_6$ alkyl

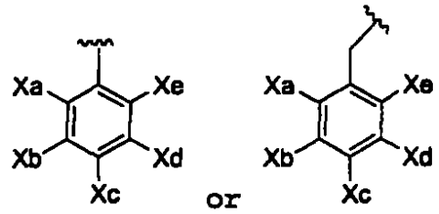
In this embodiment, it is preferred that at least one of $Z_1$, $Z_2$, and $Z_3$ is not hydrogen

Embodiment 36 A compound of the formula



or a pharmaceutically acceptable salt thereof, wherein

L and M are independently selected from -O-, $-CH_2-$, -S-,-NR-, -N(R)-N(R)-, C(=O)-, $-SO_2-$,



$R_5$ is or , wherein

$X_1$, $X_2$, $X_a$, $X_b$, $X_c$, $X_d$, and $X_e$ at are independently selected from $-C(O)NR_6R_7$, $-(C_1-C_4$ alkyl)$-C(O)NR_6R_7$, $-NR_6R_7$, hydroxy$(C_1-C_4)$alkyl, $C_1-C_4$ dihydroxyalkyl, H, OH, halogen, haloalkyl, alkyl, haloalkoxy, heteroaryl, heterocycloalkyl, $C_3-C_7$ cycloalkyl, $R_6R_7N-(C_1-C_6$ alkyl)-, $-CO_2-(C_1-C_6)$alkyl, $-N(R)C(O)NR_6R_7$, $-N(R)C(O)-(C_1-C_6)$alkoxy, $CO_2R-(C_1-C_6$ alkyl)-, or $-SO_2NR_6R_7$, wherein the heteroaryl and heterocycloalkyl groups are optionally substituted with $-NR_6R_7$, $-C(O)NR_6R_7$, $R_6R_7N-(C_1-C_6$ alkyl)-, $C_1-C_6$ alkyl, $C_1-C_6$ alkoxy, or halogen, or

$R_5$ is heteroaryl or heteroarylalkyl, wherein the heteroaryl and heteroaryl groups are optionally substituted with 1,2, 3, or 4 groups that are independently $-C(O)NR_6R_7$, $-(C_1-C_4$ alkyl)$-C(O)NR_6R_7$, $-NR_6R_7$, hydroxy$(C_1-C_4)$alkyl, $C_1-C_4$ dihydroxyalkyl, H, OH, halogen, haloalkyl, alkyl, haloalkoxy, $R_6R_7N-(C_1-C_6$ alkyl)-, $-CO_2-(C_1-C_6)$alkyl, $-N(R)C(O)NR_6R_7$, or $-N(R)C(O)-(C_1-C_6)$alkoxy, wherein

$R_6$ and $R_7$ are independently at each occurrence H, $C_1-C_6$ alkyl, $C_1-C_6$ alkoxy, $C_1-C_6$ alkoxy $C_1-C_6$ alkyl, $C_1-C_6$ alkoxycarbonyl, OH, $C_1-C_6$ hydroxyalkyl, $C_1-C_4$

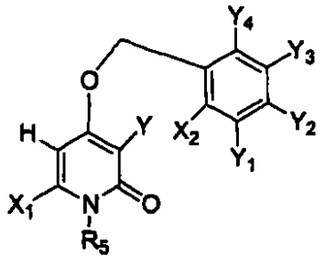
dihydroxyalkyl, $C_1$-$C_6$ thiohydroxyalkyl, -($C_1$-$C_4$)alkyl-$CO_2$-alkyl, pyridyl $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkanoyl, benzyl, phenyl $C_1$-$C_6$ alkoxy, or phenyl $C_1$-$C_6$ alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, $C_3$-$C_6$ cycloalkyl, $C_1$-$C_6$ alkoxy, piperidinyl $C_1$-$C_6$ alkyl, morpholinyl $C_1$-$C_6$ alkyl, piperazinyl $C_1$-$C_6$ alkyl, OH, SH, $NH_2$, NH(alkyl), N(alkyl)(alkyl), -O-$C_1$-$C_4$ alkanoyl, $C_1$-$C_4$ alkyl, $CF_3$, or $OCF_3$, or

$R_6$, $R_7$, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, hydroxy, hydroxy $C_1$-$C_4$ alkyl, $C_1$-$C_4$ dihydroxyalkyl, or halogen,

R at each occurrence is independently H or $C_1$-$C_6$ alkyl, and

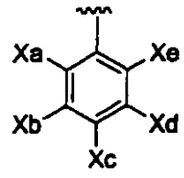
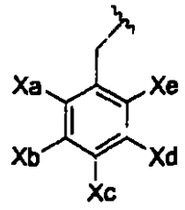
Y, $Y_1$, $Y_2$, $Y_3$, and $Y_4$ are independently selected from H, halogen, alkyl, carboxaldehyde, hydroxyalkyl, dihydroxyalkyl, alkenyl, alkynyl, CN, alkanoyl, alkoxy, alkoxyalkyl, haloalkyl, and carboxyl

Embodiment 37 Compounds according to embodiment 36 of the formula




or a pharmaceutically acceptable salt thereof

Embodiment 38 Compounds according to embodiment 37, wherein

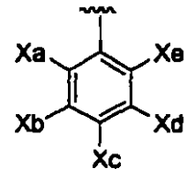
$R_5$ is  or 

Embodiment 39 Compounds according to embodiment 31, wherein

$Y_2$, $Y_4$, and Y are independently halogen, and

$Y_1$ and $Y_3$ are both hydrogen

Embodiment 40 Compounds according to embodiment 39, wherein

$R_5$ is  ,

$X_1$ and $X_2$ are independently H, methyl, $NR_6R_7$, -($C_1$-$C_4$ alkyl)-$C(O)NR_6R_7$, $R_6R_7N$-($C_1$-$C_6$ alkyl)-, -$C(O)NR_6R_7$, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ dihydroxyalkyl, or -($C_1$-$C_4$ alkyl)-morpholinyl, and

$X_a$ and $X_e$ are independently halogen, $NH_2$, $NH(C_1$-$C_6$ alkyl), $N(C_1$-$C_6$ alkyl)($C_1$-$C_6$ alkyl), methyl, or hydrogen

In this embodiment, it is preferred that one of $X_a$ and $X_e$ is not hydrogen

Embodiment 41 Compounds according to embodiment 40, wherein

one of $X_b$ and $X_c$ is hydrogen and the other is -$NR_6R_7$, $R_6R_7N$-($C_1$-$C_6$ alkyl)-, -$C(O)NR_6R_7$, -$SO_2NR_6R_7$, or halogen, where

$R_6$ and $R_7$ are independently at each occurrence H, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxycarboryl, OH, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ dihydroxyalkyl, -($C_1$-$C_4$)alkyl-$CO_2$-alkyl, pyridyl $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkanoyl, benzyl, phenyl $C_1$-$C_6$ alkoxy, or phenyl $C_1$-$C_6$ alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, $C_3$-$C_6$ cycloalkyl, $C_1$-$C_6$ alkoxy, piperidinyl $C_1$-$C_6$ alkyl, morpholinyl $C_1$-$C_6$ alkyl, piperazinyl $C_1$-$C_6$ alkyl, OH, SH, $NH_2$, NH(alkyl), N(alkyl)(alkyl), -O-$C_1$-$C_4$ alkanoyl, $C_1$-$C_4$ alkyl, $CF_3$, or $OCF_3$, or

$R_6$, $R_7$, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, hydroxy, hydroxy $C_1$-$C_4$ alkyl, $C_1$-$C_4$ dihydroxyalkyl, or halogen

Embodiment 42 Compounds according to embodiment 41, wherein

$R_6$ and $R_7$ are independently at each occurrence H, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxycarbonyl, OH, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ dihydroxyalkyl, -($C_1$-$C_4$)alkyl-$CO_2$-alkyl, pyridyl $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkanoyl, benzyl, phenyl $C_1$-$C_6$ alkoxy, or phenyl $C_1$-$C_6$ alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, $C_3$-$C_6$ cycloalkyl, $C_1$-$C_6$ alkoxy, piperidinyl $C_1$-$C_6$ alkyl, morpholinyl $C_1$-$C_6$ alkyl, piperazinyl $C_1$-$C_6$ alkyl, OH, $NH_2$, NH(alkyl), N(alkyl)(alkyl), -O-$C_1$-$C_4$ alkanoyl, $C_1$-$C_4$ alkyl, $CF_3$, or $OCF_3$

Embodiment 43 Compounds according to embodiment 42, wherein

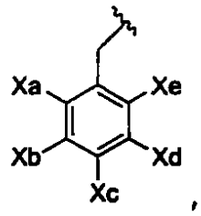
$X_a$ is hydrogen, methyl, fluorine, or chlorine,

$X_c$ and $X_d$ are both hydrogen,

$X_b$ is $-NR_6R_7$, $-(C_1-C_4$ alkyl$)-C(O)NR_6R_7$, $R_6R_7N-(C_1-C_6$ alkyl$)-$, $-C(O)NR_6R_7$, wherein

$R_6$ and $R_7$ are independently at each occurrence H, $C_1-C_6$ alkyl, $C_1-C_6$ hydroxyalkyl, $C_1-C_4$ dihydroxyalkyl, $C_1-C_6$ alkoxy, $C_1-C_6$ alkoxy $C_1-C_6$ alkyl, or $C_1-C_6$ alkanoyl, wherein each of the above is optionally substituted with 1, 2, or 3 groups that are independently OH, SH, halogen, or $C_3-C_6$ cycloalkyl

Embodiment 44 Compounds according to embodiment 39, wherein

$R_5$ is 

,

$X_a$ is H, fluoro, chloro, or methyl,

$X_e$ is hydrogen, halogen, or methyl, and

$X_b$ is H,

$X_d$ is H or halogen,

Embodiment 45 Compounds according to embodiment 44, wherein

$X_c$ is $-SO_2NR_6R_7$, or halogen, wherein

$R_6$ and $R_7$ are independently at each occurrence H, $C_1-C_6$ alkyl, $C_1-C_6$ alkoxy, $C_1-C_6$ alkoxy $C_1-C_6$ alkyl, $C_1-C_6$ alkoxycarbonyl, OH, $C_1-C_6$ hydroxyalkyl, $C_1-C_6$ dihydroxyalkyl, $-(C_1-C_4)$alkyl$-CO_2-$alkyl, pyridyl $C_1-C_6$

alkyl, $C_2$-$C_6$ alkanoyl, benzyl, phenyl $C_1$-$C_6$ alkoxy, or phenyl $C_2$-$C_6$ alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, $C_3$-$C_6$ cycloalkyl, $C_1$-$C_6$ alkoxy, piperidinyl $C_1$-$C_6$ alkyl, morpholinyl $C_1$-$C_6$ alkyl, piperazinyl $C_2$-$C_6$ alkyl, OH, SH, $NH_2$, NH(alkyl), N(alkyl)(alkyl), -O-$C_1$-$C_4$ alkanoyl, $C_1$-$C_4$ alkyl, $CF_3$, or $OCF_3$, or

$R_6$, $R_7$, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, hydroxy, hydroxy $C_1$-$C_4$ alkyl, $C_1$-$C_4$ dihydroxyalkyl, or halogen, or

$X_c$ is fluoro, chloro, $-NH_2$, -NH($C_1$-$C_6$ alkyl), -N($C_1$-$C_6$ alkyl)($C_1$-$C_6$ alkyl), $-SO_2NH_2$, $-SO_2$NH($C_1$-$C_6$ alkyl), $-SO_2$N($C_1$-$C_6$ alkyl)($C_1$-$C_6$ alkyl), or piperazinyl wherein the piperazinyl group is optionally substituted with 1 or 2 groups that are independently $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, hydroxy, hydroxy $C_1$-$C_4$ alkyl, $C_1$-$C_4$ dihydroxyalkyl, or halogen

Embodiment 46 Compounds according to embodiment 44, wherein

$X_c$ is $-C(O)NR_6R_7$, -($C_1$-$C_6$ alkyl)-$C(O)NR_6R_7$, $-NR_6R_7$, or $R_6R_7N$-($C_1$-$C_6$ alkyl)-, wherein

$R_6$ and $R_7$ are independently at each occurrence H, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxycarbonyl, OH, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ dihydroxyalkyl, $C_1$-$C_6$ dihydroxyalkyl, -($C_1$-$C_4$)alkyl-$CO_2$-alkyl, pyridyl $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkanoyl, benzyl, phenyl $C_1$-$C_6$ alkoxy, or phenyl $C_1$-$C_6$ alkanoyl,

wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, $C_3$-$C_6$ cycloalkyl, $C_1$-$C_6$ alkoxy, piperidinyl $C_1$-$C_6$ alkyl, morpholinyl $C_1$-$C_6$ alkyl, piperazinyl $C_1$-$C_6$ alkyl, OH, $-NH_2$, -NH(alkyl), -N(alkyl)(alkyl), -O-$C_1$-$C_4$ alkanoyl, $C_1$-$C_4$ alkyl, $CF_3$, or $OCF_3$, or

$R_6$, $R_7$, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, hydroxy, hydroxy $C_1$-$C_4$ alkyl, $C_1$-$C_4$ dihydroxyalkyl, or halogen

Embodiment 47 Compounds according to embodiment 46, wherein

$R_6$ is hydrogen, and

$R_7$ is $C_1$-$C_6$ alkyl or $C_1$-$C_6$ alkanoyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently $NH_2$, NH($C_1$-$C_6$ alkyl), N($C_1$-$C_6$ alkyl)($C_1$-$C_6$ alkyl), OH, SH, cyclopropyl, or $C_1$-$C_4$ alkoxy,

Embodiment 48 Compounds according to embodiment 47, wherein

$X_c$ is $-C(O)NR_6R_7$

Embodiment 49 Compounds according to embodiment 47, wherein

$X_c$ is $NR_6R_7$, or $R_6R_7N$-($C_1$-$C_6$ alkyl)-

Embodiment 50 Compounds according to embodiment 38, wherein

$X_a$ is hydrogen,

two of $X_b$, $X_c$, and $X_d$ are hydrogen and the other is $-C(O)NR_6R_7$ $-(C_1-C_6$ alkyl$)-C(O)NR_6R_7$, $-NR_6R_7$, $R_6R_7N-(C_1-C_6$ alkyl$)-$ or $-CO_2-(C_1-C_6)$alkyl, wherein

$R_6$ and $R_7$ are independently at each occurrence H, $C_1-C_6$ alkyl, $C_1-C_6$ alkoxy, $C_1-C_6$ alkoxy $C_1-C_6$ alkyl, $C_1-C_6$ alkoxycarbonyl, OH, $C_1-C_6$ hydroxyalkyl, $C_1-C_6$ dihydroxyalkyl, $-(C_1-C_4)$alkyl$-CO_2-$alkyl, pyridyl $C_1-C_6$ alkyl, $C_1-C_6$ alkanoyl, benzyl, phenyl $C_1-C_6$ alkoxy, or phenyl $C_1-C_6$ alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, $C_3-C_6$ cycloalkyl, $C_1-C_6$ alkoxy, piperidinyl $C_1-C_6$ alkyl, morpholinyl $C_1-C_6$ alkyl, piperazinyl $C_1-C_6$ alkyl, OH, $NH_2$, NH(alkyl), N(alkyl)(alkyl), $-O-C_1-C_4$ alkanoyl, $C_1-C_4$ alkyl, $CF_3$, or $OCF_3$, or

$R_6$, $R_7$, and the nitrogen to which they are attached form a morpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently $C_1-C_4$ alkyl, $C_1-C_4$ alkoxy, hydroxy, hydroxy $C_1-C_4$ alkyl, $C_1-C_4$ dihydroxyalkyl, or halogen, and

$X_a$ is hydrogen, methyl, $C_1-C_2$ alkoxy, or halogen

Embodiment 51 Compounds according to embodiment 50, wherein

$X_b$ is $-C(O)NR_6R_7$ $-(C_1-C_6$ alkyl$)-C(O)NR_6R_7$, $-NR_6R_7$, or $R_6R_7N-(C_1-C_6$ alkyl$)-$ wherein

$R_6$ is hydrogen or $C_1-C_4$ alkyl,

$R_7$ is OH, $C_1-C_6$ alkyl or $C_1-C_6$ alkanoyl, wherein the alkyl and alkanoyl groups substituted with 1, 2, or 3 groups that are independently $NH_2$, NH($C_1-C_6$ alkyl), N($C_1-C_6$ alkyl)($C_1-C_6$ alkyl), $C_3-C_6$ cycloalkyl, OH, or $C_1-C_4$ alkoxy

Embodiment 52 Compounds according to embodiment 38, wherein

$X_a$ is halogen or methyl,

$X_b$ is H, $-NR_6R_7$, $R_6R_7N-(C_1-C_6$ alkyl)-, $-C(O)NR_6R_7$, or $-CO_2-(C_1-C_6)$alkyl,

$X_c$ is $-NR_6R_7$, $R_6R_7N-(C_1-C_6$ alkyl)-, $-C(O)NR_6R_7$, halogen, $-CO_2-(C_1-C_6)$alkyl, $NH_2$, $NH(C_1-C_6$ alkyl), $N(C_1-C_6$ alkyl)$(C_1-C_6$ alkyl), $-SO_2NH_2$, $-SO_2NH(C_1-C_6$ alkyl), $-SO_2N(C_1-C_6$ alkyl)$(C_1-C_6$ alkyl), or piperazinyl, wherein the piperazinyl group is optionally substituted with 1 or 2 groups that are independently $C_1-C_4$ alkyl, $C_1-C_4$ alkoxy, hydroxy, hydroxy $C_1-C_4$ alkyl, $C_1-C_4$ dihydroxyalkyl, or halogen,

$X_d$ is hydrogen,

$X_e$ is H, methyl, $NH_2$, $NH(C_1-C_6$ alkyl) or $N(C_1-C_6$ alkyl)$(C_1-C_6$ alkyl)

Embodiment 53 Compounds according to embodiment 38, wherein

$X_1$, $X_2$, $X_a$, $X_b$, $X_c$, $X_d$, and $X_e$ are independently selected from H, OH, halogen, $CF_3$, alkyl, $OCF_3$, pyridyl, pyridazinyl, pyrimidyl, pyrazinyl, thienyl, furyl, pyrrolyl, piperidinyl, piperazinyl, or $C_3-C_7$ cycloalkyl, wherein each of the above is optionally substituted with $-NR_6R_7$, $-C(O)NR_6R_7$, $-(C_1-C_4$ alkyl)$-C(O)NR_6R_7$, $R_6R_7N-(C_1-C_6$ alkyl)-, $C_1-C_6$ alkyl, $C_1-C_6$ alkoxy, or halogen

Embodiment 54 Compounds according to embodiment 37, wherein

$R_5$ is a heteroaryl or heteroarylalkyl group, where each heteroaryl is pyrazolyl, imidazolyl, furanyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrazolyl, imidazolyl, dihydroindolyl, dihydroisoindolyl, indolon-2-yl, quinolinyl, isoquinolinyl, tetrahydroisoquinolinyl,

dihydroisoquinolinyl, or indolyl, each of which is optionally substituted with 1, 2, 3, or 4 groups that are independently -C(O)$NR_6R_7$, -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$, -$NR_6R_7$, hydroxy($C_1$-$C_4$)alkyl, $C_1$-$C_4$ dihydroxyalkyl, hydrogen, hydroxy, halogen, haloalkyl, alkyl, haloalkoxy, $R_6R_7N$-($C_1$-$C_6$ alkyl)-, -$CO_2$-($C_1$-$C_6$)alkyl, -N(R)C(O)$NR_6R_7$, or -N(R)C(O)-($C_1$-$C_6$)alkoxy, wherein

$R_6$ and $R_7$ are independently at each occurrence H, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxycarbonyl, OH, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ dihydroxyalkyl, $C_1$-$C_6$ thiohydroxyalkyl, -($C_1$-$C_4$)alkyl-$CO_2$-alkyl, pyridyl $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkanoyl, benzyl, phenyl $C_1$-$C_6$ alkoxy, or phenyl $C_1$-$C_6$ alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, $C_3$-$C_6$ cycloalkyl, $C_1$-$C_6$ alkoxy, piperidinyl $C_1$-$C_6$ alkyl, morpholinyl $C_1$-$C_6$ alkyl, piperazinyl $C_1$-$C_6$ alkyl, OH, SH, $NH_2$, NH(alkyl), N(alkyl)(alkyl), -O-$C_1$-$C_4$ alkanoyl, $C_1$-$C_4$ alkyl, $CF_3$, or OCF

Embodiment 55 Compounds according to embodiment 54, wherein

$Y_2$, $Y_4$, and Y are independently halogen, and

$Y_1$ and $Y_3$ are both hydrogen

Embodiment 56 Compounds according to embodiment 55, wherein

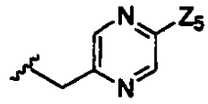
$X_1$ and $X_2$ are independently H, methyl, -$NR_6R_7$, $R_6R_7N$-($C_1$-$C_6$ alkyl)-, -C(O)$NR_6R_7$, -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ dihydroxyalkyl, or -($C_1$-$C_4$ alkyl)-morpholinyl

Embodiment 57 Compounds according to embodiment 56, wherein

$R_5$ is pyridyl $C_1$-$C_6$ alkyl, pyrimidinyl $C_1$-$C_6$ alkyl, or pyrazinyl $C_1$-$C_6$ alkyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently hydroxy($C_1$-$C_4$)alkyl, $C_1$-$C_4$ dihydroxyalkyl, OH, halogen, $CF_3$, ($C_1$-$C_4$)alkyl, $OCF_3$, $-NR_6R_7$, $-(C_1$-$C_4$ alkyl)$-C(O)NR_6R_7$, $R_6R_7N-(C_1$-$C_6$ alkyl)-, or $-C(O)NR_6R_7$

Embodiment 58 Compounds according to embodiment 57, wherein

$R_5$ is of the formula



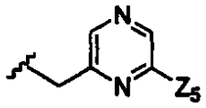
wherein

$Z_5$ is hydroxy($C_1$-$C_4$)alkyl, $C_1$-$C_4$ dihydroxyalkyl, OH, halogen, $CF_3$, ($C_1$-$C_4$)alkyl, $OCF_3$, $-NR_6R_7$, $R_6R_7N-(C_1$-$C_6$ alkyl)-, $-(C_1$-$C_4$ alkyl)$-C(O)NR_6R_7$, or $-C(O)NR_6R_7$, wherein

$R_6$ and $R_7$ at each occurrence are independently H, $C_1$-$C_6$ alkyl optionally substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkoxycarbonyl, halogen, $C_3$-$C_6$ cycloalkyl, OH, SH, or $C_1$-$C_4$ alkoxy

Embodiment 59 Compounds according to embodiment 57, wherein

$R_5$ is of the formula

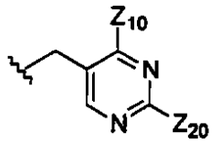


wherein

$Z_5$ is hydroxy($C_1$-$C_4$)alkyl, $C_1$-$C_4$ dihydroxyalkyl, OH, halogen, $CF_3$, ($C_1$-$C_4$)alkyl, $OCF_3$, $-NR_6R_7$, $R_6R_7N-(C_1$-$C_6$ alkyl)-, $-(C_1$-$C_4$ alkyl)$-C(O)NR_6R_7$, or $-C(O)NR_6R_7$, wherein

$R_6$ and $R_7$ at each occurrence are independently H, $C_1$-$C_6$ alkyl optionally substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkoxycarbonyl, halogen, $C_3$-$C_6$ cycloalkyl, OH, SH, or $C_1$-$C_4$ alkoxy

Embodiment 60 Compounds according to embodiment 57, wherein

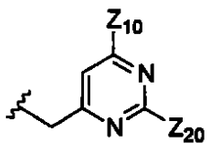
$R_5$ is of the formula  , wherein

$Z_{10}$ is H or methyl, and

$Z_{20}$ is -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$, hydroxy($C_1$-$C_4$)alkyl, $C_1$-$C_4$ dihydroxyalkyl, OH, halogen, $CF_3$, ($C_1$-$C_4$)alkyl, $OCF_3$, -$NR_6R_7$, $R_6R_7N$-($C_1$-$C_6$ alkyl)-, or -C(O)$NR_6R_7$, wherein

$R_6$ and $R_7$ at each occurrence are independently H, $C_1$-$C_6$ alkyl optionally substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkoxycarbonyl, halogen, $C_3$-$C_6$ cycloalkyl, OH, SH, or $C_1$-$C_4$ alkoxy

Embodiment 61 Compounds according to embodiment 57, wherein

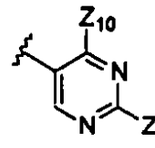
$R_5$ is of the formula  , wherein

$Z_{10}$ is H or methyl, and

$Z_{20}$ is -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$, hydroxy($C_1$-$C_4$)alkyl, $C_1$-$C_4$ dihydroxyalkyl, OH, halogen, $CF_3$, ($C_1$-$C_4$)alkyl, $OCF_3$, -$NR_6R_7$, $R_6R_7N$-($C_1$-$C_6$ alkyl)-, or -C(O)$NR_6R_7$, wherein

$R_6$ and $R_7$ at each occurrence are independently H, $C_1$-$C_6$ alkyl optionally substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkoxycarbonyl, halogen, $C_3$-$C_6$ cycloalkyl, OH, SH, or $C_1$-$C_4$ alkoxy

Embodiment 62 Compounds according to embodiment 57, wherein

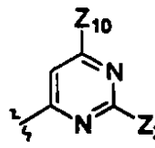
$R_5$ is of the formula  , wherein

$Z_{10}$ is H or methyl, and

$Z_{20}$ is -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$, hydroxy($C_1$-$C_4$)alkyl, $C_1$-$C_4$ dihydroxyalkyl, OH, halogen, $CF_3$, ($C_1$-$C_4$)alkyl, $OCF_3$, -$NR_6R_7$, $R_6R_7N$-($C_1$-$C_6$ alkyl)-, or -C(O)$NR_6R_7$, wherein

$R_6$ and $R_7$ at each occurrence are independently H, $C_1$-$C_6$ alkyl optionally substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkoxycarbonyl, halogen, $C_3$-$C_6$ cycloalkyl, OH, SH, or $C_1$-$C_4$ alkoxy

Embodiment 63 Compounds according to embodiment 57, wherein

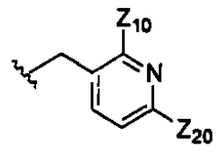
$R_5$ is of the formula  , wherein

$Z_{10}$ is H or methyl, and

$Z_{20}$ is -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$, hydroxy($C_1$-$C_4$)alkyl, $C_1$-$C_4$ dihydroxyalkyl, OH, halogen, $CF_3$, ($C_1$-$C_4$)alkyl, $OCF_3$, -$NR_6R_7$, $R_6R_7N$-($C_1$-$C_6$ alkyl)-, or -C(O)$NR_6R_7$, wherein

$R_6$ and $R_7$ at each occurrence are independently H, $C_1$-$C_6$ alkyl optionally substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkoxycarbonyl, halogen, $C_3$-$C_6$ cycloalkyl, OH, SH, or $C_1$-$C_4$ alkoxy

Embodiment 64 Compounds according to embodiment 57, wherein

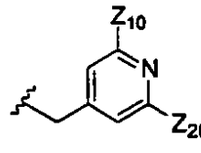
$R_5$ is of the formula  , wherein

$Z_{10}$ is H or methyl, and

$Z_{20}$ is -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$, hydroxy($C_1$-$C_4$)alkyl, $C_1$-$C_4$ dihydroxyalkyl, OH, halogen, $CF_3$, ($C_1$-$C_4$)alkyl, $OCF_3$, -$NR_6R_7$, $R_6R_7N$-($C_1$-$C_6$ alkyl)-, or -C(O)$NR_6R_7$, wherein

$R_6$ and $R_7$ at each occurrence are independently H, $C_1$-$C_6$ alkyl optionally substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkoxycarbonyl, halogen, $C_3$-$C_6$ cycloalkyl, OH, SH, or $C_1$-$C_4$ alkoxy

Embodiment 65 Compounds according to embodiment 57, wherein

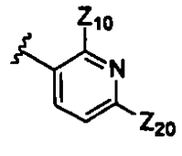
$R_5$ is of the formula  , wherein

$Z_{10}$ is H or methyl, and

$Z_{20}$ is -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$, hydroxy($C_1$-$C_4$)alkyl, $C_1$-$C_4$ dihydroxyalkyl, OH, halogen, $CF_3$, ($C_1$-$C_4$)alkyl, $OCF_3$, -$NR_6R_7$, $R_6R_7N$-($C_1$-$C_6$ alkyl)-, or -C(O)$NR_6R_7$, wherein

$R_6$ and $R_7$ at each occurrence are independently H, $C_1$-$C_6$ alkyl optionally substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkoxycarbonyl, halogen, $C_3$-$C_6$ cycloalkyl, OH, SH, or $C_1$-$C_4$ alkoxy

Embodiment 66 Compounds according to embodiment 57, wherein

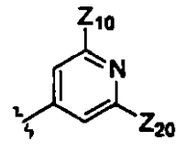
$R_5$ is of the formula  , wherein

$Z_{10}$ is H or methyl, and

$Z_{20}$ is -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$, hydroxy($C_1$-$C_4$)alkyl, $C_1$-$C_4$ dihydroxyalkyl, OH, halogen, $CF_3$, ($C_1$-$C_4$)alkyl, $OCF_3$, -$NR_6R_7$, $R_6R_7N$-($C_1$-$C_6$ alkyl)-, or -C(O)$NR_6R_7$, wherein

$R_6$ and $R_7$ at each occurrence are independently H, $C_1$-$C_6$ alkyl optionally substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkoxycarbonyl, halogen, $C_3$-$C_6$ cycloalkyl, OH, SH, or $C_1$-$C_4$ alkoxy

Embodiment 67 Compounds according to embodiment 57, wherein

$R_5$ is of the formula  , wherein

$Z_{10}$ is H or methyl, and

$Z_{20}$ is -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$, hydroxy($C_1$-$C_4$)alkyl, $C_1$-$C_4$ dihydroxyalkyl, OH, halogen, $CF_3$, ($C_1$-$C_4$)alkyl, $OCF_3$, -$NR_6R_7$, $R_6R_7N$-($C_1$-$C_6$ alkyl)-, or -C(O)$NR_6R_7$, wherein

$R_6$ and $R_7$ at each occurrence are independently H, $C_1$-$C_6$ alkyl optionally substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkoxycarbonyl, halogen, $C_3$-$C_6$ cycloalkyl, OH, SH, or $C_1$-$C_4$ alkoxy

Embodiment A7 Compounds according to embodiment 1 wherein

$R_1$ is H, halogen, alkyl optionally substituted with $C_1$-$C_4$ alkoxycarbonyl, $C_2$-$C_6$ alkenyl optionally substituted with $C_1$-$C_4$ alkoxycarbonyl, $C_2$-$C_4$ alkynyl, $C_1$-$C_4$ haloalkyl, carboxaldehyde, $C_1$-$C_4$ hydroxyalkyl, phenyl($C_1$-$C_6$)alkoxy, benzyl, phenethyl, phenpropyl, CN, or phenyl($C_1$-$C_6$)alkanoyl,

wherein the phenyl groups are unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, nitro, CN, $CF_3$, $OCF_3$ or $CO_2H$,

$R_2$ is OH, benzyloxy, phenyloxy, phenyloxy($C_1$-$C_6$)alkyl, phenyl($C_1$-$C_4$) thioalkoxy, -OC(O)NH($CH_2$)$_n$phenyl, -OC(O)N(alkyl)($CH_2$)$_n$phenyl, di($C_1$-$C_6$)alkylamino, $C_2$-$C_6$ alkynyl, pyridyl, pyrimidyl, pyridazyl, pyrazolyl, imidazolyl, pyrrolyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, tetrazolyl, pyrazinyl, benzimidazolyl, triazinyl, tetrahydrofuryl, piperidinyl, hexahydropyrimidinyl, thiazolyl, thienyl, or $CO_2H$, wherein n is 0, 1, 2, 3, 4, 5 or 6,

each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, $NR_6R_7$, ($C_1$-$C_4$) haloalkyl, ($C_1$-$C_4$) haloalkoxy, ($C_1$-$C_6$) alkyl, pyridyl -($C_1$-$C_6$)alkyl-N(R)-$CO_2R_{30}$, or $NR_6R_7$-($C_1$-$C_6$ alkyl)-,

$R_4$ is H, alkyl optionally substituted with one or two groups that are independently $CO_2H$, -$CO_2$alkyl, -C(O)NRR, -N($R_{30}$)C(O)NRR, -N($R_{30}$)C(O)-($C_1$-$C_6$)alkoxy, or -$NR_6R_7$, phenyl($C_1$-$C_6$)alkoxy, phenyl($C_1$-$C_6$)alkyl, hydroxyalkyl, wherein the phenyl groups are unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, hydroxy, alkoxy, alkyl, nitro, $CF_3$, or $OCF_3$, and

$R_5$ is phenyl($C_1$-$C_6$)alkyl, ($C_1$-$C_6$)alkyl, phenyl, piperidinyl($C_1$-$C_6$) alkyl, thienyl($C_1$-$C_6$) alkyl, indolyl, quinolinyl, isoquinolinyl, isoindolyl, indol-2-onyl, indazolyl, indolyl ($C_1$-$C_6$) alkyl, quinolinyl($C_1$-$C_6$) alkyl, isoquinolinyl($C_1$-$C_6$) alkyl, isoindolyl($C_1$-$C_6$) alkyl, indol-2-onyl($C_1$-$C_6$) alkyl, naphthyl($C_1$-$C_6$)alkyl, pyridyl($C_1$-

$C_6$)alkyl, pyrimidyl($C_1$-$C_6$)alkyl, pyrazinyl($C_1$-$C_6$)alkyl, or wherein

each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, halogen, alkoxy, benzyloxy, thioalkoxy, -$CO_2$($C_1$-$C_5$ alkyl), $CO_2H$, CN, amidinooxime, $NR_8R_9$, $NR_6R_7$-($C_1$-$C_6$ alkyl)-, -C(O)$NR_6R_7$, amidino, $CF_3$, or $OCF_3$,

$R_8$ is hydrogen, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkanoyl, phenyl $C_1$-$C_6$ alkyl and phenyl $C_1$-$C_6$ alkanoyl, and

$R_9$ is aminoalkyl, mono $C_1$-$C_6$ alkylamino $C_1$-$C_6$ alkyl, di $C_1$-$C_6$ alkylamino $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkanoyl, phenyl $C_1$-$C_4$ alkyl, indazolyl, and phenyl $C_1$-$C_4$ alkanoyl

In this embodiment, it is preferred that when $R_2$ is benzyloxy, $R_4$ is H, and $R_5$ is benzyl or methyl, $R_1$ is not hydrogen, and

no more than two of $R_1$, $R_2$, $R_4$, and $R_5$ are simultaneously hydrogen

Embodiment A8 Compounds according to embodiment A7 wherein

$R_1$ is H, halogen, $C_1$-$C_4$ alkyl optionally substituted with $C_1$-$C_4$ alkoxycarbonyl, $C_2$-$C_4$ alkenyl optionally substituted with $C_1$-$C_4$ alkoxycarbonyl, $C_2$-$C_4$ alkynyl, or carboxaldehyde,

$R_2$ is benzyloxy, OH, phenyloxy, phenyloxy($C_1$-$C_6$)alkyl, phenyl ($C_1$-$C_4$) thioalkoxy, or pyridyl, wherein each of the above is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, -($C_1$-$C_6$)alkyl-N(R)-$CO_2R_{30}$, $NR_6R_7$, ($C_1$-$C_4$) haloalkyl, ($C_1$-$C_4$) haloalkoxy, ($C_1$-$C_6$) alkyl, pyridyl, or $NR_6R_7$-($C_1$-$C_6$ alkyl)-

Embodiment A9 Compounds according to embodiment A7 wherein

$R_4$ is H, ($C_1$-$C_6$)alkyl optionally substituted with one or two groups that are independently $CO_2H$, -$CO_2$alkyl, -C(O)NRR, -N($R_{30}$)C(O)NRR, -N $R_{30}$)C(O)-($C_1$-$C_6$)alkoxy, or -$NR_6R_7$, phenyl($C_1$-$C_6$)alkoxy, or hydroxy($C_1$-$C_6$)alkyl, wherein the phenyl groups are unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, hydroxy, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkyl, nitro, $CF_3$, $OCF_3$, and

$R_5$ is benzyl, phenethyl, phenpropyl, phenbutyl, ($C_1$-$C_6$)alkyl, phenyl, pyridyl, pyrimidyl, indolyl, indazolyl, indolyl ($C_1$-$C_6$) alkyl, naphthyl($C_1$-$C_6$)alkyl, thienyl($C_1$-$C_6$)alkyl, pyridyl($C_1$-$C_6$)alkyl, pyrimidyl($C_1$-$C_6$)alkyl, or pyrazinyl($C_1$-$C_6$)alkyl, and wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently alkyl, halogen, alkoxy, benzyloxy, thioalkoxy, -$CO_2$($C_1$-$C_5$ alkyl), $CF_3$, $OCF_3$, $CO_2$h, CN, amidinooxime

In this embodiment, it is preferred that when $R_2$ is benzyloxy, $R_4$ is H, and $R_5$ is benzyl or methyl, $R_1$ is not hydrogen, and

no more than two of $R_1$, $R_2$, $R_4$, and $R_5$ are simultaneously hydrogen

Embodiment A10 Compounds according to embodiment A7, wherein

$R_4$ is H, ($C_1$-$C_4$) alkyl optionally substituted with one or two groups that are independently $CO_2H$, -$CO_2$alkyl, -C(O)NRR, -N($R_{30}$)C(O)NRR, -N($R_{30}$)C(O)-($C_1$-$C_6$)alkoxy, or -$NR_6R_7$, phenyl($C_1$-$C_6$)alkoxy, benzyl, phenethyl, phenpropyl, or hydroxy($C_1$-$C_6$)alkyl, wherein

the phenyl groups are unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen,

hydroxy, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkyl, nitro, $CF_3$, $OCF_3$, and

$R_5$ is indolyl, quinolinyl, isoquinolinyl, isoindolyl, indol-2-onyl, indolyl($C_1$-$C_6$) alkyl, quinolinyl($C_1$-$C_6$) alkyl, isoquinolinyl($C_1$-$C_6$) alkyl, isoindolyl($C_1$-$C_6$) alkyl, indol-2-onyl($C_1$-$C_6$) alkyl, each of which is unsubstituted or substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkyl, halogen, $CF_3$, $OCF_3$, $-CO_2CH_3$, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ alkoxy, $-CO_2(C_1$-$C_5$ alkyl), benzyloxy, $-NR_8R_9$, $NR_6R_7$-($C_1$-$C_6$ alkyl)-, $-C(O)NR_6R_7$, or amidinooxime, wherein

$R_6$ and $R_7$ are independently at each occurrence H, alkyl, hydroxyalkyl, alkoxy, alkoxyalkyl, alkanoyl, phenylalkyl, phenylalkoxy, or phenylalkanoyl, wherein each is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, hydroxy, $C_1$-$C_4$ alkoxy, OH, SH, $C_3$-$C_6$ cycloalkyl, $C_1$-$C_4$ alkyl, $CF_3$, or $OCF_3$, or

$R_6$, $R_7$, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently $C_1$-$C_4$ alkyl, hydroxy, hydroxy $C_1$-$C_4$ alkyl, or halogen

Embodiment A11 Compounds according to embodiment A7 wherein

$R_1$ is chloro, bromo, iodo, or H, and

$R_5$ is benzyl, phenethyl, phenpropyl, phenyl, quinolinyl, indolyl, isoquinolinyl, isoindolyl, indol-2-onyl, indolyl($C_1$-$C_6$) alkyl, quinolinyl($C_1$-$C_6$) alkyl, isoquinolinyl($C_1$-$C_6$) alkyl, isoindolyl($C_1$-$C_6$) alkyl, indol-2-onyl($C_1$-$C_6$) alkyl, piperidinyl $C_1$-$C_4$ alkyl, thienyl $C_1$-$C_4$ alkyl, $-CH_2$-pyridyl, or pyridyl, each of which is

unsubstituted or substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkyl, halogen, $CF_3$, $OCF_3$, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ alkoxy, -$CO_2$($C_1$-$C_5$ alkyl), benzyloxy, $NR_8R_9$, $NR_6R_7$ $C_1$-$C_4$ alkyl, -$C(O)NR_6R_7$, and amidinooxime, wherein

$R_6$ and $R_7$ are independently at each occurrence H, alkyl, hydroxyalkyl, alkoxy, alkoxyalkyl, alkanoyl, phenylalkyl, phenylalkoxy, or phenylalkanoyl, wherein each is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, hydroxy, $C_1$-$C_4$ alkoxy, OH, SH, $C_3$-$C_6$ cycloalkyl, $C_1$-$C_4$ alkyl, $CF_3$, or $OCF_3$, or

$R_6$, $R_7$, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently $C_1$-$C_4$ alkyl, hydroxy, hydroxy $C_1$-$C_4$ alkyl, or halogen

Embodiment A12 Compounds according to embodiment A11, wherein

$R_5$ is benzyl, phenethyl, phenpropyl, or phenyl, each of which is unsubstituted or substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkyl, halogen, $CF_3$, $OCF_3$, -$CO_2CH_3$, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ alkoxy, -$CO_2$($C_1$-$C_5$ alkyl), benzyloxy, $NR_8R_9$, $NR_6R_7$ $C_1$-$C_4$ alkyl, -$C(O)NR_6R_7$, and amidinooxime

Embodiment A13 Compounds according to embodiment A11, wherein

$R_5$ is quinolinyl, indolyl isoquinolinyl isoindolyl, indol-2-onyl, indolyl($C_1$-$C_6$) alkyl, quinolinyl($C_1$-$C_6$) alkyl, isoquinolinyl($C_1$-$C_6$) alkyl, isoindolyl($C_1$-$C_6$) alkyl, indol-2-onyl($C_1$-$C_6$) alkyl, piperidinyl $C_1$-$C_4$ alkyl, thienyl $C_1$-$C_4$

alkyl, -$CH_2$-pyridyl, or pyridyl, each of which is unsubstituted or substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkyl, halogen, $CF_3$, $OCF_3$, -$CO_2CH_3$, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ alkoxy, -$CO_2$($C_1$-$C_5$ alkyl), benzyloxy, $NR_8R_9$, $NR_6R_7$ $C_1$-$C_4$ alkyl, -$C(O)NR_6R_7$, and amidinooxime

Embodiment A14 Compounds according to any one of embodiments A11, A12, or A13 wherein

$R_2$ is benzyloxy, or phenethyloxy,

each of the above is unsubstituted or substituted with 1, 2, or 3, groups that are independently -($C_1$-$C_6$)alkyl-N(R)-$CO_2R_{30}$, fluoro, chloro, bromo, $CF_3$, or ($C_1$-$C_4$)alkyl

Embodiment A15 Compounds according to any one of embodiments A11, A12 or A13 wherein

$R_2$ is phenyloxy($C_1$-$C_6$)alkyl, wherein the phenyl group is unsubstituted or substituted with 1, 2, or 3, groups that are independently -($C_1$-$C_6$)alkyl-N(R)-$CO_2R_{30}$, fluoro, chloro, bromo, $CF_3$, or ($C_1$-$C_4$)alkyl

Embodiment A16 Compounds according to embodiment A1, wherein

$R_1$ is H, halogen, $C_1$-$C_4$ alkyl optionally substituted with $C_1$-$C_4$ alkoxycarbonyl, $C_2$-$C_4$ alkenyl optionally substituted with $C_1$-$C_4$ alkoxycarbonyl, $C_2$-$C_4$ alkynyl, or carboxaldehyde

Embodiment A17 Compounds according to embodiment A16, wherein

$R_2$ is benzyloxy, OH, phenyloxy, phenyloxy($C_1$-$C_6$)alkyl, or phenyl ($C_1$-$C_4$) thioalkoxy, wherein each of the above is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, -($C_1$-$C_6$)alkyl-N(R)-$CO_2R_{30}$, $NR_6R_7$,

($C_1$-$C_4$) haloalkyl, ($C_1$-$C_4$) haloalkoxy, ($C_1$-$C_6$) alkyl, pyridyl, or $NR_6R_7$-($C_1$ $C_6$ alkyl)-

Embodiment A18 Compounds according to embodiment A17, wherein

$R_4$ is H, or ($C_1$-$C_4$) alkyl optionally substituted with one or two groups that are independently $CO_2H$, -$CO_2$alkyl, -C(O)NRR, -N($R_{30}$)C(O)NRR, -N($R_{30}$)C(O)-($C_1$-$C_5$)alkoxy, OH, or -$NR_6R_7$

Embodiment A19 Compounds according to embodiment A18, wherein

$R_5$ is phenyl, naphthyl, indolyl, pyridyl, quinolinyl, isoquinolinyl, isoindolyl, indol-2-onyl, indolyl($C_1$-$C_6$) alkyl, quinolinyl($C_1$-$C_6$) alkyl, isoquinolinyl($C_1$-$C_6$) alkyl, isoindolyl($C_1$-$C_6$) alkyl, indol-2-oryl($C_1$-$C_6$) alkyl, pyridazinyl, pyrimidinyl, or pyrazinyl, pyridazinyl($C_1$-$C_6$) alkyl, pyrimidinyl($C_1$-$C_6$) alkyl, or pyrazinyl($C_1$-$C_6$) alkyl, each of which is unsubstituted or substituted with 1, 2, 3, 4 or 5 groups that are independently $C_1$-$C_4$ alkyl, halogen, $CF_3$, $OCF_3$, -$CO_2CH_3$, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ alkoxy, -$CO_2$($C_1$-$C_5$ alkyl), benzyloxy, -$NR_8R_9$, -C(O)$NR_6R_7$, $NR_6R_7$ $C_1$-$C_4$ alkyl, and amidinooxime, wherein

$R_6$ and $R_7$ are independently at each occurrence H, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkoxy $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkanoyl, phenyl $C_1$-$C_4$ alkyl, phenyl $C_1$-$C_4$ alkoxy, or phenyl $C_1$-$C_4$ alkanoyl, wherein each is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, hydroxy, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkyl, OH, SH, $C_3$-$C_6$ cycloalkyl, $CF_3$, or $OCF_3$, or

$R_6$, $R_7$, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, or piperazinyl ring

which is optionally substituted with 1 or 2 groups that are independently $C_1$-$C_4$ alkyl, hydroxy, hydroxy $C_1$-$C_4$ alkyl, or halogen

Embodiment A20 Compounds according to embodiment A19, wherein

$R_1$ is H, halogen, methyl, ethyl, $C_2$-$C_4$ alkenyl $C_2$-$C_4$ alkynyl, or carboxaldehyde,

$R_2$ is benzyloxy, OH, phenyloxy, phenyloxy($C_1$-$C_6$)alkyl, or phenyl ($C_1$-$C_4$) thioalkoxy, wherein each of the above is optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, -($C_1$-$C_6$)alkyl-N(R)-$CO_2R_{30}$, $NR_6R_7$, $NR_6R_7$ $C_1$-$C_4$ alkyl, ($C_1$-$C_4$) haloalkyl, ($C_1$-$C_4$) haloalkoxy, ($C_1$-$C_6$) alkyl, or pyridyl, and

$R_4$ is H, ($C_1$-$C_4$) alkyl optionally substituted with one or two groups that are independently $CO_2H$, -$CO_2$alkyl, -C(O)NRR, -N($R_{30}$)C(O)NRR, -N($R_{30}$)C(O)-($C_1$-$C_6$)alkoxy, OH, or -$NR_6R_7$

Embodiment A21 Compounds according to embodiment A20, wherein

$R_5$ is phenyl optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, $C_1$-$C_6$ alkyl, -$NR_{10}R_{11}$, $C_1$-$C_4$ alkoxy, -C(O)$NR_{10}R_{11}$, -$CO_2H$, $NR_{10}R_{11}$ $C_1$-$C_4$ alkyl, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxycarbonyl, $C_1$-$C_6$ alkoxy, CHO, -$SO_2NH_2$, $C_1$-$C_4$ haloalkyl, $C_1$-$C_6$ hydroxyalkyl, -$C_1$-$C_4$ alkyl-$NR_{12}$C(O)$NR_{13}R_{14}$, -$C_1$-$C_4$ alkyl-$NR_{12}$C(O)-($C_1$-$C_4$ alkyl)-$NR_{13}R_{14}$, -$C_1$-$C_4$ alkyl-$NR_{12}$C(O)$OR_{15}$, or -$C_1$-$C_4$ alkyl-$NR_{12}$C(O)-($C_1$-$C_4$ alkyl)-$R_{15}$, wherein

$R_{10}$ and $R_{11}$ at each occurrence are independently H, $C_1$-$C_6$ alkyl, amino $C_1$-$C_4$ alkyl, NH($C_1$-$C_6$ alkyl)alkyl, N($C_1$-$C_6$ alkyl)($C_1$-$C_6$ alkyl) $C_1$-$C_6$ alkyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, OH, -$SO_2$ ($C_1$-$C_6$ alkyl), or $C_1$-$C_6$ alkanoyl, or

$R_{10}$, $R_{11}$, and the nitrogen to which they are attached form a piperidinyl, pyrrolidinyl, piperazinyl, or a morpholinyl ring optionally substituted with 1 or 2 groups that are independently alkyl or halogen,

$R_{12}$ is H or $C_1$-$C_6$ alkyl,

$R_{13}$ and $R_{14}$ are independently H or $C_1$-$C_6$ alkyl or

$R_{13}$ and $R_{14}$ and the nitrogen to which they are attached form a morpholinyl ring, and

$R_{15}$ is $C_1$-$C_6$ alkoxy, -OC(O)$C_1$-$C_6$ alkyl, OH

Embodiment A22 Compounds according to embodiment A21, wherein

$R_5$ is phenyl optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, $C_1$-$C_6$ alkyl, -$NR_{10}R_{11}$, $NR_{10}R_{11}$ $C_1$-$C_6$ alkyl, $C_1$-$C_4$ alkoxy, or -C(O)$NR_{10}R_{11}$, -$CO_2H$, -$C_1$-$C_4$ alkyl-$NR_{10}R_{11}$, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxycarbonyl, $C_1$ $C_6$ alkoxy, CHO, -$SO_2NH_2$, $C_1$-$C_4$ haloalkyl, $C_1$-$C_6$ hydroxyalkyl, -$C_1$-$C_4$ alkyl-$NR_{12}C(O)NR_{13}R_{14}$, -$C_1$-$C_4$ alkyl-$NR_{12}C(O)$-($C_1$-$C_4$ alkyl)-$NR_{13}R_{14}$, -$C_1$-$C_4$ alkyl-$NR_{12}C(O)OR_{15}$, or -$C_1$-$C_4$ alkyl-$NR_{12}C(O)$-($C_1$-$C_4$ alkyl)-$R_{15}$ wherein

$R_{10}$ and $R_{11}$ at each occurrence are independently H, $C_1$-$C_6$ alkyl, amino $C_1$-$C_4$ alkyl, NH($C_1$-$C_6$ alkyl)alkyl, N($C_1$-$C_6$ alkyl)($C_1$-$C_6$ alkyl) $C_1$-$C_6$ alkyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, OH, -$SO_2$ ($C_1$-$C_6$ alkyl), or $C_1$-$C_6$ alkanoyl,

$R_{12}$ is H or $C_1$-$C_6$ alkyl,

$R_{13}$ and $R_{14}$ are independently H or $C_1$-$C_6$ alkyl, or

$R_{13}$ and $R_{14}$ and the nitrogen to which they are attached form a morpholinyl ring, and

$R_{15}$ is $C_1$-$C_6$ alkoxy, -OC(O)$C_1$-$C_6$ alkyl, OH

Embodiment A23 Compounds according to embodiment A22, wherein

$R_5$ is phenyl optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, $C_1$-$C_6$ alkyl, -$NR_{10}R_{11}$, $NR_{10}R_{11}$ $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, -$C(O)NR_{10}R_{11}$, wherein

$R_{10}$ and $R_{11}$ at each occurrence are independently H, $C_1$-$C_6$ alkyl, amino $C_1$-$C_4$ alkyl, $NH(C_1$-$C_6$ alkyl)alkyl, $N(C_1$-$C_6$ alkyl)($C_1$-$C_6$ alkyl) $C_1$-$C_6$ alkyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, OH, -$SO_2$ ($C_1$-$C_6$ alkyl), $C_1$-$C_6$ alkanoyl

Embodiment A24 Compounds according to embodiment A23, wherein

$R_5$ is phenyl optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, $C_1$-$C_6$ alkyl, -$NR_{10}R_{11}$, or $C_1$-$C_4$ alkoxy

Embodiment A25 Compounds according to embodiment A23, wherein

$R_5$ is substituted with at least one -$C(O)NR_{10}R_{11}$

Embodiment A26 Compounds according to embodiment A25, wherein

$R_{10}$ and $R_{11}$ at each occurrence are independently H, $C_1$-$C_6$ alkyl, amino $C_1$-$C_4$ alkyl, $NH(C_1$-$C_6$ alkyl)alkyl, $N(C_1$-$C_6$ alkyl)($C_1$-$C_6$ alkyl) $C_1$-$C_6$ alkyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl

Embodiment 27 Compounds according to embodiment A26, wherein

$R_{10}$ is H

Embodiment A28 Compounds according to embodiment A25, wherein

$R_{10}$ and $R_{11}$ at each occurrence are independently H, $C_1$-$C_6$ alkyl, OH, $-SO_2$ ($C_1$-$C_6$ alkyl), $C_1$-$C_6$ alkanoyl

Embodiment A29 Compounds according to embodiment A20, wherein

$R_5$ is phenyl optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, $C_1$-$C_6$ alkyl, $NH_2$, $NH(C_1$-$C_6$ alkyl), $N(C_1$-$C_6$ alkyl)($C_1$-$C_6$ alkyl), $C_1$-$C_4$ alkoxy, $-C(O)NR_{10}R_{11}$, wherein each of the above alkyl groups is optionally substituted with 1 or 2 groups that are independently OH, or methoxy, wherein

$R_{10}$, $R_{11}$, and the nitrogen to which they are attached form a piperidinyl, pyrrolidinyl, piperazinyl, or a morpholinyl ring optionally substituted with 1 or 2 groups that are independertly alkyl or halogen

Embodiment A30 Compounds according to embodiment A20, wherein

$R_5$ is phenyl optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, $C_1$-$C_6$ alkyl, $C_1$-$C_4$ alkoxy, $-CO_2H$, $-C_1$-$C_4$ alkyl-$NR_{10}R_{11}$, $C_1$-$C_6$ alkoxycarbonyl, $C_1$-$C_6$ alkoxy, CHO, $-SO_2NH_2$, $C_1$-$C_4$ haloalkyl, $C_1$-$C_6$ hydroxyalkyl, $-C_1$-$C_4$ alkyl-$NR_{12}C(O)NR_{13}R_{14}$, $-C_1$-$C_4$ alkyl-$NR_{12}C(O)$-($C_1$-$C_4$ alkyl)-$NR_{13}R_{14}$, $-C_1$-$C_4$ alkyl-$NR_{12}C(O)OR_{15}$, or $-C_1$-$C_4$ alkyl-$NR_{12}C(O)$ ($C_1$-$C_4$ alkyl)-$R_{15}$, $-OC(O)C_1$-$C_6$ alkyl, or OH wherein

$R_{12}$ is H or $C_1$-$C_6$ alkyl,

$R_{13}$ and $R_{14}$ are independently H or $C_1$-$C_6$ alkyl, or

$R_{13}$ and $R_{14}$ and the nitrogen to which they are attached form a morpholinyl ring,

$R_{15}$ is $C_1$-$C_6$ alkoxy

Embodiment A31 Compounds according to embodiment A30, wherein

$R_5$ is phenyl optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, -$CO_2H$, $C_1$-$C_4$ alkoxycarbonyl, $C_1$-$C_4$ alkoxy, CHO, -$SO_2NH_2$, $C_1$-$C_4$ haloalkyl, $C_1$-$C_4$ hydroxyalkyl

Embodiment A32 Compounds according to embodiment A30, wherein

$R_5$ is phenyl optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, -$CO_2H$, -$C_1$-$C_4$ alkyl-$NR_{10}R_{11}$, -$C_1$-$C_4$ alkyl-$NR_{12}C(O)NR_{13}R_{14}$, -$C_1$-$C_4$ alkyl-$NR_{12}C(O)$-($C_1$-$C_4$ alkyl)-$NR_{13}R_{14}$, -$C_1$-$C_4$ alkyl-$NR_{12}C(O)OR_{15}$, or -$C_1$-$C_4$ alkyl-$NR_{12}C(O)$-($C_1$-$C_4$ alkyl)-$R_{15}$, or -$OC(O)C_1$-$C_6$ alkyl, wherein

$R_{12}$ is H or $C_1$-$C_6$ alkyl,

$R_{13}$ and $R_{14}$ are independently H or $C_1$-$C_6$ alkyl, or

$R_{13}$ and $R_{14}$ and the nitrogen to which they are attached form a morpholinyl ring,

$R_{15}$ is $C_1$-$C_6$ alkoxy

Embodiment A33 Compounds according to embodiment A31, wherein

$R_5$ is phenyl optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, -$CO_2H$, -$C_1$-$C_4$ alkyl-$NR_{10}R_{11}$, -$C_1$-$C_4$ alkyl-$NR_{12}C(O)NR_{13}R_{14}$, -$C_1$-$C_4$ alkyl-$NR_{12}C(O)$-($C_1$-$C_4$ alkyl)-$NR_{13}R_{14}$, wherein

$R_{12}$ is H or $C_1$-$C_6$ alkyl,

$R_{13}$ and $R_{14}$ are independently H or $C_1$-$C_6$ alkyl, or

$R_{13}$ and $R_{14}$ and the nitrogen to which they are attached form a morpholinyl ring

Embodiment A34 Compounds according to any one of embodiments A30, A31, A32, or A33, wherein the phenyl group is substituted with two groups that are meta to each other

Embodiment A35 Compounds according to any one of embodiments A30, A31, A32, or A33, wherein the phenyl group is substituted with two groups that are para to each other

Embodiment A36 Compounds according to embodiment A20, wherein

$R_5$ is indolyl, pyridyl, pyridazinyl, pyrimidinyl, indazolyl, quinolinyl, isoquinolinyl, isoindolyl, indol-2-onyl, pyridoazinyl, pyrimidinyl, or pyrazinyl, , each of which is unsubstituted or substituted with 1, 2, 3, 4 or 5 groups that are independently $C_1$-$C_4$ alkyl, halogen, $CF_3$, $OCF_3$, $-CO_2CH_3$, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ alkoxy, $-CO_2(C_1$-$C_5$ alkyl), benzyloxy, $NR_8R_9$, $NR_8R_7$ $C_1$-$C_4$ alkyl, $-C(O)NR_6R_7$, or amidinooxime, wherein

$R_6$ and $R_7$ are independently at each occurrence H, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkoxy $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkanoyl, phenyl $C_1$-$C_4$ alkyl, phenyl $C_1$-$C_4$ alkoxy, or phenyl $C_1$-$C_4$ alkanoyl, wherein each is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, OH, SH, $C_3$-$C_6$ cycloalkyl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkyl, OH, $CF_3$, or $OCF_3$, or

$R_6$, $R_7$, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently $C_1$-$C_4$ alkyl, hydroxy, hydroxy $C_1$-$C_4$ alkyl, or halogen

Embodiment A38 Compounds according to embodiment A36, wherein

$R_5$ is indolyl, pyridyl, pyrimidinyl, indazolyl, or pyrazinyl, each of which is unsubstituted or substituted with 1, 2, 3, or 4 groups that are independently $C_1$-$C_4$ alkyl, halogen, $CF_3$, $OCF_3$, $-CO_2CH_3$, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ alkoxy, $-CO_2(C_1$-$C_5$ alkyl), benzyloxy, $-C(O)NR_6R_7$, $-NR_8R_9$, $NR_6R_7$ $C_1$-$C_4$ alkyl, and amidinooxime, wherein

$R_6$ and $R_7$ are independently at each occurrence H, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkoxy $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkanoyl, phenyl $C_1$-$C_4$ alkyl, phenyl $C_1$-$C_4$ alkoxy, or phenyl $C_1$-$C_4$ alkanoyl, wherein each is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, OH, SH, $C_3$-$C_6$ cycloalkyl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkyl, OH, $CF_3$, or $OCF_3$

Embodiment A39 Compounds according to embodiment A38, wherein

$R_5$ is indolyl, pyridyl, or pyrazinyl, each of which is unsubstituted or substituted with 1, 2, 3, or 4 groups that are independently $C_1$-$C_4$ alkyl, halogen, $CF_3$, $OCF_3$, $-CO_2CH_3$, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ alkoxy, $-CO_2(C_1$-$C_5$ alkyl), benzyloxy, $-C(O)NR_6R_7$, $NR_8R_9$, $NR_6R_7$-$C_1$-$C_4$ alkyl-, and amidinooxime, wherein

$R_6$ and $R_7$ are independently at each occurrence H, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkoxy $C_1$-$C_4$ alkyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently halogen, OH, SH, $C_3$-$C_6$ cycloalkyl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkyl, OH, $CF_3$, or $OCF_3$

Embodiment A40 Compounds according to embodiment A36, wherein

$R_5$ is indolyl, pyridyl, pyridazinyl, pyrimidinyl, or pyrazinyl, each of which is unsubstituted or substituted with 1, 2, 3, 4 or 5 groups that are independently $C_1$-$C_4$ alkyl, halogen, $CF_3$, $OCF_3$, $-CO_2CH_3$, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ alkoxy, $-CO_2(C_1$-$C_5$ alkyl), benzyloxy, $-C(O)NH_2$, $-C(O)N(C_1$-$C_6$ alkyl) wherein the alkyl group is optionally substituted with OH or methoxy, $-C(O)N(C_1$-$C_6$ alkyl) ($C_1$-$C_6$ alkyl) wherein each alkyl group is independently and optionally substituted with OH or methoxy, $-C(O)NR_6R_7$, $NR_8R_9$, $NR_6R_7$ $C_1$-$C_4$ alkyl, $-C_1$-$C_4$ alkyl-$NH_2$, $-C_1$-$C_4$ alkyl-$NH(C_1$-$C_6$ alkyl) wherein each alkyl group is independently and optionally substituted with OH or methoxy, $-C_1$-$C_4$ alkyl-$N(C_1$-$C_6$ alkyl)($C_1$-$C_6$ alkyl) wherein each alkyl group is independently and optionally substituted with OH or methoxy, and amidinooxime, wherein

$R_6$, $R_7$, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently $C_1$-$C_4$ alkyl, hydroxy, hydroxy $C_1$-$C_4$ alkyl, or halogen

Embodiment A42 Compounds according to any one of embodiments A37, A38, A39, or A40, , wherein

$R_1$ is H, halogen, methyl, or carboxaldehyde,

$R_2$ is benzyloxy, phenyloxy, phenyloxy($C_1$-$C_6$)alkyl, or phenyl ($C_1$-$C_4$) thioalkoxy, wherein each of the above is optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, -($C_1$-$C_6$)alkyl-N(R)-$CO_2R_{30}$, $NR_6R_7$, ($C_1$-$C_4$) haloalkyl, ($C_1$-$C_4$) haloalkoxy, ($C_1$-$C_6$) alkyl, $NR_6R_7(C_1$-$C_6$)alkyl, pyridyl, morpholinyl, thiomorpholinyl, piperazinyl pyridyl($C_1$-$C_6$)alkyl, morpholinyl($C_1$-$C_6$)alkyl,

thiomorpholinyl($C_1$-$C_6$)alkyl, or piperazinyl($C_1$-$C_6$)alkyl wherein the pyridyl, morpholinyl, thiomorpholinyl, and piperazinyl rings are optionally substituted with 1 or 2 groups that are independently $C_1$-$C_4$ alkyl, or halogen, wherein

$R_6$ and $R_7$ are independently at each occurrence H, $C_1$-$C_4$ alkyl optionally substituted with 1 or two groups that are independently OH, halogen or methoxy, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkoxy $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkanoyl, benzyl, benzyloxy, or phenyl $C_1$-$C_4$ alkanoyl, wherein each is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, OH, SH, $C_3$-$C_6$ cycloalkyl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkyl, $CF_3$, or $OCF_3$, and

$R_4$ is H, ($C_1$-$C_3$) alkyl optionally substituted with one or two groups that are independently $CO_2H$, -$CO_2$alkyl, -C(O)NRR, -N($R_{30}$)C(O)NRR, -N($R_{30}$)C(O)-($C_1$-$C_6$)alkoxy, -$NR_6R_7$, $NR_6R_7C_1$-$C_4$ alkyl, or hydroxy($C_1$-$C_3$)alkyl

Embodiment A43 Compounds according to embodiment A42, wherein

$R_1$ is H or halogen

Embodiment A44 Compounds according to embodiment A18, wherein

$R_5$ is phenyl($C_1$-$C_6$)alkyl, ($C_1$-$C_6$)alkyl, piperidinyl($C_1$-$C_6$) alkyl, thienyl($C_1$-$C_6$) alkyl, indolyl ($C_1$-$C_6$) alkyl, naphthyl($C_1$-$C_6$)alkyl, pyridyl($C_1$-$C_6$)alkyl, pyrimidyl($C_1$-$C_6$)alkyl, quinolinyl($C_1$-$C_6$) alkyl, isoquinolinyl($C_1$-$C_6$) alkyl, isoindolyl($C_1$-$C_6$) alkyl, indol-2-onyl($C_1$-$C_6$) alkyl, pyridazinyl($C_1$-$C_6$) alkyl, pyrazinyl($C_1$-$C_6$) alkyl, or pyrazinyl($C_1$-$C_6$)alkyl, wherein

each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, halogen, alkoxy, benzyloxy, hydroxyalkyl, thioalkoxy, $-CO_2(C_1-C_5$ alkyl), $CO_2H$, CN, amidinooxime, $NR_8R_9$, $NR_6R_7-(C_1-C_6$ alkyl)-, $-C(O)NR_6R_7$, amidino, $CF_3$, or $OCF_3$,

$R_8$ is hydrogen, $C_1-C_6$ alkyl, $C_1-C_6$ alkanoyl, phenyl $C_1-C_6$ alkyl and phenyl $C_1-C_6$ alkanoyl, and

$R_9$ is aminoalkyl, mono $C_1-C_6$ alkylamino $C_1-C_6$ alkyl, di $C_1-C_6$ alkylamino $C_1-C_6$ alkyl, $C_1-C_6$ alkyl, $C_1-C_6$ alkanoyl, phenyl $C_1-C_4$ alkyl, indazolyl, and phenyl $C_1-C_4$ alkanoyl

In this embodiment, it is preferred that when $R_2$ is benzyloxy, $R_4$ is H, and $R_5$ is benzyl or methyl, $R_1$ is not hydrogen, and

no more than two of $R_1$, $R_2$, $R_4$, and $R_5$ are simultaneously hydrogen

Embodiment A45 Compounds according to embodiment A44, wherein

$R_5$ is phenyl$(C_1-C_6)$alkyl, which is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, halogen, alkoxy, benzyloxy, thioalkoxy, $-CO_2(C_1-C_5$ alkyl), $CO_2H$, CN, amidinooxime, $NR_8R_9$, $NR_6R_7-(C_1-C_6$ alkyl)-, $-C(O)NR_6R_7$, amidino, $CF_3$, or $OCF_3$, wherein

$R_6$ and $R_7$ are independently at each occurrence H, $C_1-C_4$ alkyl, $C_1-C_4$ hydroxyalkyl, $C_1-C_4$ alkoxy, $C_1-C_4$ alkoxy $C_1-C_4$ alkyl, $C_1-C_4$ alkanoyl, phenyl $C_1-C_4$ alkyl, phenyl $C_1-C_4$ alkoxy, or phenyl $C_1-C_4$ alkanoyl, wherein each is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, OH, SH, $C_3-C_6$ cycloalkyl, $C_1-C_4$ alkoxy, $C_1-C_4$ alkyl, $CF_3$, or $OCF_3$, or

$R_6$, $R_7$, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently $C_1$-$C_4$ alkyl, hydroxy, hydroxy $C_1$-$C_4$ alkyl, or halogen,

$R_8$ is hydrogen, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkanoyl, phenyl $C_1$-$C_6$ alkyl and phenyl $C_1$-$C_6$ alkanoyl, and

$R_9$ is aminoalkyl, mono $C_1$-$C_6$ alkylamino $C_1$-$C_6$ alkyl, di $C_1$-$C_6$ alkylamino $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkanoyl, phenyl $C_1$-$C_4$ alkyl, indazolyl, and phenyl $C_1$-$C_4$ alkanoyl

Embodiment A46 Compounds according to embodiment A45, wherein

$R_5$ is phenyl($C_1$-$C_6$)alkyl, which is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently CN, halogen, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ thioalkoxy, $C_1$-$C_4$ haloalkyl, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ haloalkyl, $C_1$-$C_4$ haloalkoxy, $-C(O)NR_{20}R_{21}$, wherein

$R_{20}$ and $R_{21}$ are independently H, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, or

$R_{20}$, $R_{21}$, and the nitrogen to which they are attached form a piperazinyl, or morpholinyl ring, each of which is optionally substituted with 1 or 2 groups that are independently alkyl or halogen

Embodiment A47 Compounds according to embodiment A46, wherein

$R_5$ is phenyl($C_1$-$C_4$)alkyl, which is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently CN, halogen, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ haloalkyl, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ haloalkoxy, $-C(O)NR_{20}R_{21}$, wherein

$R_{20}$ and $R_{21}$ are independently H, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, or

$R_{20}$, $R_{21}$, and the nitrogen to which they are attached form a piperazinyl, or morpholinyl ring, each of which is optionally substituted with 1 or 2 groups that are independently alkyl or halogen

Embodiment A48 Compounds according to embodiment A47, wherein

$R_5$ is benzyl or phenethyl, each of which is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently CN, halogen, $C_1$-$C_4$ alkoxy, $CF_3$, $OCF_3$, $C_1$-$C_4$ alkyl, $-C(O)NR_{20}R_{21}$, wherein

$R_{20}$ and $R_{21}$ are independently H, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, or

$R_{20}$, $R_{21}$, and the nitrogen to which they are attached form a piperazinyl, or morpholinyl ring, each of which is optionally substituted with 1 or 2 groups that are independently alkyl or halogen

Embodiment A49 Compounds according to embodiment A48, wherein

$R_5$ is benzyl or phenethyl, each of which is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, methoxy, ethoxy, $CF_3$, $OCF_3$, methyl, ethyl, or $-C(O)NR_{20}R_{21}$, wherein

$R_{20}$ and $R_{21}$ are independently H, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl,

Embodiment A50 Compounds according to embodiment A48, wherein

$R_5$ is benzyl or phenethyl, each of which is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are

independently halogen, methoxy, ethoxy, $CF_3$, $OCF_3$, methyl, ethyl, or $-C(O)NR_{20}R_{21}$, wherein

$R_{20}$, $R_{21}$, and the nitrogen to which they are attached form a piperazinyl, or morpholinyl ring, each of which is optionally substituted with 1 or 2 groups that are independently alkyl or halogen

Embodiment A51 Compounds according to embodiment A49, wherein

$R_5$ is substituted on the phenyl ring with 1, 2, 3, 4, or 5 groups and wherein there is a group at the para position of the phenyl

Embodiment A52 Compounds according to embodiment A43, wherein

$R_5$ is piperidinyl$(C_1-C_6)$ alkyl, thienyl$(C_1-C_6)$ alkyl, indolyl $(C_1-C_6)$ alkyl, pyridyl$(C_1-C_6)$alkyl, pyrimidyl$(C_1-C_6)$alkyl, quinolinyl$(C_1-C_6)$ alkyl, isoquinolinyl$(C_1-C_6)$ alkyl, isoindolyl$(C_1-C_6)$ alkyl, indol-2-onyl$(C_1-C_6)$ alkyl, pyridazinyl$(C_1-C_6)$ alkyl, or pyrazinyl$(C_1-C_6)$ alkyl, or pyrazinyl$(C_1-C_6)$alkyl, or pyrazinyl$(C_1-C_6)$alkyl, wherein each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently $C_1-C_6$ alkyl, halogen, $C_1-C_6$ alkoxy, $C_1-C_6$ hydroxyalkyl, benzyloxy, $C_1-C_6$ thioalkoxy, $-CO_2(C_1-C_5$ alkyl), $CO_2H$, CN, amidinooxime, $NR_8R_9$, $NR_6R_7-(C_1-C_6$ alkyl)-, $-C(O)NR_6R_7$, amidino, $CF_3$, or $OCF_3$,

$R_8$ is hydrogen, $C_1-C_6$ alkyl, $C_1-C_6$ alkanoyl, phenyl $C_1-C_6$ alkyl and phenyl $C_1-C_6$ alkanoyl, and

$R_9$ is aminoalkyl, mono $C_1-C_6$ alkylamino $C_1-C_6$ alkyl, di $C_1-C_6$ alkylamino $C_1-C_6$ alkyl, $C_1-C_6$ alkyl, $C_1-C_6$ alkanoyl, phenyl $C_1-C_4$ alkyl, indazolyl, and phenyl $C_1-C_4$ alkanoyl

In this embodiment, it is preferred that when $R_2$ is benzyloxy, $R_4$ is H, and $R_5$ is benzyl or methyl, $R_1$ is not hydrogen, and

no more than two of $R_1$, $R_2$, $R_4$, and $R_5$ are simultaneously hydrogen

Embodiment A53 Compounds according to embodiment A52, wherein

$R_5$ is piperidinyl($C_1$-$C_4$) alkyl, thienyl($C_1$-$C_4$) alkyl, indolyl ($C_1$-$C_4$) alkyl, pyridyl($C_1$-$C_4$)alkyl, pyrimidyl($C_1$-$C_4$)alkyl, or pyrazinyl($C_1$-$C_4$)alkyl, each of which is unsubstituted

Embodiment A54 Compounds according to embodiment A52, wherein

$R_5$ is indolyl ($C_1$-$C_4$) alkyl, pyrimidyl($C_1$-$C_4$)alkyl, or pyrazinyl($C_1$-$C_4$)alkyl, wherein

each of the above is unsubstituted or substituted with 1, 2, 3, or 4 groups that are independently $C_1$-$C_6$ alkyl, halogen, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ hydroxyalkyl, benzyloxy, $C_1$-$C_6$ thioalkoxy, -$CO_2$($C_1$-$C_5$ alkyl), $CO_2H$, CN, amidinooxime, $NR_8R_9$, $NR_6R_7$-($C_1$-$C_6$ alkyl)-, amidino, -C(O)$NR_{20}R_{21}$, $CF_3$, or $OCF_3$, wherein

$R_6$ and $R_7$ are independently at each occurrence H, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkoxy $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkanoyl, benzyl, benzyloxy, or phenyl $C_1$-$C_4$ alkanoyl, wherein each is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, OH, SH, $C_3$-$C_6$ cycloalkyl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkyl, $CF_3$, or $OCF_3$, or

$R_6$, $R_7$, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups

that are independently $C_1$-$C_4$ alkyl, hydroxy, hydroxy $C_1$-$C_4$ alkyl, or halogen,

$R_8$ is hydrogen, $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkanoyl, pheryl $C_1$-$C_4$ alkyl and phenyl $C_2$-$C_4$ alkanoyl, and

$R_9$ is aminoalkyl, mono $C_1$-$C_6$ alkylamino $C_1$-$C_6$ alkyl, di $C_1$-$C_6$ alkylamino $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkyl, $C_1$-$C_6$ alkanoyl, phenyl $C_1$-$C_4$ alkyl, indazolyl, and phenyl $C_1$-$C_4$ alkanoyl,

$R_{20}$ and $R_{21}$ are independently H, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, or

$R_{20}$, $R_{21}$, and the nitrogen to which they are attached form a piperazinyl, or morpholinyl ring, each of which is optionally substituted with 1 or 2 groups that are independently alkyl or halogen

Embodiment A55 Compounds according to embodiment A54, wherein

$R_5$ is indolyl ($C_1$-$C_4$) alkyl, or pyrazinyl($C_1$-$C_4$)alkyl, wherein each of the above is unsubstituted or substituted with 1, 2, 3, or 4 groups that are independently $C_1$-$C_6$ alkyl, halogen, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ hydroxyalkyl, benzyloxy, $C_1$-$C_6$ thioalkoxy, -$CO_2$($C_1$-$C_5$ alkyl), $CO_2H$, CN, -C(O)$NR_{20}R_{21}$, $CF_3$, or $OCF_3$, wherein

$R_{20}$ and $R_{21}$ are independently H, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, or

$R_{20}$, $R_{21}$, and the nitrogen to which they are attached form a piperazinyl, or morpholinyl ring, each of which is optionally substituted with 1 or 2 groups that are independently alkyl or halogen

Embodiment A56 Compounds according to embodiment A52, wherein

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$R_5$ is isoquinolinyl, isoindolyl, indol-2-onyl, quinolinyl($C_1$-$C_6$) alkyl, isoquinolinyl($C_1$-$C_6$) alkyl, isoindolyl($C_1$-$C_6$) alkyl, indol-2-onyl($C_1$-$C_6$) alkyl, wherein

each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently $C_1$-$C_6$ alkyl, halogen, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ hydroxyalkyl, benzyloxy, $C_1$-$C_6$ thioalkoxy, -$CO_2$($C_1$-$C_5$ alkyl), $CO_2H$, CN, amidinooxime, $NR_8R_9$, $NR_6R_7$-($C_1$-$C_6$ alkyl)-, -$C(O)NR_6R_7$, amidino, $CF_3$, or $OCF_3$

Embodiment A57 Compounds according to embodiment A1, wherein

$R_1$ is H, halogen, methyl, ethyl, $C_2$-$C_4$ alkenyl, $C_2$-$C_4$ alkynyl, or carboxaldehyde,

$R_2$ is benzyloxy, OH, phenyloxy, phenyloxy($C_1$-$C_6$)alkyl, or phenyl ($C_1$-$C_4$) thioalkoxy, wherein each of the above is optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, -($C_1$-$C_6$)alkyl-N(R)-$CO_2R_{30}$, $NR_6R_7$, ($C_1$-$C_4$) haloalkyl, ($C_1$-$C_4$) haloalkoxy, ($C_1$-$C_6$) alkyl, pyridyl, or $NR_6R_7$-($C_1$-$C_6$ alkyl)-, and

$R_4$ is H, ($C_1$-$C_4$) alkyl optionally substituted with one or two groups that are independently $CO_2H$, -$CO_2$alkyl, -C(O)NRR, -$N(R_{30})C(O)$NRR, -$N(R_{30})C(O)$-($C_1$-$C_6$)alkoxy, or -$NR_6R_7$, or hydroxy($C_1$-$C_4$)alkyl,

$R_5$ is $C_3$-$C_7$ cycloalkyl or $C_3$-$C_7$ cycloalkylalkyl, each of which is optionally substituted with 1 or 2 groups that are independently alkyl, alkoxy, halogen, -$NR_6R_7$, or $NR_6R_7$-($C_1$-$C_6$ alkyl)-, wherein each of the alkyl groups is optionally substituted with 1 or 2 groups that are independently OH, methoxy, $NH_2$, or halogen

Embodiment A58 Compounds according to embodiment A57, wherein

$R_5$ is $C_3$-$C_7$ cycloalkyl or $C_3$-$C_7$ cycloalkyl $C_1$-$C_4$ alkyl, each of which is optionally substituted with 1 or 2 groups that are independently $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, halogen, -$NR_6R_7$, or $NR_6R_7$-($C_1$-$C_6$ alkyl)- wherein each of the alkyl groups is optionally substituted with 1 or 2 groups that are independently OH, methoxy, or $NH_2$,

$R_6$ and $R_7$ are independently at each occurrence H, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkoxy $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkanoyl, benzyl, benzyloxy, or phenyl $C_1$-$C_4$ alkanoyl, wherein each is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, OH, SH, $C_3$-$C_6$ cycloalkyl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkyl, $CF_3$, or $OCF_3$, or

$R_6$, $R_7$, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently $C_1$-$C_4$ alkyl, hydroxy, hydroxy $C_1$-$C_4$ alkyl, or halogen

Embodiment A59 Compounds according to embodiment A58, wherein

$R_1$ is H, halogen, methyl, ethyl,

$R_2$ is benzyloxy, phenyloxy, phenyloxy($C_1$-$C_6$)alkyl, or phenyl ($C_1$-$C_4$) thioalkoxy, wherein each of the above is optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, -($C_1$-$C_6$)alkyl-N(R)-$CO_2R_{30}$, amino, mono or dialkylamino, -$NR_6R_7$, ($C_1$-$C_4$) haloalkyl, ($C_1$-$C_4$) haloalkoxy, ($C_1$-$C_6$) alkyl, or $NR_6R_7$-($C_1$-$C_6$ alkyl)-, and

$R_4$ is H, methyl, ($C_1$-$C_4$)alkyl optionally substituted with one or two groups that are independently $CO_2H$, -$CO_2$alkyl, -C(O)NRR, -N($R_{30}$)C(O)NRR, -N($R_{30}$)C(O)-($C_1$-$C_6$)alkoxy, or -$NR_6R_7$ or hydroxy($C_1$-$C_2$)alkyl

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Embodiment A60 Compounds according to embodiment A59, wherein

$R_2$ is substituted with two halogens and is further optionally substituted with 1 or 2 groups that are independently halogen, $-(C_1-C_6)$alkyl-$N(R)-CO_2R_{10}$, amino, mono or dialkylamino, $-NR_8R_7$, $(C_1-C_4)$ haloalkyl, $(C_1-C_4)$ haloalkoxy, $(C_1-C_6)$ alkyl, or $NR_6R_7-(C_1-C_6$ alkyl)

Embodiment A61 Compounds according to embodiment A1, wherein

$R_5$ is H, alkyl optionally substituted with 1, 2, or 3 groups that are independently phenylalkoxycarbonyl, $-NR_8R_9$, halogen, $-C(O)NR_8R_9$, alkoxycarbonyl, or alkanoyl, alkoxyalkyl optionally substituted with one trimethylsilyl group, alkoxycarbonyl, amino, hydroxyalkyl, alkenyl optionally substituted with alkoxycarbonyl, alkynyl, $-SO_2$-alkyl, or alkoxy optionally substituted with one trimethylsilyl group, wherein

each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, halogen, alkoxy, phenylalkoxy, thioalkoxy, $-SO_2$alkyl, alkoxycarbonyl, phenylalkoxycarbonyl, $CO_2H$, CN, OH, amidinooxime, $NR_8R_9$, $NR_6R_7-(C_1-C_6$ alkyl)-, $-C(O)NR_6R_7$, amidino, hydroxyalkyl, carboxaldehyde, $-NR_6R_7$, haloalkyl, or haloalkoxy,

wherein $R_8$ is hydrogen, alkyl, alkanoyl, phenylalkyl and arylalkanoyl, and

wherein $R_9$ is alkyl, alkanoyl, phenylalkyl, heteroaryl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, and arylalkanoyl

In this embodiment, it is preferred that when $R_2$ is benzyloxy, $R_4$ is H, and $R_5$ is benzyl or methyl, $R_1$ is not hydrogen, and

no more than two of $R_1$, $R_2$, $R_4$, and $R_5$ are simultaneously hydrogen

Embodiment A62 Compounds according to embodiment A1, wherein

$R_5$ is H, alkyl optionally substituted with 1, 2, or 3 groups that are independently phenylalkoxycarbonyl, $-NR_8R_9$, halogen, $-C(O)NR_8R_9$, alkoxycarbonyl, or alkanoyl, alkoxyalkyl optionally substituted with one trimethylsilyl group, alkoxycarbonyl, amino, hydroxyalkyl, alkenyl optionally substituted with alkoxycarbonyl, alkynyl, $-SO_2$-alkyl, alkoxy optionally substituted with one trimethylsilyl group, wherein

each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, halogen, alkoxy, phenylalkoxy, thioalkoxy, $-SO_2$alkyl, alkoxycarbonyl, phenylalkoxycarbonyl, $CO_2H$, CN, OH, amidinooxime, $NR_8R_9$, $NR_6R_7$-($C_1$-$C_6$ alkyl)-, $-C(O)NR_6R_7$, amidino, hydroxyalkyl, carboxaldehyde, $-NR_6R_7$, haloalkyl, or haloalkoxy,

wherein $R_8$ is hydrogen, alkyl, alkanoyl, phenylalkyl and arylalkanoyl, and

wherein $R_9$ is alkyl, alkanoyl, phenylalkyl, heteroaryl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, and arylalkanoyl

In this embodiment, it is preferred that when $R_2$ is benzyloxy, $R_4$ is H, and $R_5$ is benzyl or methyl, $R_1$ is not hydrogen, and

no more than two of $R_1$, $R_2$, $R_4$, and $R_5$ are simultaneously hydrogen

Embodiment A63 Compounds according to embodiment A62, wherein

$R_1$ is H, halogen, methyl, ethyl, $C_2$-$C_4$ alkenyl, $C_2$-$C_4$ alkynyl, or carboxaldehyde,

$R_2$ is benzyloxy, OH, phenyloxy, phenyloxy($C_1$-$C_6$)alkyl, or phenyl ($C_1$-$C_4$) thioalkoxy, wherein each of the above is optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, -($C_1$-$C_6$)alkyl-N(R)-$CO_2R_{30}$, $NR_6R_7$, ($C_1$-$C_4$) haloalkyl, ($C_1$-$C_4$) haloalkoxy, ($C_1$-$C_6$) alkyl, pyridyl, or $NR_6R_7$-($C_1$-$C_6$ alkyl)-, and

$R_4$ is H, ($C_1$-$C_4$) alkyl optionally substituted with one or two groups that are independently $CO_2H$, -$CO_2$alkyl, -C(O)NRR, -N($R_{30}$)C(O)NRR, -N($R_{30}$)C(O)-($C_1$-$C_6$)alkoxy, or -$NR_6R_7$, or hydroxy($C_1$-$C_4$)alkyl

Embodiment A64 Compounds according to embodiment A63, wherein

$R_5$ is H, alkyl optionally substituted with 1, 2, or 3 groups that are independently phenylalkoxycarbonyl, -$NR_8R_9$, halogen, -C(O)$NR_8R_9$, alkoxycarbonyl, or alkanoyl, alkoxyalkyl optionally substituted with one trimethylsilyl group, alkoxycarbonyl, amino, hydroxyalkyl, alkenyl optionally substituted with alkoxycarbonyl, alkynyl, -$SO_2$-alkyl, alkoxy optionally substituted with one trimethylsilyl group, wherein

wherein $R_8$ is hydrogen, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkanoyl, phenyl $C_1$-$C_4$ alkyl and phenyl $C_1$-$C_4$ alkanoyl,

wherein $R_9$ is $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkanoyl, phenyl $C_1$-$C_4$ alkyl, pyridyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, and phenyl $C_1$-$C_4$ alkanoyl

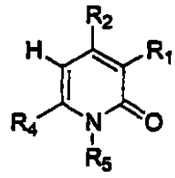
Embodiment A65 Compounds according to embodiment A64, wherein

$R_5$ is $C_1$-$C_6$ alkyl optionally substituted with 1, 2, or 3 groups that are independently phenyl $C_1$-$C_4$ alkoxycarbonyl, $NH_2$,

mono $C_1$-$C_4$ alkylamino, di $C_1$-$C_4$ alkylamino, halogen, -C(O)$NH_2$, -C(O)NH($C_1$-$C_6$ alkyl) wherein the alkyl is optionally substituted with OH, $NH_2$, or methoxy, -C(O)N($C_1$-$C_6$ alkyl) ($C_1$-$C_6$ alkyl) wherein each alkyl is optionally substituted with OH, $NH_2$, or methoxy, $C_1$-$C_4$ alkoxycarbonyl, and $C_1$-$C_4$ alkanoyl, or

$R_5$ is $C_1$-$C_4$ alkoxy $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxycarbonyl, amino, $C_1$-$C_4$ hydroxyalkyl, $C_2$-$C_4$ alkenyl optionally substituted with $C_1$-$C_4$ alkoxycarbonyl, $C_2$-$C_4$ alkynyl, -$SO_2$- $C_1$-$C_4$ alkyl, or $C_1$-$C_4$ alkoxy

Embodiment A66 A compound of the formula



or a pharmaceutically acceptable salt thereof, wherein

$R_1$ is halogen, $NO_2$, alkyl, carboxaldehyde, hydroxyalkyl, arylalkoxy, arylalkyl, CN, aryl, alkanoyl, alkoxy, alkoxyalkyl, haloalkyl, or arylalkanoyl,

wherein the aryl portion of arylalkoxy, arylalkyl, and arylalkanoyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, ($C_1$-$C_4$)alkyl, ($C_1$-$C_4$) alkoxy, nitro, CN, haloalkyl, haloalkoxy or $CO_2H$,

wherein the alkyl portion of the alkyl, hydroxyalkyl, arylalkoxy, arylalkyl, alkanoyl, alkoxy, alkoxyalkyl and arylalkanoyl groups is unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkoxycarbonyl, or spirocyclopropyl,

$R_2$ is aryl, heteroaryl, arylalkenyl, arylalkoxy, aryloxyalkyl, arylalkyl, OH, alkynyl, aryloxy, aryloxyalkyl,

arylthioalkoxy, alkoxy, -OC(O)NH-$(CH_2)_n$aryl, -OC(O)N(alkyl)$(CH_2)_n$aryl, -$OSO_2$($C_1$-$C_6$)alkyl, -$OSO_2$aryl, alkyl, alkoxyalkoxy, $NR_8R_9$, or $CO_2H$, wherein

n is 0, 1, 2, 3, 4, 5 or 6,

each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, -($C_1$-$C_6$)alkyl-N(R)-$CO_2R_{30}$, alkoxy, alkoxycarbonyl, CN, $NR_6R_7$, haloalkyl, haloalkoxy, alkyl, heteroaryl, heteroarylalkyl, $NR_6R_7$-($C_1$-$C_6$ alkyl)-, phenyl, -$SO_2$-phenyl wherein the phenyl groups are optionally substituted with 1, 2, or 3 groups that are independently halogen or $NO_2$, or -OC(O)$NR_6R_7$, wherein

$R_6$ and $R_7$ are independently at each occurrence H, alkyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, -$SO_2$-alkyl, OH, hydroxyalkyl, -($C_1$-$C_4$)alkyl-$CO_2$-alkyl, heteroarylalkyl, alkanoyl, arylalkyl, arylalkoxy, or arylalkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, alkoxy, heterocycloalkyl, OH, SH, $C_3$-$C_6$ cycloalkyl, $NH_2$, NH(alkyl), N(alkyl)(alkyl), -O-alkanoyl, alkyl, haloalkyl, or haloalkoxy, or

$R_6$, $R_7$, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, hydroxy, hydroxy $C_1$-$C_4$ alkyl, or halogen,

R at each occurrence is independently H or $C_1$-$C_6$ alkyl,

$R_{30}$ is $C_1$-$C_6$ alkyl optionally substituted with 1 or 2 groups that are independently OH, SH, halogen,

amino, monoalkylamino, dialkylamino or $C_3$-$C_6$ cycloalkyl,

$R_4$ is H, alkyl optionally substituted with one or two groups that are independently $CO_2H$, $-CO_2$alkyl, $-C(O)NRR$, $-N(R_{30})C(O)NRR$, $-N(R_{30})C(O)-(C_1-C_6)$alkoxy or $-NR_6R_7$, arylalkoxy, arylalkyl, hydroxyalkyl, haloalkyl, alkoxy, carboxaldehyde, $CO_2H$, alkoxyalkyl, or alkoxyalkoxy, wherein

the aryl portion of arylalkoxy, arylalkyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, hydroxy, alkoxy, alkyl, nitro, haloalkyl, or haloalkoxy, and

$R_5$ is H, arylalkyl, alkyl, aryl, alkoxy, heterocycloalkylalkyl, heteroarylalkyl, heterocycloalkyl, cycloalkyl, cycloalkylalkyl, -alkyl-S-aryl, -alkyl-$SO_2$-aryl, $-(C_1-C_4)$alkyl-C(O)-heterocycloalkyl, $-SO_2$-aryl, or heteroaryl, wherein

each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, halogen, alkoxy, aryl, arylalkoxy, thioalkoxy, alkoxycarbonyl, arylalkoxycarbonyl, OH, $CO_2H$, CN, amidinooxime, $NR_8R_9$, $NR_6R_7$-($C_1$-$C_6$ alkyl)-, $-C(O)NR_6R_7$, $-(C_1-C_4$ alkyl)$-C(O)NR_6R_7$ amidino, hydroxyalkyl, $-SO_2$alkyl, $-SO_2H$, $-SO_2NR_6R_7$, $-NR_6R_7$, alkanoyl wherein the alkyl portion is optionally substituted with OH, halogen or alkoxy, haloalkyl, $-(C_1-C_4$ alkyl)$-NR_{15}C(O)NR_{16}R_{17}$, $-(C_1-C_4$ alkyl)$-NR_{15}C(O)R_{18}$, $-O-CH_2-O$, $-O-CH_2CH_2-O-$, or haloalkoxy, wherein

$R_9$ at each occurrence is independently hydrogen, alkyl, alkanoyl, arylalkyl and arylalkanoyl wherein each of the above is optionally substituted with 1, 2, 3, 4, or 5 groups that

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are independently alkyl, alkoxy, alkoxycarbonyl, halogen, or haloalkyl, and

$R_9$ at each occurrence is independently alkyl, alkanoyl, arylalkyl cycloalkyl, alkenyl, heteroaryl, cycloalkylalkyl, arylalkanoyl, $-SO_2$-phenyl, and aryl wherein each of the above is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, alkoxy, alkoxycarbonyl, halogen, or haloalkyl

$R_{15}$ is H or $C_1$-$C_6$ alkyl,

$R_{16}$ and $R_{17}$ are independently H or $C_1$-$C_6$ alkyl, or

$R_{16}$, $R_{17}$, and the nitrogen to which they are attached form a morpholinyl ring, and

$R_{18}$ is $C_1$-$C_6$ alkyl optionally substituted with $-O-(C_2$-$C_6$ alkanoyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, amino $C_1$-$C_6$ alkyl, mono or dialkylamino $C_1$-$C_6$ alkyl

In this embodiment, it is preferred that

$R_6$ and $R_7$ are not simultaneously OH,

$R_6$ and $R_7$ are not simultaneously $-SO_2(C_1$-$C_6$ alkyl),

when $R_2$ is OH, $R_4$ is methyl and $R_5$ is phenyl, $R_1$ is not acetyl, and

$R_4$ and $R_5$ are not simultaneously hydrogen

Embodiment A71 Compounds according to embodiment A66 wherein

$R_1$ is halogen, $C_1$-$C_6$ alkyl, phenyl, carboxaldehyde, $C_1$-$C_6$ hydroxyalkyl, phenyl $C_1$-$C_6$ alkoxy, phenyl $C_1$-$C_6$ alkyl, CN, $C_1$-$C_6$ alkanoyl, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, $C_1$-$C_6$ haloalkyl, or phenyl $C_1$-$C_6$ alkanoyl,

wherein the above phenyl groups are unsubstituted or substituted with 1, 2, or 3 groups that are

independently halogen, ($C_1$-$C_4$)alkyl, ($C_1$-$C_4$) alkoxy, nitro, CN, $C_1$-$C_4$ haloalkyl, $C_1$-$C_4$ haloalkoxy or $CO_2H$, wherein the above alkyl groups are unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, methoxy, or ethoxy,

$R_2$ is phenylalkoxy, OH, phenyloxy, phenyloxy($C_1$-$C_6$)alkyl, phenylthio($C_1$-$C_4$)alkoxy, alkoxy, alkenyl, phenethyl, -OC(O)NH$(CH_2)_n$phenyl, -OC(O)N(alkyl)$(CH_2)_n$phenyl, alkyl, alkoxyalkoxy, $NR_8R_9$, pyridyl, pyrimidyl, pyridazyl, pyrazolyl, imidazolyl, pyrrolyl, tetrahydroquinolinyl, amino, tetrahydroisoquinolinyl, tetrazolyl, pyrazinyl, benzimidazolyl, triazinyl, tetrahydrofuryl, piperidinyl, hexahydropyrimidinyl, thiazolyl, thienyl, or $CO_2H$, wherein n is 0, 1, 2, or 3,

each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, -($C_1$-$C_6$)alkyl-N(R)-$CO_2R_{30}$, haloalkyl, haloalkoxy, alkyl, thienyl, pyridyl, or phenyl optionally substituted with 1, 2, or 3 halogens,

$R_6$ and $R_7$ are independently at each occurrence H, alkyl, alkoxy, alkoxyalkyl, hydroxyalkyl, alkoxycarbonyl, -($C_1$-$C_4$)alkyl-$CO_2$-alkyl, alkanoyl, phenylalkyl, phenylalkoxy, or phenylalkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, OH, SH, $C_3$-$C_6$ cycloalkyl, alkoxy, $NH_2$, NH($C_1$-$C_6$ alkyl), N($C_1$-$C_6$ alkyl)($C_1$-$C_6$ alkyl), alkyl, $CF_3$ or $OCF_3$, or

$R_6$, $R_7$, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently $C_1$-$C_4$ alkyl, hydroxy, hydroxy $C_1$-$C_4$ alkyl, or halogen,

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$R_4$ is H, alkyl optionally substituted with one or two groups that are independently $CO_2H$, $-CO_2$alkyl, $-C(O)NRR$, $-N(R_{30})C(O)NRR$, $-N(R_{30})C(O)-(C_1-C_6)$alkoxy or $-NR_6R_7$, phenylalkoxy, phenylalkyl, hydroxyalkyl, carboxaldehyde, haloalkyl, alkoxy, alkoxyalkyl, or alkoxyalkoxy, wherein the above phenyl groups are unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, hydroxy, alkoxy, alkyl, nitro, haloalkyl, or haloalkoxy, and

$R_5$ is benzyl, phenethyl, $(C_1-C_6)$alkyl, phenyl, naphthyl, alkoxy, piperidinyl, pyrrolidinyl, imidazolidinyl, piperazinyl, isoquinolinyl, tetrahydroisoquinolinyl, indolyl, 1H-indazolyl, pyridyl, pyrimidyl, pyridazyl, pyrazinyl, piperidinyl$(C_1-C_6)$alkyl, pyrrolidinyl$(C_1-C_6)$alkyl, imidazolidinyl$(C_1-C_6)$alkyl, piperazinyl$(C_1-C_6)$alkyl, pyridyl$(C_1-C_6)$alkyl, pyrimidyl$(C_1-C_6)$alkyl, pyridazyl$(C_1-C_6)$alkyl, pyrazinyl$(C_1-C_6)$alkyl, isoquinolinyl$(C_1-C_6)$alkyl, tetrahydroisoquinolinyl$(C_1-C_6)$alkyl, indolyl$(C_1-C_6)$alkyl, or 1H-indazolyl$(C_1-C_6)$alkyl, and wherein

each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, halogen, alkoxy, hydroxyalkyl, phenylalkoxy, thioalkoxy, alkoxycarbonyl, phenylalkoxycarbonyl, OH, $CO_2H$, CN, amidinooxime, $NR_8R_9$, $NR_6R_7-(C_1-C_6$ alkyl)-, $-C(O)NR_6R_7$, amidino, piperazinyl, morpholinyl, $-SO_2(C_1-C_6)$ alkyl, $-SO_2NH_2$, $-SO_2NH(C_1-C_6)$alkyl, $-SO_2N(C_1-C_6)$alkyl $(C_1-C_6$alkyl, haloalkyl, or haloalkoxy

In this embodiment, it is preferred that when $R_2$ is OH, $R_4$ is methyl and $R_5$ is phenyl, $R_1$ is not acetyl, and

$R_4$ and $R_5$ are not simultaneously hydrogen

Embodiment A72 Compounds according to embodiment A71 wherein

$R_1$ is halogen, alkyl, carboxaldehyde, hydroxyalkyl, phenylalkoxy, phenyl, benzyl, phenethyl, phenpropyl, phenbutyl, CN, $(C_2-C_6)$alkanoyl, haloalkyl, or phenylCO-, phenyl$CH_2$CO-, phenyl$CH_2CH_2$CO-,

wherein the above phenyl groups are unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, $(C_1-C_4)$alkyl, $(C_1-C_4)$ alkoxy, nitro, CN, haloalkyl, haloalkoxy or $CO_2H$,

wherein the above alkyl groups are unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, methoxy, or ethoxy,

$R_2$ is benzyloxy, phenethyloxy, phenpropyloxy, OH, phenyloxy, phenyloxy$(C_1-C_6)$alkyl, phenylthio$(C_1-C_4)$alkoxy, $NR_8R_9$, $(C_1-C_6)$alkyl, alkynyl, phenethyl, -OC(O)N$(CH_3)CH_2$phenyl, alkoxyalkoxy, pyridyl, pyrimidyl, pyridazyl, pyrazolyl, imidazolyl, pyrrolyl, pyrazinyl, piperidinyl, hexahydropyrimidinyl, benzimidazolyl, or thienyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, -$(C_1-C_6)$alkyl-N(R)-$CO_2R_{30}$, $CF_3$, $OCF_3$, $(C_1-C_4)$alkyl, thienyl, pyridyl, or phenyl optionally substituted with 1, 2, or 3 halogens,

$R_6$ and $R_7$ are independently at each occurrence H, $(C_1-C_6)$alkyl, $(C_1-C_6)$alkoxy, $(C_1-C_6)$alkoxy$(C_1-C_6)$alkyl, $(C_1-C_6)$alkoxycarbonyl, hydroxy$(C_1-C_6)$alkyl, -$(C_1-C_4)$alkyl-$CO_2$-alkyl, $(C_1-C_6)$alkanoyl, phenyl$(C_1-C_6)$alkyl, phenyl$(C_1-C_6)$alkoxy, or phenyl$(C_1-C_6)$alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, $(C_1-C_6)$alkoxy, $NH_2$,

OH, SH, $C_3$-$C_6$ cycloalkyl, ($C_1$-$C_6$)alkyl, $CF_3$ or $OCF_3$, or

$R_6$, $R_7$, and the nitrogen to which they are attached form a morpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently $C_1$-$C_4$ alkyl, hydroxy, hydroxy $C_1$-$C_4$ alkyl, or halogen,

$R_4$ is H, alkyl optionally substituted with one or two groups that are independently $CO_2H$, -$CO_2$alkyl, -C(O)NRR, -N($R_{30}$)C(O)NRR, -N($R_{30}$)C(O)-($C_1$-$C_6$)alkoxy, or -$NR_6R_7$, benzyloxy, phenethyloxy, phenpropyloxy, benzyl, phenethyl, phenpropyl, hydroxyalkyl, halo($C_1$-$C_4$)alkyl, carboxaldehyde, alkoxy, alkoxyalkyl, or alkoxyalkoxy, wherein

the above phenyl groups are unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, hydroxy, alkoxy, alkyl, nitro, $CF_3$ or $OCF_3$, and

$R_5$ is benzyl, phenethyl, phenpropyl, phenbutyl, ($C_1$-$C_6$)alkyl, phenyl, piperidinyl, pyrrolidinyl, imidazolidinyl, piperidinyl($C_1$-$C_6$)alkyl, pyrrolidinyl($C_1$-$C_6$)alkyl, imidazolidinyl($C_1$-$C_6$)alkyl, pyridyl, pyrimidyl, pyridazyl, pyrazinyl, pyridyl($C_1$-$C_6$)alkyl, pyrimidyl($C_1$-$C_6$)alkyl, pyridazyl($C_1$-$C_6$)alkyl, or pyrazinyl($C_1$-$C_6$)alkyl wherein

each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, halogen, haloalkyl, $NR_8R_9$, $NR_6R_7$-($C_1$-$C_6$ alkyl)-, carboxaldehyde, morpholinyl, $SO_2NH_2$, $SO_2NH$(alkyl), $SO_2N$(alkyl)(alkyl), alkoxy, hydroxyalkyl, benzyloxy, thioalkoxy, OH, $CO_2H$, CN, -$CO_2$($C_1$-$C_5$ alkyl), phenylalkoxycarbonyl, amidinooxime, amidino, -C(O)$NR_6R_7$, $CF_3$, $CF_2CF_3$, $ClCH_2$, or $OCF_3$

In this embodiment, it is preferred that when $R_2$ is OH, $R_4$ is methyl and $R_5$ is phenyl, $R_1$ is not acetyl

Embodiment A73 Compounds according to embodiment A72 wherein

$R_1$ is halogen, alkyl, carboxaldehyde, hydroxy($C_1$-$C_4$)alkyl, phenylalkoxy, benzyl, phenethyl, -C(O)$CH_3$, phenylCO-, or phenyl$CH_2$CO-,

wherein the above phenyl groups are unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, ($C_1$-$C_4$)alkyl, ($C_1$-$C_4$) alkoxy, nitro, CN, $CF_3$, or $OCF_3$,

wherein the above alkyl groups are unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, methoxy, or ethoxy,

$R_2$ is benzyloxy, phenethyloxy, phenpropyloxy, OH, phenyloxy, phenyloxy($C_1$-$C_6$)alkyl, phenethyl, $NR_8R_9$, -S-benzyl, or ($C_1$-$C_6$)alkyl, wherein

each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, -($C_1$-$C_6$)alkyl-N(R)-$CO_2R_{30}$, $CF_3$, $OCF_3$, alkyl, thienyl, or pyridyl,

$R_6$ and $R_7$ are independently at each occurrence H, ($C_1$-$C_6$)alkyl, ($C_1$-$C_6$)alkoxy, ($C_1$-$C_6$)alkoxy($C_1$-$C_6$)alkyl, ($C_1$-$C_6$)alkoxycarbonyl, hydroxy($C_1$-$C_6$)alkyl, -($C_1$-$C_4$)alkyl-$CO_2$-alkyl, ($C_1$-$C_6$)alkanoyl, phenyl($C_1$-$C_6$)alkyl, phenyl($C_1$-$C_6$)alkoxy, or phenyl($C_1$-$C_6$)alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, ($C_1$-$C_6$)alkoxy, $NH_2$, OH, SH, $C_3$-$C_6$ cycloalkyl, ($C_1$-$C_6$)alkyl, $CF_3$ or $OCF_3$, or

$R_6$, $R_7$, and the nitrogen to which they are attached form a morpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently $C_1$-$C_4$ alkyl, hydroxy, hydroxy $C_1$-$C_4$ alkyl, or halogen,

$R_4$ is H, alkyl optionally substituted with one or two groups that are independently $CO_2H$, $-CO_2$alkyl, $-C(O)NRR$, $-N(R_{30})C(O)NRR$, $-N(R_{30})C(O)-(C_1-C_6)$alkoxy, or $-NR_6R_7$, benzyloxy, phenethyloxy, phenpropyloxy, benzyl, or hydroxyalkyl, wherein

the above phenyl groups are unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, hydroxy, alkoxy, alkyl, nitro, $CF_3$ or $OCF_3$, and

$R_5$ is benzyl, phenethyl, phenpropyl, phenbutyl, $(C_1-C_6)$alkyl, phenyl, pyridyl, pyrazinyl, pyrimidinyl, pyrazinyl$(C_1-C_6)$alkyl, pyrimidinyl$(C_1-C_6)$alkyl, or pyridyl$(C_1-C_4)$alkyl, wherein

each of the above is unsubstituted or substituted with 1, 2 3, 4, or 5 groups that are independently alkyl, halogen, haloalkyl, morpholinyl, $-SO_2$ $(C_1-C_6)$ alkyl, $-SO_2NH_2$, $-SO_2NH(C_1-C_6)$, $-SO_2N(C_1-C_6)(C_1-C_6)$, $(C_1-C_4)$alkoxy, phenyl$(C_1-C_4)$alkoxy, thio$(C_1-C_4)$alkoxy, $(C_1-C_4)$alkoxycarbonyl, OH, $CO_2H$, CN, amidinooxime, amidino, $NR_8R_9$, $NR_6R_7$-$(C_1-C_6$ alkyl)-, hydroxyalkyl, $CONR_6R_7$, $CF_3$, or $OCF_3$

Embodiment A74 Compounds according to embodiment A73 wherein

$R_1$ is halogen, alkyl, carboxaldehyde, or hydroxyalkyl,

$R_2$ is benzyloxy, phenethyloxy, phenpropyloxy, OH, phenyloxy, phenyloxy$(C_1-C_6)$alkyl, phenethyl, phenylthioalkoxy, or $(C_1-C_6)$alkyl, wherein

each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, -($C_1$-$C_6$)alkyl-N(R)-$CO_2R_{30}$, $CF_3$, $OCF_3$, alkyl, thienyl, or pyridyl,

$R_4$ is H, ($C_1$-$C_4$) alkyl optionally substituted with one or two groups that are independently $CO_2H$, -$CO_2$alkyl, -C(O)NRR, -N($R_{30}$)C(O)NRR, -N($R_{30}$)C(O)-($C_1$-$C_6$)alkoxy, or -$NR_6R_7$, benzyloxy, or phenethyloxy, wherein

the above phenyl groups are unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, hydroxy, ($C_1$-$C_4$)alkoxy, ($C_1$-$C_4$)alkyl, nitro, $CF_3$ or $OCF_3$, and

$R_5$ is benzyl, phenethyl, ($C_1$-$C_6$)alkyl, phenyl, indazolyl, or pyridyl, wherein each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently ($C_1$-$C_4$)alkyl, halogen, OH, $CO_2H$, CN, ($C_1$-$C_4$)alkoxy, -C(O)pyrrolidine, -$SO_2$ ($C_1$-$C_6$) alkyl, benzyloxy, -$CO_2$($C_1$-$C_5$ alkyl), amidino, thio($C_1$-$C_4$)alkoxy, amidinooxime, $CF_3$, $NR_8R_9$, $NR_6R_7$-($C_1$-$C_6$ alkyl)-, $CONR_6R_7$, or $OCF_3$

Embodiment A75 Compounds according to embodiment A74 wherein

$R_1$ is chloro, bromo, iodo, methyl, $C_2$-$C_3$ alkenyl, $C_2$-$C_3$ alkynyl, and

$R_5$ is benzyl, phenethyl, phenpropyl, phenyl, or pyridyl, each of which is unsubstituted or substituted with 1, 2, or 3 groups that are independently alkyl, OH, halogen, alkoxy, $NH_2$, NH($C_1$-$C_6$)alkyl, N($C_1$-$C_6$)alkyl($C_1$-$C_6$)alkyl, $NR_8R_9$, $NR_6R_7$-($C_1$-$C_6$ alkyl)-, $CONR_6R_7$, and amidinooxime, wherein

$R_6$ and $R_7$ are independently H, $C_1$-$C_4$ alkyl, $C_1$-$C_6$ alkanoyl, wherein the alkyl and alkanoyl groups are optionally

substituted with 1, 2, or 3 groups that are independently OH, halogen, or $C_3$-$C_7$ cyclopropyl

Embodiment A76 Compounds according to embodiment A75 wherein

$R_2$ is benzyloxy, phenethyl, phenyloxy($C_1$-$C_6$)alkyl, or phenethyloxy, each of which is unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, -($C_1$-$C_6$)alkyl-N(R)-$CO_2R_{30}$, $CF_3$, $OCF_3$, or ($C_1$-$C_4$)alkyl

Embodiment A77 Compounds according to embodiment A66, wherein

$R_5$ is benzyl, phenethyl, thienyl($C_1$-$C_6$ alkyl), piperidinyl($C_1$-$C_6$)alkyl, pyrrolidinyl($C_1$-$C_6$)alkyl, imidazolidinyl($C_1$-$C_6$)alkyl, piperazinyl($C_1$-$C_6$)alkyl, pyridyl($C_1$-$C_6$)alkyl, pyrimidyl($C_1$-$C_6$)alkyl, pyridazyl($C_1$-$C_6$)alkyl, pyrazinyl($C_1$-$C_6$)alkyl, isoquinolinyl($C_1$-$C_6$)alkyl, tetrahydroisoquinolinyl($C_1$-$C_6$)alkyl, indolyl($C_1$-$C_6$)alkyl, or 1H-indazolyl($C_1$-$C_6$)alkyl, wherein

each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently ($C_1$-$C_6$)alkyl, halogen, ($C_1$-$C_6$)alkoxy, ($C_1$-$C_6$)hydroxyalkyl, phenyl($C_1$-$C_6$)alkoxy, ($C_1$-$C_6$)thioalkoxy, ($C_1$-$C_6$)alkoxycarbonyl, phenyl($C_1$-$C_6$)alkoxycarbonyl, OH, $CO_2H$, CN, amidinooxime, $NR_8R_9$, $NR_6R_7$-($C_1$-$C_6$ alkyl)-, -$C(O)NR_6R_7$, amidino, piperazinyl, morpholinyl, -$SO_2$($C_1$-$C_6$) alkyl, -$SO_2NH_2$, -$SO_2NH$($C_1$-$C_6$)alkyl, -$SO_2N$($C_1$-$C_6$)alkyl ($C_1$-$C_6$)alkyl, ($C_1$-$C_4$)haloalkyl, -($C_1$-$C_4$ alkyl)-$NR_{15}C(O)NR_{16}R_{17}$, -($C_1$-$C_4$ alkyl)-$NR_{15}C(O)R_{18}$, -O-$CH_2$-O, -O-$CH_2CH_2$-O-, or ($C_1$-$C_4$)haloalkoxy, wherein

$R_6$ and $R_7$ are independently at each occurrence H, ($C_1$-$C_6$)alkyl, ($C_1$-$C_6$)alkoxy, ($C_1$-$C_6$)alkoxy($C_1$-

$C_6$)alkyl, ($C_1$-$C_6$)alkoxycarbonyl, ($C_1$-$C_6$)hydroxyalkyl, -($C_1$-$C_4$)alkyl-$CO_2$-($C_1$-$C_6$)alkyl, ($C_1$-$C_6$)alkanoyl, phenyl($C_1$-$C_6$)alkyl, phenyl($C_1$-$C_6$)alkoxy, or phenyl($C_1$-$C_6$)alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, ($C_1$-$C_4$)alkoxy, $NH_2$, OH, SH, $C_3$-$C_6$ cycloalkyl, NH($C_1$-$C_6$ alkyl), N($C_1$-$C_6$ alkyl)($C_1$-$C_6$ alkyl), ($C_1$-$C_4$)alkyl, $CF_3$ or $OCF_3$, or

$R_6$, $R_7$, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently $C_1$-$C_4$ alkyl, hydroxy, hydroxy $C_1$-$C_4$ alkyl, or halogen, and

$R_{18}$ is $C_1$-$C_6$ alkyl optionally substituted with -O-($C_2$-$C_6$ alkanoyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, amino $C_1$-$C_6$ alkyl, mono or dialkylamino $C_1$-$C_6$ alkyl

In this embodiment, it is preferred that $R_6$ and $R_7$ are not simultaneously OH, and

$R_6$ and $R_7$ are not simultaneously -$SO_2$($C_1$-$C_6$ alkyl)

Embodiment A78 Compounds according to embodiment A77, wherein

$R_1$ is halogen, methyl, ethyl, $C_2$-$C_4$ alkenyl, $C_2$-$C_4$ alkynyl, or carboxaldehyde,

$R_2$ is benzyloxy, OH, phenyloxy, phenyloxy($C_1$-$C_6$)alkyl, or phenyl ($C_1$-$C_4$) thioalkoxy, wherein each of the above is optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, -($C_1$-$C_6$)alkyl-N(R)-$CO_2R_{30}$, $NR_6R_7$,

$(C_1-C_4)$ haloalkyl, $(C_1-C_4)$ haloalkoxy, $(C_1-C_6)$ alkyl, or pyridyl, and

$R_4$ is H, $(C_1-C_4)$ alkyl optionally substituted with one or two groups that are independently $CO_2H$, $-CO_2$alkyl, $-C(O)NRR$, $-N(R_{30})C(O)NRR$, $-N(R_{30})C(O)-(C_1-C_6)$alkoxy, or $-NR_6R_7$, or hydroxy$(C_1-C_4)$alkyl

Embodiment A79 Compounds according to embodiment A78, wherein

$R_5$ is benzyl, or phenethyl, wherein each is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently $(C_1-C_6)$alkyl, halogen, $(C_1-C_6)$alkoxy, $(C_1-C_6)$hydroxyalkyl, phenyl$(C_1-C_6)$alkoxy, $(C_1-C_6)$thioalkoxy, $(C_1-C_6)$alkoxycarbonyl, phenyl$(C_1-C_6)$alkoxycarbonyl, OH, $CO_2H$, CN, amidinooxime, $NR_8R_9$, $NR_6R_7-(C_1-C_6$ alkyl)-, $-C(O)NR_6R_7$, $-(C_1-C_4$ alkyl)$-C(O)NR_6R_7$amidino, piperazinyl, morpholinyl, $-SO_2$ $(C_1-C_6)$ alkyl, $-SO_2NH_2$, $-SO_2NH(C_1-C_6)$alkyl, $-SO_2N(C_1-C_6)$alkyl $(C_1-C_6)$alkyl, $(C_1-C_4)$haloalkyl, $-(C_1-C_4$ alkyl$)-NR_{15}C(O)R_{18}$, $-O-CH_2-O$, $-O-CH_2CH_2-O-$, or $(C_1-C_4)$haloalkoxy, wherein

$R_6$ and $R_7$ are independently at each occurrence H, $(C_1-C_6)$alkyl, $(C_1-C_6)$alkoxy, $(C_1-C_6)$alkoxy$(C_1-C_6)$alkyl, $(C_1-C_6)$alkoxycarbonyl, $(C_1-C_6)$hydroxyalkyl, $-(C_1-C_4)$alkyl$-CO_2-(C_1-C_6)$alkyl, $(C_1-C_6)$alkanoyl, phenyl$(C_1-C_6)$alkyl, phenyl$(C_1-C_6)$alkoxy, or phenyl$(C_1-C_6)$alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, $(C_1-C_4)$alkoxy, $NH_2$, OH, SH, $C_3-C_6$ cycloalkyl, $NH(C_1-C_6$ alkyl), $N(C_1-C_6$ alkyl$)(C_1-C_6$ alkyl), $(C_1-C_4)$alkyl, $CF_3$ or $OCF_3$, or

$R_6$, $R_7$, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is

optionally substituted with 1 or 2 groups that are independently $C_1$-$C_4$ alkyl, hydroxy, hydroxy $C_1$-$C_4$ alkyl, or halogen, and

$R_{18}$ is $C_1$-$C_6$ alkyl optionally substituted with -O-($C_2$-$C_6$ alkanoyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, amino $C_1$-$C_6$ alkyl, or mono or dialkylamino $C_1$-$C_6$ alkyl

In this embodiment, it is preferred that $R_6$ and $R_7$ are not simultaneously OH, and

$R_6$ and $R_7$ are not simultaneously -$SO_2$($C_1$-$C_6$ alkyl)

Embodiment A80 Compounds according to embodiment A79, wherein

$R_5$ is benzyl or phenethyl, wherein each is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently $C_1$-$C_6$ alkyl, -C(O)$NR_6R_7$ -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$, $NR_8R_9$, halogen, $C_1$-$C_6$ alkoxy, $CO_2H$, -($C_1$-$C_4$ alkyl)-$CO_2H$, $C_1$-$C_6$ thioalkoxy, amidinooxime, $C_1$-$C_6$ alkoxycarbonyl, -($C_1$-$C_4$ alkyl)-$C_1$-$C_6$ alkoxycarbonyl, $C_1$-$C_6$ hydroxyalkyl, -($C_1$-$C_4$ alkyl)-CN, CN, phenyl $C_1$-$C_6$ alkoxy, OH, $C_1$-$C_4$ haloalkyl, $C_1$-$C_4$ haloalkoxy, $NR_6R_7$-($C_1$-$C_6$ alkyl)-, -($C_1$-$C_4$ alkyl)-$NR_{15}$C(O)$R_{18}$, amidinooxime, -$SO_2$($C_1$-$C_6$ alkyl), -O-$CH_2$-O-, -O-$CH_2CH_2$-O-, phenyl $C_1$-$C_4$ alkoxy, or phenyl, wherein

$R_6$ and $R_7$ at each occurrence are independently H, OH, $C_1$-$C_6$ alkyl, amino $C_1$-$C_4$ alkyl, NH($C_1$-$C_6$ alkyl)alkyl, N($C_1$-$C_6$ alkyl)($C_1$-$C_6$ alkyl) $C_1$-$C_6$ alkyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, -$SO_2$($C_1$-$C_6$ alkyl) each of which is optionally substituted with 1, 2, or 3 groups that are independently halogen, OH, SH, $C_3$-$C_6$ cycloalkyl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkyl, OH, $CF_3$, or $OCF_3$,

or

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$R_6$, $R_7$, and the nitrogen to which they are attached form a piperidinyl, pyrrolidinyl, piperazinyl, or a morpholinyl, thiomorpholinyl, ring optionally substituted with 1 or 2 groups that are independently alkyl, hydroxy, hydroxy $C_1$-$C_4$ alkyl, or halogen,

$R_{18}$ is $C_1$-$C_6$ alkyl optionally substituted with -O-($C_2$-$C_6$ alkanoyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, amino $C_1$-$C_6$ alkyl, mono or dialkylamino C -$C_6$ alkyl

In this embodiment, it is preferred that $R_6$ and $R_7$ are not simultaneously OH, and

$R_6$ and $R_7$ are not simultaneously -$SO_2$($C_1$-$C_6$ alkyl)

Embodiment A81 Compounds according to embodiment A80, wherein

$R_5$ is benzyl or phenethyl, wherein each is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently $C_1$-$C_6$ alkyl, -C(O)$NR_6R_7$ -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$, halogen, $C_1$-$C_6$ alkoxy, $CO_2H$, -($C_1$-$C_4$ alkyl)-$CO_2H$, $C_1$-$C_6$ thioalkoxy, amidinooxime, $C_1$-$C_6$ alkoxycarbonyl, -($C_1$-$C_4$ alkyl)-$C_1$-$C_6$ alkoxycarbonyl, $C_1$-$C_6$ hydroxyalkyl, -($C_1$-$C_4$ alkyl)-CN, CN, phenyl $C_1$-$C_6$ alkoxy, OH, $C_1$-$C_4$ haloalkyl, $C_1$-$C_4$ haloalkoxy, $NR_6R_7$-($C_1$-$C_6$ alkyl)-, $NR_8R_9$, -($C_1$-$C_4$ alkyl)-$NR_{15}$C(O)$R_{16}$, amidinooxime, -$SO_2$($C_1$-$C_6$ alkyl), -O-$CH_2$-O-, -O-$CH_2CH_2$-O-, phenyl $C_1$-$C_4$ alkoxy, or phenyl, wherein

$R_6$ and $R_7$ at each occurrence are independently H, OH, $C_1$-$C_6$ alkyl, amino $C_1$-$C_4$ alkyl, NH($C_1$-$C_6$ alkyl)alkyl, N($C_1$-$C_6$ alkyl)($C_1$-$C_6$ alkyl) $C_1$-$C_6$ alkyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, -$SO_2$($C_1$-$C_6$ alkyl) each of which is optionally substituted with 1, 2, or 3 groups that are independently halogen, OH, SH, $C_3$-$C_6$

cycloalkyl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkyl, OH, $CF_3$, or $OCF_3$, and

$R_{18}$ is $C_1$-$C_6$ alkyl optionally substituted with -O-($C_2$-$C_6$ alkanoyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, amino $C_1$-$C_6$ alkyl, mono or dialkylamino $C_1$-$C_6$ alkyl

In this embodiment, it is preferred that $R_6$ and $R_7$ are not simultaneously OH, and

$R_6$ and $R_7$ are not simultaneously -$SO_2$($C_1$-$C_6$ alkyl)

Embodiment A82 Compounds according to embodiment A81, wherein

$R_5$ is benzyl which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently $C_1$-$C_4$ alkyl, -C(O)$NR_6R_7$ -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$, halogen, $C_1$-$C_4$ alkoxy, $CO_2H$, $C_1$-$C_4$ thioalkoxy, $C_1$-$C_4$ alkoxycarbonyl, $C_1$-$C_6$ hydroxyalkyl, CN, OH, $NR_6R_7$-($C_1$-$C_6$ alkyl)-, $NR_8R_9$, -$SO_2$($C_1$-$C_6$ alkyl), or benzyloxy, wherein

$R_6$ and $R_7$ at each occurrence are independently H, OH, $C_1$-$C_6$ alkyl, amino $C_1$-$C_4$ alkyl, NH($C_1$-$C_6$ alkyl)alkyl, N($C_1$-$C_6$ alkyl)($C_1$-$C_6$ alkyl) $C_1$-$C_6$ alkyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, -$SO_2$($C_1$-$C_6$ alkyl) each of which is optionally substituted with 1, 2, or 3 groups that are independently halogen, OH, SH, $C_3$-$C_6$ cycloalkyl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkyl, OH, $CF_3$, or $OCF_3$

In this embodiment, it is preferred that $R_6$ and $R_7$ are not simultaneously OH, and

$R_6$ and $R_7$ are not simultaneously -$SO_2$($C_1$-$C_6$ alkyl)

Embodiment A83 Compounds according to embodiment A82, wherein

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$R_5$ is benzyl which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently $C_1$-$C_4$ alkyl, $-C(O)NR_6R_7$, $-(C_1$-$C_4$ alkyl$)-C(O)NR_6R_7$, halogen, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ thioalkoxy, $C_1$-$C_4$ alkoxycarboryl, $C_1$-$C_6$ hydroxyalkyl, CN, $NR_8R_9$, or $NR_6R_7$-($C_1$-$C_6$ alkyl)-, wherein

$R_6$ and $R_7$ at each occurrence are independently H, OH, $C_1$-$C_6$ alkyl, amino $C_1$-$C_4$ alkyl, $NH(C_1$-$C_6$ alkyl$)$alkyl, $N(C_1$-$C_6$ alkyl$)(C_1$-$C_6$ alkyl$)$ $C_1$-$C_6$ alkyl, $C_1$-$C_6$ hydroxyalkyl, or $C_1$-$C_4$ alkoxy $C_1$-$C_4$ alkyl each of which is optionally substituted with 1, 2, or 3 groups that are independently halogen, OH, SH, $C_3$-$C_6$ cycloalkyl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkyl, OH, $CF_3$, or $OCF_3$

In this embodiment, it is preferred that $R_6$ and $R_7$ are not simultaneously OH

Embodiment A84 Compounds according to embodiment A83, wherein

the $R_5$ group is disubstituted with two groups that are meta to each other

Embodiment A86 Compounds according to embodiment A80, wherein

$R_5$ is benzyl which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently $C_1$-$C_4$ alkyl, $-C(O)NR_6R_7$, $-(C_1$-$C_4$ alkyl$)-C(O)NR_6R_7$, $NR_8R_9$, $NR_6R_7$-($C_1$-$C_6$ alkyl)-, halogen, $C_1$-$C_4$ alkoxy, $CO_2H$, $-(C_1$-$C_4$ alkyl$)-CO_2H$, $-(C_1$-$C_4$ alkyl$)-C_1$-$C_6$ alkoxycarbonyl, $-(C_1$-$C_4$ alkyl$)-CN$, CN, phenyl $C_1$-$C_6$ alkoxy, $CF_3$, $OCF_3$, $-(C_1$-$C_4$ alkyl$)-NR_{15}C(O)R_{18}$, amidinooxime, $-O-CH_2-O-$, $-O-CH_2CH_2-O-$, or phenyl, wherein

$R_6$ and $R_7$ at each occurrence are independently H, $C_1$-$C_4$ alkyl, amino $C_1$-$C_4$ alkyl, $NH(C_1$-$C_4$ alkyl$)$alkyl, $N(C_1$-$C_4$ alkyl$)(C_1$-$C_4$ alkyl$)$ $C_1$-$C_4$ alkyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_4$ alkoxy $C_1$-$C_4$ alkyl, or OH, each of which is

optionally substituted with 1, 2, or 3 groups that are independently halogen, OH, SH, $C_3$-$C_6$ cycloalkyl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkyl, OH, $CF_3$, or $OCF_3$, and

$R_{18}$ is $C_1$-$C_6$ alkyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ alkoxy, $C_1$-$C_4$ alkoxy $C_1$-$C_6$ alkyl, amino $C_1$-$C_6$ alkyl, mono or dialkylamino $C_1$-$C_6$ alkyl

In this embodiment, it is preferred that $R_6$ and $R_7$ are not simultaneously OH

Embodiment A87 Compounds according to embodiment A80, wherein

$R_5$ is benzyl or phenethyl, wherein each is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently $C_1$-$C_6$ alkyl, $-C(O)NR_6R_7$ $-(C_1$-$C_4$ alkyl)-$C(O)NR_6R_7$, halogen, $C_1$-$C_6$ alkoxy, $CO_2H$, $-(C_1$-$C_4$ alkyl)-$CO_2H$, $C_1$-$C_6$ thioalkoxy, amidinooxime, $C_1$-$C_6$ alkoxycarbonyl, $-(C_1$-$C_4$ alkyl)-$C_1$-$C_6$ alkoxycarbonyl, $C_1$-$C_6$ hydroxyalkyl, $-(C_1$-$C_4$ alkyl)-CN, CN, phenyl $C_1$-$C_6$ alkoxy, OH, $C_1$-$C_4$ haloalkyl, $C_1$-$C_4$ haloalkoxy, $NR_8R_9$, $NR_6R_7$-($C_1$-$C_6$ alkyl)-, $-(C_1$-$C_4$ alkyl)-$NR_{15}C(O)R_{18}$, amidinooxime, $-SO_2(C_1$-$C_6$ alkyl), $-O-CH_2-O-$, $-O-CH_2CH_2-O-$, phenyl $C_1$-$C_4$ alkoxy, or phenyl, wherein

$R_6$, $R_7$, and the nitrogen to which they are attached form a piperidinyl, pyrrolidinyl, piperazinyl, or a morpholinyl, thiomorpholinyl, ring optionally substituted with 1 or 2 groups that are independently alkyl, hydroxy, hydroxy $C_1$-$C_4$ alkyl, or halogen,

$R_{18}$ is $C_1$-$C_6$ alkyl optionally substituted with $-O-(C_2$-$C_6$ alkanoyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, amino $C_1$-$C_6$ alkyl, mono or dialkylamino $C_1$-$C_6$ alkyl

In this embodiment, it is preferred that $R_6$ and $R_7$ are not simultaneously OH, and

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$R_6$ and $R_7$ are not simultaneously $-SO_2(C_1-C_6$ alkyl)

Embodiment A88 Compounds according to embodiment A87, wherein

$R_5$ is benzyl which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently $C_1-C_4$ alkyl, $-C(O)NR_8R_7$ $-(C_1-C_4$alkyl$)-C(O)NR_6R_7$ halogen, $C_1-C_4$ alkoxy, $CO_2H$, $C_1-C_4$ thioalkoxy, $C_1-C_4$ alkoxycarbonyl, $C_1-C_6$ hydroxyalkyl, CN, OH, $NR_8R_9$, $NR_6R_7-(C_1-C_6$ alkyl$)-$, $-SO_2(C_1-C_6$ alkyl), or benzyloxy, and wherein

$R_6$ and $R_7$ at each occurrence are independently H, OH, $C_1-C_6$ alkyl, amino $C_1-C_4$ alkyl, $NH(C_1-C_6$ alkyl$)$alkyl, $N(C_1-C_6$ alkyl$)(C_1-C_6$ alkyl$)$ $C_1-C_6$ alkyl, $C_1-C_6$ hydroxyalkyl, $C_1-C_6$ alkoxy $C_1-C_6$ alkyl, or $-SO_2(C_1-C_6$ alkyl), each of which is optionally substituted with 1, 2, or 3 groups that are independently halogen, OH, SH $C_3-C_6$ cycloalkyl, $C_1-C_4$ alkoxy, $C_1-C_4$ alkyl, OH, $CF_3$, or $OCF_3$

In this embodiment, it is preferred that $R_6$ and $R_7$ are not simultaneously OH, and

$R_6$ and $R_7$ are not simultaneously $-SO_2(C_1-C_6$ alkyl)

Embodiment A89 Compounds according to embodiment A80, wherein

$R_5$ is benzyl which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently $C_1-C_4$ alkyl, $-C(O)NR_6R_7$ $-(C_1-C_4$alkyl$)-C(O)NR_6R_7$ $NR_6R_7-(C_1-C_6$ alkyl$)-$, $NR_8R_9$, halogen, $C_1-C_4$ alkoxy, $C_1-C_4$ thioalkoxy, $C_1-C_4$ alkoxycarbonyl, $C_1-C_6$ hydroxyalkyl, or CN, wherein

$R_6$ and $R_7$ at each occurrence are independently H, OH, $C_1-C_6$ alkyl, amino $C_1-C_4$ alkyl, $NH(C_1-C_6$ alkyl$)$alkyl, $N(C_1-C_6$ alkyl$)(C_1-C_6$ alkyl$)$ $C_1-C_6$ alkyl, $C_1-C_6$ hydroxyalkyl, or $C_1-C_4$ alkoxy $C_1-C_4$ alkyl, each of which is

optionally substituted with 1, 2, or 3 groups that are independently halogen, OH, SH, $C_3$-$C_8$ cycloalkyl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkyl, OH, $CF_3$, or $OCF_3$

In this embodiment, it is preferred that $R_6$ and $R_7$ are not simultaneously OH

Embodiment A90 Compounds according to embodiment A89, wherein

the $R_5$ group is disubstituted with two groups that are meta to each other

Embodiment A91 Compounds according to embodiment A78, wherein

$R_5$ is phenyl, which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently $C_1$-$C_4$ alkyl, $-C(O)NR_6R_7$, $-NR_6R_7$, $NR_6R_7(C_1$-$C_6$ alkyl), $NR_8R_9$, $C_1$-$C_6$ hydroxyalkyl, halogen, $C_1$-$C_4$ alkoxy, $CO_2H$, OH, $C_1$-$C_6$ alkoxycarbonyl, carboxaldehyde, $C_1$-$C_4$ haloalkyl, $-(C_1$-$C_4$ alkyl)-$NR_{15}C(O)NR_{16}R_{17}$, $-(C_1$-$C_4$ alkyl)$-NR_{15}C(O)R_{18}$, wherein

$R_6$ and $R_7$ at each occurrence are independently H, OH, $C_1$-$C_6$ alkyl, amino $C_1$-$C_4$ alkyl, $NH(C_1$-$C_6$ alkyl)alkyl, $N(C_1$-$C_6$ alkyl)$(C_1$-$C_6$ alkyl) $C_1$-$C_6$ alkyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, $-SO_2(C_1$-$C_6$ alkyl), $-SO_2NH_2$, $-SO_2NH(C_1$-$C_6$ alkyl), $-SO_2N(C_1$-$C_6$ alkyl)$(C_1$-$C_6$ alkyl), or $C_1$-$C_6$ alkanoyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently halogen, OH, SH, $C_3$-$C_6$ cycloalkyl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkyl, OH, $CF_3$, or $OCF_3$, or

$R_6$, $R_7$, and the nitrogen to which they are attached form a piperidinyl, pyrrolidinyl, piperazinyl, or a morpholinyl ring optionally substituted with 1 or 2 groups that are independently alkyl, hydroxy, hydroxy $C_1$-$C_4$ alkyl, or halogen,

$R_{15}$ is H or $C_1$-$C_6$ alkyl,

$R_{16}$ and $R_{17}$ are independently H or $C_1$-$C_6$ alkyl, or

$R_{16}$, $R_{17}$, and the nitrogen to which they are attached form a morpholinyl ring,

$R_{18}$ is $C_1$-$C_6$ alkyl optionally substituted with -O-($C_2$-$C_6$ alkanoyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, amino $C_1$-$C_6$ alkyl, mono or dialkylamino $C_1$-$C_6$ alkyl

In this embodiment, it is preferred that $R_6$ and $R_7$ are not simultaneously OH

Embodiment A92 Compounds according to embodiment A91, wherein

$R_5$ is phenyl, which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently $C_1$-$C_4$ alkyl, -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$ -C(O)$NR_6R_7$, -$NR_6R_7$, $NR_6R_7$($C_1$-$C_6$ alkyl), $NR_8R_9$, $C_1$-$C_6$ hydroxyalkyl, halogen, $C_1$-$C_4$ alkoxy, $CO_2H$, OH, $C_1$-$C_6$ alkoxycarbonyl, carboxaldehyde, $C_1$-$C_4$ haloalkyl, -($C_1$-$C_4$ alkyl)-$NR_{15}$C(O)$NR_{16}R_{17}$, -($C_1$-$C_4$ alkyl)-$NR_{15}$C(O)$R_{18}$, wherein

$R_6$ and $R_7$ at each occurrence are independently H, OH, $C_1$-$C_6$ alkyl, amino $C_1$-$C_4$ alkyl, NH($C_1$-$C_6$ alkyl)alkyl, N($C_1$-$C_6$ alkyl)($C_1$-$C_6$ alkyl) $C_1$-$C_6$ alkyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, -$SO_2$($C_1$-$C_6$ alkyl), -$SO_2NH_2$, -$SO_2$NH($C_1$-$C_6$ alkyl), -$SO_2$N($C_1$-$C_6$ alkyl)($C_1$-$C_6$ alkyl), or $C_1$-$C_6$ alkanoyl each of which is optionally substituted with 1, 2, or 3 groups that are independently halogen, OH, SH, $C_3$-$C_6$ cycloalkyl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkyl, OH, $CF_3$, or $OCF_3$,

$R_{15}$ is H or $C_1$-$C_6$ alkyl,

$R_{16}$ and $R_{17}$ are independently H or $C_1$-$C_6$ alkyl, or

$R_{16}$, $R_{17}$, and the nitrogen to which they are attached form a morpholinyl ring,

$R_{18}$ is $C_1$-$C_6$ alkyl optionally substituted with -O-($C_2$-$C_6$ alkanoyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, amino $C_1$-$C_6$ alkyl, mono or dialkylamino $C_1$-$C_6$ alkyl

Embodiment A93 Compounds according to embodiment A92, wherein

$R_1$ is halogen, methyl, ethyl, $C_2$-$C_4$ alkenyl, $C_2$-$C_4$ alkynyl, or carboxaldehyde,

$R_2$ is benzyloxy, OH, phenyloxy, phenyloxy($C_1$-$C_6$)alkyl, or phenyl ($C_1$-$C_4$) thioalkoxy, wherein each of the above is optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, -($C_1$-$C_6$)alkyl-N(R)-$CO_2R_{30}$, $NR_6R_7$, ($C_1$-$C_4$) haloalkyl, ($C_1$-$C_4$) haloalkoxy, ($C_1$-$C_6$) alkyl, pyridyl, or $NR_6R_7$-($C_1$-$C_6$ alkyl)-, and

$R_4$ is H, ($C_1$-$C_4$) alkyl optionally substituted with one or two groups that are independently $CO_2H$, -$CO_2$alkyl, -C(O)NRR, -N($R_{30}$)C(O)NRR, -N($R_{30}$)C(O)-($C_1$-$C_6$)alkoxy, or -$NR_6R_7$, or hydroxy($C_1$-$C_4$)alkyl

Embodiment A94 Compounds according to embodiment A93, wherein

$R_5$ is phenyl, which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently $C_1$-$C_4$ alkyl, -C(O)$NR_6R_7$, -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$ -$NR_6R_7$, $NR_6R_7$($C_1$-$C_6$ alkyl), $C_1$-$C_6$ hydroxyalkyl, halogen, $C_1$-$C_4$ alkoxy, $CO_2H$, OH, $C_1$-$C_6$ alkoxycarbonyl, carboxaldehyde, $C_1$-$C_4$ haloalkyl, wherein

$R_6$ and $R_7$ at each occurrence are independently H, OH, $C_1$-$C_6$ alkyl, amino $C_1$-$C_4$ alkyl, NH($C_1$-$C_6$ alkyl)alkyl, N($C_1$-$C_6$ alkyl)($C_1$-$C_6$ alkyl) $C_1$-$C_6$ alkyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, -$SO_2$($C_1$-$C_6$ alkyl), -$SO_2NH_2$, -$SO_2$NH($C_1$-$C_6$ alkyl), -$SO_2$N($C_1$-$C_6$ alkyl)($C_1$-$C_6$ alkyl), or $C_1$-$C_6$ alkanoyl, each of which is optionally

substituted with 1, 2, or 3 groups that are independently halogen, OH, SH, $C_3$-$C_6$ cycloalkyl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkyl, OH, $CF_3$, or $OCF_3$,

Embodiment A101 Compounds according to embodiment A66, wherein

$R_5$ is thienyl($C_1$-$C_6$ alkyl), piperidinyl($C_1$-$C_6$)alkyl, pyrrolidinyl($C_1$-$C_6$)alkyl, imidazolidinyl($C_1$-$C_6$)alkyl, piperazinyl($C_1$-$C_6$)alkyl, pyridyl($C_1$-$C_6$)alkyl, pyrimidyl($C_1$-$C_6$)alkyl, pyridazyl($C_1$-$C_6$)alkyl, pyrazinyl($C_1$-$C_6$)alkyl, isoquinolinyl($C_1$-$C_6$)alkyl, tetrahydroisoquinolinyl($C_1$-$C_6$)alkyl, indolyl($C_1$-$C_6$)alkyl, 1H-indazolyl($C_1$-$C_6$)alkyl, dihydroindolonyl($C_1$-$C_6$ alkyl), indolinyl($C_1$-$C_6$ alkyl), dihydroisoindolyl($C_1$-$C_6$ alkyl), dihydrobenzimdazolyl($C_1$-$C_6$ alkyl), or dihydrobenzoimidazolonyl($C_1$-$C_6$ alkyl), wherein each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently ($C_1$-$C_6$)alkyl, halogen, ($C_1$-$C_6$)alkoxy, ($C_1$-$C_6$)hydroxyalkyl, phenyl($C_1$-$C_6$)alkoxy, ($C_1$-$C_6$)thioalkoxy, ($C_1$-$C_6$)alkoxycarbonyl, phenyl($C_1$-$C_6$)alkoxycarbonyl, OH, $CO_2H$, CN, amidinooxime, $NR_8R_9$, $NR_6R_7$-($C_1$-$C_6$ alkyl)-, -$C(O)NR_6R_7$, -($C_1$-$C_4$ alkyl)-$C(O)NR_6R_7$ amidino, piperazinyl, morpholinyl, -$SO_2$ ($C_1$-$C_6$) alkyl, -$SO_2NH_2$, -$SO_2NH$($C_1$-$C_6$)alkyl, -$SO_2N$($C_1$-$C_6$)alkyl ($C_1$-$C_6$)alkyl, ($C_1$-$C_4$)haloalkyl, -($C_1$-$C_4$ alkyl)-$NR_{15}C(O)NR_{16}R_{17}$, -($C_1$-$C_4$ alkyl)-$NR_{15}C(O)R_{18}$, -O-$CH_2$-O, -O-$CH_2CH_2$-O-, or ($C_1$-$C_4$)haloalkoxy, wherein

$R_6$ and $R_7$ are independently at each occurrence H, ($C_1$-$C_6$)alkyl, ($C_1$-$C_6$)alkoxy, ($C_1$-$C_6$)alkoxy($C_1$-$C_6$)alkyl, ($C_1$-$C_6$)alkoxycarbonyl, ($C_1$-$C_6$)hydroxyalkyl, -($C_1$-$C_4$)alkyl-$CO_2$-($C_1$-$C_6$)alkyl,

($C_1$-$C_6$)alkanoyl, phenyl($C_1$-$C_6$)alkyl, phenyl($C_1$-$C_6$)alkoxy, or phenyl($C_1$-$C_6$)alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, ($C_1$-$C_4$)alkoxy, OH, SH, $C_3$-$C_6$ cycloalkyl, $NH_2$, $NH(C_1$-$C_6$ alkyl), $N(C_1$-$C_6$ alkyl)($C_1$-$C_6$ alkyl), ($C_1$-$C_4$)alkyl, $CF_3$ or $OCF_3$, or

$R_6$, $R_7$, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups tnat are independently $C_1$-$C_4$ alkyl, hydroxy, hydroxy $C_1$-$C_4$ alkyl, or halogen, and

$R_{18}$ is $C_1$-$C_6$ alkyl optionally substituted with -O-($C_2$-$C_6$ alkanoyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, amino $C_1$-$C_6$ alkyl, mono or dialkylamino $C_1$-$C_6$ alkyl

In this embodiment, it is preferred that $R_6$ and $R_7$ are not simultaneously OH, and

$R_6$ and $R_7$ are not simultaneously $-SO_2(C_1$-$C_6$ alkyl)

Embodiment A102 Compounds according to embodiment A101, wherein

$R_1$ is halogen, methyl, ethyl, $C_2$-$C_4$ alkenyl, $C_2$-$C_4$ alkynyl, or carboxaldehyde,

$R_2$ is benzyloxy, OH, phenyloxy, phenyloxy($C_1$-$C_6$)alkyl, or phenyl ($C_1$-$C_4$) thioalkoxy, wherein each of the above is optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, -($C_1$-$C_6$)alkyl-N(R)-$CO_2R_{30}$, $NR_6R_7$, ($C_1$-$C_4$) haloalkyl, ($C_1$-$C_4$) haloalkoxy, ($C_1$-$C_6$) alkyl, pyridyl, or $NR_6R_7$-($C_1$-$C_6$ alkyl)-, and

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$R_4$ is H, ($C_1$-$C_4$) alkyl optionally substituted with one or two groups that are independently $CO_2H$, -$CO_2$alkyl, -C(O)NRR, -N($R_{30}$)C(O)NRR, -N($R_{30}$)C(O)-($C_1$-$C_6$)alkoxy, or -$NR_8R_7$, or hydroxy($C_1$-$C_4$)alkyl

Embodiment A103 Compounds according to embodiment A102, wherein

$R_5$ is thienyl($C_1$-$C_6$ alkyl), indolyl($C_1$-$C_6$ alkyl), pyridinyl($C_1$-$C_6$ alkyl), piperazinyl($C_1$-$C_6$ alkyl), or pyrazinyl($C_1$-$C_6$ alkyl) each of which is optionally substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkyl, $C_1$-$C_4$ hydroxyalkyl, halogen, -C(O)$NR_6R_7$, -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$ $C_1$-$C_6$ alkoxycarbonyl, -$NR_6R_7$, $NR_6R_7$-($C_1$-$C_6$ alkyl)-, haloalkyl, $C_1$-$C_6$ alkanoyl,

$R_6$ and $R_7$ at each occurrence are independently H, $C_1$-$C_6$ alkyl optionally substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkoxycarbonyl, halogen, $C_3$-$C_6$ cycloalkyl OH, SH, or $C_1$-$C_4$ alkoxy,

or

$R_6$, $R_7$, and the nitrogen to which they are attached form a piperidinyl, pyrrolidinyl, piperazinyl, or a morpholinyl ring optionally substituted with 1 or 2 groups that are independently alkyl, hydroxy, hydroxy $C_1$-$C_4$ alkyl, or halogen

Embodiment A104 Compounds according to embodiment A103, wherein

$R_5$ is thienyl($C_1$-$C_6$ alkyl), indolyl($C_1$-$C_6$ alkyl), pyridinyl($C_1$-$C_6$ alkyl), piperazinyl($C_1$-$C_6$ alkyl), or pyrazinyl($C_1$-$C_6$ alkyl)

Embodiment A105 Compounds according to embodiment A103, wherein

$R_4$ is H, methyl, ethyl, or $-CH_2OH$,

$R_5$ is pyridinyl($C_1$-$C_6$ alkyl), or pyrazinyl($C_1$-$C_6$ alkyl) each of which is optionally substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkyl, $C_1$-$C_4$ hydroxyalkyl, halogen, $-C(O)NR_6R_7$, $-(C_1$-$C_4$ alkyl$)-C(O)NR_6R_7$ $C_1$-$C_6$ alkoxycarbonyl, $-NR_6R_7$, $NR_6R_7-(C_1$-$C_6$ alkyl$)-$, $CF_3$, $C_1$-$C_6$ alkanoyl, wherein

$R_6$ and $R_7$ at each occurrence are independently H, $C_1$-$C_6$ alkyl optionally substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkoxycarbonyl, halogen, $C_3$-$C_6$ cycloalkyl, OH, SH, or $C_1$-$C_4$ alkoxy,

or

$R_6$, $R_7$, and the nitrogen to which they are attached form a piperidinyl, pyrrolidinyl, piperazinyl, or a morpholinyl ring optionally substituted with 1 or 2 groups that are independently alkyl, hydroxy, hydroxy $C_1$-$C_4$ alkyl, or halogen

Embodiment A106 Compounds according to embodiment A105, wherein

$R_4$ is H, alkyl substituted with one or two groups that are independently $CO_2H$, $-CO_2-(C_1$-$C_6)$alkyl, $-C(O)NRR$, $-N(R_{30})C(O)NRR$, $-N(R_{30})C(O)-(C_1$-$C_6)$alkoxy, or $-NR_6R_7$

Embodiment A112 Compounds according to embodiment 16, wherein

$R_1$ is halogen, or methyl,

$R_2$ is benzyloxy, which is optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, $-(C_1$-$C_6)$alkyl-$N(R)-CO_2R_{30}$, $CF_3$, $OCF_3$, or ($C_1$-$C_4$) alkyl,, and

$R_4$ is H, methyl, ethyl, $-CH_2OH$, $-CH_2CO_2-(C_1$-$C_4$ alkyl), or $C_2$ hydroxyalkyl

Embodiment A113 Compounds according to any one of embodiments A85, A95, A97, A98, A99, A100, 16 or 17, wherein

$R_1$ is halogen, or methyl,

$R_2$ is benzyloxy, which is optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, -($C_1$-$C_6$)alkyl-N(R)-$CO_2R_{30}$, $CF_3$, $OCF_3$, or ($C_1$-$C_4$) alkyl,, and

$R_4$ is alkyl substituted with one group that is $CO_2H$, -$CO_2$-($C_1$-$C_6$)alkyl, -C(O)NRR, -N($R_{30}$)C(O)NRR, -N($R_{30}$)C(O)-($C_1$-$C_6$)alkoxy, or -$NR_6R_7$

Embodiment A114 Compounds according to embodiment A66, wherein

$R_5$ is isoquinolinyl($C_1$-$C_6$ alkyl), tetrahydroisoquinolinyl($C_1$-$C_6$ alkyl), 1H-indazolyl($C_1$-$C_6$ alkyl), dihydroindolonyl($C_1$-$C_6$ alkyl), indolinyl($C_1$-$C_6$ alkyl), dihydroisoindolyl($C_1$-$C_6$ alkyl), dihydrobenzimdazolyl($C_1$-$C_6$ alkyl), dihydrobenzoimidazolonyl($C_1$-$C_6$ alkyl), each of which is unsubstituted or substituted with 1, 2, or 3 groups that are independently alkyl, alkoxy, halogen, $C_1$-$C_6$ alkoxycarbonyl, alkanoyl optionally substituted with 1 or 2 groups that are independently selected from the group consisting of OH, $NH_2$, NH($C_1$-$C_6$ alkyl), and N($C_1$-$C_6$ alkyl)($C_1$-$C_6$ alkyl), -C(O)$NR_6R_7$, -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$ $NR_6R_7$-($C_1$-$C_6$ alkyl)-, -$NR_6R_7$, or $SO_2H$, or

piperidinyl $C_1$-$C_4$ alkyl optionally substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, halogen, -C(O)$NR_6R_7$, -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$ $NR_6R_7$-($C_1$-$C_6$ alkyl)-, or -$NR_6R_7$, or $C_1$-$C_6$ alkoxycarbonyl

Embodiment A115 Compounds according to embodiment A114, wherein

$R_5$ is isoquinolinyl($C_1$-$C_4$ alkyl), piperidinyl $C_1$-$C_4$ alkyl, tetrahydroisoquinolinyl($C_1$-$C_4$ alkyl), 1H-indazolyl($C_1$-$C_4$ alkyl), dihydroindolonyl($C_1$-$C_4$ alkyl), indolinyl($C_1$-$C_4$ alkyl), dihydroisoindolyl($C_1$-$C_4$ alkyl), dihydrobenzimdazolyl($C_1$-$C_4$ alkyl), or dihydrobenzoimidazolonyl($C_1$-$C_4$ alkyl)

Embodiment A116 Compounds according to embodiment A114, wherein

$R_5$ is piperidinyl $C_1$-$C_4$ alkyl optionally substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, halogen, or $C_1$-$C_6$ alkoxycarbonyl

Embodiment A117 Compounds according to embodiment A66, wherein

$R_5$ is pyrimidyl, indolinyl, indolyl, 1H-isoindolyl, isoquinolinyl, tetrahydroisoquinolinyl, benzimidazolyl, dihydro-1H-benzimidazolyl, pyrrolyl, imidazolyl, or each of which is optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of

$C_1$-$C_6$ alkoxycarbonyl, $C_1$-$C_4$ thioalkoxy, each of which is unsubstituted or substituted with 1, 2, or 3 groups that are independently $-C(O)NR_6R_7$, $-(C_1$-$C_4$ alkyl)-$C(O)NR_6R_7$ $NR_6R_7$-($C_1$-$C_6$ alkyl)-, $-NR_6R_7$, alkyl, alkoxy, halogen, $C_1$-$C_6$ alkoxycarbonyl, or alkanoyl optionally substituted with 1 or 2 groups that are independently selected from the group consisting of OH, $NH_2$, $NH(C_1$-$C_6$ alkyl), and $N(C_1$-$C_6$ alkyl) ($C_1$-$C_6$ alkyl), and $SO_2H$, or

pyridyl, pyrazolyl, optionally substituted with 1, 2, or 3 groups that are independently $-C(O)NR_6R_7$, $-(C_1$-$C_4$ alkyl)-$C(O)NR_6R_7$ $NR_6R_7$-($C_1$-$C_6$ alkyl)-, $-NR_6R_7$, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ hydroxyalkyl, halogen, $C_1$-$C_6$

alkoxycarbonyl, $-NR_6R_7$, $NR_6R_7-(C_1-C_6$ alkyl)-, $CF_3$, $C_1-C_6$ alkanoyl, wherein

$R_6$ and $R_7$ at each occurrence are independently H, $C_1-C_6$ alkyl optionally substituted with 1, 2, or 3 groups that are independently $C_1-C_4$ alkoxycarbonyl, halogen, $C_3-C_6$ cycloalkyl, OH, SH, or $C_1-C_4$ alkoxy,

or

$R_6$, $R_7$, and the nitrogen to which they are attached form a piperidinyl, pyrrolidinyl, piperazinyl, or a morpholinyl ring optionally substituted with 1 or 2 groups that are independently alkyl, hydroxy, hydroxy $C_1-C_4$ alkyl, or halogen

Embodiment A118 Compounds according to embodiment A117, wherein

$R_5$ is pyrimidyl, pyrrolyl, imidazolyl, or pyrazolyl, each of which is optionally substituted with 1, 2, or 3 groups independently selected from $C_1-C_6$ alkoxycarbonyl, $C_1-C_4$ thioalkoxy, each of which is unsubstituted or substituted with 1, 2, or 3 groups that are independently alkyl, alkoxy, halogen, $C_1-C_6$ alkoxycarbonyl, $-C(O)NR_6R_7$, $-(C_1-C_4$ alkyl) $C(O)NR_6R_7$ $NR_6R_7-(C_1-C_6$ alkyl)-, or $-NR_6R_7$, or $C_1-C_4$ alkanoyl optionally substituted with 1 or 2 groups that are independently selected from the group consisting of OH, $NH_2$, $NH(C_1-C_6$ alkyl), and $N(C_1-C_6$ alkyl) $(C_1-C_6$ alkyl), or $SO_2H$

Embodiment A119 Compounds according to embodiment A117, wherein

$R_5$ is pyridyl or pyrazolyl, optionally substituted with 1, 2, or 3 groups that are independently $C_1-C_4$ alkyl, $C_1-C_4$ hydroxyalkyl, halogen, $-C(O)NR_6R_7$, $-(C_1-C_4$ alkyl)$-C(O)NR_6R_7$

$NR_6R_7$-($C_1$-$C_6$ alkyl)-, or -$NR_6R_7$, $C_1$-$C_6$ alkoxycarbonyl, -$NR_6R_7$, $NR_6R_7$-($C_1$-$C_6$ alkyl)-, $CF_3$, $C_1$-$C_6$ alkanoyl, wherein

$R_6$ and $R_7$ at each occurrence are independently H, $C_1$-$C_6$ alkyl optionally substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkoxycarbonyl, halogen, $C_3$-$C_6$ cycloalkyl, OH, SH, or $C_1$-$C_4$ alkoxy,

or

$R_6$, $R_7$, and the nitrogen to which they are attached form a piperidinyl, pyrrolidinyl, piperazinyl, or a morpholinyl ring optionally substituted with 1 or 2 groups that are independently alkyl, hydroxy, hydroxy $C_1$-$C_4$ alkyl, or halogen

Embodiment A120 Compounds according to embodiment A119, wherein

$R_5$ is pyridyl or pyrazolyl, optionally substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkyl, $C_1$-$C_4$ hydroxyalkyl, halogen, -$C(O)NR_6R_7$, -($C_1$-$C_4$ alkyl)-$C(O)NR_6R_7$ $NR_6R_7$-($C_1$-$C_6$ alkyl)-, -$NR_6R_7$, $C_1$-$C_6$ alkoxycarbonyl, $CF_3$, $C_1$-$C_6$ alkanoyl, wherein

$R_6$ and $R_7$ at each occurrence are independently H, $C_1$-$C_6$ alkyl optionally substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkoxycarbonyl, halogen, $C_3$-$C_6$ cycloalkyl, OH, SH, or $C_1$-$C_4$ alkoxy

Embodiment A121 Compounds according to embodiment A119, wherein

$R_5$ is pyridyl or pyrazolyl, optionally substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkyl, $C_1$-$C_4$ hydroxyalkyl, halogen, -$C(O)NR_6R_7$, -($C_1$-$C_4$ alkyl)-$C(O)NR_6R_7$ $NR_6R_7$-($C_1$-$C_6$ alkyl)-, -$NR_6R_7$, $C_1$-$C_6$ alkoxycarbonyl, $CF_3$, $C_1$-$C_6$ alkanoyl, wherein

$R_6$, $R_7$, and the nitrogen to which they are attached form a piperidinyl, pyrrolidinyl, piperazinyl, or a morpholinyl ring optionally substituted with 1 or 2 groups that are independently alkyl, hydroxy, hydroxy $C_1$-$C_4$ alkyl, or halogen

Embodiment A122 Compounds according to any one of embodiments A114, A115, A116, or A117 wherein

$R_1$ is halogen, methyl, ethyl, $C_2$-$C_4$ alkenyl, $C_2$-$C_4$ alkynyl, or carboxaldehyde,

$R_2$ is benzyloxy, OH, phenyloxy, phenyloxy($C_1$-$C_6$)alkyl, or phenyl ($C_1$-$C_4$) thioalkoxy, wherein each of the above is optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, -($C_1$-$C_6$)alkyl-N(R)-$CO_2R_{30}$, $NR_6R_7$, ($C_1$-$C_4$) haloalkyl, ($C_1$-$C_4$) haloalkoxy, ($C_1$-$C_6$) alkyl, pyridyl, or $NR_6R_7$-($C_1$-$C_6$ alkyl)-, and

$R_4$ is H, ($C_1$-$C_4$) alkyl substituted with one group that is $CO_2H$, -$CO_2$-($C_1$-$C_6$)alkyl, -C(O)NRR, -N($R_{30}$)C(O)NRR, -N($R_{30}$)C(O)-($C_1$-$C_6$)alkoxy, or -$NR_6R_7$, hydroxy($C_1$-$C_4$)alkyl

Embodiment A123 Compounds according to embodiment A66, wherein

$R_5$ is $C_1$-$C_6$ alkyl optionally substituted with 1 or 2, groups that are independently $C_1$-$C_4$ alkoxycarbonyl, or halogen, or

$R_5$ is $C_1$-$C_4$ alkoxy, ethyl, methyl, cyclopropylmethyl, cycloalkyl, or alkynyl, or

$R_5$ is $C_2$-$C_6$ alkenyl optionally substituted with $C_1$-$C_4$ alkoxycarbonyl or cyclohexyl

Embodiment A124 Compounds according to embodiment A123, wherein

$R_1$ is halogen, methyl, ethyl, $C_2$-$C_4$ alkenyl, $C_2$-$C_4$ alkynyl, or carboxaldehyde,

$R_2$ is benzyloxy, OH, phenyloxy, phenyloxy($C_1$-$C_6$)alkyl, or phenyl ($C_1$-$C_4$) thioalkoxy, wherein each of the above is optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, -($C_1$-$C_6$)alkyl-N(R)-$CO_2R_{30}$, $NR_6R_7$, ($C_1$-$C_4$) haloalkyl, ($C_1$-$C_4$) haloalkoxy, ($C_1$-$C_6$) alkyl, pyridyl, or $NR_6R_7$-($C_1$-$C_6$ alkyl)-, and

$R_4$ is H, ($C_1$-$C_4$) alkyl substituted with one group that is $CO_2H$, -$CO_2$-($C_1$-$C_6$)alkyl, -C(O)NRR, -N($R_{30}$)C(O)NRR, -N($R_{30}$)C(O)-($C_1$-$C_6$)alkoxy, or -$NR_6R_7$, hydroxy($C_1$-$C_4$)alkyl, wherein

$R_6$ and $R_7$ at each occurrence are independently H, $C_1$-$C_6$ alkyl optionally substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkoxycarbonyl, halogen, $C_3$-$C_6$ cycloalkyl, OH, SH, or $C_1$-$C_4$ alkoxy,

or

$R_6$, $R_7$, and the nitrogen to which they are attached form a piperidinyl, pyrrolidinyl, piperazinyl, or a morpholinyl ring optionally substituted with 1 or 2 groups that are independently alkyl, hydroxy, hydroxy $C_1$-$C_4$ alkyl, or halogen

Embodiment A125 Compounds according to embodiment A124, wherein

$R_5$ is $C_1$-$C_6$ alkyl optionally substituted with 1 or 2, groups that are independently $C_1$-$C_4$ alkoxycarbonyl, or halogen, or

$R_5$ is $C_1$-$C_4$ alkoxy, ethyl, methyl, cyclopropylmethyl, cyclohexyl, cyclopentyl, $C_2$-$C_6$ alkynyl, or

$R_5$ is $C_2$-$C_6$ alkenyl optionally substituted with $C_1$-$C_4$ alkoxycarbonyl or cyclohexyl

Embodiment A126 Compounds according to embodiment A66, wherein

$R_2$ is phenylalkynyl, $-OC(O)NH(CH_2)_n$aryl, $-OC(O)N$(alkyl)$(CH_2)_n$aryl, $-OSO_2(C_1-C_6)$alkyl, $-OSO_2$aryl, or $NR_8R_9$, wherein

n is 0, 1, 2, 3, 4, 5 or 6,

each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, $-(C_1-C_6)$alkyl$-N(R)-CO_2R_{30}$, alkoxy, alkoxycarbonyl, CN, $NR_6R_7$, haloalkyl, haloalkoxy, alkyl, heteroaryl, heteroarylalkyl, $NR_6R_7-(C_1-C_6$ alkyl)-, phenyl, $-SO_2-$phenyl wherein the phenyl groups are optionally substituted with 1, 2, or 3 groups that are independently halogen or $NO_2$, or $-OC(O)NR_6R_7$, wherein

$R_6$ and $R_7$ are independently at each occurrence H, alkyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, $-SO_2-$alkyl, OH, hydroxyalkyl, $-(C_1-C_4)$alkyl$-CO_2-$alkyl, heteroarylalkyl, alkanoyl, arylalkyl, arylalkoxy, or arylalkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, alkoxy, heterocycloalkyl, OH, $NH_2$, $C_3-C_6$ cycloalkyl, NH(alkyl), N(alkyl)(alkyl), -O-alkanoyl, alkyl, $C_1-C_4$ haloalkyl, or $C_1-C_4$ haloalkoxy, or

$R_6$, $R_7$, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently $C_1-C_4$ alkyl, $C_1-C_4$ alkoxy, hydroxy, hydroxy $C_1-C_4$ alkyl, or halogen

Embodiment A127 Compounds according to embodiment A126, wherein

$R_1$ is halogen, methyl, ethyl, $C_2$-$C_4$ alkenyl, $C_2$-$C_4$ alkynyl, or carboxaldehyde, and

$R_4$ is H, ($C_1$-$C_4$) alkyl substituted with one group that is $CO_2H$, $-CO_2-(C_1-C_6)$alkyl, $-C(O)NRR$, $-N(R_{30})C(O)NRR$, $-N(R_{30})C(O)-(C_1-C_6)$alkoxy, $-NR_6R_7$, $NR_6R_7-(C_1-C_6$ alkyl)-, or hydroxy($C_1$-$C_4$)alkyl

Embodiment A128 Compounds according to embodiment A127, wherein

$R_5$ is phenyl, optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, $CF_3$, $OCF_3$, $-(C_1-C_4$ alkyl)$-C(O)NR_6R_7$ $NR_6R_7-(C_1-C_6$ alkyl)-, $-NR_6R_7$, or $C(O)NR_6R_7$, wherein

$R_6$ and $R_7$ are independently at each occurrence H, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxycarbonyl, OH, $C_1$-$C_6$ hydroxyalkyl, $-(C_1-C_4)$alkyl$-CO_2-$alkyl, pyridyl $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkanoyl, benzyl, phenyl $C_1$-$C_6$ alkoxy, or phenyl $C_1$-$C_6$ alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, $C_1$-$C_6$ alkoxy, piperidinyl $C_1$-$C_6$ alkyl, morpholinyl $C_1$-$C_6$ alkyl, piperazinyl $C_1$-$C_6$ alkyl, OH, SH, $C_3$-$C_6$ cycloalkyl, $NH_2$, NH(alkyl), N(alkyl)(alkyl), $-O-C_1-C_4$ alkanoyl, $C_1$-$C_4$ alkyl, $CF_3$, or $OCF_3$, or

$R_6$, $R_7$, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, hydroxy, hydroxy $C_1$-$C_4$ alkyl, or halogen, or

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$R_5$ is benzyl optionally substituted with 1 ,2 ,3 ,4 or 5 groups that are independently halogen, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, CN, $CF_3$, $OCF_3$, -($C_1$-$C_4$ alkyl)-$C(O)NR_6R_7$ $NR_6R_7$-($C_1$-$C_6$ alkyl)-, $-NR_6R_7$, or $C(O)NR_6R_7$

Embodiment A129 Compounds according to embodiment A128, wherein

$R_2$ is $NR_8R_9$, or $NR_8R_9$-($C_1$-$C_4$ alkyl)-, wherein

$R_8$ at each occurrence is independently hydrogen, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkanoyl, phenyl($C_1$-$C_6$)alkyl or phenyl($C_1$-$C_6$)alkanoyl wherein each of the above is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ alkoxycarbonyl, halogen, or $C_1$-$C_4$ haloalkyl, and

$R_9$ at each occurrence is independently $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkanoyl, phenyl($C_1$-$C_6$)alkyl, $C_3$-$C_7$ cycloalkyl, $C_2$-$C_6$ alkenyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, imidazolyl, $C_3$-$C_7$ cycloalkyl($C_1$-$C_6$)alkyl, phenyl($C_1$-$C_6$)alkanoyl, -$SO_2$-phenyl and phenyl wherein each of the above is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ alkoxycarbonyl, halogen, or $C_1$-$C_4$ haloalkyl

Embodiment A130 Compounds according to embodiment A129, wherein

$R_8$ is H

Embodiment A131 Compounds according to embodiment A130, wherein

$R_2$ is -NH-benzyl option substituted with 1, 2, or 3 groups that are independently halogen, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, $CF_3$, $OCF_3$,

or

$R_2$ is -NH-C(O)phenyl, wherein the phenyl group is optionally substituted with 1, 2, or 3 groups that are independently halogen, $C_1$-$C_4$ alkyl, or $C_1$-$C_4$ alkoxy, or

$R_2$ is -NH-allyl

Embodiment A132 Compounds according to embodiment A131, wherein

$R_1$ is chloro, bromo, iodo, or methyl, and

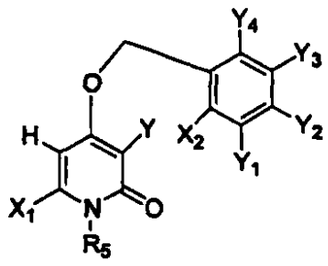
$R_5$ is benzyl optionally substituted with 1 ,2 ,3 ,4, or 5 groups that are independently halogen, -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$ $NR_6R_7$-($C_1$-$C_6$ alkyl)-, -$NR_6R_7$, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, CN, $CF_3$, $OCF_3$, or C(O)$NR_6R_7$

Embodiment A133 Compounds according to embodiment A131, wherein

$R_1$ is chloro, bromo, iodo, or methyl, and

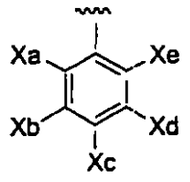
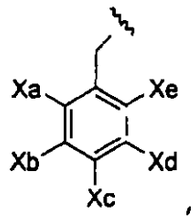
$R_5$ is phenyl, optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$ $NR_6R_7$-($C_1$-$C_6$ alkyl)-, -$NR_6R_7$, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, $CF_3$, $OCF_3$, or C(O)$NR_6R_7$

Embodiment A134 A compound of the formula




or pharmaceutically acceptable salts thereof, wherein

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$R_5$ is  or  , wherein

$X_1$, $X_2$, $X_a$, $X_b$, $X_c$, $X_d$, and $X_e$ at are independently selected from -C(O)$NR_6R_7$, -$NR_6R_7$, hydroxy($C_1$-$C_4$)alkyl, H, OH, halogen, haloalkyl, alkyl, haloalkoxy, heteroaryl, heterocycloalkyl, $C_3$-$C_7$ cycloalkyl, $NR_6R_7$-($C_1$-$C_6$ alkyl)-, -$CO_2$-($C_1$-$C_6$)alkyl, -N(R)C(O)$NR_6R_7$, -N(R)C(O)-($C_1$-$C_6$)alkoxy, $CO_2$H-($C_1$-$C_6$ alkyl)-, or -$SO_2NR_6R_7$, wherein

the heteroaryl and heterocycloalkyl groups are optionally substituted with -$NR_6R_7$, -C(O)$NR_6R_7$, $NR_6R_7$-($C_1$-$C_6$ alkyl)-, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, or halogen,

$R_6$ and $R_7$ are independently at each occurrence H, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxycarbonyl OH, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ thiohydroxyalkyl, -($C_1$-$C_4$)alkyl-$CO_2$-alkyl, pyridyl $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkanoyl, benzyl, phenyl $C_1$-$C_6$ alkoxy, or phenyl $C_1$-$C_6$ alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, $C_3$-$C_6$ cycloalkyl, $C_1$-$C_6$ alkoxy, piperidinyl $C_1$-$C_6$ alkyl, morpholinyl $C_1$-$C_6$ alkyl, piperazinyl $C_1$-$C_6$ alkyl, OH, SH, $NH_2$, NH(alkyl), N(alkyl)(alkyl), -O-$C_1$-$C_4$ alkanoyl, $C_1$-$C_4$ alkyl, $CF_3$, or $OCF_3$, or

$R_6$, $R_7$, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, hydroxy, hydroxy $C_1$-$C_4$ alkyl, or halogen,

R at each occurrence is independently H or $C_1$-$C_6$ alkyl, and

Y, $Y_1$, $Y_2$, $Y_3$, and $Y_4$ are independently selected from H, halogen, alkyl, carboxaldehyde, hydroxyalkyl, alkenyl, alkynyl, CN, alkanoyl, alkoxy, alkoxyalkyl, haloalkyl, and carboxyl

Embodiment A135 Compounds according to embodiment A134, wherein

$Y_2$, $Y_4$, and Y are independently halogen, and

$Y_1$ and $Y_3$ are both hydrogen

Embodiment A136 Compounds according to embodiment A135, wherein

$X_1$ is H, methyl, $-NR_6R_7$, $NR_6R_7$-($C_1$-$C_6$ alkyl)-, $-C(O)NR_6R_7$, $C_1$-$C_6$ hydroxyalkyl, or -($C_1$-$C_4$ alkyl)-morpholinyl

Embodiment A137 Compounds according to embodiment A136, wherein

$X_a$ and $X_e$ are independently halogen, is $NH_2$, NH($C_1$-$C_6$ alkyl), N($C_1$-$C_6$ alkyl)($C_1$-$C_6$ alkyl) or methyl

Embodiment A138 Compounds according to embodiment A137, wherein

$X_b$ or $X_c$ is $-NR_6R_7$, $NR_6R_7$-($C_1$-$C_6$ alkyl)-, $-C(O)NR_6R_7$, $-SO_2NR_6R_7$, or halogen, wherein

$R_6$ and $R_7$ are independently at each occurrence H, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxycarbonyl, OH, $C_1$-$C_6$ hydroxyalkyl, -($C_1$-$C_4$)alkyl-$CO_2$-alkyl, pyridyl $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkanoyl, benzyl, phenyl $C_1$-$C_6$ alkoxy, or phenyl $C_1$-$C_6$ alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are

independently, halogen, $C_3$-$C_6$ cycloalkyl, $C_1$-$C_6$ alkoxy, piperidinyl $C_1$-$C_6$ alkyl, morpholinyl $C_1$-$C_6$ alkyl, piperazinyl $C_1$-$C_6$ alkyl, OH, SH, $NH_2$, NH(alkyl), N(alkyl)(alkyl), -O-$C_1$-$C_4$ alkanoyl, $C_1$-$C_4$ alkyl, $CF_3$, or $OCF_3$, or

$R_6$, $R_7$, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, hydroxy, hydroxy $C_1$-$C_4$ alkyl, or halogen

Embodiment A139 Compounds according to embodiment A138, wherein

$R_6$, $R_7$, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, hydroxy, hydroxy $C_1$-$C_4$ alkyl, or halogen

Embodiment A140 Compounds according to embodiment A138, wherein

$R_6$, $R_7$, and the nitrogen to which they are attached form a piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, hydroxy, hydroxy $C_1$-$C_4$ alkyl, or halogen

Embodiment A141 Compounds according to embodiment A138, wherein

$R_6$ and $R_7$ are independently at each occurrence H, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxycarbonyl, OH, $C_1$-$C_6$ hydroxyalkyl, -($C_1$-$C_4$)alkyl-$CO_2$-alkyl, pyridyl $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkanoyl, benzyl, phenyl

$C_1$-$C_6$ alkoxy, or phenyl $C_1$-$C_6$ alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, $C_3$-$C_6$ cycloalkyl, $C_1$-$C_6$ alkoxy, piperidinyl $C_1$-$C_6$ alkyl, morpholinyl $C_1$-$C_6$ alkyl, piperazinyl $C_1$-$C_6$ alkyl, OH, $NH_2$, NH(alkyl), N(alkyl)(alkyl), -O-$C_1$-$C_4$ alkanoyl, $C_1$-$C_4$ alkyl, $CF_3$, or $OCF_3$

Embodiment A142 Compounds according to embodiment A138, wherein

$R_6$ and $R_7$ are independently at each occurrence H, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, or $C_1$-$C_6$ alkanoyl, wherein each of the above is optionally substituted with 1, 2, or 3 groups that are independently OH, SH, halogen, or $C_3$-$C_6$ cycloalkyl

Embodiment A143 Compounds according to embodiment A137, wherein

$X_a$ and $X_e$ are independently fluoro, chloro, or methyl, and

$X_c$ is hydrogen or halogen

Embodiment A144 Compounds according to embodiment A137, wherein

$X_a$ is halogen,

$X_e$ is $NH_2$, NH($C_1$-$C_6$ alkyl) or N($C_1$-$C_6$ alkyl)($C_1$-$C_6$ alkyl),

$X_b$ and $X_d$ are both hydrogen

Embodiment A145 Compounds according to embodiment A144, wherein

$X_c$ is -$NR_6R_7$, $NR_6R_7$ $C_1$-$C_6$ alkyl, -$SO_2NR_6R_7$, or halogen, wherein

$R_6$ and $R_7$ are independently at each occurrence H, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxycarbonyl, OH, $C_1$-$C_6$ hydroxyalkyl, -($C_1$-$C_4$)alkyl-

$CO_2$-alkyl, pyridyl $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkanoyl, benzyl, phenyl $C_1$-$C_6$ alkoxy, or phenyl $C_1$-$C_6$ alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, $C_3$-$C_6$ cycloalkyl, $C_1$-$C_6$ alkoxy, piperidinyl $C_1$-$C_6$ alkyl, morpholinyl $C_1$-$C_6$ alkyl, piperazinyl $C_1$-$C_6$ alkyl, OH, SH, $NH_2$, NH(alkyl), N(alkyl)(alkyl), -O-$C_1$-$C_4$ alkanoyl, $C_1$-$C_4$ alkyl, $CF_3$, or $OCF_3$, or

$R_6$, $R_7$, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, hydroxy, hydroxy $C_1$-$C_4$ alkyl, or halogen

Embodiment A146 Compounds according to embodiment A145, wherein

$X_c$ is fluoro, chloro, $NH_2$, NH($C_1$-$C_6$ alkyl), N($C_1$-$C_6$ alkyl)($C_1$-$C_6$ alkyl), -$SO_2NH_2$, -$SO_2$NH($C_1$-$C_6$ alkyl) -$SO_2$N($C_1$-$C_6$ alkyl)($C_1$-$C_6$ alkyl), or piperazinyl, wherein the piperazinyl group is optionally substituted with 1 or 2 groups that are independently $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, hydroxy, hydroxy $C_1$-$C_4$ alkyl, or halogen

Embodiment A147 Compounds according to either embodiment A137 or A144, wherein

$X_c$ is -C(O)$NR_6R_7$, -($C_1$-$C_6$ alkyl)-C(O)$NR_6R_7$, $NR_6R_7$, or $NR_6R_7$-($C_1$-$C_6$ alkyl)-, wherein

$R_6$ and $R_7$ are independently at each occurrence H, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxycarbonyl, OH, $C_1$-$C_6$ hydroxyalkyl, -($C_1$-$C_4$)alkyl-$CO_2$-alkyl, pyridyl $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkanoyl,

benzyl, phenyl $C_1$-$C_6$ alkoxy, or phenyl $C_1$-$C_6$ alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, $C_3$-$C_6$ cycloalkyl, $C_1$-$C_6$ alkoxy, piperidinyl $C_1$-$C_6$ alkyl, morpholinyl $C_1$-$C_6$ alkyl, piperazinyl $C_1$-$C_6$ alkyl, OH, $NH_2$, NH(alkyl), N(alkyl)(alkyl), -O-$C_1$-$C_4$ alkanoyl, $C_1$-$C_4$ alkyl, $CF_3$, or $OCF_3$, or

$R_6$, $R_7$, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, hydroxy, hydroxy $C_1$-$C_4$ alkyl, or halogen

Embodiment A148 Compounds according to embodiment A147, wherein

$R_6$ is hydrogen, and

$R_7$ is $C_1$-$C_6$ alkyl or $C_1$-$C_6$ alkanoyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently $NH_2$, NH($C_1$-$C_6$ alkyl), N($C_1$-$C_6$ alkyl)($C_1$-$C_6$ alkyl), OH, SH, cyclopropyl, or $C_1$-$C_4$ alkoxy

Embodiment A148a Compounds according to embodiment A148, wherein

$R_7$ is $C_1$-$C_6$ alkanoyl optionally substituted with 1, 2, or 3 groups that are independently OH, cyclopropyl, or $NH_2$

Embodiment A149 Compounds according to embodiment A135, wherein

$X_a$ is hydrogen,

$X_b$, $X_c$, or $X_d$ is -C(O)$NR_6R_7$ -($C_1$-$C_6$ alkyl)-C(O)$NR_6R_7$, $NR_6R_7$, $NR_6R_7$-($C_1$-$C_6$ alkyl)- or -$CO_2$-($C_1$-$C_6$)alkyl, wherein

$R_6$ and $R_7$ are independently at each occurrence H, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxycarbonyl, OH, $C_1$-$C_6$ hydroxyalkyl, -($C_1$-$C_4$)alkyl-$CO_2$-alkyl, pyridyl $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkanoyl, benzyl, phenyl $C_1$-$C_6$ alkoxy, or phenyl $C_1$-$C_6$ alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, $C_3$-$C_6$ cycloalkyl, $C_1$-$C_6$ alkoxy, piperidinyl $C_1$-$C_6$ alkyl, morpholinyl $C_1$-$C_6$ alkyl, piperazinyl $C_1$-$C_6$ alkyl, OH, $NH_2$, NH(alkyl), N(alkyl)(alkyl) -O-$C_1$-$C_4$ alkanoyl, $C_1$-$C_4$ alkyl, $CF_3$, or $OCF_3$, or

$R_6$, $R_7$, and the nitrogen to which they are attached form a morpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, hydroxy, hydroxy $C_1$-$C_4$ alkyl, or halogen, and

$X_e$ is hydrogen, methyl, $C_1$-$C_2$ alkoxy, or halogen

Embodiment A150 Compounds according to embodiment A149, wherein

$X_b$ is $NR_6R_7$, or $NR_6R_7$-($C_1$-$C_6$ alkyl)-, -C(O)$NR_6R_7$ or -$CO_2$-($C_1$-$C_6$)alkyl, wherein

$R_6$ is hydrogen or $C_1$-$C_4$ alkyl,

$R_7$ is OH, $C_1$-$C_6$ alkyl or $C_1$-$C_6$ alkanoyl, wherein the alkyl and alkanoyl groups substituted with 1, 2, or 3 groups that are independently $NH_2$, NH($C_1$-$C_6$ alkyl), N($C_1$-$C_6$ alkyl)($C_1$-$C_6$ alkyl), $C_3$-$C_6$ cycloalkyl, OH, or $C_1$-$C_4$ alkoxy

Embodiment A151 Compounds according to embodiment A137, wherein

$X_a$ is halogen,

$X_b$ is $NR_6R_7$, $NR_6R_7$-($C_1$-$C_6$ alkyl)-, -C(O)$NR_6R_7$, or -$CO_2$-($C_1$-$C_6$)alkyl,

$X_c$ is $NR_6R_7$, $NR_6R_7$-($C_1$-$C_6$ alkyl)-, -C(O)$NR_6R_7$, halogen, -$CO_2$-($C_1$-$C_6$)alkyl, $NH_2$, NH($C_1$-$C_6$ alkyl), N($C_1$-$C_6$ alkyl)($C_1$-$C_6$ alkyl), -$SO_2NH_2$, -$SO_2$NH($C_1$-$C_6$ alkyl), -$SO_2$N($C_1$-$C_6$ alkyl)($C_1$-$C_6$ alkyl), or piperazinyl, wherein the piperazinyl group is optionally substituted with 1 or 2 groups that are independently $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, hydroxy, hydroxy $C_1$-$C_4$ alkyl, or halogen,

$X_d$ is hydrogen,

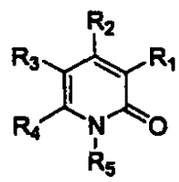
$X_e$ is H, methyl, $NH_2$, NH($C_1$-$C_6$ alkyl) or N($C_1$-$C_6$ alkyl)($C_1$-$C_6$ alkyl)

Embodiment A152 Compounds according to embodiment A135, wherein

$X_1$, $X_2$, $X_a$, $X_b$, $X_c$, $X_d$, and $X_e$ are independently selected from H, OH, halogen, $CF_3$, alkyl, $OCF_3$, pyridyl, pyridazinyl, pyrimidyl, pyrazinyl, thienyl, furyl, pyrrolyl, piperidinyl, piperazinyl, or $C_3$-$C_7$ cycloalkyl, wherein each of the above is optionally substituted with -$NR_6R_7$, -C(O)$NR_6R_7$, $NR_6R_7$-($C_1$-$C_6$ alkyl)-, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, or halogen

Embodiment A153 Compounds according to embodiment A152, wherein at least three of $X_1$, $X_2$, $X_a$, $X_b$, $X_c$, $X_d$, and $X_e$ are hydrogen

Embodiment A154 A compound of the formula




or a pharmaceutically acceptable salt thereof, wherein

$R_1$ is alkanoyl, halogen, arylalkanoyl, arylalkyl, alkoxyalkyl, hydroxyalkyl, or carboxaldehyde, wherein

the aryl portion of arylalkyl, and arylalkanoyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, nitro, CN, haloalkyl, haloalkoxy or $CO_2H$,

the alkyl portion of the hydroxyalkyl, arylalkyl, alkanoyl, alkoxyalkyl and arylalkanoyl groups are unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, methoxy, ethoxy or spirocyclopropyl,

$R_2$ is arylalkoxy, aryloxy, phenyloxy$(C_1$-$C_6)$alkyl, OH, halogen, arylthioalkoxy, alkoxy, -OC(O)NH$(CH_2)_n$aryl, -OC(O)N(alkyl)$(CH_2)_n$aryl, alkyl, alkoxyalkoxy, dialkylamino, pyridyl, pyrimidyl, pyridazyl, pyrazolyl, imidazolyl, pyrrolyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, tetrazolyl, pyrazinyl, benzimidazolyl, triazinyl, tetrahydrofuryl, piperidinyl, hexahydropyrimidinyl, thiazolyl, thienyl, or $CO_2H$, wherein n is 0, 1, 2, 3, 4, 5 or 6,

the aryl portion of arylalkoxy, aryloxy, arylthioalkoxy, -OC(O)NH$(CH_2)_n$aryl, and -OC(O)N(alkyl)$(CH_2)_n$aryl or the heteroaryl and heterocycloalkyl groups is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, -$(C_1$-$C_6)$alkyl-N(R)-$CO_2R_{30}$, haloalkyl heteroaryl, heteroarylalkyl, $NR_6R_7$, $NR_6R_7$-$(C_1$-$C_6$ alkyl)-, -OC(O)$NR_6R_7$, wherein

$R_6$ and $R_7$ are independently at each occurrence H, alkyl, alkoxy alkanoyl, arylalkyl, arylalkoxy, or arylalkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, OH, SH,

$C_3$-$C_6$ cycloalkyl, alkoxy, alkyl, haloalkyl, or haloalkoxy, or

$R_6$, $R_7$, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, thiomorpholinyl S-oxide, thiomorpholinyl S,S-dioxide, piperidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently $C_1$-$C_4$ alkyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, or halogen,

R at each occurrence is independently H or $C_1$-$C_6$ alkyl,

$R_{30}$ is $C_1$-$C_6$ alkyl optionally substituted with 1 or 2 groups that are independently OH, SH, halogen, amino, monoalkylamino, dialkylamino or $C_3$-$C_6$ cycloalkyl,

$R_3$ is halogen, arylalkoxycarbonyl, aryloxycarbonyl, arylalkyl, $-OC(O)NH(CH_2)_naryl$, arylalkoxy,——$-OC(O)N(alkyl)(CH_2)_naryl$, aryloxy, arylthio, thioalkoxy, arylthioalkoxy, alkenyl, $NR_6R_7$, $NR_6R_7$-($C_1$-$C_6$ alkyl)-, or alkyl, wherein

the aryl portion of arylalkoxycarbonyl, aryloxycarbonyl, arylalkyl, $-OC(O)NH(CH_2)_naryl$, arylalkoxy, $-OC(O)N(alkyl)(CH_2)_naryl$, and arylthioalkoxy, is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, alkoxy, alkyl, haloalkyl, or haloalkoxy,

wherein n is 0, 1, 2, 3, 4, 5, or 6, or

$R_4$ is H, alkyl substituted with one group selected from $CO_2H$, $-CO_2$-($C_1$-$C_6$)alkyl, -C(O)NRR, $-N(R_{30})C(O)NRR$, $-N(R_{30})C(O)$-($C_1$-$C_6$)alkoxy, and $-NR_6R_7$, arylalkoxy, arylalkyl, hydroxyalkyl, haloalkyl, alkoxy, alkoxyalkyl, or alkoxyalkoxy, wherein

the aryl portion of arylalkoxy, arylalkyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, hydroxy, alkoxy, alkyl, nitro, haloalkyl, or haloalkoxy, and

$R_5$ is arylalkyl, alkyl aryl, alkoxy, heterocycloalkylalkyl, heteroarylalkyl, arylthioalkyl, heterocycloalkyl, or heteroaryl, wherein

each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, halogen, alkoxy, arylalkoxy, thioalkoxy, alkoxycarbonyl, arylalkoxycarbonyl, $CO_2H$, CN, amidinooxime, $NR_6R_7$, $NR_6R_7$-($C_1$-$C_6$ alkyl)-, $-C(O)NR_6R_7$, amidino, haloalkyl, or haloalkoxy

Embodiment A160 Compounds according to embodiment A154 wherein

$R_1$ is halogen, ($C_1$-$C_6$)alkanoyl, phenyl($C_1$-$C_6$)alkanoyl, naphthyl($C_1$-$C_6$)alkanoyl, naphthyl($C_1$-$C_6$)alkyl, phenyl($C_1$-$C_6$)alkyl, alkoxyalkyl, hydroxyalkyl, or carboxaldehyde, wherein

the phenyl and naphthyl portions of the above are unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, nitro, CN, $CF_3$, $OCF_3$ or $CO_2H$,

the alkyl portion of the above groups are unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, methoxy, or ethoxy

$R_2$ is phenylalkoxy, aryloxy, phenyloxy($C_1$-$C_6$)alkyl, OH, halogen, phenylthioalkoxy, alkoxy, alkyl, alkoxyalkoxy, $-OC(O)NH(CH_2)_n$phenyl, $-OC(O)N(alkyl)(CH_2)_n$phenyl, pyridyl, pyrimidyl, pyridazyl, pyrazolyl, or thienyl, wherein

n is 0, 1, 2, 3, or 4, and

the above groups are unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, -($C_1$-$C_6$)alkyl-N(R)-$CO_2R_{30}$, halo($C_1$-$C_4$)alkyl, or thienyl,

$R_3$ is halogen, phenylalkoxycarbonyl, phenyloxycarbonyl, phenyl($C_1$-$C_6$)alkyl, phenylalkoxy, phenyloxy, phenylthio, thioalkoxy, arylthioalkoxy, ($C_2$-$C_6$)alkenyl, $NR_6R_7$, $NR_6R_7$-($C_1$-$C_6$ alkyl)-, or alkyl, wherein

the phenyl, naphthyl, and aryl portions of arylalkoxycarbonyl, aryloxycarbonyl, arylalkyl, -OC(O)NH($CH_2$)$_n$aryl, arylthioalkoxy, arylalkoxy, and-OC(O)N(alkyl)($CH_2$)$_n$aryl, are unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, alkoxy, alkyl, $CF_3$, or $OCF_3$,

wherein n is 0, 1, 2, 3, 4, 5, or 6, or

$R_4$ is H, ($C_1$-$C_6$) alkyl substituted with one group that is $CO_2H$, -$CO_2$-($C_1$-$C_6$)alkyl, -C(O)NRR, -N($R_{30}$)C(O)NRR, -N($R_{30}$)C(O)-($C_1$-$C_6$)alkoxy, or -$NR_6R_7$, phenylalkoxy, phenyl($C_1$-$C_6$)alkyl, hydroxyalkyl, haloalkyl, alkoxyalkyl, or alkoxyalkoxy, wherein

the phenyl portion of the above groups are unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, hydroxy, alkoxy, alkyl, nitro, $CF_3$, or $OCF_3$

$R_5$ is phenyl($C_1$-$C_6$)alkyl, ($C_1$-$C_6$)alkyl, phenyl, naphthyl, pyridyl, ($C_1$-$C_6$)alkoxy, piperidinyl($C_1$-$C_6$)alkyl, pyrrolyl($C_1$-$C_6$)alkyl, imidazolidinyl($C_1$-$C_6$)alkyl, pyrazolyl($C_1$-$C_6$)alkyl, imidazolyl($C_1$-$C_6$)alkyl, tetrahydropyridinyl($C_1$-$C_6$)alkyl, thienyl($C_1$-$C_6$)alkyl, phenylthio($C_1$-$C_6$)alkyl, or pyridyl($C_1$-$C_6$)alkyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently ($C_1$-$C_4$)alkyl,

fluoro, chloro, bromo, $(C_1-C_4)$alkoxy, phenyl$(C_1-C_4)$alkoxy, thio$(C_1-C_4)$alkoxy, $(C_1-C_4)$alkoxycarbonyl, phenyl$(C_1-C_4)$alkoxycarbonyl, $CO_2H$, CN, amidinooxime, $NR_6R_7$, $NR_6R_7$-$(C_1-C_6$ alkyl)-, $-C(O)NR_6R_7$, amidino, $CF_3$, $-CF_2CF_3$, $OCF_3$ or $OCF_2CF_3$

Embodiment A161 Compounds according to embodiment A160 wherein

$R_1$ is halogen, $(C_1-C_4)$alkanoyl, phenyl$(C_1-C_4)$alkanoyl, benzyl, phenethyl, phenpropyl, hydroxyalkyl, or carboxaldehyde, wherein

the above phenyl groups are unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, $C_1-C_4$ alkyl, $C_1-C_4$ alkoxy, nitro, CN, $CF_3$, $OCF_3$ or $CO_2H$,

the alkyl portion of the above groups are unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, methoxy, or ethoxy,

$R_2$ is benzyloxy, phenethyloxy, phenpropyloxy, phenbutyloxy, phenyloxy, phenyloxy$(C_1-C_6)$alkyl, OH, halogen, phenylthioalkoxy, alkoxy, alkyl, alkoxyalkoxy, wherein

n is 0, 1, 2, 3, or 4, and

the above groups are unsubstituted or substituted with 1, 2, or 3, groups that are independently halogen, $-(C_1-C_6)$alkyl-N(R)-$CO_2R_{30}$, halo$(C_1-C_4)$alkyl, or thienyl,

$R_3$ is halogen, phenylalkoxycarbonyl, phenyloxycarbonyl, phenyl$(C_1-C_6)$alkyl, phenylalkoxy, phenyloxy, phenylthio, thioalkoxy, phenylthioalkoxy, $(C_2-C_6)$alkenyl, $NR_6R_7$, $NR_6R_7$ $C_1-C_6$ alkyl, or alkyl, wherein

the above phenyl groups are unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, alkoxy, $(C_1-C_4)$alkyl, $CF_3$, or $OCF_3$,

$R_4$ is H, $(C_1-C_6)$ alkyl substituted with one group that is $CO_2H$, $-CO_2-(C_1-C_6)$alkyl, $-C(O)NRR$, $-N(R_{30})C(O)NRR$, $-N(R_{30})C(O)-(C_1-C_6)$alkoxy, or $-NR_6R_7$, phenylalkoxy, benzyl, phenethyl, hydroxyalkyl, haloalkyl, alkoxyalkyl, or alkoxyalkoxy, wherein

the phenyl portion of the above groups are unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, hydroxy, $(C_1-C_4)$alkoxy, $(C_1-C_4)$alkyl, nitro, $CF_3$, or $OCF_3$

$R_5$ is benzyl, phenethyl, phenpropyl, phenbutyl, $(C_1-C_6)$alkyl, phenyl, or pyridyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently $(C_1-C_4)$alkyl, fluoro, chloro, bromo, $(C_1-C_4)$alkoxy, phenyl$(C_1-C_4)$alkoxy, thio$(C_1-C_4)$alkoxy, $(C_1-C_4)$alkoxycarbonyl, $CO_2H$, CN, amidinooxime, $NR_6R_7$, $NR_6R_7-(C_1-C_6$ alkyl)-, $-C(O)NR_6R_7$, amidino, $CF_3$, or $OCF_3$

Embodiment A162 Compounds according to embodiment A161 wherein

$R_1$ is bromo, phenyl$(C_1-C_4)$alkanoyl, benzyl, phenethyl, phenpropyl, hydroxyalkyl, or carboxaldehyde, wherein

the above phenyl groups are unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, $C_1-C_4$ alkyl, $C_1-C_4$ alkoxy, nitro, CN, $CF_3$, $OCF_3$ or $CO_2H$,

$R_2$ is benzyloxy, phenethyloxy, phenpropyloxy, phenbutyloxy, phenyloxy, phenyloxy$(C_1-C_6)$alkyl, OH, halogen, or phenylthioalkoxy, wherein

n is 0, 1, 2, 3, or 4, and

the above groups are unsubstituted or substituted with 1, 2, or 3, groups that are independently halogen, $-(C_1-C_6)$alkyl-N(R)-$CO_2R_{30}$, halo$(C_1-C_4)$alkyl, or thienyl,

$R_3$ is bromo, phenylalkoxycarbonyl, phenyloxycarbonyl, phenyl($C_1$-$C_6$)alkyl, phenylalkoxy, pheryloxy, pheryl thio, thioalkoxy, phenylthioalkoxy, ($C_2$-$C_6$)alkenyl, $NR_6R_7$, $NR_6R_7$ $C_1$-$C_6$ alkyl, or alkyl, wherein

the above phenyl groups are unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, alkoxy, ($C_1$-$C_4$)alkyl, $CF_3$, or $OCF_3$,

$R_4$ is H, ($C_1$-$C_6$) alkyl substituted with one group that is $CO_2H$, $-CO_2$-($C_1$-$C_6$)alkyl, -C(O)NRR, $-N(R_{30})C(O)NRR$, $-N(R_{30})C(O)$-($C_1$-$C_6$)alkoxy, or $-NR_6R_7$, phenylalkoxy, benzyl, or phenethyl, wherein

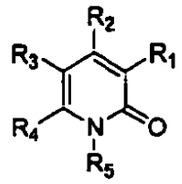
the phenyl portion of the above groups are unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, hydroxy, ($C_1$-$C_4$)alkoxy, ($C_1$-$C_4$)alkyl, nitro, $CF_3$, or $OCF_3$

$R_5$ is benzyl, phenethyl, phenpropyl, ($C_1$-$C_6$)alkyl, phenyl, or pyridyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently ($C_1$-$C_4$)alkyl, fluoro, chloro, bromo, ($C_1$-$C_4$)alkoxy, $CO_2H$, CN, amidinooxime, amidino, $CF_3$, $OCF_3$, $NR_6R_7$, $NR_6R_7$-($C_1$-$C_6$ alkyl)-, or $-C(O)NR_6R_7$, wherein

$R_6$ and $R_7$ are independently hydrogen, OH, $C_1$-$C_4$ alkoxy, $C_1$-$C_6$ alkanoyl, or $C_1$-$C_6$ alkyl, wherein each of the above is optionally substituted with 1 or 2 groups that are independently OH, $NH_2$, $C_3$-$C_6$ cycloalkyl, or halogen, or

$R_6$, $R_7$, and the nitrogen to which they are attached form a morpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, hydroxy, hydroxy $C_1$-$C_4$ alkyl, or halogen

Embodiment A163 Compounds of the formula



or pharmaceutically acceptable salts thereof, wherein

$R_1$ is H, halogen, alkyl, carboxaldehyde, hydroxyalkyl, arylalkoxy, arylalkyl, CN, alkanoyl, alkoxy, alkoxyalkyl, or arylalkanoyl,

wherein the aryl portion of arylalkoxy, arylalkyl, and arylalkanoyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, nitro, CN, haloalkyl, haloalkoxy or $CO_2H$,

wherein the alkyl portion of the alkyl, hydroxyalkyl, arylalkoxy, arylalkyl, alkanoyl, alkoxy, alkoxyalkyl and arylalkanoyl groups is unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, methoxy, ethoxy or spirocyclopropyl,

$R_2$ is H, arylthio, $-OC(O)NH(CH_2)_n$aryl, arylalkyl, $-OC(O)N(alkyl)(CH_2)_n$aryl, or arylthioalkoxy, wherein n is 1, 2, 3, 4, or 5, wherein the aryl groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, $-(C_1$-$C_6)$alkyl-$N(R)-CO_2R_{30}$, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkyl, $CF_3$, or $OCF_3$,

R at each occurrence is independently H or $C_1$-$C_6$ alkyl,

$R_{30}$ is $C_1$-$C_6$ alkyl optionally substituted with 1 or 2 groups that are independently OH, SH, halogen, amino, monoalkylamino, dialkylamino or $C_3$-$C_6$ cycloalkyl,

$R_3$ is halogen, alkoxycarbonyl, arylalkoxycarbonyl, aryloxycarbonyl, arylalkyl, $-OC(O)NH(CH_2)_n$aryl,

arylalkoxy, -OC(O)N(alkyl)$(CH_2)_n$aryl, aryloxy, arylthio, thioalkoxy, arylthioalkoxy, alkenyl, $NR_6R_7$ $C_1$-$C_6$ alkyl, $NR_6R_7$ or alkyl, wherein

the aryl portion of arylalkoxycarbonyl, aryloxycarbonyl, arylalkyl, -OC(O)NH$(CH_2)_n$aryl, arylalkoxy, -OC(O)N(alkyl)$(CH_2)_n$aryl, and arylthioalkoxy, is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, alkoxy, alkyl, haloalkyl, or haloalkoxy,

wherein n is 0, 1, 2, 3, 4, 5, or 6, or

$R_4$ is H, alkyl substituted with one group that is $CO_2H$, -$CO_2$-($C_1$-$C_6$)alkyl, -C(O)NRR, -N($R_{30}$)C(O)NRR, -N($R_{30}$)C(O)-($C_1$-$C_6$)alkoxy, or -$NR_6R_7$, arylalkoxy, arylalkyl, hydroxyalkyl, haloalkyl, alkoxy, alkoxyalkyl, or alkoxyalkoxy, wherein

the aryl portion of arylalkoxy, arylalkyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, hydroxy, alkoxy, alkyl, nitro, haloalkyl, or haloalkoxy, and

$R_5$ is arylalkyl, alkyl, aryl, alkoxy, heterocycloalkylalkyl, heteroarylalkyl, arylthioalkyl, heterocycloalkyl, or heteroaryl, wherein each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, halogen, alkoxy, arylalkoxy, thioalkoxy, alkoxycarbonyl, arylalkoxycarbonyl, $CO_2H$, CN, amidinooxime, $NR_6R_7$ $NR_6R_7$-($C_1$-$C_6$ alkyl)-, -C(O)$NR_6R_7$, amidino, haloalkyl, or haloalkoxy, wherein

$R_6$ and $R_7$ are independently at each occurrence H, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxycarbonyl, OH, $C_1$-$C_6$ hydroxyalkyl, -($C_1$-$C_4$)alkyl-$CO_2$-alkyl, pyridyl $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkanoyl, benzyl, phenyl $C_1$-$C_6$ alkoxy, or phenyl $C_1$-$C_6$ alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are

independently, halogen, $C_3$-$C_6$ cycloalkyl, $C_1$-$C_6$ alkoxy, piperidinyl $C_1$-$C_6$ alkyl, morpholinyl $C_1$-$C_6$ alkyl, piperazinyl $C_1$-$C_6$ alkyl, OH, SH, $NH_2$, NH(alkyl), N(alkyl)(alkyl), -O-$C_1$-$C_4$ alkanoyl, $C_1$-$C_4$ alkyl, $CF_3$, or $OCF_3$, or

$R_6$, $R_7$, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, hydroxy, hydroxy $C_1$-$C_4$ alkyl, or halogen

Embodiment A168 Compounds according to embodiment A163 wherein

$R_5$ is benzyl, phenethyl, phenpropyl, phenbutyl, alkyl, phenyl, alkoxy, pyridyl($C_1$-$C_6$)alkyl, phenyl($C_1$-$C_6$)thioalkyl, pyrrolyl, pyrrolyl($C_1$-$C_6$)alkyl, or pyridyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently ($C_1$-$C_6$)alkyl, halogen, ($C_1$-$C_6$)alkoxy, phenyl($C_1$-$C_6$)alkoxy, ($C_1$-$C_6$)thioalkoxy, alkoxycarbonyl, $CO_2H$, CN, amidinooxime, amidino, $CF_3$, or $OCF_3$

Embodiment A169 Compounds according to embodiment A163 wherein

$R_1$ is H, Cl, Br, ($C_1$-$C_6$)alkyl, carboxaldehyde, hydroxy($C_1$-$C_6$)alkyl,

wherein the alkyl portion of above is unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, methoxy, or ethoxy

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$R_2$ is H, phenylthio, $-OC(O)NH(CH_2)_n$aryl, phenylalkyl $-OC(O)N(alkyl)(CH_2)_n$aryl, or phenylthio$(C_1-C_6)$alkoxy, wherein n is 1, 2, 3, or 4,

wherein the aryl groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, $-(C_1-C_6)$alkyl$-N(R)-CO_2R_{30}$, $C_1-C_4$ alkoxy, $C_1-C_4$ alkyl, $CF_3$, or $OCF_3$,

$R_3$ is bromo, alkoxycarbonyl, pherylalkoxycarbonyl, phenyloxycarbonyl phenylalkyl, phenylalkoxy, phenyloxy, phenylthio, thioalkoxy, phenylthioalkoxy, alkenyl $NR_6R_7$ or alkyl, wherein

the phenyl portion of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen $(C_1-C_4)$alkoxy, $(C_1-C_4)$alkyl, halo$(C_1-C_4)$alkyl, or halo$(C_1-C_4)$alkoxy,

wherein n is 0, 1, 2, 3, or 4,

$R_4$ is H, alkyl substituted with one group that is $CO_2H$, $-CO_2-(C_1-C_6)$alkyl, $-C(O)NRR$, $-N(R_{30})C(O)NRR$, $-N(R_{30})C(O)-(C_1-C_6)$alkoxy, or $-NR_6R_7$, phenylalkoxy, phenylalkyl, hydroxyalkyl, haloalkyl, alkoxy, alkoxyalkyl, or wherein

the phenyl portion of phenylalkoxy, phenylalkyl is unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, hydroxy, alkoxy, alkyl, nitro, haloalkyl, or haloalkoxy

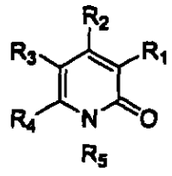
$R_5$ is benzyl, phenethyl, phenpropyl, phenbutyl, alkyl, phenyl, phenyl$(C_1-C_6)$thioalkyl, pyrrolyl, or pyridyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently $(C_1-C_6)$alkyl, halogen, $(C_1-C_6)$alkoxy, benzyloxy, $(C_1-C_6)$thioalkoxy, alkoxycarbonyl, $CO_2H$, CN, amidinooxime, amidino, $CF_3$, or $OCF_3$,

$R_6$ and $R_7$ are independently hydrogen, OH, $C_1-C_4$ alkoxy, $C_1-C_6$ alkanoyl, or $C_1-C_6$ alkyl, wherein each of the

above is optionally substituted with 1 or 2 groups that are independently OH, $NH_2$, $C_3$-$C_6$ cycloalkyl, or halogen, or

$R_6$, $R_7$, and the nitrogen to which they are attached form a morpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, hydroxy, hydroxy $C_1$-$C_4$ alkyl, or halogen

Embodiment A170 Compounds according to embodiment 1



or a pharmaceutically acceptable salt thereof, wherein

$R_1$ is H, halogen, alkyl, carboxaldehyde, hydroxyalkyl, arylalkoxy, arylalkyl, CN, alkanoyl, alkoxy, alkoxyalkyl, or arylalkanoyl,

wherein the aryl portion of arylalkoxy, arylalkyl, and arylalkanoyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, nitro, CN, haloalkyl, haloalkoxy or $CO_2H$,

wherein the alkyl portion of the alkyl, hydroxyalkyl, arylalkoxy, arylalkyl, alkanoyl, alkoxy, alkoxyalkyl and arylalkanoyl groups is unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, methoxy, ethoxy or spirocyclopropyl,

$R_2$ is arylalkoxy, aryloxy, aryloxyalkyl, OH, halogen, arylthioalkoxy, alkoxy, $-OC(O)NH(CH_2)_n$aryl,

-OC(O)N(alkyl)$(CH_2)_n$aryl, alkyl, alkoxyalkoxy, dialkylamino, or $CO_2H$, wherein

n is 0, 1, 2, 3, 4, 5 or 6,

the aryl portion of arylalkoxy, aryloxy, aryloxyalkoxy, -OC(O)N-$(CH_2)_n$aryl, and -OC(O)N(alkyl)(C-)aryl or the heteroary and heterocycloalkyl groups is unsubstituted or substituted with 1, 2, 3 -, or 5 groups that are independently halogen, -$(C_-C_6)$alkyl-N(R)-$CO_2R_{30}$, naloalkyl, heteroaryl, heteroarylalkyl, $NR_6R_7$, $NR_6R_7$-$(C_1$ $C_6$ alkyl)-, -OC(O)$NR_6R_7$, wherein

$R_6$ and $R_7$ are independently at each occurrence H, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxycarbonyl, OH, $C_1$-$C_6$ hydroxyalkyl, -$(C_1$-$C_4)$alkyl-$CO_2$-alkyl, pyridyl $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkanoyl, benzyl, phenyl $C_1$-$C_6$ alkoxy, or phenyl $C_1$-$C_6$ alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, $C_3$-$C_6$ cycloalkyl, $C_1$-$C_6$ alkoxy, piperidinyl $C_1$-$C_6$ alkyl, morpholinyl $C_1$-$C_6$ alkyl, piperazinyl $C_1$-$C_6$ alkyl, OH, SH, $NH_2$, NH(alkyl), N(alkyl)(alkyl), -O-$C_1$-$C_4$ alkanoyl, $C_1$-$C_4$ alkyl, $CF_3$, or $OCF_3$, or

$R_6$, $R_7$, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, hydroxy, hydroxy $C_1$-$C_4$ alkyl, or halogen,

R at each occurrence is independently H or $C_1$-$C_6$ alkyl,

$R_{30}$ is $C_1$-$C_6$ alkyl optionally substituted with 1 or 2 groups that are independently OH, SH, halogen, amino, monoalkylamino, dialkylamino or $C_3$-$C_6$ cycloalkyl,

$R_3$ is halogen, alkoxycarbonyl, arylalkoxycarbonyl, aryloxycarbonyl, arylalkyl, $-OC(O)NH(CH_2)_naryl$, arylalkoxy, $-OC(O)N(alkyl)(CH_2)_naryl$, aryloxy, arylthio, thioalkoxy, arylthioalkoxy, alkenyl, $NR_6R_7$ $C_1$-$C_6$ alkyl, $NR_6R_7$ or alkyl, wherein

the aryl portion of arylalkoxycarboryl, aryloxycarbonyl, arylalkyl, $-OC(O)NH(CH_2)_naryl$, arylalkoxy, $-OC(O)N(alkyl)(CH_2)_naryl$, and arylthioalkoxy, is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, alkoxy, alkyl, haloalkyl, or haloalkoxy,

wherein n is 0, 1, 2, 3, 4, 5, or 6, or

$R_4$ is H, alkyl substituted with one group that is $CO_2H$, $-CO_2-(C_1-C_6)$alkyl, $-C(O)NRR$, $-N(R_{30})C(O)NRR$, $-N(R_{30})C(O)-(C_1-C_6)$alkoxy, or $-NR_6R_7$, arylalkoxy, arylalkyl, hydroxyalkyl, haloalkyl, alkoxy, alkoxyalkyl, or alkoxyalkoxy, wherein

the aryl portion of arylalkoxy, arylalkyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, hydroxy, alkoxy, alkyl, nitro, haloalkyl, or haloalkoxy, and

$R_5$ is aryl, heterocycloalkylalkyl, heteroarylalkyl, arylthioalkyl, heterocycloalkyl, or heteroaryl, wherein each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, halogen, alkoxy, arylalkoxy, thioalkoxy, alkoxycarbonyl, arylalkoxycarbonyl, $CO_2H$, CN, amidinooxime, $NR_6R_7$, $NR_6R_7$-($C_1$-$C_6$ alkyl)-, $-C(O)NR_6R_7$, amidino, haloalkyl, or haloalkoxy

Embodiment A173 Compounds according to embodiment A170 wherein

$R_1$ is H, halogen, alkyl, carboxaldehyde, hydroxyalkyl, benzyloxy, phenethyloxy, phenpropyloxy, benzyl, phenethyl, phenpropyl, CN, alkanoyl, alkoxy, or phenylC(O)-, phenylCH$_2$C(O)-, or phenylCH$_2$CH$_2$C(O),

wherein the above phenyl groups are unsubstituted or substituted with 1, 2 or 3 groups that are independently halogen, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy nitro, CN, $CF_3$, $OCF_3$ or $CO_2H$,

wherein the above alkyl groups are unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, methoxy, or ethoxy,

$R_2$ is benzyloxy, phenethyloxy, phenpropyloxy, phenyloxy, phenyloxy($C_1$-$C_6$)alkyl, OH, halogen, phenylthioalkoxy, alkyl, alkoxy, -OC(O)NH(CH$_2$)$_n$phenyl, -OC(O)N(alkyl)(CH$_2$)$_n$phenyl, dialkylamino, or $CO_2H$, wherein n is 0, 1, 2, 3, or 4,

the above aryl groups are unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, -($C_1$ $C_6$)alkyl-N(R)-$CO_2R_{30}$, $CF_3$ pyridyl, thienyl, $NR_6R_7$, or $NR_6R_7$-($C_1$-$C_6$ alkyl)-, wherein

$R_6$ and $R_7$ are independently at each occurrence H, alkyl, alkanoyl, benzyl, or phenylC(O)-, wherein the phenyl portion of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, OH, $C_3$-$C_6$ cycloalkyl, alkoxy, alkyl, $CF_3$, or $OCF_3$,

$R_3$ is halogen, alkoxycarbonyl, phenylalkoxycarbonyl, phenyloxycarbonyl, phenylalkyl, -OC(O)NH(CH$_2$)$_n$phenyl, phenylalkoxy, -OC(O)N(alkyl)(CH$_2$)$_n$phenyl, phenyloxy, phenylthio, thioalkoxy, phenylthioalkoxy, alkenyl, $NR_6R_7$ or alkyl, wherein

the phenyl portion of the above is unsubstituted or substituted with 1, 2, or 3 groups that are

independently, halogen, alkoxy, alkyl, haloalkyl, or haloalkoxy,

wherein n is 0, 1, 2, 3,or 4,

$R_4$ is H, alkyl substituted with one group that is $CO_2H$, $-CO_2-(C_1-C_6)$alkyl, $-C(O)NRR$, $-N(R_{30})C(O)NRR$ $-N(R_{30})C(O)-(C_1-C_6)$alkoxy, or $-NR_6R_7$, phenylalkoxy, phenylalkyl, hydroxyalkyl, haloalkyl, alkoxy, alkoxyalkyl, or alkoxyalkoxy, wherein

the phenyl portion of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, hydroxy, alkoxy, alkyl, nitro, haloalkyl, or haloalkoxy, and

$R_5$ is phenyl, naphthyl, pyrrolylalkyl, piperidinylalkyl pyridinylalkyl, pyrimidinylalkyl, phenylthioalkyl, pyrrolyl, piperidinyl, pyridyl, or thienylalkyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently alkyl, halogen, alkoxy, phenylalkoxy, thioalkoxy, alkoxycarbonyl, phenylalkoxycarbonyl, $CO_2H$, CN, amidinooxime, $NR_6R_7$, $NR_6R_7-(C_1-C_6$ alkyl)-, $-C(O)NR_6R_7$, amidino, haloalkyl, or haloalkoxy

Embodiment A174 Compounds according to embodiment A173 wherein

$R_1$ is H, halogen, alkyl, carboxaldehyde, hydroxyalkyl, benzyloxy, phenethyloxy, benzyl, phenethyl, CN, $(C_1-C_6)$alkanoyl, alkoxy, or phenylC(O)-, or phenyl$CH_2$C(O)-,

wherein the above phenyl groups are unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, $C_1-C_4$ alkyl, $C_1-C_4$ alkoxy, nitro, CN, $CF_3$, $OCF_3$ or $CO_2H$,

$R_2$ is benzyloxy, phenethyloxy, phenpropyloxy, phenyloxy, phenyloxy$(C_1-C_6)$alkyl, halogen, phenyl$(C_1-C_4)$thioalkoxy,

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-OC(O)NH(CH$_2$)$_n$phenyl, -OC(O)N(alkyl)(CH$_2$)$_n$phenyl, or dialkylamino, wherein

n is 0, 1, 2, 3, or 4,

the above phenyl groups are unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, $CF_3$, $NR_6R_7$, or $NR_6R_7$-($C_1$-$C_6$ alkyl)-, wherein

$R_6$ and $R_7$ are independently at each occurrence -, ($C_1$-$C_6$)alkyl, acetyl, benzyl, or phenylC(O)-, wherein the phenyl portion of the above is unsubstituted or substituted with 1 2, or 3 groups that are independently, halogen, OH, cyclopropyl, alkoxy, alkyl, $CF_3$, or $OCF_3$,

$R_3$ is halogen, alkoxycarbonyl, phenylalkoxycarbonyl, phenyloxycarbonyl, phenylalkyl, phenylalkoxy, phenyloxy, phenylthio, thioalkoxy, phenylthioalkoxy, alkenyl, $NR_6R_7$ or alkyl, wherein

the phenyl portion of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, alkoxy, alkyl, haloalkyl, or haloalkoxy,

wherein n is 0, 1, 2, 3,or 4,

$R_4$ is H, alkyl substituted with one group that is $CO_2H$, -$CO_2$-($C_1$-$C_6$)alkyl, -C(O)NRR, -N($R_{30}$)C(O)NRR, -N($R_{30}$)C(O)-($C_1$-$C_6$)alkoxy, or -$NR_6R_7$, phenylalkoxy, phenylalkyl, hydroxyalkyl, haloalkyl, alkoxy, alkoxyalkyl, or alkoxyalkoxy, wherein

the phenyl portion of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, hydroxy, alkoxy, alkyl, nitro, haloalkyl, or haloalkoxy, and

$R_5$ is phenyl, phenyl($C_1$-$C_4$)thioalkyl, pyridyl, or thienyl($C_1$-$C_4$)alkyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently

($C_1$-$C_4$)alkyl, fluoro, chloro, bromo, ($C_1$-$C_4$)alkoxy, CN, amidinooxime, amino, $CF_3$, or $OCF_3$

Embodiment A175 Compounds according to embodiment A174 wherein

$R_5$ is substituted with at least one group selected from fluoro, chloro, bromo, and methyl

In another aspect, the invention provides pharmaceutical compositions comprising at least one pharmaceutically acceptable carrier, solvent, adjuvant or excipient and a compound of formula I, embodiment A66, or embodiment A154

The invention further provides pharmaceutical compositions comprising at least one pharmaceutically acceptable carrier, solvent, adjuvant or excipient and compounds according to any of the preceding embodiments

As noted above, the invention encompasses methods of treating a TNF mediated disorder, a p38 kinase mediated disorder, inflammation and/or arthritis in a subject, the method comprising treating a subject having or susceptible to such disorder or condition with a therapeutically-effective amount of a compound of formula I or embodiment A1

More specifically, the invention provides methods for treating or preventing inflammation, arthritis, rheumatoid arthritis, spondylarthropathies, gouty arthritis, osteoarthritis, systemic lupus erthematosus, juvenile arthritis, and other arthritic conditions, neuroinflammation, allergy, Th2 mediated diseases, pain, neuropathic pain, fever, pulmonary disorders, lung inflammation, adult respiratory distress syndrome, pulmonary sarcoisosis, asthma, silicosis, chronic pulmonary inflammatory disease, and chronic obstructive pulmonary disease (COPD), cardiovascular disease,

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arteriosclerosis, myocardial infarction (including post-myocardial infarction indications), thrombosis, congestive heart failure, cardiac reperfusion injury, as well as complications associated with hypertension and/or heart failure such as vascular organ damage, restenosis, cardiomyopathy, stroke including ischemic and hemorrhagic stroke, reperfusion injury, renal reperfusion injury, ischemia including stroke and brain ischemia, and ischemia resulting from cardiac/coronary bypass, neurotrauma and brain trauma including closed head injury, brain edema, neurodegenerative disorders, liver disease and nephritis, gastrointestinal conditions, inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome, ulcerative colitis, ulcerative diseases, gastric ulcers, ophthalmic diseases, retinitis, retinopathies, uveitis, ocular photophobia, acute injury to the eye tissue and ocular traumas such as post-traumatic glaucoma, traumatic optic neuropathy, and central retinal artery occlusion (CRAO), periodontal disease, ophthalmological conditions, retinitis, retinopathies (including diabetic retinopathy), uveitis, ocular photophobia, nonglaucomatous optic nerve atrophy, and age related macular degeneration (ARMD) (including ARMD-atrophic form), corneal graft rejection, ocular neovascularization, retinal neovascularization, neovascularization following injury or infection, retrolental fibroplasias, neovascular glaucoma, glaucoma including primary open angle glaucoma (POAG), juvenile onset primary open-angle glaucoma, angle-closure glaucoma, pseudoexfoliative glaucoma, anterior ischemic optic neuropathy (AION), ocular hypertension, Reiger's syndrome, normal tension glaucoma, neovascular glaucoma, ocular inflammation and corticosteroid-induced glaucoma, diabetes, diabetic nephropathy, skin-related conditions, psoriasis, eczema, burns, dermatitis, keloid formation, scar tissue

formation, angiogenic disorders, viral and bacterial infections, sepsis, septic shock, gram negative sepsis, malaria, meningitis, HIV infection, opportunistic infections, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDS related complex), pneumonia, herpes virus, myalgias due to infection, influenza, endotoxic shock, toxic shock syndrome, autoimmune disease, graft vs host reaction and allograft rejections, treatment of bone resorption diseases, osteoporosis, multiple sclerosis, disorders of the female reproductive system, endometriosis, hemaginomas, infantile hemagionmas, angiofibroma of the nasopharynx, avascular necrosis of bone, benign and malignant tumors/neoplasia, cancer, colorectal cancer, brain cancer, bone cancer, epithelial call-derived neoplasia (epithelial carcinoma), basal cell carcinoma, adenocarcinoma, gastrointestinal cancer, lip cancer, mouth cancer, esophageal cancer, small bowel cancer, stomach cancer, colon cancer liver cancer, bladder cancer, pancreas cancer, ovarian cancer, cervical cancer, lung cancer, breast cancer, skin cancer, squamus cell and/or basal cell cancers, prostate cancer, renal cell carcinoma, and other known cancers that affect epithelial cells throughout the body, leukemia, lymphoma, systemic lupus erthrematosis (SLE), angiogenesis including neoplasia, metastasis, central nervous system disorders, central nervous system disorders having an inflammatory or apoptotic component, Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, spinal cord injury, and peripheral neuropathy, Canine B-Cell Lymphoma Compounds of the invention are also useful for preventing the production or expression of cyclooxygenase-2, or cyclooxygenase-2 activity

In this aspect, the invention encompasses methods of treating a p38 kinase or TNF-alpha mediated disorder

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comprising administering to a patient in need thereof a therapeutically effective amount of Compounds according to embodiment 1 and at least one pharmaceutically acceptable carrier, adjuvant, solvent or excipient

Representative compounds of the invention are

1-benzyl-4-(benzyloxy)-3-bromopyridin-2(1*H*)-one,

3-bromo-1-(4-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-dimethylphenyl)-6-methylpyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-(4-fluorobenzyl)pyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(3-fluorobenzyl)pyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1*H*)-one,

4-bromo-2-(2,6-dichlorophenyl)-5-[(2,4-difluorobenzyl)oxy]pyridazin-3(2*H*)-one,

3-bromo-1-(2,6-dichlorophenyl)-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-bromo-1-(3-fluorobenzyl)-4-[(3-methylbenzyl)oxy]pyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(pyridin-4-ylmethyl)pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-(3-fluorobenzyl)pyridin-2(1*H*)-one,

1-benzyl-4-(benzyloxy)-3-bromo-6-methylpyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2-methoxy-6-methylphenyl)-6-methylpyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2-fluorobenzyl)pyridin-2(1*H*)-one,

3-bromo-4-[(4-fluorobenzyl)oxy]-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1*H*)-one,

3-bromo-1-(2,6-dichlorophenyl)-4-[(4-fluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-(4-methylbenzyl)pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-(4-chlorobenzyl)pyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(3-methoxybenzyl)pyridin-2(1*H*)-one,

4-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]methyl}benzoic acid,

4-(benzyloxy)-3-bromo-1-(2-fluorobenzyl)pyridin-2(1*H*)-one,

3-bromo-1-(2,6-dimethylphenyl)-4-[(4-fluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-[4-(methylthio)benzyl]pyridin-2(1*H*)-one,

1-benzyl-4-(benzyloxy)-3-chloropyridin-2(1*H*)-one,

4-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]methyl}-*N*'-hydroxybenzenecarboximidamide,

methyl 4-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]methyl}benzoate,

3-bromo-4-[(3-chlorobenzyl)oxy]-1-(3-fluorobenzyl)pyridin-2(1*H*)-one,

3-bromo-1-(3-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one,

4-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]methyl}benzonitrile,

4-(benzyloxy)-3-bromo-1-(2,6-dichlorophenyl)-6-methylpyridin-2(1*H*)-one,

3-bromo-4-[(4-fluorobenzyl)oxy]-1-(pyridin-4-ylmethyl)pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-(4-bromobenzyl)pyridin-2(1*H*)-one,

4-{[3-bromo-4-[(4-fluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}benzonitrile,

1-(3-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]-3-iodopyridin-2(1*H*)-one,

4-bromo-2-(2,6-dichlorophenyl)-5-{[2-(hydroxymethyl)benzyl]oxy}pyridazin-3(2*H*)-one

3-bromo-4-[(4-fluorobenzyl)oxy]-1-(pyridin-3-ylmethyl)pyridin-2(1*H*)-one,

3-bromo-1-(2,4-difluorobenzyl)-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-bromo-4-[(4-fluorobenzyl)oxy]-6-methyl-1-(pyridin-2-ylmethyl)pyridin-2(1*H*)-one, or a pharmaceutically acceptable salt thereof

Embodiment 57 Compounds according to embodiment 1 or embodiment A1, which is

3-bromo-4-[(4-chlorobenzyl)oxy]-1-(4-fluorobenzyl)pyridin-2(1*H*)-one,

1-benzyl-3-bromo-4-[(4-chlorobenzyl)oxy]pyridin-2(1*H*)-one,

3-bromo-1-(4-chlorobenzyl)-4-[(4-chlorobenzyl)oxy]pyridin-2(1*H*)-one,

3-bromo-4-[(4-chlorobenzyl)oxy]-1-[2-(phenylthio)ethyl]pyridin-2(1*H*)-one,

3-bromo-4-[(4-chlorobenzyl)oxy]-1-(2-phenylethyl)pyridin-2(1*H*)-one,

3-bromo-4-hydroxy-1-(4-hydroxybenzyl)pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-(piperidin-3-ylmethyl)pyridin-2(1*H*)-one hydrochloride,

3-bromo-1-(4-methoxybenzyl)-4-phenoxypyridin-2(1*H*)-one,

1-benzyl-2-oxo-4-phenoxy-1,2-dihydropyridine-3-carbaldehyde,

3-bromo-4-[(4-chlorobenzyl)oxy]-1-(4-methoxybenzyl)pyridin-2(1*H*)-one,

3-bromo-4-[(4-fluorobenzyl)oxy]-1-(3-phenylpropyl)pyridin-2(1*H*)-one,

4-(benzyloxy)-1-[4-(benzyloxy)benzyl]-3-bromopyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-[2-(trifluoromethyl)benzyl]pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-[3-(trifluoromethyl)benzyl]pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-(piperidin-4-ylmethyl)pyridin-2(1*H*)-one hydrochloride,

1-benzyl-3-bromo-4-{[2-(trifluoromethyl)benzyl]oxy}pyridin-2(1*H*)-one,

1-benzyl-4-[(2,6-dichlorobenzyl)oxy]pyridin-2(1*H*)-one,

1-benzyl-4-(benzyloxy)-3-(hydroxymethyl)pyridin-2(1*H*)-one,

1-benzyl-3-bromo-4-[(2,6-dichlorobenzyl)oxy]pyridin-2(1*H*)-one,

1-benzyl-4-[(3-chlorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

1-benzyl-3-bromo-4-[(3-chlorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

1-benzyl-3-bromo-4-[(2-chlorobenzyl)oxy]pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-ethylpyridin-2(1*H*)-one,

4-(benzyloxy)-1-(4-bromobenzyl)pyridin-2(1*H*)-one,

3-bromo-1-(4-methylbenzyl)-4-[(4-methylbenzyl)oxy]pyridin-2(1*H*)-one,

methyl 4-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]methyl}benzoate,

4-(benzyloxy)-3-bromo-1-(2-thien-3-ylethyl)pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-(2-thien-2-ylethyl)pyridin-2(1*H*)-one,

1-benzyl-4-[(3-chlorobenzyl)oxy]pyridin-2(1*H*)-one,

3-bromo-1-(4-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one,

4-(benzyloxy)-1-(3-fluorobenzyl)pyridin-2(1*H*)-one,

4-(benzyloxy)-1-(2-fluorobenzyl)pyridin-2(1*H*)-one

4-(benzyloxy)-3-bromo-1-methylpyridin-2(1*H*)-one hydrobromide,

4-(benzyloxy)-3-bromo-1-methylpyridin-2(1*H*)-one,

3-bromo-1-(3-chlorobenzyl)-4-[(4-chlorobenzyl)oxy]pyridin 2(1*H*)-one,

3-bromo-1-(3-chlorobenzyl)-4-[(4-fluorobenzyl)oxy]pyridin 2(1*H*)-one,

4-(benzyloxy)-1-(4-chlorobenzyl)pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-[4-(trifluoromethoxy)benzyl]pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-(4-tert-butylbenzyl)pyridin-2(1*H*)-one,

1-benzyl-4-(benzyloxy)-6-methylpyridin-2(1*H*)-one,

1-benzyl-4-(benzyloxy)-3,5-dibromo-6-methylpyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-[4-(trifluoromethyl)benzyl]pyridin-2(1*H*)-one,

1-benzyl-4-[(2-chlorobenzyl)oxy]pyridin-2(1*H*)-one,

1-(2-bromobenzyl)-3-[(2-bromobenzyl)oxy]pyridin-2(1*H*)-one,

methyl 5-chloro-1-(4-chlorobenzyl)-6-oxo-1,6-dihydropyridine-3-carboxylate,

3-benzyl-4-hydroxy-1-(2-phenylethyl)pyridin-2(1*H*)-one,

5-bromo-1-(2-chloro-6-fluorobenzyl)-3-methylpyridin-2(1*H*)-one,

1-(2-bromobenzyl)-3-[(2-bromobenzyl)oxy]pyridin-2(1*H*)-one,

1-benzyl-4-(benzyloxy)pyridin-2(1*H*)-one,

1-benzyl-4-(benzyloxy)-3-bromopyridin-2(1*H*)-one,

1-benzyl-4-(benzyloxy)-2-oxo-1,2-dihydropyridine-3-carbaldehyde,

1-benzyl-4-chloro-2-oxo-1,2-dihydropyridine-3-carbaldehyde,

1-benzyl-4-hydroxy-2-oxo-1,2-dihydropyridine-3-carbaldehyde,

1-benzyl-4-(benzyloxy)-3-methylpyridin-2(1*H*)-one,

4-(benzyloxy)-1-(4-fluorobenzyl)pyridin-2(1*H*)-one,

1-benzyl-4-(benzyloxy)-3,5-dibromopyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-[4-(methylthio)benzyl]pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-(4-fluorobenzyl)pyridin-2(1*H*)-one,

1-benzyl-4-(benzyloxy)-3-chloropyridin-2(1*H*)-one,

3-bromo-1-(4-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one,

1-benzyl-3-bromo-2-oxo-1,2-dihydropyridin-4-yl methyl(phenyl)carbamate,

1-benzyl-3-bromo-4-(2-phenylethyl)pyridin-2(1*H*)-one,

1-benzyl-3-bromo-4-(3-phenylpropyl)pyridin-2(1*H*)-one,

1-benzyl-3-methyl-4-(2-phenylethyl)pyridin-2(1*H*)-one,

1-benzyl-3-methyl-4-(3-phenylpropyl)pyridin-2(1*H*)-one,

1-benzyl-4-(benzylthio)-3-methylpyridin-2(1*H*)-one,

1-benzyl-4-(benzylthio)-3-bromopyridin-2(1*H*)-one,

1-benzyl-2-oxo-1,2-dihydropyridin-4-yl methanesulfonate,

3-acetyl-4-hydroxy-6-methyl-1-[choro]phenylpyridin-2(1*H*)-one,

6-(benzyloxy)-1-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile,

3-benzoyl-6-(benzyloxy)-1-methylpyridin-2(1*H*)-one,

3-benzyl-6-(benzyloxy)-1-methylpyridin-2(1*H*)-one,

1-benzyl-4-hydroxypyridin-2(1*H*)-one,

1-benzyl-4-(benzylthio)pyridin-2(1*H*)-one

4-amino-1-benzylpyridin-2(1*H*)-one,

1-benzyl-4-(benzyloxy)pyridin-2(1*H*)-one,

1-benzyl-4-hydroxypyridin-2(1*H*)-one,

1-benzyl-2-oxo-1,2-dihydropyridin-4-yl methyl(phenyl)carbamate,

or a pharmaceutically acceptable thereof

Embodiment 58 Compounds according to embodiment 1 or embodiment A1, which is

4-(benzyloxy)-1-(4-methylbenzyl)pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromopyridin-2(1*H*)-one,

methyl 4-{[4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl]methyl} benzoate,

methyl-4-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]methyl} benzoate,

4-{[4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl]methyl} benzonitrile,

4-(benzyloxy)-1-(4-tert-butylbenzyl)pyridin-2(1*H*)-one,

4-(benzyloxy)-1-[4-(trifluoromethyl)benzyl]pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-[4-(trifluoromethyl) benzyl]pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-[3-(trifluoromethyl) benzyl]pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-[2-(trifluoromethyl) benzyl]pyridin-2(1*H*)-one,

4-(benzyloxy)-1-[4-(trifluoromethoxy)benzyl]pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-[4-(trifluoromethoxy) benzyl]pyridin-2(1*H*)-one,

1-benzyl-4-hydroxy-6-methylpyridin-2(1H)-one,

1-benzyl-6-methyl-2-oxo-1,2-dihydropyridin-4-yl 4-bromobenzenesulfonate,

1-benzyl-3-bromo-4-[(3-chlorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

1-benzyl-6-methyl-2-oxo-1,2-dihydropyridin-4-yl 4-bromobenzenesulfonate,

1-benzyl-3-bromo-4-[(3-chlorobenzyl)oxy]-6-methylpyridin-2(1H)-one,

1-Benzyl-4-[2,6-(dichlorobenzyl)oxy]pyridin-2(1H)-one,

4-[(2,6-dichlororbenzyl)oxy]pyridine-1-oxide,

4-[(2,6-dichlorobenzyl)oxy]pyridine 1-oxide,

1-Benzyl-3-bromo-4-[2,6-(dichlorobenzyl)oxy]pyridin-2(1*H*)-one,

1-Benzyl-3-bromo-4-[(4-methylbenzyl)oxy]pyridin-2(1H)-one,

1-Benzyl-4-[benzylthio]-3-bromopyridin-2(1H)-one,

1-benzyl-4-(benzyloxy)-3-iodopyridin-2(1H)-one,

1-benzyl-4-(benzyloxy)-3-vinylpyridin-2(1H)-one,

1-benzyl-4-(benzyloxy)-3-ethylpyridin-2(1H)-one,

3-acetyl-4-(benzyloxy)-1-(2-chlorophenyl)-6-methylpyridin-2(1H)-one,

3-acetyl-1-(2-chlorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one,

1-benzyl-3-bromo-4-hydroxypyridin-2(1H)-one,

1-benzyl-3-bromo-2-oxo-1,2-dihydropyridin-4-yl trifluoromethanesulfonate,

1-benzyl-3-bromo-4-(phenylethynyl)pyridin-2(1H)-one,

3-bromo-1-(3-fluorobenzyl)-6-methyl-4-(2-phenylethyl)pyridin-2(1H)-one,

1-(3-fluorobenzyl)-4-hydroxy-6-methylpyridin-2(1H)-one,

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3-bromo-1-(3-fluorobenzyl)-4-hydroxy-6-methylpyridin-2(1H)-one,

3-bromo-1-(3-fluorobenzyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl trifluoromethanesulfonate,

3-bromo-1-(3-fluorobenzyl)-6-methyl-4-(phenylethynyl)pyridin-2(1H)-one,

3-acetyl-1-(2,6-dichlorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one,

1-(2,6-dichlorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one,

4-(benzyloxy)-1-(2,6-dichlorophenyl)-6-methylpyridin-2(1H)-one,

3-bromo-1-(3-fluorobenzyl)-4-(2-phenylethynyl)pyridin-2(1H)-one,

3-bromo-1-(3-fluorobenzyl)-4-hydroxypyridin-2(1H)-one,

3-bromo-1-(3-fluorobenzyl)-2-oxo-1,2-dihydropyridin-4-yl trifluoromethanesulfonate,

3-bromo-1-(3-fluorobenzyl)-4-(phenylethynyl)pyridin-2(1H)-one,

4-(benzyloxy)-3-ethynyl-1-(3-fluorobenzyl)pyridin-2(1H)-one,

4-(benzyloxy)-1-(3-fluorobenzyl)-3-iodopyridin-2(1H)-one,

4-(benzyloxy)-1-(3-fluorobenzyl)-3-[(trimethylsilyl)ethynyl]pyridin-2(1H)-one,

4-(benzylamino)-3-bromo-1-(3-fluorobenzyl)pyridin-2(1H)-one,

1-(3-fluorobenzyl)-4-hydroxypyridin-2(1H)-one,

4-(benzylamino)-1-(3-fluorobenzyl)pyridin-2(1H)-one,

or a pharmaceutically acceptable salt thereof

Embodiment 59 Compounds according to embodiment 1 or embodiment A1, which is

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2-fluorobenzyl)pyridin-2(1*H*)-one,

3-bromo-4-[(4-fluorobenzyl)oxy]-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1*H*)-one,

3-bromo-4-[(4-fluorobenzyl)oxy]-6-methyl-1-(pyridin-4-ylmethyl)pyridin-2(1*H*)-one,

3-bromo-1-(2,6-dichlorophenyl)-4-[(4-fluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(3-methoxybenzyl)pyridin-2(1*H*)-one,

3-bromo-1-(2,6-dimethylphenyl)-4-[(4-fluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-bromo-4-[(3-chlorobenzyl)oxy]-1-(3-fluorobenzyl)pyridin-2(1*H*)-one,

3-bromo-4-[(4-fluorobenzyl)oxy]-1-(pyridin-4-ylmethyl)pyridin-2(1*H*)-one,

3-bromo-1-(3-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one,

4-{[3-bromo-4-[(4-fluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}benzonitrile,

1-(3-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]-3-iodopyridin-2(1*H*)-one,

3-bromo-4-[(4-fluorobenzyl)oxy]-1-(pyridin-3-ylmethyl)pyridin-2(1*H*)-one,

3-bromo-1-(2,4-difluorobenzyl)-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-bromo-4-[(4-fluorobenzyl)oxy]-6-methyl-1-(pyridin-2-ylmethyl)pyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(3-fluorobenzyl)pyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1*H*)-one,

3-bromo-1-(2,6-dichlorophenyl)-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-bromo-1-(3-fluorobenzyl)-4-[(3-methylbenzyl)oxy]piperidin-2-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(pyridin-4-ylmethyl)pyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2-methoxy-6-methylphenyl)-6-methylpyridin-2(1*H*)-one,

or a pharmaceutically acceptable salt thereof

Embodiment 60 Compounds according to embodiment 1, which is

1-(1-acetyl-2,3-dihydro-1*H*-indol-5-yl)-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(1-glycoloyl-2,3-dihydro-1*H*-indol-5-yl)-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-indol-5-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[1-(*N*-methylglycyl)-2,3-dihydro-1*H*-indol-5-yl]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-indol-5-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1*H*-indol-5-yl]-6-methylpyridin-2(1*H*)-one,

5-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]indoline-1-carboxamide,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[1-(methylsulfonyl)-2,3-dihydro-1*H*-indol-5-yl]pyridin-2(1*H*)-one,

1-(1-acetyl-1*H*-indol-5-yl)-3-chloro-4-[(2,4-

difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(1-glycoloyl-1*H*-indol-5-yl)-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(2-hydroxy-2-methylpropanoyl)-1*H*-indol-5-yl]-6-methylpyridin-2(1*H*)-one

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[1-(*N*-methylglycyl)-1*H*-indol-5-yl]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(3-hydroxypropanoyl)-1*H*-indol-5-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(3-hydroxy-3-methylbutanoyl)-1*H*-indol-5-yl]-6-methylpyridin-2(1*H*)-one,

5-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-1*H*-indole-1-carboxamide,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[1-(methylsulfonyl)-1*H*-indol-5-yl]pyridin-2(1*H*)-one,

1-(2-acetyl-2,3-dihydro-1*H*-isoindol-5-yl)-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(2-glycoloyl-2,3-dihydro-1*H*-isoindol-5-yl)-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[2-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-isoindol-5-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[2-(*N*-methylglycyl)-2,3-dihydro-1*H*-isoindol-5-yl]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[2-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-isoindol-5-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[2-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1*H*-isoindol-5-yl]-6-methylpyridin-2(1*H*)-one,

5-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-1,3-dihydro-2*H*-isoindole-2-carboxamide,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[2-(methylsulfonyl)-2,3-dihydro-1*H*-isoindol-5-yl]pyridin-2(1*H*)-one,

1-(2-acetyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(2-glycoloyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[2-(2-hydroxy-2-methylpropanoyl)-1,2,3,4 tetrahydroisoquinolin-6-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[2-(*N*-methylglycyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[2-(3-hydroxypropanoyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[2-(3-hydroxy-3-methylbutanoyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-6-methylpyridin-2(1*H*)-one,

6-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-3,4-dihydroisoquinoline-2(1*H*)-carboxamide,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[2-(methylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]pyridin-2(1*H*)-one,

1-(2-acetyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(2-glycoloyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[2-(2-hydroxy-2-methylpropanoyl)-1,2,3,4-tetrahydroisoquinolin-7-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[2-(*N*-methylglycyl)-1,2,3,4-tetrahydroisoquinolin-7-yl]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[2-(3-hydroxypropanoyl)-1,2,3,4-tetrahydroisoquinolin-7-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[2-(3-hydroxy-3-methylbutanoyl)-1,2,3,4-tetrahydroisoquinolin-7-yl]-6-methylpyridin-2(1*H*)-one,

7-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-3,4-dihydroisoquinoline-2(1*H*)-carboxamide,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[2-(methylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-7-yl]pyridin-2(1*H*)-one,

1-(1-acetyl-1*H*-benzimidazol-5-yl)-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(1-glycoloyl-1*H*-benzimidazol-5-yl)-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(2-hydroxy-2-methylpropanoyl)-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[1-(*N*-methylglycyl)-1*H*-benzimidazol-5-yl]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(3-hydroxypropanoyl)-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(3-hydroxy-3-methylbutanoyl)-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

5-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-1*H*-benzimidazole-1-carboxamide,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[1-(methylsulfonyl)-1*H*-benzimidazol-5-yl]pyridin-2(1*H*)-one,

3-chloro-1-(1,3-diacetyl-2,3-dihydro-1*H*-benzimidazol-5-yl)-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

1-(3-acetyl-1-glycoloyl-2,3-dihydro-1*H*-benzimidazol-5-yl)-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

1-[3-acetyl-1-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

1-[3-acetyl-1-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one

1-[3-acetyl-1-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

1-[3-acetyl-1-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-acetyl-5-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

1-(1-acetyl-3-glycoloyl-2,3-dihydro-1*H*-benzimidazol-5-yl)-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4 difluorobenzyl)oxy]-1-(1,3-diglycoloyl-2,3-dihydro-1*H*-benzimidazol-5-yl)-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[3-glycoloyl-1-(2-hydroxy-2-methylpropanoyl)-2 3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[3-glycoloyl-1-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-

methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[3-glycoloyl-1-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

5-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-3-glycoloyl-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[3-glycoloyl-1-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[3-glycoloyl-1-(methylsulfonyl)-2 3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

1-[1-acetyl-3-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-glycoloyl-3-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

1-[1,3-bis(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[3-(2-hydroxy-2-methylpropanoyl)-1-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[3-(2-hydroxy-2-methylpropanoyl)-1-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(3-hydroxy-3-methylbutanoyl)-3-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

5-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-

oxopyridin-1(2*H*)-yl]-3-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-benzimidazole 1-carboxamide,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[3-(2-hydroxy-2-methylpropanoyl)-1-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

1-[1-acetyl-3-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-glycoloyl-3-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(2-hydroxy-2-methylpropanoyl)-3-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

1-[1,3-bis(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(3-hydroxypropanoyl)-3-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(3-hydroxy-3-methylbutanoyl)-3-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

5-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-3-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[3-(*N*-methylglycyl)-1-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]pyridin-2(1*H*)-one,

1-[1-acetyl-3-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-glycoloyl-3-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(2-hydroxy-2-methylpropanoyl)-3-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[3-(3-hydroxypropanoyl)-1-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

1-[1,3-bis(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(3-hydroxy-3-methylbutanoyl)-3-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

5-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-3-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[3-(3-hydroxypropanoyl)-1-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

1-[1-acetyl-3-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-glycoloyl-3-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[3-(3-hydroxy-3-methylbutanoyl)-1-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[3-(3-hydroxy-3-methylbutanoyl)-1-(*N*-methylglycyl)-2,3-dihydro-1*H*-

benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[3-(3-hydroxy-3-methylbutanoyl)-1-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

1-[1,3-bis(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

5-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-3-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[3-(3-hydroxy-3-methylbutanoyl)-1-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

3-acetyl-6-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

6-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-3-glycoloyl-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

6-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-3-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

6-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-3-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

6-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-3-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

6-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-3-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

5-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-

oxopyridin-1(2*H*)-yl]-1*H*-benzimidazole-1,3(2*H*)-dicarboxamide,

6-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-3-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

1-[1-acetyl-3-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-glycoloyl-3-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(2-hydroxy-2-methylpropanoyl)-3-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[1-(*N*-methylglycyl)-3-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(3-hydroxypropanoyl)-3-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(3-hydroxy-3-methylbutanoyl)-3-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

5-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-3-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

1-[1,3-bis(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

1-[3-acetyl-1-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

1-(1-acetyl-1*H*-pyrrol-3-yl)-3-chloro-4-[(2,4-

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difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(1-glycoloyl-1*H*-pyrrol-3-yl)-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(2-hydroxy-2-methylpropanoyl)-1*H*-pyrrol-3-yl]-6-methylpyridin-2(1*H*)-one

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[1-(*N*-methylglycyl)-1*H*-pyrrol-3-yl]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(3-hydroxypropanoyl)-1*H*-pyrrol-3-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(3-hydroxy-3-methylbutanoyl)-1*H*-pyrrol-3-yl]-6-methylpyridin-2(1*H*)-one,

3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-1*H*-pyrrole-1-carboxamide,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[1-(methylsulfonyl)-1*H*-pyrrol-3-yl]pyridin-2(1*H*)-one,

1-(1-acetyl-1*H*-imidazol-4-yl)-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(1-glycoloyl-1*H*-imidazol-4-yl)-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(2-hydroxy-2-methylpropanoyl)-1*H*-imidazol-4-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[1-(*N*-methylglycyl)-1*H*-imidazol-4-yl]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(3-hydroxypropanoyl)-1*H*-imidazol-4-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(3-hydroxy-3-methylbutanoyl)-1*H*-imidazol-4-yl]-6-methylpyridin-2(1*H*)-one,

4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-1*H*-imidazole-1-carboxamide,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[1-(methylsulfonyl)-1*H*-imidazol-4-yl]pyridin-2(1*H*)-one,

1-(1-acetyl-1*H*-pyrazol-4-yl)-3-chloro-4-[(2,4-

difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(1-glycoloyl-1*H*-pyrazol-4-yl)-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(2-hydroxy-2-methylpropanoyl)-1*H*-pyrazol-4-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[1-(*N*-methylglycyl)-1*H*-pyrazol-4-yl]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(3-hydroxypropanoyl)-1*H*-pyrazol-4-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(3-hydroxy-3-methylbutanoyl)-1*H*-pyrazol-4-yl]-6-methylpyridin-2(1*H*)-one,

4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-1*H*-pyrazole-1-carboxamide,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[1-(methylsulfonyl)-1*H*-pyrazol-4-yl]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-isoquinolin-7-yl-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(isoquinolin-6-ylmethyl)pyridin-2(1*H*)-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1,3-dihydro-2*H*-indol-2-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(2,3-dihydro-1*H*-indol-5-ylmethyl)pyridin-2(1*H*)-one,

1-[(1-acetyl-2,3-dihydro-1*H*-indol-5-yl)methyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[(1-glycoloyl-2,3-dihydro-1*H*-indol-5-yl)methyl]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-indol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(*N*-methylglycyl)-2,3-dihydro-1*H*-indol-5-yl]methyl}pyridin-2(1*H*)-

one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-indol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1*H*-indol-5-yl]methyl}pyridin-2(1*H*)-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}indoline-1-carboxamide

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(methylsulfonyl)-2,3-dihydro-1*H*-indol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(2,3-dihydro-1*H*-isoindol-5-ylmethyl)pyridin-2(1*H*)-one,

1-[(2-acetyl-2,3-dihydro-1*H*-isoindol-5-yl)methyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[(2-glycoloyl-2,3-dihydro-1*H*-isoindol-5-yl)methyl]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[2-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-isoindol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4 difluorobenzyl)oxy]-1-{[2-(*N*-methylglycyl)-2,3-dihydro-1*H*-isoindol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[2-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-isoindol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[2-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1*H*-isoindol-5-yl]methyl}pyridin-2(1*H*)-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1,3-dihydro-2*H*-isoindole-2-carboxamide,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[2-(methylsulfonyl)-2,3-dihydro-1*H*-isoindol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(1,2,3,4-tetrahydroisoquinolin-6-ylmethyl)pyridin-2(1*H*)-one,

1-[(2-acetyl-1,2,3,4-tetrahydroisoquinolin-6-yl)methyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[(2-glycoloyl-1,2,3,4-tetrahydroisoquinolin-6-yl)methyl]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[2-(2-hydroxy-2-methylpropanoyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[2-(*N*-methylglycyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[2-(3-hydroxypropanoyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[2-(3-hydroxy-3-methylbutanoyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]methyl}pyridin-2(1*H*)-one,

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3,4-dihydroisoquinoline-2(1*H*)-carboxamide,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[2-(methylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(1,2,3,4-tetrahydroisoquinolin-5-ylmethyl)pyridin-2(1*H*)-one,

1-[(2-acetyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[(2-glycoloyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[2-(2-hydroxy-2-methylpropanoyl)-1,2,3,4 tetrahydroisoquinolin-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[2-(*N*-methylglycyl)-1,2,3,4-tetrahydroisoquinolin-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[2-(3-hydroxypropanoyl)-1,2,3,4-tetrahydroisoquinolin-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[2-(3-hydroxy-3-methylbutanoyl)-1,2,3,4-tetrahydroisoquinolin-5-yl]methyl}pyridin-2(1*H*)-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3,4-dihydroisoquinoline-2(1*H*)-carboxamide,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[2-(methylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(2,3-dihydro-1*H*-benzimidazol-5-ylmethyl)pyridin-2(1*H*)-one,

1-[(1-acetyl-2,3-dihydro-1*H*-benzimidazol-5-yl)methyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[(1-glycoloyl-2,3-dihydro-1*H*-benzimidazol-5-yl)methyl]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

1-[(3-acetyl-2,3-dihydro-1*H*-benzimidazol-5-yl)methyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-chloro-1-[(1,3-diacetyl-2,3-dihydro-1*H*-benzimidazol-5-yl)methyl]-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one,

1-[(3-acetyl-1-glycoloyl-2,3-dihydro-1*H*-benzimidazol-5-yl)methyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one,

1-{[3-acetyl-1-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one,

1-{[3-acetyl-1-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one,

1-{[3-acetyl-1-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one,

1-{[3-acetyl-1-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-acetyl-5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

1-{[3-acetyl-1-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}-3-chloro-4-[(2,4-

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difluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[(3-glycoloyl-2,3-dihydro-1*H*-benzimidazol-5-yl)methyl]pyridin-2(1*H*)-one,

1-[(1-acetyl-3-glycoloyl-2,3-dihydro-1*H*-benzimidazol-5-yl)methyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[(1,3-diglycoloyl-2,3-dihydro-1*H*-benzimidazol-5-yl)methyl]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-glycoloyl-1-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-glycoloyl-1-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-glycoloyl-1-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-glycoloyl-1-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-glycoloyl-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-glycoloyl-1-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

1-{[1-acetyl-3-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-glycoloyl-3-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

1-{[1,3-bis(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-(2-hydroxy-2-methylpropanoyl)-1-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-(2-hydroxy-2-methylpropanoyl)-1-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(3-hydroxy-3-methylbutanoyl)-3-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-(2-hydroxy-2-methylpropanoyl)-1-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

1-{[1-acetyl-3-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-glycoloyl-3-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(2-hydroxy-2-methylpropanoyl)-3-(*N*-methylglycyl)-2,3-dihydro-1*H*-

benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

1-{[1,3-bis(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(3-hydroxypropanoyl)-3-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(3-hydroxy-3-methylbutanoyl)-3-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl pyridin-2(1*H*)-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-(*N*-methylglycyl)-1-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

1-{[1-acetyl-3-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-glycoloyl-3-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(2-hydroxy-2-methylpropanoyl)-3-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-(3-hydroxypropanoyl)-1-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

1-{[1,3-bis(3-hydroxypropanoyl)-2,3-dihydro-1*H*-

benzimidazol-5-yl]methyl}-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(3-hydroxy-3-methylbutanoyl)-3-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-(3-hydroxypropanoyl)-1-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

1-{[1-acetyl-3-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-glycoloyl-3-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-(3-hydroxy-3-methylbutanoyl)-1-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-(3-hydroxy-3-methylbutanoyl)-1-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-(3-hydroxy-3-methylbutanoyl)-1-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

1-{[1,3-bis(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1H)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-(3-hydroxy-3-methylbutanoyl)-1-(3-hydroxypropanoyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}pyridin-2(1H)-one,

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]methyl}-2,3-dihydro-1H-benzimidazole-1-carboxamide,

3-acetyl-6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]methyl}-2,3-dihydro-1H-benzimidazole-1-carboxamide,

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]methyl}-3-glycoloyl-2,3-dihydro-1H-benzimidazole-1-carboxamide,

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]methyl}-3-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1H-benzimidazole-1-carboxamide,

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]methyl}-3-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]methyl}-3-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]methyl}-3-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]methyl}-1*H*-benzimidazole-1,3(2*H*)-dicarboxamide,

6-{[3-chloro-4-[(2 4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]methyl}-3-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-

(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

1-{[1-acetyl-3-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-glycoloyl-3-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(2-hydroxy-2-methylpropanoyl)-3-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(*N*-methylglycyl)-3-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(3-hydroxypropanoyl)-3-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(3-hydroxy-3-methylbutanoyl)-3-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

1-{[1,3-bis(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1,3-dihydro-2*H*-benzimidazol-2-one,

1-acetyl-5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-glycoloyl-1,3-dihydro-2*H*-benzimidazol-2-

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5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(2-hydroxy-2-methylpropanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(*N*-methylglycyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(3-hydroxypropanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(3-hydroxy-3-methylbutanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(methylsulfonyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

1-acetyl-6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1,3-dihydro-2*H*-benzimidazol-2-one,

1,3-diacetyl-5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1,3-dihydro-2*H*-benzimidazol-2-one,

3-acetyl-5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-glycoloyl-1,3-dihydro-2*H*-benzimidazol-2-one,

3-acetyl-5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(2-hydroxy-2-methylpropanoyl)-1 3-dihydro-2*H*-benzimidazol-2-one,

3-acetyl-5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(*N*-methylglycyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

3-acetyl-5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(3-hydroxypropanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

3-acetyl-5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(3-hydroxy-3-methylbutanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

3-acetyl-5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

3-acetyl-5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(methylsulfonyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-glycoloyl-1,3-dihydro-2*H*-benzimidazol-2-one,

1-acetyl-5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-glycoloyl-1 3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1,3-diglycoloyl-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-glycoloyl-1-(2-hydroxy-2-methylpropanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-glycoloyl-1-(*N*-methylglycyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-glycoloyl-1-(3-hydroxypropanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-glycoloyl-1-(3-hydroxy-3-methylbutanoyl)-

1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-glycoloyl-2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-glycoloyl-1-(methylsulfonyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(2-hydroxy-2-methylpropanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

1-acetyl-5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(2-hydroxy-2-methylpropanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-glycoloyl-3-(2-hydroxy-2-methylpropanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1,3-bis(2-hydroxy-2-methylpropanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(2-hydroxy-2-methylpropanoyl)-1-(*N*-methylglycyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(2-hydroxy-2-methylpropanoyl)-1-(3-hydroxypropanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(3-hydroxy-3-methylbutanoyl)-3-(2-hydroxy-2-methylpropanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(2-hydroxy-2-methylpropanoyl)-2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-

1(2*H*)-yl]methyl}-3-(2-hydroxy-2-methylpropanoyl)-1-(methylsulfonyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(*N*-methylglycyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

1-acetyl-5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(*N*-methylglycyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-glycoloyl-3-(*N*-methylglycyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(2-hydroxy-2-methylpropanoyl)-3-(*N*-methylglycyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1,3-bis(*N*-methylglycyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(3-hydroxypropanoyl)-3-(*N*-methylglycyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(3-hydroxy-3-methylbutanoyl)-3-(*N*-methylglycyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(*N*-methylglycyl)-2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(*N*-methylglycyl)-1-(methylsulfonyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(3-hydroxypropanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

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1-acetyl-5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]methyl}-3-(3-hydroxypropanoyl)-1,3-dihydro-2H-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]methyl}-1-glycoloyl-3-(3-hydroxypropanoyl)-1,3-dihydro-2H-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]methyl}-1-(2-hydroxy-2-methylpropanoyl)-3-(3-hydroxypropanoyl)-1,3-dihydro-2H-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]methyl}-3-(3-hydroxypropanoyl)-1-(N-methylglycyl)-1,3-dihydro-2H-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]methyl}-1,3-bis(3-hydroxypropanoyl)-1,3-dihydro-2H-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]methyl}-1-(3-hydroxy-3-methylbutanoyl)-3-(3-hydroxypropanoyl)-1,3-dihydro-2H-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]methyl}-3-(3-hydroxypropanoyl)-2-oxo-2,3-dihydro-1H-benzimidazole-1-carboxamide,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]methyl}-3-(3-hydroxypropanoyl)-1-(methylsulfonyl)-1,3-dihydro-2H-benzimidazol-2-one,

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]methyl}-1-(3-hydroxy-3-methylbutanoyl)-1,3-dihydro-2H-benzimidazol-2-one,

1-acetyl-5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]methyl}-3-(3-hydroxy-3-methylbutanoyl)-1,3-dihydro-2H-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]methyl}-1-glycoloyl-3-(3-hydroxy-3-methylbutanoyl)-

1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(3-hydroxy-3-methylbutanoyl)-1-(2-hydroxy-2-methylpropanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(3-hydroxy-3-methylbutanoyl)-1-(*N*-methylglycyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(3-hydroxy-3-methylbutanoyl)-1-(3-hydroxypropanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1,3-bis(3-hydroxy-3-methylbutanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(3-hydroxy-3-methylbutanoyl)-2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(3-hydroxy-3-methylbutanoyl)-1-(methylsulfonyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

3-acetyl-6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-glycoloyl-2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(2-hydroxy-2-methylpropanoyl)-2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-

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Hz

1(2*H*)-yl]methyl}-3-(*N*-methylglycyl)-2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(3-hydroxypropanoyl)-2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carboxamide

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(3-hydroxy-3-methylbutanoyl)-2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-2-oxo-1*H*-benzimidazole-1,3(2*H*)-dicarboxamide,

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(methylsulfonyl)-2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(methylsulfonyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

1-acetyl-5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(methylsulfonyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-glycoloyl-3-(methylsulfonyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(2-hydroxy-2-methylpropanoyl)-3-(methylsulfonyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(*N*-methylglycyl)-3-(methylsulfonyl)-1,3-dihydro-2*H*-benzimidazol 2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(3-hydroxypropanoyl)-3-(methylsulfonyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-

1(2*H*)-yl]methyl}-1-(3-hydroxy-3-methylbutanoyl)-3-(methylsulfonyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(methylsulfonyl)-2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1,3-bis(methylsulfonyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

3-benzyl-4-hydroxy-1-(2-phenylethyl)pyridin-2(1*H*)-one,

1-benzyl-4-hydroxy-2-oxo-1,2-dihydropyridine-3-carbaldehyde,

1-benzyl-4-chloro-2-oxo-1,2-dihydropyridine-3-carbaldehyde,

methyl 5-chloro-1-(4-chlorobenzyl)-6-oxo-1,6-dihydropyridine-3-carboxylate,

5-bromo-1-(2-chloro-6-fluorobenzyl)-3-methylpyridin-2(1*H*)-one,

3-bromo-1-(2,6-dichlorophenyl)-4-[(4-fluorophenyl)ethynyl]-6-methylpyridin-2(1*H*)-one,

3-bromo-1-(2,6-dichlorophenyl)-4-[(4-fluorophenyl)ethynyl]-6-methylpyridin-2(1*H*)-one,

methyl 3-chloro-4-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzoate,

4-[(2,4-difluorobenzyl)oxy]-1-(3-fluorobenzyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile,

4-[(2,4-difluorobenzyl)oxy]-6-(hydroxymethyl)-1-(2,4,6-trifluorophenyl)pyridin-2(1*H*)-one,

4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[2-(trifluoromethyl)phenyl]pyridin-2(1*H*)-one,

3-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzaldehyde,

4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluoro-4-morpholin-

4-ylphenyl)-6-methylpyridin-2(1*H*)-one,

4-[(2,4-difluorobenzyl)oxy]-1-[2,6-difluoro-4-(4-methylpiperazin-1-yl)phenyl]-6-methylpyridin-2(1*H*)-one,

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzoic acid

4-[(2,4-difluorobenzyl)oxy]-1-[4-(dimethylamino)-2,6-difluorophenyl]-6-methylpyridin-2(1*H*)-one,

4-[(2,4-difluorobenzyl)oxy]-1-{2,6-difluoro-4-[(2-hydroxyethyl)(methyl)amino]phenyl}-6-methylpyridin-2(1*H*)-one,

methyl 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzoate,

3-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-4-methylbenzoic acid,

4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-(hydroxymethyl)pyridin-2(1*H*)-one,

3-bromo-1-{[5-(chloromethyl)pyrazin-2-yl]methyl}-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

1-[2-chloro-5-(hydroxymethyl)phenyl]-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one

4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluoro-4-hydroxyphenyl)-6-methylpyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[4-(hydroxymethyl)-2-methoxyphenyl]-6-methylpyridin-2(1*H*)-one,

methyl 3-[3-bromo-4-[(2 4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-4-methylbenzoate,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-{3-[(4-methylpiperazin-1-yl)carbonyl]phenyl}pyridin-2(1*H*)-one,

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*-[2-(dimethylamino)ethyl]benzamide,

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N* (2-methoxyethyl)benzamide,

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-

oxopyridin-1(2*H*)-yl]-*N*-[2-(dimethylamino)ethyl]-*N*-methylbenzamide,

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*-(2-hydroxyethyl)-*N*-methylbenzamide,

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*-(2-methoxyethyl)-*N*-methylbenzamide,

4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzamide,

methyl 3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-4-fluorobenzoate,

4-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-3-methylbenzoic acid,

1-(4-bromo-2-methylphenyl)-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

1-[(1-acetyl-1*H*-indol-5-yl)methyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[(5-methylpyrazin-2-yl)methyl]pyridin-2(1*H*)-one,

methyl 2-({[3-bromo-1-(2,6-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl]oxy}methyl)-3,5-difluorobenzylcarbamate,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-{[5-(hydroxymethyl)pyrazin-2-yl]methyl}-6-methylpyridin-2(1*H*)-one,

4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}-*N*,*N*-dimethylbenzamide,

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*-(2-hydroxyethyl)-4-methylbenzamide,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-{4-[(4-methylpiperazin-1-yl)carbonyl]benzyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(1*H*-indol-5-ylmethyl)pyridin-2(1*H*)-one,

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-

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oxopyridin-1(2*H*)-yl]-*N*-methylbenzamide,

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzamide,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[5-(hydroxymethyl)pyrazin-2-yl]methyl}-6-methylpyridin-2(1*H*)-one,

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*-(2-methoxyethyl)-4-methylbenzamide

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*,4-dimethylbenzamide,

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*,*N*,4-trimethylbenzamide,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[2-methyl-5-(morpholin-4-ylcarbonyl)phenyl]pyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[5-(1-hydroxy-1-methylethyl)-2-methylphenyl]-6-methylpyridin-2(1*H*)-one,

1-(2-bromobenzyl)-3-[(2-bromobenzyl)oxy]pyridin-2(1*H*)-one,

1-(2-bromobenzyl)-3-[(2-bromobenzyl)oxy]pyridin-2(1*H*)-one,

3-bromo-1-(4-methoxybenzyl)-4-phenoxypyridin-2(1*H*)-one,

1-benzyl-2-oxo-4-phenoxy-1,2-dihydropyridine-3-carbaldehyde,

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-(3-dimethylaminomethyl-benzyl)-6-methyl-1H-pyridin-2-one,

N-{3-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-benzyl}-2-hydroxy-acetamide,

3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1-[4-(piperidine-1-carbonyl)-benzyl]-1H-pyridin-2-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-[(ethoxyamino)methyl]pyridin-2(1*H*)-one,

4-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-N-isopropyl-benzamide,

*N*-(3-aminopropyl)-4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}benzamide hydrochloride,

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*,4-dimethylbenzamide,

4-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2*H*-pyridin-1-ylmethyl]-N,N-bis-(2-hydroxy-ethyl)-benzamide,

3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1-[4-(pyrrolidine-1-carbonyl)-benzyl]-1H-pyridin-2-one,

4-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-N-hydroxy-benzamide,

4-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-N-methyl-benzamide,

4-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-N-(2-dimethylamino-ethyl)-benzamide,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(1*H*-indazol-5-ylmethyl)pyridin-2(1*H*)-one,

3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1-[4-(4-methyl-piperazine-1-carbonyl)-benzyl]-1H-pyridin-2-one,

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-4-methylbenzaldehyde,

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-(4-dimethylaminomethyl-benzyl)-6-methyl-1H-pyridin-2-one,

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*-(2-methoxyethyl)-4-methylbenzamide,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[2-(dimethylamino)-4,6-difluorophenyl]-6-methylpyridin-2(1*H*)-one hydrochloride,

*N*-(2-aminoethyl)-4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}benzamide hydrochloride,

4-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-N-(2-hydroxy-ethyl)-benzamide,

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-(4-hydroxymethyl-

benzyl)-6-methyl-1H-pyridin-2-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[2,6-difluoro-4-(4-methylpiperazin-1-yl)phenyl]-6-methylpyridin-2(1H)-one

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[2-(dimethylamino)-4,6-difluorophenyl]-6-methylpyridin-2(1H)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[2,6-difluoro-4-(4-methylpiperazin-1-yl)phenyl]-6-methylpyridin-2(1H)-one

4-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-N-(2-methoxy-ethyl)-benzamide,

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-{4-[(2-hydroxy-ethylamino)-methyl]-benzyl}-6-methyl-1H-pyridin-2-one

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-[(dimethylamino)methyl]pyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[2-methyl-5-(morpholin-4-ylcarbonyl)phenyl]pyridin-2(1*H*)-one,

3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1-(4-methylaminomethyl-benzyl)-1H-pyridin-2-one,

3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1-[4-(morpholine-4-carbonyl)-benzyl]-1H-pyridin-2-one,

*N*-(2-aminoethyl)-3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzamide,

*N*-(3-aminopropyl)-3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzamide hydrochloride,

4-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-N-(2-methoxy-ethyl)-N-methyl-benzamide,

1-(4-Aminomethyl-benzyl)-3-bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1H-pyridin-2-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[4-(piperazin-1-ylcarbonyl)benzyl]pyridin-2(1*H*)-one hydrochloride,

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-[4-(isopropylamino-methyl)-benzyl]-6-methyl-1H-pyridin-2-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-dimethylphenyl)-6-methylpyridin-2(1*H*)-one,

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-{3-[(2-hydroxy-ethylamino)-methyl]-benzyl}-6-methyl-1H-pyridin-2-one,

1-(3-Aminomethyl-benzyl)-3-bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1H-pyridin-2-one,

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-(4-hydroxy-benzyl)-6-methyl-1H-pyridin-2-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-[(dimethylamino)methyl]pyridin-2(1*H*)-one,

N-{3-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-benzyl}-acetamide,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-{2,6-difluoro-4-[(2-hydroxyethyl)(methyl)amino]phenyl}-6-methylpyridin-2(1*H*)-one,

ethyl 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzoate,

1-[3-(aminomethyl)benzyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one trifluoroacetate,

1-(3-{[Bis-(2-hydroxy-ethyl)-amino]-methyl}-benzyl)-3-bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1H-pyridin-2-one,

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-[3-(isopropylamino-methyl)-benzyl]-6-methyl-1H-pyridin-2-one,

{3-[3-Bromo-4-(2,4-difluoro-benzyloxy)-2-oxo-2H-pyridin-1-ylmethyl]-benzyl}-carbamic acid tert-butyl ester,

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzamide,

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-[4-(1-hydroxy-1-methyl-ethyl)-benzyl]-6-methyl-1H-pyridin-2-one,

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-(3-dimethylaminomethyl-benzyl)-1H-pyridin-2-one,

3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1-(3-

piperidin-1-ylmethyl-benzyl)-1H-pyridin-2-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluoropnenyl)-6-{[(2-methoxyethyl)amino]methyl}pyridin-2(1*H*)-one,

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*-methylbenzamide,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-{2,4-difluoro-6-[(2-hydroxyetryl)(methyl)amino]pheryl}-6-methylpyridin-2(1*H*)-one

3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1-(3-morpholin-4-ylmethyl-benzyl)-1H-pyridin-2-one,

3-bromo-1-(2,6-dimethylphenyl)-6-methyl-4-[(2,4,6-trifluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-bromo-1-(2,6-dimethylphenyl)-6-methyl-4-[(2,4,6-trifluorobenzyl)oxy]pyridin-2(1*H*)-one,

1-(4-{[Bis-(2-hydroxy-ethyl)-amino]-methyl}-benzyl)-3-bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1H-pyridin-2-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluoro-4-morpholin-4-ylphenyl)-6-methylpyridin-2(1*H*)-one,

4-Benzyloxy-3-bromo-1-(4-fluoro-benzyl)-1H-pyridin-2-one,

4-[3-Chloro-4-(2,4-difluoro-benzyloxy)-2-oxo-2H-pyridin-1-ylmethyl]-benzamide,

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*,*N*,4-trimethylbenzamide,

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*-isopropylbenzamide,

4-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-benzamide,

3-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-benzonitrile,

3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1-(3-piperazin-1-ylmethyl-benzyl)-1H-pyridin-2-one,

4-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-N-(2-hydroxy-ethyl)-N-methyl-benzamide,

methyl 4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-3-chlorobenzoate,

3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1-[3-(morpholine-4-carbonyl)-benzyl]-1H-pyridin-2-one,

3-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-N,N-bis-(2-hydroxy-ethyl)-benzamide,

4-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-benzoic acid methyl ester,

3-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-N-hydroxy-benzamide,

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-(3-hydroxymethyl-benzyl)-6-methyl-1H-pyridin-2-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(3-fluorobenzyl)pyridin-2(1*H*)-one,

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-(3-fluoro-benzyl)-1H-pyridin-2-one,

N-{3-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-benzyl}-methanesulfonamide,

3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1-[3-(pyrrolidine-1-carbonyl)-benzyl]-1H-pyridin-2-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1*H*)-one,

*N*-(3-aminopropyl)-3-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}benzamide hydrochloride,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1*H*)-one,

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-(3-methylaminomethyl-benzyl)-1H-pyridin-2-one,

4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-

oxopyridin-1(2*H*)-yl]-3,5-dichlorobenzenesulfonamide,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[4-(dimethylamino)-2,6-difluorophenyl]-6-methylpyridin-2(1*H*)-one,

3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1-(4-piperidin-1-ylmethyl-benzyl)-1H-pyridin-2-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(pyridin-4-ylmethyl)pyridin-2(1*H*)-one,

*N*-(2-aminoethyl)-3-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}benzamide hydrochloride,

3-bromo-1-[2-chloro-5-(hydroxymethyl)phenyl]-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-methylpyridin-2(1*H*)-one,

3-chloro-1-[2-chloro-5-(hydroxymethyl)phenyl]-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*-(2-hydroxyethyl)-4-methylbenzamide,

2-{3-[3-Bromo-4-(2,4-difluoro-benzyloxy)-2-oxo-2H-pyridin-1-ylmethyl]-phenyl}-acetamide,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[3-(piperazin-1-ylcarbonyl)benzyl]pyridin-2(1*H*)-one hydrochloride,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-methylpyridin-2(1*H*)-one,

4-[3-Bromo-4-(2,4-difluoro-benzyloxy)-2-oxo-2H-pyridin-1-ylmethyl]-benzoic acid methyl ester,

1-(3-Aminomethyl-2-fluoro-benzyl)-3-bromo-4-(2,4-difluoro-benzyloxy)-1H-pyridin-2-one,

3-bromo-4-[(2,4 difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-(morpholin-4-ylmethyl)pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-(4-fluorobenzyl)pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(1*H*-indol-5-ylmethyl)pyridin-2(1*H*)-one,

1-[3-(aminomethyl)benzyl]-3-bromo-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one trifluoroacetate,

1-[3-(2-aminoethyl)benzyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one trifluoroacetate,

1-[3-(aminomethyl)benzyl]-3-bromo-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-bromo-1-(2,6-dichlorophenyl)-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*-(2-hydroxyethyl)benzamide,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(pyridin-4-ylmethyl)pyridin-2(1*H*)-one,

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-(4-methoxy-benzyl)-6-methyl-1*H*-pyridin-2-one,

4-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-N,N-dimethyl-benzamide,

3-bromo-6-methyl-1-(pyridin-4-ylmethyl)-4-[(2,4,6-trifluorobenzyl)oxy]pyridin-2(1*H*)-one,

4-[3-Bromo-4-(2,4-difluoro-benzyloxy)-2-oxo-2H-pyridin-1-ylmethyl]-benzamide,

3-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-N-methyl-benzamide,

{3-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-benzyl}-carbamic acid methyl ester,

3-bromo-4-[(2,6-difluorobenzyl)oxy]-1-(2,6-dimethylphenyl)-6-methylpyridin-2(1*H*)-one,

4-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-benzonitrile,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(pyridin-4-ylmethyl)pyridin-2(1*H*)-one,

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1-benzyl-4-(benzyloxy)-3-bromo-6-methylpyridin-2(1H)-one,

1-Benzyl-4-benzyloxy-3-bromo-6-methyl-1H-pyridin-2-one

1-benzyl-4-(benzyloxy)-3-bromo-6-methylpyridin-2(1H)-one,

1-Benzyl-3-bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1H-pyridin-2-one,

{3-[3-Bromo-4-(2,4-difluoro-benzyloxy)-2-oxo-2H-pyridin-1-ylmethyl]-phenyl}-acetonitrile,

3-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-N-(2-hydroxy-ethyl)-benzamide,

3-Chloro-4-(2,4-difluoro-benzyloxy)-1-(3-fluoro-benzyl)-1H-pyridin-2-one,

1-Allyl-3-chloro-4-(2,4-difluoro-benzyloxy)-6-methyl-1H-pyridin-2-one,

3-Chloro-4-(2,4-difluoro-benzyloxy)-1-[4-(isopropylamino-methyl)-benzyl]-1H-pyridin-2-one,

methyl 3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-4-methylbenzoate,

3-bromo-4-[(2,4-difluoroberzyl)oxy]-6-(hydroxymethyl)-1-(2,4,6-trifluorophenyl)pyridin-2(1*H*)-one,

3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1-(4-piperazin-1-ylmethyl-benzyl)-1H-pyridin-2-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-(hydroxymethyl)pyridin-2(1*H*)-one,

3-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-N,N-dimethyl-benzamide,

3-bromo-1-(3-fluorobenzyl)-4-[(3-methylbenzyl)oxy]pyridin-2(1*H*)-one,

3-Bromo-1-(3-fluoro-benzyl)-4-(3-methyl-benzyloxy)-1H-pyridin-2-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(1,2,3,4-tetrahydroisoquinolin-5-ylmethyl)pyridin-2(1*H*)-one,

3-bromo-1-(3-fluorobenzyl)-4-[(3-

methylbenzyl)oxy]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(isoquinolin-5-ylmethyl)pyridin-2(1*H*)-one trifluoroacetate,

3-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-benzamide,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-({5-[(4-methylpiperazin-1-yl)carbonyl]pyrazin-2-yl}methyl)pyridin-2(1*H*)-one trifluoroacetate,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[5-(hydroxymethyl)-2-methylphenyl]-6-methylpyridin-2(1*H*)-one,

1-allyl-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(pyridin-3-ylmethyl)pyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2-methoxy-6-methylphenyl)-6-methylpyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2-methoxy-6-methylphenyl)-6-methylpyridin-2(1*H*)-one,

3-[3-Bromo-4-(2,4-difluoro-benzyloxy)-2-oxo-2H-pyridin-1-ylmethyl]-benzamide,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-(hydroxymethyl)-1-(2,4,6-trifluorophenyl)pyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[2-(trifluoromethyl)phenyl]pyridin-2(1*H*)-one,

4-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-benzoic acid,

3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1-(4-morpholin-4-ylmethyl-benzyl)-1H-pyridin-2-one,

4-(2,4-Difluoro-benzyloxy)-1-(3-fluoro-benzyl)-3-iodo-1H-pyridin-2-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(2,4,6-trifluorophenyl)pyridin-2(1*H*)-one,

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3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*-hydroxybenzamide,

3-bromo-1-(2,6-dichlorophenyl)-4-[(2,6-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-(4-Benzyloxy-3-bromo-2-oxo-2H-pyridin-1-ylmethyl)-benzonitrile,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[3-(pyrrolidin-1-ylcarbonyl)phenyl]pyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2-fluorobenzyl)pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-(4-methylbenzyl)pyridin-2(1*H*)-one,

3-{[3-chloro-4-[(2,4-difluorobenzyl)amino]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}benzonitrile,

3-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-N-isopropyl-benzamide,

3-bromo-1-(4-bromo-2,6-difluorophenyl)-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-bromo-4-[(4-fluorobenzyl)oxy]-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1*H*) one,

3-bromo-4-[(4-fluorobenzyl)oxy]-6-methyl-1-(pyridin-4-ylmethyl)pyridin-2(1*H*)-one,

3-bromo-4-[(4-fluorobenzyl)oxy]-6-methyl-1-(pyridin-4-ylmethyl)pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-(4-chlorobenzyl)pyridin-2(1*H*)-one,

4-Benzyloxy-3-bromo-1-(4-chloro-benzyl)-1H-pyridin-2-one,

3-bromo-1-(4-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-bromo-1-(2,6-dichlorophenyl)-4-[(4-fluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-Bromo-1-(4-fluoro-benzyl)-4-(4-fluoro-benzyloxy)-1H-

pyridin-2-one,

methyl 4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzoate,

4-(4-Benzyloxy-3-bromo-2-oxo-2H-pyridin-1-ylmethyl)-benzoic acid,

4-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]methyl}benzoic acid,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(2,4,6-trifluorophenyl)pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-(2-fluorobenzyl)pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-(hydroxymethyl)pyridin-2(1*H*)-one,

*N*-(2-aminoethyl)-4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzamide hydrochloride,

4-Benzyloxy-3-bromo-1-(4-methylsulfanyl-benzyl)-1H-pyridin-2-one,

1-Benzyl-4-benzyloxy-3-chloro-1H-pyridin-2-one,

4-(benzyloxy)-3-bromo-1-[4-(methylthio)benzyl]pyridin-2(1*H*)-one,

1-benzyl-4-(benzyloxy)-3-chloropyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-{[5-(hydroxymethyl)pyrazin-2-yl]methyl}-6-methylpyridin-2(1*H*)-one,

3-bromo-1-(2,6-dimethylphenyl)-4-[(4-fluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-bromo-1-(2,6-dimethylphenyl)-4-[(4-fluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-[3-(isopropylamino-methyl)-benzyl]-1H-pyridin-2-one,

3-[3-Chloro-4-(2,4-difluoro-benzyloxy)-2-oxo-2H-pyridin-1-ylmethyl]-2-fluoro-benzamide,

5-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-

oxopyridin-1(2*H*)-yl]methyl}-*N*-(2,3-dihydroxypropyl)pyrazine-2-carboxamide,

{3-[3-Bromo-4-(2,4-difluoro-benzyloxy)-2-oxo-2*H*-pyridin-1-ylmethyl]-phenyl}-acetic acid ethyl ester,

4-(4-Benzyloxy-3-bromo-2-oxo-2*H*-pyridin-1-ylmethyl)-*N*-hydroxy-benzamidine,

4-{[4-(benzyloxy)-3 bromo-2-oxopyridin-1(2*H*)-yl]methyl}-*N*'-hydroxybenzenecarboximidamide,

ethyl 5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}pyrazine-2-carboxylate,

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-(3-methoxy-benzyl)-1H-pyridin-2-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[(5-methylpyrazin-2-yl)methyl]pyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(3-methoxybenzyl)pyridin-2(1*H*)-one,

4-(4-Benzyloxy-3-bromo-2-oxo-2H-pyridin-1-ylmethyl)-benzoic acid methyl ester,

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-(4-dimethylaminomethyl-benzyl)-1H-pyridin-2-one,

3-Chloro-4-(2,4-difluoro-benzyloxy)-1-(3-methanesulfonyl-benzyl)-1H-pyridin-2-one,

4-(4-Benzyloxy-3 bromo-2-oxo-2H-pyridin-1-ylmethyl)-benzoic acid methyl ester,

methyl 4-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]methyl}benzoate,

ethyl 5-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}pyrazine-2-carboxylate,

4-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]methyl}benzonitrile,

4-(4-Benzyloxy-3-bromo-2-oxo-2H-pyridin-1-ylmethyl)-benzonitrile,

{3-[3-Bromo-4-(4-fluoro-benzyloxy)-2-oxo-2H-pyridin-1-ylmethyl]-benzyl}-carbamic acid tert-butylester,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[5-(1-hydroxy-1-methylethyl)-2-methylphenyl]-6-methylpyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-(2,6-dichlorophenyl)-6-methylpyridin-2(1*H*)-one,

1-(3-Aminomethyl-benzyl)-4-benzyloxy-3-bromo-1H-pyridin-2-one,

3-bromo-4-[(4-fluorobenzyl)oxy]-1-(pyridin-4-ylmethyl)pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-(4-bromobenzyl)pyridin-2(1*H*)-one,

4-Benzyloxy-3-bromo-1-(4-bromo-benzyl)-1H-pyridin-2-one,

5-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-oxo-1,6-dihydropyridine-2-carbaldehyde,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[5-(hydroxymetnyl)pyrazin-2-yl]methyl}-6-methylpyridin-2(1*H*)-one,

4-(4-Benzyloxy-3-bromo-2-oxo-2H-pyridin-1-ylmethyl)-benzamide,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[3-(piperazin-1-ylcarbonyl)phenyl]pyridin-2(1*H*)-one hydrochloride;

3-bromo-4-[(2,4-difluorobenzyl)amino]-1-(3-fluorobenzyl)pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[(5-methylpyrazin-2-yl)methyl]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[5-(hydroxymethyl)-2-methylphenyl]-6-methylpyridin-2(1*H*)-one,

3-bromo-1-(3-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-Bromo-1-(3-fluoro-benzyl)-4-(4-fluoro-benzyloxy)-1H-pyridin-2-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[3-

(morpholin-4-ylcarbonyl)phenyl]pyridin-2(1*H*)-one,

3-(4-Benzyloxy-3-bromo-2-oxo-2*H*-pyridin-1-ylmethyl)-benzoic acid methyl ester,

3-bromo-1-(3-fluorobenzyl)-4-{[2-(hydroxymethyl)benzyl]oxy}pyridin-2(1*H*)-one,

3-Bromo-1-(3-fluoro-benzyl)-4-(2-hydroxymethyl-benzyloxy)-1*H*-pyridin-2-one,

1-Benzo[1,3]dioxol-5-ylmethyl-3-bromo-4-(2,4-difluoro-benzyloxy)-1*H*-pyridin-2-one,

3-bromo-4-[(2,6-difluorobenzyl)oxy]-6-methyl-1-(pyridin-4-ylmethyl)pyridin-2(1*H*)-one,

3-bromo-4-[(3-chlorobenzyl)oxy]-1-(3-fluorobenzyl)pyridin-2(1*H*)-one,

3-bromo-4-[(3-chlorobenzyl)oxy]-1-(3-fluorobenzyl)pyridin-2(1*H*)-one,

3-Bromo-4-(3-chloro-benzyloxy)-1-(3-fluoro-benzyl)-1*H*-pyridin-2-one,

4-(benzyloxy)-3-bromo-1-(3-fluorobenzyl)pyridin-2(1*H*)-one,

4-Benzyloxy-3-bromo-1-(3-fluoro-benzyl)-1*H*-pyridin-2-one,

3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1-[3-(piperidine-1-carbonyl)-benzyl]-1*H*-pyridin-2-one,

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*,*N*-dimethylbenzamide,

3-[3-Chloro-4-(2,4-difluoro-benzyloxy)-2-oxo-2*H*-pyridin-1-ylmethyl]-2-fluoro-benzoic acid methyl ester,

1-(3-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]-3-iodopyridin-2(1*H*)-one,

1-(3-Fluoro-benzyl)-4-(4-fluoro-benzyloxy)-3-iodo-1*H*-pyridin-2-one,

*N*-(3-aminopropyl)-4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzamide hydrochloride,

4-{[3-bromo-4-[(4-fluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}benzonitrile,

4-[3-Bromo-4-(4-fluoro-benzyloxy)-2-oxo-2H-pyridin-1-ylmethyl]-benzonitrile,

3-Bromo-1-(3-fluoro-benzyl)-4-(2,3,4-trifluoro-benzyloxy)-1H-pyridin-2-one,

1-benzyl-4-(benzyloxy)-3-bromopyridin-2(1*H*)-one,

5-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}-*N*-(2-hydroxyethyl)-*N*-methylpyrazine-2-carboxamide,

4-(4-Benzyloxy-3-bromo-2-oxo-2H-pyridin-1-ylmethyl)-benzonitrile,

3-bromo-1-(2,4-difluorobenzyl)-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-Bromo-1-(2,4-difluoro-benzyl)-4-(2,4-difluoro-benzyloxy)-1H-pyridin-2-one,

4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*-(2-hydroxyethyl)benzamide,

3-bromo-4-[(4-fluorobenzyl)oxy]-1-(pyridin-3-ylmethyl)pyridin-2(1*H*)-one,

1-Benzyl-4-benzyloxy-3-bromo-1H-pyridin-2-one,

3-bromo-1-(cyclopropylmethyl)-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

1-(4-Aminomethyl-benzyl)-4-benzyloxy-3-bromo-1H-pyridin-2-one,

3-bromo-1-(4-fluorobenzyl)-4-[(4-fluorobenzyl)amino]-6-methylpyridin-2(1*H*)-one,

3-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-benzoic acid methyl ester,

5-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}-*N*,*N*-dimethylpyrazine-2-carboxamide,

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3-bromo-4-[(4-fluorobenzyl)oxy]-6-methyl-1-(pyridin-2-ylmethyl)pyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-dimethylphenyl)-6-methylpyridin-2(1*H*)-one,

3-bromo-1-(2,6-dichlorophenyl)-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

4-(benzyloxy)-1-(4-bromobenzyl)pyridin-2(1*H*)-one,

3-bromo-4-hydroxy-1-(4-hydroxybenzyl)pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-[2-(trifluoromethyl)benzyl]pyridin-2(1*H*)-one,

1-benzyl-4-[(3-chlorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-(piperidin-3-ylmethyl)pyridin-2(1*H*)-one hydrochloride,

1-benzyl-3-bromo-2-oxo-1,2-dihydropyridin-4-yl methyl(phenyl)carbamate,

4-(benzylamino)-1-(3-fluorobenzyl)-6-methyl-3-nitropyridin-2(1*H*)-one,

*tert*-butyl 4-[3-bromo-1-(3-fluorobenzyl)-2-oxo-1,2-dihydropyridin-4-yl]piperazine-1-carboxylate,

ethyl [4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]acetate,

*N*-[3-bromo-1-(3-fluorobenzyl)-2-oxo-1,2-dihydropyridin-4-yl]benzenesulfonamide,

3-bromo-4-[(4-tert butylbenzyl)oxy]-1-(3-fluorobenzyl)pyridin-2(1*H*)-one,

*N*-[3-bromo-1-(3-fluorobenzyl)-2-oxo-1,2-dihydropyridin-4-yl]-1-phenylmethanesulfonamide,

1-(biphenyl-2-ylmethyl)-3-bromo-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one,

4-(biphenyl-2-ylmethoxy)-3-bromo-1-(3-fluorobenzyl)pyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorophenyl)amino]-1-(3-fluorobenzyl)pyridin-2(1*H*)-one,

4-anilino-3-bromo-1-(3-fluorobenzyl)pyridin-2(1*H*)-one,

methyl 4-{[3-bromo-1-(3-fluorobenzyl)-2-oxo-1,2-dihydropyridin-4-yl]amino}benzoate,

3-bromo-1-(3-fluorobenzyl)-4-[(3,4,5-trimethoxyphenyl)amino]pyridin-2(1*H*)-one,

3-bromo-1-(3-fluorobenzyl)-4-[4-(4-fluorophenyl)piperazin-1-yl]pyridin-2(1*H*)-one,

3-bromo-1-(3-fluorobenzyl)-4-(4-methylpiperazin-1-yl)pyridin-2(1*H*)-one trifluoroacetate,

*N*-[3-bromo-1-(3-fluorobenzyl)-2-oxo-1,2-dihydropyridin-4-yl]-2,5-difluorobenzamide,

*N*-[3-bromo-1-(3-fluorobenzyl)-2-oxo-1,2-dihydropyridin-4-yl]-2,4-difluorobenzamide,

3-bromo-1-(cyclohexylmethyl)-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]propanoic acid,

*N*-[3-bromo-1-(3-fluorobenzyl)-2-oxo-1,2-dihydropyridin-4-yl]-*N'*-(2,4-difluorophenyl)urea,

3-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]propanamide,

4-(benzyloxy)-3-bromo-1-(3-morpholin-4-yl-3-oxopropyl)pyridin-2(1*H*)-one,

*N*-(3-aminopropyl)-3-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]propanamide hydrochloride,

4-(benzyloxy)-3-bromo-1-(3-oxo-3-piperazin-1-ylpropyl)pyridin-2(1*H*)-one hydrochloride,

4-(benzyloxy)-3-bromo-1-(2-morpholin-4-ylethyl)pyridin-2(1*H*)-one,

3-bromo-1-(3-fluorobenzyl)-4-{[4-fluoro-2-

(trifluoromethyl)benzyl]amino}pyridin-2(1*H*)-one,

*N*-(2-aminoethyl)-3-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]propanamide hydrochloride,

[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]acetic acid,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(tetrahydrofuran-2-ylmethyl)pyridin-2(1*H*)-one,

4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(tetrahydrofuran-2-ylmethyl)pyridin-2(1*H*)-one,

methyl 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridine-1(2*H*)-carboxylate,

1-allyl-3-(2,4-difluorobenzyl)-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

4-(benzyloxy)-1-(2,2-diethoxyethyl)pyridin-2(1*H*)-one,

methyl *N*-acetyl-3-[4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl]alaninate,

benzyl *N*-acetyl-3-[4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl]alaninate,

benzyl *N*-[(benzyloxy)carbonyl]-3-[4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl]alaninate,

4-(benzyloxy)-1-(2-oxopropyl)pyridin-2(1*H*)-one,

5-{[4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl]methyl}-5-methylimidazolidine-2,4-dione,

ethyl [4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl]acetate,

2-[4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl]acetamide,

1-benzyl-4-(benzyloxy)-3,5-dibromopyridin-2(1*H*)-one,

4-(benzyloxy)-1-ethylpyridin-2(1*H*)-one,

4-(benzyloxy)-1-(4-tert-butylbenzyl)pyridin-2(1*H*)-one,

4-{[4-(benzyloxy)-2 oxopyridin-1(2*H*)-yl]methyl}benzonitrile,

tert-butyl 3-{[4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl]methyl}piperidine-1-carboxylate,

1,3-dibenzyl-4-hydroxy-6-methylpyridin-2(1*H*)-one,

1-benzyl-6-methyl-2-oxo-1,2-dihydropyridin-4-yl methanesulfonate,

4-(benzyloxy)-1-(4-bromobenzyl)pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromopyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-[2-(trifluoromethyl)benzyl]pyridin-2(1*H*)-one,

1-benzyl-4-(1-naphthylmethoxy)pyridin-2(1*H*)-one,

1-benzyl-4-(benzylthio)-3,5-dibromopyridin-2(1*H*)-one,

1-benzyl-4-[(2,6-dichlorobenzyl)oxy]pyridin-2(1*H*)-one,

1-benzyl-3-[(benzylamino)methyl]-4-(benzyloxy)pyridin-2(1*H*)-one,

1-benzyl-4-(benzyloxy)-3-{[(2-cyclonexylethyl)amino]methyl}pyridin-2(1*H*)-one,

1-benzyl-4-(benzylthio)-5-methylpyridin-2(1*H*)-one,

1-benzyl-3-bromo-6-methyl-2-oxo-1 2-dihydropyridin-4-yl methanesulfonate,

1-benzyl-3-bromo-6-methyl-4-{[2-(trifluoromethyl)benzyl]oxy}pyridin-2(1*H*)-one,

1-benzyl-6-methyl-2-oxo-1,2-dihydropyridin-4-yl 4-bromobenzenesulfonate,

1-benzyl-4-[(3-chlorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

1-benzyl-3-bromo-6-methyl-2-oxo-1,2-dihydropyridin-4-yl 4-bromobenzenesulfonate,

4-phenoxy-1-{[2-(trimethylsilyl)ethoxy]methyl}pyridin-2(1*H*)-one,

1-benzyl-4-phenoxypyridin-2(1*H*)-one,

1-(4-methoxybenzyl)-4-phenoxypyridin-2(1*H*)-one,

3-bromo-4-hydroxy-1-(4-hydroxybenzyl)pyridin-2(1*H*)-one hydrochloride,

4-(benzyloxy)-3-bromo-1-(piperidin-3-ylmethyl)pyridin-

2(1*H*)-one,

1-benzyl-4-[(2,6-dichlorobenzyl)oxy]pyridin-2(1*H*)-one,

1-benzyl-4-(benzyloxy)-3,5-dibromopyridin-2(1*H*)-one,

3-bromo-1-(3-fluorobenzyl)-4-[(*E*)-2-(4-fluorophenyl)vinyl]pyridin-2(1*H*)-one,

1-benzyl-4-(benzyloxy)-2-oxo-1,2-dihydropyridine-3-carbaldehyde,

1-benzyl-4-(benzyloxy)pyridin-2(1*H*)-one,

1-benzyl-4-(benzyloxy)pyridin-2(1*H*)-one,

1-benzyl-4-(benzylthio)pyridin-2(1*H*)-one,

methyl 4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]benzoate,

benzyl (5-nitro-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl)acetate,

ethyl 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxo-2*H*-1,2'-bipyridine-5'-carboxylate,

4-(benzyloxy)-1-(4-methylbenzyl)pyridin-2(1*H*)-one,

[5-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-2-methyl-6-oxo-1,6-dihydropyridin-3-yl]methyl carbamate,

4-(benzyloxy)-1-(4-chlorobenzyl)pyridin-2(1*H*)-one,

methyl (2*E*)-4-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]but-2-enoate,

4-(benzyloxy)-1-(2-fluorobenzyl)pyridin-2(1*H*)-one,

tert-butyl 4-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]methyl}piperidine-1-carboxylate,

4-(benzyloxy)-1-(3-fluorobenzyl)pyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-5-(1,2-dihydroxyethyl)-6-methylpyridin-2(1*H*)-one,

1-benzyl-4-hydroxy-6-methylpyridin-2(1*H*)-one,

4-({[3-bromo-1-(3-fluorobenzyl)-2-oxo-1,2-dihydropyridin-

4-yl]oxy}methyl)benzonitrile,

1-benzyl-4-(benzyloxy)-6-methylpyridin-2(1*H*)-one,

5-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-2-methyl-6-oxo-1,6-dihydropyridine-3-carbaldehyde oxime,

1-benzyl-4-(benzylthio)-3-methylpyridin-2(1*H*)-one,

1-benzyl-4-[(4-methylbenzyl)oxy]pyridin-2(1*H*)-one,

1-benzyl-4-(benzyloxy)-3,5-dibromo-6-methylpyridin-2(1*H*)-one,

1-benzyl-4-(benzyloxy)-3,5-dibromo-6-methylpyridin-2(1*H*)-one,

3-bromo-1-(3-fluorobenzyl)-4-(1-phenylethoxy)pyridin-2(1*H*)-one,

4-(benzyloxy)-1-[4-(trifluoromethyl)benzyl]pyridin-2(1*H*)-one,

2-({[3-bromo-2-oxo-1-(pyridin-3-ylmethyl)-1,2-dihydropyridin-4-yl]oxy}methyl)-5-fluorobenzonitrile,

5-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-2-methyl-6-oxo-1,6-dihydropyridine-3-carbonitrile,

4-(benzyloxy)-1-(3-fluorobenzyl)-3-(trifluoromethyl)pyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-methyl-5-oxiran-2-ylpyridin-2(1*H*)-one,

1-benzyl-4-[(3-chlorobenzyl)oxy]pyridin-2(1*H*)-one,

1-benzyl-4-[(3-chlorobenzyl)oxy]pyridin-2(1*H*)-one,

5-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-2-methyl-6-oxo-1,6-dihydropyridine-3-carbaldehyde,

tert-butyl 3-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]methyl}piperidine-1-carboxylate,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-

difluorophenyl)-6-methyl-5-vinylpyridin-2(1*H*)-one,

4-(benzyloxy)-1-[4-(trifluoromethoxy)benzyl]pyridin-2(1*H*)-one,

3-bromo-4-[(4-chlorobenzyl)oxy]-1-[2-(phenylthio)ethyl]pyridin-2(1*H*)-one,

3-Bromo-4-(4-chloro-benzyloxy)-1-(2-phenylsulfanyl-ethyl)-1H-pyridin-2-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(2-morpholin-4-ylethyl)pyridin-2(1*H*)-one,

4-[(2,4-difluorobenzyl)oxy]-6-(hydroxymethyl)-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one,

4-{[2-(Aminomethyl)-4-fluorobenzyl]oxy}-3-bromo-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one trifluoroacetate,

4-(benzyloxy)-1-(4 fluorobenzyl)pyridin-2(1*H*)-one,

4-(benzyloxy)-1-(4-fluorobenzyl)pyridin-2(1*H*)-one,

4-Benzyloxy-3-bromo-1-methanesulfonyl-1*H*-pyridin-2-one,

*tert*-butyl 4-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]piperidine-1-carboxylate,

1-benzyl-4-(benzyloxy)-3-vinylpyridin-2(1*H*)-one,

4-(benzyloxy)-1-[4 (methylthio)benzyl]pyridin-2(1*H*)-one,

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-(2-methyl-4-methylamino-pyrimidin-5-ylmethyl)-1H-pyridin-2-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

1-benzyl-3-bromo-4-{[2-(trifluoromethyl)benzyl]oxy}pyridin-2(1*H*)-one,

1-benzyl-3-bromo-4-{[2-(trifluoromethyl)benzyl]oxy}pyridin-2(1*H*)-one,

4-[(2,4-difluorobenzyl)oxy]-1-[5-(hydroxymethyl)-2-methylphenyl]-6-methylpyridin-2(1*H*)-one,

4-(benzyloxy)-1-[4-(methylsulfonyl)benzyl]pyridin-2(1*H*)-one,

4-Phenoxy-1H-pyridin-2-one,

1-benzyl-4-[(2-chlorobenzyl)oxy]pyridin-2(1*H*)-one

1-benzyl-4-[(2-chlorobenzyl)oxy]pyridin-2(1*H*)-one,

methyl 4-{[4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl]methyl}benzoate,

4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-methylpyridin-2(1*H*)-one,

1-(3-fluorobenzyl)-4-(phenylethynyl)pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-(piperidin-4-ylmethyl)pyridin-2(1*H*)-one hydrochloride,

4-(benzyloxy)-3-bromo-1-(piperidin-4-ylmethyl)pyridin-2(1*H*)-one hydrochloride,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[2-(methylthio)pyrimidin-4-yl]pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-piperidin-4-ylpyridin-2(1*H*)-one hydrochloride,

4-Benzyloxy-1-difluoromethyl-1H-pyridin-2-one,

4-Benzyloxy-3-bromo-1-(2-chloro-phenyl)-6-methyl-1H-pyridin-2-one,

3-Bromo-6-methyl-1-pyridin-3-ylmethyl-4-[(pyridin-3-ylmethyl)-amino]-1H-pyridin-2-one,

1-(3,4-Dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (2,4-difluoro-phenyl)-amide,

1-(2,6-Dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (2,4-difluoro-phenyl)-amide,

5-Chloro-1-(2,6-dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (2,4-difluoro-phenyl)-amide,

5-Chloro-1-(2,6-dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid methyl-phenyl-amide,

1-(2,6-Dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid benzylamide,

1-(2,6-Dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-

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carboxylic acid (3-dimethylamino-propyl)-amide,

1-(2,6-Dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (2-morpholin-4-yl-ethyl)-amide,

N-[5-Acetyl-1-(4-chloro-benzyl)-6-methyl-2-oxo-1,2-dihydro-pyridin-3-yl]-4-chloro-benzamide,

1-(2,6-Dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid N'-(3-chloro-5-trifluoromethyl-pyridin-2-yl)-hydrazide,

*N*-allyl-2-[(1-benzyl-6-oxo-1,6-dihydropyridin-3-yl)carbonyl]hydrazinecarbothioamide,

1-Benzyl-5-[5-(3,4-dichloro-benzylsulfanyl)-[1,3,4]oxadiazol-2-yl]-1H-pyridin-2-one,

*N*'-{[(1-benzyl-6-oxo-1,6-dihydropyridin-3-yl)carbonyl]oxy}pyridine-4-carboximidamide,

1-(2,6-Dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid 3-trifluoromethyl-benzylamide,

1-Benzyl-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (2-morpholin-4-yl-ethyl)-amide,

5-[4-(3-Chloro-phenyl)-piperazine-1-carbonyl]-1-(3,4-dichloro-benzyl)-1H-pyridin-2-one,

5-Chloro-1-(2,6-dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid benzylamide,

1-(4-Chloro-benzyl)-5-[3-(4-chloro-phenyl)-[1,2,4]oxadiazol-5-yl]-1H-pyridin-2-one,

1-(4-Chloro-benzyl)-5-[3-(4-chloro-phenyl)-[1,2,4]oxadiazol-5-yl]-1H-pyridin-2-one,

2-Chloro-N-[1-(2,6-dichloro-benzyl)-6-oxo-5-trifluoromethyl-1,6-dihydro-pyridin-3-yl]-4-fluoro-benzamide,

N-[1-(2,6-Dichloro benzyl)-6-oxo-5-trifluoromethyl-1,6-dihydro-pyridin-3-yl]-4-isopropoxy-benzamidE,

1-(2,6-Dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (4-trifluoromethoxy-phenyl)-amide,

1-(2,6-Dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (3-trifluoromethyl-phenyl)-amide,

5-Chloro-1-(2,6-dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (3-trifluoromethyl-phenyl)-amide,

1-(2,6-Dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (4-chloro-phenyl)-amide,

1-(2,6-Dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (2-dimethylamino-ethyl)-amide,

5-Methyl-1-phenyl-1H-pyridin-2-one,

3-Bromo-1-(3-fluoro-benzyl)-4-(3-methoxy-phenyl)-1H-pyridin-2-one,

3-Bromo-1-(3-fluoro-benzyl)-4-(3-isopropyl-phenyl)-1H-pyridin-2-one,

3'-Bromo-1'-(3-fluoro-benzyl)-6-methoxy-1'H-[3,4']bipyridinyl-2'-one,

4-Benzo[1,3]dioxol-5-yl-3-bromo-1-(3-fluoro-benzyl)-1H-pyridin-2-one,

3-Bromo-1-(3-fluoro-benzyl)-4-thiophen-3-yl-1H-pyridin-2-one,

3-Bromo-1-(3-fluoro-benzyl)-4-(3-trifluoromethyl-phenyl)-1H-pyridin-2-one,

3-Bromo-1-(3-fluoro-benzyl)-4-naphthalen-2-yl-1H-pyridin-2-one,

3-Bromo-1-(3-fluoro-benzyl)-4-(4-fluoro-phenyl)-1H-pyridin-2-one,

1-Benzenesulfonyl-4-benzyloxy-3-bromo-1H-pyridin-2-one,

4-[3-Amino-1-(2,4-difluoro-phenyl)-propoxy]-3-bromo-6-methyl-1-pyridin-3-ylmethyl-1H-pyridin-2-one,

1-(4-Bromo-2,6-difluoro-phenyl)-4-(2,4-difluoro-benzyloxy)-6-methyl-1H-pyridin-2-one,

2-[1-(4-Amino-2-methyl-pyrimidin-5-ylmethyl)-3-bromo-6-methyl-2-oxo-1,2-dihydro-pyridin-4-yloxymethyl]-5-fluoro-

benzonitrile,

4-(2,4-Difluoro-benzyloxy)-6-methyl-1-(2,4,6-trifluoro-phenyl)-1H-pyridin-2-one,

1-(2-Chloro-4-hydroxy-phenyl)-4-(2,4-difluoro-benzyloxy)-6-methyl-1H-pyridin-2-one,

3-[4-(2,4-Difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-yl]-benzoic acid methyl ester,

3-Bromo-1-(2,6-difluoro-phenyl)-4-methoxy-6-methyl-5-vinyl-1H-pyridin-2-one,

3-Bromo-1-(2,6-difluoro-phenyl)-4-methoxy-6-methyl-5-styryl-1H-pyridin-2-one,

1-(2,6-Difluoro-phenyl)-4-methoxy-6-methyl-5-phenethyl-1H-pyridin-2-one,

3-Bromo-1-(2,6-difluoro-phenyl)-4-methoxy-6-methyl-5-phenethyl-1H-pyridin-2-one

1-(1*H*-indazol-5-yl)-4-(1*H*-indazol-5-ylamino)-6-methylpyridin-2(1*H*)-one,

5-Bromo-4-(2,4-difluoro-benzyloxy)-1-(2,6-difluoro-phenyl)-2-[2-(2,4-difluoro-phenyl)-ethyl]-6-oxo-1,6-dihydro-pyridine-3-carbaldehyde,

4-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-yl]-pyrimidine-2-carbonitrile,

3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-[1,2']bipyridinyl-5'-carboxylic acid,

3-Bromo-4-(5-carboxy-pyridin-2-yloxy)-6-methyl-2-oxo-2H-[1,2']bipyridinyl-5'-carboxylic acid,

3-Bromo-4-(2,4-difluoro-benzyloxy)-6,6'-dimethyl-2-oxo-2H-[1,2']bipyridinyl-3'-carbonitrile,

3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-[1,2']bipyridinyl-5'-carboxylic acid methylamide,

3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-[1,2']bipyridinyl-5'-carboxylic acid (2-hydroxy-ethyl)-amide,

3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-[1,2']bipyridinyl-5'-carboxylic acid (2-methoxy-ethyl)-amide,

3-Bromo-1-(2,6-difluoro-phenyl)-4-methoxy-6-methyl-5-(--methyl-benzyl)-1H-pyridin-2-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-5-(1,2-dihydroxy-2-phenylethyl)-6-methylpyridin-2(1H)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-5'-(1-hydroxy-1-methylethyl)-6-methyl-2H-1,2'-bipyridin-2-one,

4-Benzyloxy-1H-pyridin-2-one,

4-Benzyloxy-3-methyl-1H-pyridin-2-one,

2-Oxo-6-phenethyl-1,2-dihydro-pyridine-3-carbonitrile,

2-Oxo-6-phenyl-1,2-dihydro-pyridine-3-carbonitrile,

6-Oxo-1,6-dihydro-[2,3']bipyridinyl-5-carbonitrile,

6-Oxo-1,6-dihydro-[2,3']bipyridinyl-5-carboxylic acid,

3-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]methyl}benzamide,

3-bromo-4-[(4-fluorobenzyl)oxy]-1-(4-methoxybenzyl)pyridin-2(1*H*)-one,

3-bromo-4-[(4-fluorobenzyl)oxy]-1-(4-methoxybenzyl)pyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[2-fluoro-5-(hydroxymethyl)phenyl]-6-methylpyridin-2(1*H*)-one,

3-chloro-1-(4-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-chloro-1-(4-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-bromo-1-(3-chlorobenzyl)-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-bromo-4-[(3,4-difluorobenzyl)oxy]-1-(3-fluorobenzyl)pyridin-2(1*H*)-one,

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-

oxopyridin-1(2*H*)-yl]-4-methylbenzoic acid,

3-bromo-1-(3-chlorobenzyl)-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-bromo-1-(3-chlorobenzyl)-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one,

4-{[3-chloro-4-[(2,4-difluorobenzyl)amino]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}benzonitrile trifluoroacetate,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-{[5-(1-hydroxy-1-methylethyl)pyrazin-2-yl]methyl}-6-methylpyridin-2(1*H*)-one,

4-(benzylamino)-3-bromo-1-(3-fluorobenzyl)pyridin-2(1*H*)-one,

4-(benzylamino)-3-bromo-1-(3-fluorobenzyl)pyridin-2(1*H*)-one,

2-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}benzonitrile,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[2-fluoro-6-(4-methylpiperazin-1-yl)phenyl]-6-methylpyridin-2(1*H*)-one trifluoroacetate,

4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*-methylbenzamide,

1-[2-(aminomethyl)benzyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-bromo-1-(4-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one,

1-[2-(aminomethyl)benzyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[3-(piperidin-1-ylcarbonyl)phenyl]pyridin-2(1*H*)-one,

1-benzyl-3-bromo-4-[(4-chlorobenzyl)oxy]pyridin-2(1*H*)-one,

4-[(2,4-difluorobenzyl)oxy]-1-(3-fluorobenzyl)-3-methylpyridin-2(1*H*)-one,

4-(benzyloxy)-1-[4-(benzyloxy)benzyl]-3-bromopyridin-2(1*H*)-one,

4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*-hydroxybenzamide,

4-(benzyloxy)-3-bromo-1-[4-(trifluoromethyl)benzyl]pyridin-2(1*H*)-one,

3-bromo-1-(cyclopropylmethyl)-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-bromo-1-(cyclopropylmethyl)-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one,

1-benzyl-3-bromo-4-[(3-chlorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

1-benzyl-3-bromo-4-[(3-chlorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

1-benzyl-3-bromo-4-[(3-chlorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

2-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}benzonitrile,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-({5-[(methylamino)methyl]pyrazin-2-yl}methyl)pyridin-2(1*H*)-one trifluoroacetate,

3-bromo-1-(3-fluorobenzyl)-4-[(2-methylbenzyl)oxy]pyridin-2(1*H*)-one,

3-bromo-1-(3-fluorobenzyl)-4-[(2-methylbenzyl)oxy]pyridin-2(1*H*)-one,

methyl 3-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}benzoate,

3-bromo-1-(3-fluorobenzyl)-6-methyl-4-(2-phenylethyl)pyridin-2(1*H*)-one,

3-bromo-1-(3-fluorobenzyl)-6-methyl-4-(2-phenylethyl)pyridin-2(1*H*)-one,

1-benzyl-3-bromo-4-[(4-methylbenzyl)oxy]pyridin-2(1*H*)-

one,

4-(benzyloxy)-1-(3-fluorobenzyl)-3-iodopyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[3-(hydroxymethyl)phenyl]-6-methylpyridin-2(1*H*)-one,

4-(benzyloxy)-1-(3-fluorobenzyl)-3-iodopyridin-2(1*H*)-one

3-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}benzoic acid,

3-bromo-4-[(4-fluorobenzyl)oxy]-1-[2-(hydroxymethyl)benzyl]pyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[(5-{[(2-hydroxyethyl)(methyl)amino]methyl}pyrazin-2-yl)methyl]-6-methylpyridin-2(1*H*)-one trifluoroacetate (salt),

4-(benzyloxy)-3-bromo-1-[(6-fluoropyridin-3-yl)methyl]pyridin-2(1*H*)-one,

3-bromo-4-[(4-chlorobenzyl)oxy]-1-(4-fluorobenzyl)pyridin-2(1*H*)-one,

3-bromo-4-[(4-chloro-2-fluorobenzyl)amino]-1-(3-fluorobenzyl)pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-ethylpyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-ethylpyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-ethylpyridin-2(1*H*)-one,

2-(2-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}phenyl)acetamide,

1-benzyl-3-bromo 4-[(2-chlorobenzyl)oxy]pyridin-2(1*H*)-one,

1-benzyl-3-bromo-4-[(2-chlorobenzyl)oxy]pyridin-2(1*H*)-one,

methyl 2-{[3-bromo-4-[(4-fluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}benzoate,

3-bromo-1-(2,6-dichlorophenyl)-4-[2-(4-fluorophenyl)ethyl]-6-methylpyridin-2(1*H*)-one,

3-bromo-1-(2,6-dichlorophenyl)-4-[2-(4-

fluorophenyl)ethyl]-6-methylpyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-{5-[(isopropylamino)methyl]-2-methylphenyl}-6-methylpyridin-2(1*H*)-one hydrochloride,

3-bromo-1-(3-fluorobenzyl)-4-(2-phenylethyl)pyridin-2(1*H*)-one,

*N*-{3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzyl}-*N'*-methylurea,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[3-(hydroxymethyl)phenyl]-6-methylpyridin-2(1*H*)-one,

3-bromo-1-(3-fluorobenzyl)-4-[(3-fluorobenzyl)oxy]pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-[2-(2-thienyl)ethyl]pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-[2-(2-thienyl)ethyl]pyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)amino]-1-(2,6-difluorophenyl)-6-methylpyridin-2(1*H*)-one trifluoroacetate,

3-bromo-4-[(2,4-difluorobenzyl)amino]-1-(2,6-difluorophenyl)-6-methylpyridin-2(1*H*)-one trifluoroacetate,

3-bromo-4-[(4-chlorobenzyl)oxy]-1-(4-methoxybenzyl)pyridin-2(1*H*)-one,

3-bromo-4-[(4-chlorobenzyl)oxy]-1-(4-methoxybenzyl)pyridin-2(1*H*)-one,

3-bromo-1-(4-chlorobenzyl)-4-[(4-chlorobenzyl)oxy]pyridin-2(1*H*)-one,

3-bromo-1-(3-fluorobenzyl)-4-[(4-methoxybenzyl)oxy]pyridin-2(1*H*)-one,

3-bromo-1-(3,5-dibromo-2,6-difluoro-4-hydroxyphenyl)-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-[4-(trifluoromethoxy)benzyl]pyridin-2(1*H*)-one,

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4-(benzyloxy)-3-bromo-1-[4-(trifluoromethoxy)benzyl]pyridin-2(1*H*)-one,

*N*'-{3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzyl}-*N*,*N*-dimethylurea,

3-bromo-4-[(4-fluorobenzyl)oxy]-1-[4-(trifluoromethyl)benzyl]pyridin-2(1*H*)-one,

2-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}benzamide,

*N*-{3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzyl}morpholine-4-carboxamide,

*N*-{3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzyl}methanesulfonamide,

4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*-isopropylbenzamide,

4-(allylamino)-3-bromo-1-(2,6-difluorophenyl)-5-iodo-6-methylpyridin-2(1*H*)-one,

4-(allylamino)-3-bromo-1-(2,6-difluorophenyl)-5-iodo-6-methylpyridin-2(1*H*)-one,

(4-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]methyl}phenyl)acetic acid,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[4-(pyrrolidin-1-ylcarbonyl)phenyl]pyridin-2(1*H*)-one,

1-benzyl-4-(benzyloxy)-3-iodopyridin-2(1*H*)-one,

1-(biphenyl-4-ylmethyl)-3-bromo-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one,

4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzoic acid,

4-(benzyloxy)-3-bromo-1-[2-(3-thienyl)ethyl]pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-[2-(3-thienyl)ethyl]pyridin-2(1*H*)-one,

3-bromo-4-[(4-fluorobenzyl)oxy]-1-[3-

(trifluoromethyl)benzyl]pyridin-2(1*H*)-one,

*N*-[3-bromo-1-(3-fluorobenzyl)-2-oxo-1,2-dihydropyridin-4-yl]-4-fluorobenzamide,

methyl 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzylcarbamate,

1-benzyl-4-(benzylthio)-3-bromopyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-(4-*tert*-butylbenzyl)pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-(4-*tert*-butylbenzyl)pyridin-2(1*H*)-one,

*N*-{3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzyl}-2-methoxyacetamide,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-({5-[(dimethylamino)methyl]pyrazin-2-yl}methyl)-6-methylpyridin-2(1*H*)-one trifluoroacetate,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[4-(piperazin-1-ylcarbonyl)phenyl]pyridin-2(1*H*)-one hydrochloride,

4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*,*N*-bis(2-hydroxyethyl)benzamide,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-{5-[(dimethylamino)methyl]-2-methylphenyl}-6-methylpyridin-2(1*H*)-one hydrochloride,

1-benzyl-3-bromo-4-(2-phenylethyl)pyridin-2(1*H*)-one,

1-(3-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]-3-methylpyridin-2(1*H*)-one,

4-(benzyloxy)-1-(piperidin-3-ylmethyl)pyridin-2(1*H*)-one trifluoroacetate,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[4-(morpholin-4-ylcarbonyl)phenyl]pyridin-2(1*H*)-one,

4-(benzyloxy)-1-(3-fluorobenzyl)-3-methylpyridin-2(1*H*)-one,

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*N*$^1$-{3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzyl}glycinamide hydrochloride,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-5-oxo-6-methylpyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[4-(piperidin-1-ylcarbonyl)phenyl]pyridin-2(1*H*)-one,

*N*-[3-bromo-1-(3-fluorobenzyl)-2-oxo-1,2-dihydropyridin-4-yl]-2,6-difluorobenzamide,

2-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]methyl}benzonitrile,

5-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}-*N*-methylpyrazine-2-carboxamide,

3-chloro-4-[(2,4-difluorobenzyl)amino]-1-(2,6-difluorophenyl)-6-methylpyridin-2(1*H*)-one,

3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzoic acid,

3-bromo-1-(3-fluorobenzyl)-4-[(3-fluorobenzyl)amino]pyridin-2(1*H*)-one,

3-bromo-1-(3-fluorobenzyl)-4-[(3-methoxybenzyl)oxy]pyridin-2(1*H*)-one,

3-bromo-1-(4-tert-butylbenzyl)-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one,

*N*-{3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzyl}acetamide,

2-({3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzyl}amino)-2-oxoethyl acetate,

1-benzyl-4-(benzyloxy)-3-methylpyridin-2(1*H*)-one

*N*-{3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzyl}urea,

1-benzyl-4-(benzyloxy)-3-ethylpyridin-2(1*H*)-one,

*N*-{3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzyl}-2-hydroxyacetamide,

3-bromo-4-[(4-chlorobenzyl)oxy]-1-(2-phenylethyl)pyridin-2(1*H*)-one,

3-bromo-1-(3-chlorobenzyl)-4-[(4-chlorobenzyl)oxy]pyridin-2(1*H*)-one,

1-[3-(aminomethyl)phenyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

2-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]methyl}benzamide,

1-(4-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one,

1-[2-(aminomethyl)benzyl]-4-(benzyloxy)-3-bromopyridin-2(1*H*)-one,

methyl 3-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]propanoate,

1-benzyl-4-(benzyloxy)-3-methylpyridin-2(1*H*)-one,

4-(allylamino)-1-(2,6-difluorophenyl)-5-iodo-6-methylpyridin-2(1*H*)-one,

4-(allylamino)-1-(2,6-difluorophenyl)-5-iodo-6-methylpyridin-2(1*H*)-one,

3-bromo-1-(3-fluorobenzyl)-4-(phenylethynyl)pyridin-2(1*H*)-one,

4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*,*N*-dimethylbenzamide,

{4-[({4-(benzyloxy)-3-bromo-1-[4-(carboxymethyl)benzyl]-1,2-dihydropyridin-2-yl}oxy)methyl]phenyl}acetic acid,

4-(benzyloxy)-3-bromo-1-[3-(trifluoromethyl)benzyl]pyridin-2(1*H*)-one,

4-(benzyloxy)-3-ethynyl-1-(3-fluorobenzyl)pyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-{3-[(dimethylamino)methyl]phenyl}-6-methylpyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-methylpyridin-2(1*H*)-one,

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1-benzyl-3-bromo-4-(phenylethynyl)pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-methylpyridin-2(1*H*)-one,

3-bromo-1-(3-fluorobenzyl)-4-{[4-(trifluoromethyl)benzyl]oxy}pyridin-2(1*H*)-one,

4-(benzylamino)-3-bromo-1-(2,6-difluorophenyl)-5-iodo-6-methylpyridin-2(1*H*)-one,

4-[(2,4-difluorobenzyl)oxy]-1-(4-methoxybenzyl)-6-methylpyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-methylpyridin-2(1*H*)-one hydrobromide,

4-(benzyloxy)-3-bromo-1-[4-(morpholin-4-ylcarbonyl)phenyl]pyridin-2(1*H*)-one,

5-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-oxo-1,6-dihydropyridine-2-carboxylic acid,

1-benzyl-3-bromo-4-[(2,6-dichlorobenzyl)oxy]pyridin-2(1*H*)-one,

3-[3-chloro-4-[(2,4 difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-2-methylbenzoic acid,

4-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]benzoic acid,

ethyl *N*-(5-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}-2-methylpyrimidin-4-yl)glycinate trifluoroacetate,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-methyl-5-[(*E*)-2-phenylvinyl]pyridin-2(1*H*)-one,

3-bromo-1-(3-fluorobenzyl)-4-{[3-(trifluoromethyl)benzyl]amino}pyridin-2(1*H*)-one,

3-bromo-4-[(4-fluorobenzyl)oxy]-1-(3-phenylpropyl)pyridin-2(1*H*)-one,

3-bromo-1-(4-tert-butylbenzyl)-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one,

4-(allylamino)-3-bromo-1-(2,6-difluorophenyl)-6-methylpyridin-2(1*H*)-one,

1-cyclohexyl-4-[(2,4-difluorobenzyl)oxy]-3,6-dimethylpyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-5-(hydroxymethyl)-6-methylpyridin-2(1*H*)-one,

1-benzyl-4-(benzyloxy)-2-oxo-1,2-dihydropyridine-3-carbaldehyde,

4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-prop-2-yn-1-ylpyridin-2(1*H*)-one,

etnyl 3-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]propanoate,

1-benzyl-4-(benzyloxy)-3-(hydroxymethyl)pyridin-2(1*H*)-one,

or a pharmaceutically acceptable salt thereof

3-Chloro-4-(2,4-difluoro-benzyloxy)-6-methyl-1-(5-methyl-pyrazin-2-ylmethyl)-1H-pyridin-2-one

3-Chloro-4-(2,4-difluoro-benzyloxy)-1-(5-hydroxymethyl-pyrazin-2-ylmethyl)-6-methyl-1H-pyridin-2-one

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-(2,3-dihydro-1H-indol-5-ylmethyl)-1H-pyridin-2-one

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-[1-(2-hydroxy-acetyl)-2,3-dihydro-1H-indol-5-ylmethyl]-6-methyl-1H-pyridin-2-one

3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1-(1H-pyrazol-3-ylmethyl)-1H-pyridin-2-one

3-[3-Chloro-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-yl]-4,N-dimethyl-benzamide

3-[3-Chloro-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-yl]-4-methyl-benzamide

3-[3-Chloro-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-yl]-4-fluoro-N-methyl-benzamide

4-Chloro-3-[3-chloro-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-yl]-N-methyl-benzamide

3-[3-Chloro-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-yl]-4-fluoro-benzamide

4-[3-Chloro-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-yl]-3,N-dimethyl-benzamide

3-Chloro-4-(2,4-difluoro-benzyloxy)-1-[4-(1,2-dihydroxy-ethyl)-2-methyl-phenyl]-6-methyl-1H-pyridin-2-one

N-{4-[3-Chloro-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-phenyl}-2-hydroxy-acetamide

1-Hydroxy-cyclopropanecarboxylic acid 4-[3-chloro-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-benzylamide

N-{4-[3-Chloro-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-benzyl}-2-hydroxy-acetamide

N-{4-[3-Chloro-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-phenyl}-acetamide

{2-[3-Bromo-1-(2,6-difluoro-phenyl)-6-methyl-2-oxo-1,2-dihydro-pyridin-4-yloxymethyl]-5-fluoro-benzyl}-carbamic acid ethyl ester

The above names were generated using ChemDraw Ultra version 6 0 2, which is put out by CambridgeSoft com, Cambridge, MA, or ACD Namepro version 5 09, which is put out by ACDlabs com

Definitions

As used herein, the term "alkenyl" refers to a straight or branched hydrocarbon of a designed number of carbon atoms containing at least one carbon-carbon double bond Examples of "alkenyl" include vinyl, allyl, and 2-methyl-3-heptene

The term "alkoxy" represents an alkyl attached to the parent molecular moiety through an oxygen bridge Examples of

alkoxy groups include, for example, methoxy, ethoxy, propoxy and isopropoxy

The term "thioalkoxy" represents an alkyl attached to the parent molecular moiety through a sulfur atom Examples of thioalkoxy groups include, for example, thiomethoxy, thioethoxy, thiopropoxy and thioisopropoxy

As used herein, the term "alkyl" includes those alkyl groups of a designed number of carbon atoms Alkyl groups may be straight or branched Examples of "alkyl" include methyl, ethyl, propyl, isopropyl, butyl, iso-, sec- and tert-butyl, pentyl, hexyl, heptyl, 3-ethylbutyl, and the like "Cx-Cy alkyl" represents an alkyl group of the specified number of carbons For example, $C_1$-$C_4$ alkyl includes all alkyl groups that include at least one and no more than four carbon atoms It also contains subgroups, such as, for example, $C_2$-$C_3$ alkyl or $C_1$-$C_3$ alkyl

The term "aryl" refers to an aromatic hydrocarbon ring system containing at least one aromatic ring The aromatic ring may optionally be fused or otherwise attached to other aromatic hydrocarbon rings or non-aromatic hydrocarbon rings Examples of aryl groups include, for example, phenyl, naphthyl, 1,2,3,4-tetrahydronaphthalene, indanyl, and biphenyl Preferred examples of aryl groups include phenyl and naphthyl The most preferred aryl group is phenyl The aryl groups herein are unsubstituted or, as specified, substituted in one or more substitutable positions with various groups Thus, such aryl groups can be optionally substituted with groups such as, for example, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, halogen, hydroxy, cyano, nitro, amino, mono- or di-($C_1$-$C_6$)alkylamino, $C_2$-$C_6$alkenyl, $C_2$-$C_6$alkynyl, $C_1$-$C_6$ haloalkyl, $C_1$-$C_6$ haloalkoxy, amino($C_1$-$C_6$)alkyl, mono- or di($C_1$-$C_6$)alkylamino($C_1$-$C_6$)alkyl

The term "arylalkyl" refers to an aryl group, as defined above, attached to the parent molecular moiety through an alkyl group, as defined above Preferred arylalkyl groups include, benzyl, phenethyl, phenpropyl, and phenbutyl More preferred arylalkyl groups include benzyl and phenethyl The most preferred arylalkyl group is benzyl The aryl portions of these groups are unsubstituted or, as specified, substituted in one or more substitutable positions with various groups Thus, such aryl groups can be optionally substituted with groups such as, for example, $C_1$-$C_6$ alkyl $C_1$-$C_6$ alkoxy, halogen, hydroxy, cyano, nitro, amino, mono- or di-($C_1$-$C_6$)alkylamino, $C_2$-$C_6$alkenyl, $C_2$-$C_6$alkynyl, $C_1$-$C_6$ haloalkyl, $C_1$-$C_6$ haloalkoxy, amino($C_1$-$C_6$)alkyl, mono- or di($C_1$-$C_6$)alkylamino($C_1$-$C_6$)alkyl

The term "arylalkoxy" refers to an aryl group, as defined above, attached to the parent molecular moiety through an alkoxy group, as defined above Preferred arylaloxy groups include, benzyloxy, phenethyloxy, phenpropyloxy, and phenbutyloxy The most preferred arylalkoxy group is benzyloxy

The term "cycloalkyl" refers to a $C_3$-$C_8$ cyclic hydrocarbon Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl More preferred cycloalkyl groups include cyclopropyl

The term "cycloalkylalkyl," as used herein, refers to a $C_3$-$C_8$ cycloalkyl group attached to the parent molecular moiety through an alkyl group, as defined above Examples of cycloalkylalkyl groups include cyclopropylmethyl and cyclopentylethyl

The terms "halogen" or "halo" indicate fluorine, chlorine, bromine, or iodine

The term "heterocycloalkyl," refers to a non-aromatic ring system containing at least one heteroatom selected from nitrogen, oxygen, and sulfur, wherein the non-aromatic heterocycle is attached to the core The heterocycloalkyl ring may be optionally fused to or otherwise attached to other heterocycloalkyl rings, aromatic heterocycles, aromatic hydrocarbons and/or non-aromatic hydrocarbon rings Preferred heterocycloalkyl groups have from 3 to 7 members Examples of heterocycloalkyl groups include, for example, piperazine, 1,2,3,4-tetrahydroisoquinoline, morpholine, piperidine, tetranydrofuran, pyrrolidine, and pyrazole Preferred heterocycloalkyl groups include piperidinyl, piperazinyl, morpholinyl, and pyrolidinyl The heterocycloalkyl groups herein are unsubstituted or, as specified, substituted in one or more substitutable positions with various groups Thus, such heterocycloalkyl groups can be optionally substituted with groups such as, for example, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, halogen, hydroxy, cyano, nitro, amino, mono- or di-($C_1$-$C_6$)alkylamino, $C_2$-$C_6$alkenyl, $C_2$-$C_6$alkynyl, $C_1$-$C_6$ haloalkyl, $C_1$-$C_6$ haloalkoxy, amino($C_1$-$C_6$)alkyl, mono- or di($C_1$-$C_6$)alkylamino($C_1$-$C_6$)alkyl

The term "heteroaryl" refers to an aromatic ring system containing at least one heteroatom selected from nitrogen, oxygen, and sulfur The heteroaryl ring may be fused or otherwise attached to one or more heteroaryl rings, aromatic or non-aromatic hydrocarbon rings or heterocycloalkyl rings Examples of heteroaryl groups include, for example, pyridine, furan, thiophene, 5,6,7,8-tetrahydroisoquinoline and pyrimidine Preferred examples of heteroaryl groups include thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, benzimidazolyl, furanyl, benzofuranyl, thiazolyl, benzothiazolyl, isoxazolyl, oxadiazolyl, isothiazolyl, benzisothiazolyl, triazolyl, tetrazolyl,

pyrrolyl, indolyl, pyrazolyl, and benzopyrazolyl. Preferred heteroaryl groups include pyridyl. The heteroaryl groups herein are unsubstituted or, as specified, substituted in one or more substitutable positions with various groups. Thus, such heteroaryl groups can be optionally substituted with groups such as, for example, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, halogen, hydroxy, cyano, nitro, amino, mono- or di-($C_1$-$C_6$)alkylamino, $C_2$-$C_6$alkenyl, $C_2$-$C_6$alkynyl, $C_1$-$C_6$ haloalkyl, $C_1$-$C_6$ haloalkoxy, amino($C_1$-$C_6$)alkyl, mono- or di($C_1$-$C_6$)alkylamino($C_1$-$C_6$)alkyl.

The term "heteroarylalkyl" refers to a heteroaryl group, as defined above, attached to the parent molecular moiety through an alkyl group, as defined above. Preferred heteroarylalkyl groups include, pyrazolemethyl, pyrazoleethyl, pyridylmethyl, pyridylethyl, thiazolemethyl, thiazoleethyl, imidazolemethyl, imidazoleethyl, thienylmethyl, thienylethyl, furanylmethyl, furanylethyl, isoxazolemethyl, isoxazoleethyl, pyrazinemethyl and pyrazineethyl. More preferred heteroarylalkyl groups include pyridylmethyl and pyridylethyl. The heteroaryl portions of these groups are unsubstituted or, as specified, substituted in one or more substitutable positions with various groups. Thus, such heteroaryl groups can be optionally substituted with groups such as, for example, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, halogen, hydroxy, cyano, nitro, amino, mono- or di-($C_1$-$C_6$)alkylamino, $C_2$-$C_6$alkenyl, $C_2$-$C_6$alkynyl, $C_1$-$C_6$ haloalkyl, $C_1$-$C_6$ haloalkoxy, amino($C_1$-$C_6$)alkyl, mono- or di($C_1$-$C_6$)alkylamino($C_1$-$C_6$)alkyl.

If two or more of the same substituents are on a common atom, e.g., di($C_1$-$C_6$)alkylamino, it is understood that the nature of each group is independent of the other.

As used herein, the term "p38 mediated disorder" refers to any and all disorders and disease states in which p38 plays a role, either by control of p38 itself, or by p38 causing another factor to be released, such as but not limited to IL-

1, IL-6 or IL-8 A disease state in which for instance, IL-1 is a major component, and whose production or action, is exacerbated or secreted in response to p38, would therefore be considered a disorder mediated by p38

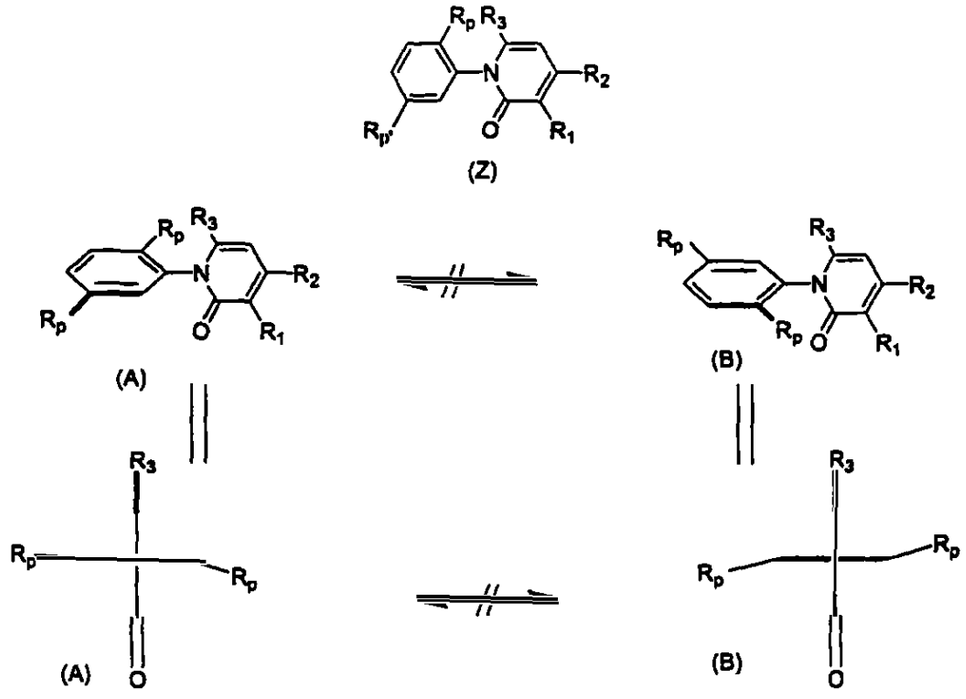
As TNF-beta has close structural homology with TNF-alpha (also known as cachectin), and since each induces similar biologic responses and binds to the same cellular receptor, the synthesis of both TNF-alpha and TNF-beta are inhibited by the compounds of the present invention and thus are herein referred to collectively as "TNF" unless specifically delineated otherwise

Non-toxic pharmaceutically acceptable salts include, but are not limited to salts of inorganic acids such as hydrochloric, sulfuric, phosphoric, diphosphoric, hydrobromic, and nitric or salts of organic acids such as formic, citric, malic, maleic, fumaric, tartaric, succinic, acetic, lactic, methanesulfonic, p-toluenesulfonic, 2-hydroxyethylsulfonic, salicylic and stearic Similarly, pharmaceutically acceptable cations include, but are not limited to sodium, potassium, calcium, aluminum, lithium and ammonium Those skilled in the art will recognize a wide variety of non-toxic pharmaceutically acceptable addition salts

The compounds of this invention may contain one or more asymmetric carbon atoms, so that the compounds can exist in different stereoisomeric forms These compounds can be, for example, racemates, chiral non-racemic or diastereomers In these situations, the single enantiomers, i e , optically active forms, can be obtained by asymmetric synthesis or by resolution of the racemates Resolution of the racemates can be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, chromatography, using, for example a chiral HPLC column, or derivatizing the racemic mixture with a resolving reagent to

generate diastereomers, separating the diastereomers via chromatography or selective crystallization, and removing the resolving agent to generate the original compound in enantiomerically enriched form. Any of the above procedures can be repeated to increase the enantiomeric purity of a compound.

The compounds of the invention may exist as atropisomers, i.e., chiral rotational isomers. The invention encompasses the racemic and the resolved atropisomers. The following illustration generically shows a compound (Z) that can exist as atropisomers as well as its two possible atropisomers (A) and (B). This illustration also shows each of atropisomers (A) and (B) in a Fischer projection. In this illustration, $R_1$, $R_2$, and $R_4$ carry the same definitions as set forth for Formula I, $R_p$ is a substituent within the definition of $R_5$, and $R_p$ is a non-hydrogen substituent within the definition of $R_5$.



When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless otherwise specified, it is intended that the compounds include the cis, trans, Z- and E- configurations Likewise, all tautomeric forms are also intended to be included

The compounds of general Formula I may be administered orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles The term parenteral as used herein includes percutaneous, subcutaneous, intravascular (e g , intravenous), intramuscular, or intrathecal injection or infusion techniques and the like In addition, there is provided a pharmaceutical formulation comprising a compound of general Formula I and a pharmaceutically acceptable carrier One or more compounds of general Formula I may be present in association with one or more non-toxic pharmaceutically acceptable carriers and/or diluents and/or adjuvants, and if desired other active ingredients The pharmaceutical compositions containing compounds of general Formula I may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, hard or soft capsule, lozenges, dispensable powders, suspension, or liquid The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient Examples of such dosage units are tablets or capsules

Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may

contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preservative agents in order to provide pharmaceutically elegant and palatable preparations Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients that are suitable for the manufacture of tablets These excipients may be for example, inert diluents such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate, granulating and disintegrating agents, for example, corn starch, or alginic acid, binding agents, for example starch, gelatin or acacia, and lubricating agents for example magnesium stearate, stearic acid or talc The tablets may be uncoated or they may be coated by known techniques In some cases such coatings may be prepared by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period For example, a time delay material such as glyceryl monosterate or glyceryl distearate may be employed

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

Formulations for oral use may also be presented as lozenges

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropyl-methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia,

dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin

Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil, or coconut oil, or in a mineral oil such as liquid paraffin The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin, or cetyl alcohol Sweetening agents and flavoring agents may be added to provide palatable oral preparations These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid

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

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Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions The oily phase may be a vegetable oil or a mineral oil or mixtures of these Suitable emulsifying agents may be naturally-occurring gums for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate The emulsions may also contain sweetening and flavoring agents

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol, glucose or sucrose Such formulations may also contain a demulcent, a preservative, and flavoring and coloring agents The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents that have been mentioned above The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides In addition, fatty acids such as oleic acid find use in the preparation of injectables

The compounds of general Formula I may also be administered in the form of suppositories, e g , for rectal administration of the drug These compositions can be

prepared by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug Such materials include cocoa butter and polyethylene glycols

Compounds of general Formula I may be administered parenterally in a sterile medium The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle Advantageously, adjuvants such as local anesthetics, preservatives, and buffering agents can be dissolved in the vehicle

The active ingredient may also be administered by injection (IV, IM, subcutaneous or jet) as a composition wherein, for example, saline, dextrose, or water may be used as a suitable carrier The pH of the composition may be adjusted, if necessary, with suitable acid, base, or buffer Suitable bulking, dispersing, wetting or suspending agents, including mannitol and PEG 400, may also be included in the composition A suitable parenteral composition can also include a compound formulated as a sterile solid substance, including lyophilized powder, in injection vials Aqueous solution can be added to dissolve the compound prior to injection

For disorders of the eye or other external tissues, e g , mouth and skin, the formulations are preferably applied as a topical gel, spray, ointment or cream, or as a suppository, containing the active ingredients in a total amount of, for example, 0 075 to 30% w/w, preferably 0 2 to 20% w/w and most preferably 0 4 to 15% w/w When formulated in an ointment, the active ingredients may be employed with either paraffinic or a water-miscible ointment base

Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base If desired, the

aqueous phase of the cream base may include, for example at least 30% w/w of a polyhydric alcohol such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol, polyethylene glycol and mixtures thereof. The topical formulation may desirably include a compound, which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide and related analogs. The compounds of this invention can also be administered by a transdermal device. Preferably topical administration will be accomplished using a patch either of the reservoir and porous membrane type or of a solid matrix variety. In either case, the active agent is delivered continuously from the reservoir or microcapsules through a membrane into the active agent permeable adhesive, which is in contact with the skin or mucosa of the recipient. If the active agent is absorbed through the skin, a controlled and predetermined flow of the active agent is administered to the recipient. In the case of microcapsules, the encapsulating agent may also function as the membrane. The transdermal patch may include the compound in a suitable solvent system with an adhesive system, such as an acrylic emulsion, and a polyester patch. The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier, it may comprise a mixture of at least one emulsifier with a fat or oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier, which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make-up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base, which forms the oily,

dispersed phase of the cream formulations Emulsifiers and emulsion stabilizers suitable for use in the formulation of the present invention include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate, and sodium lauryl sulfate, among others The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations is very low Thus, the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters may be used These may be used alone or in combination depending on the properties required Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used

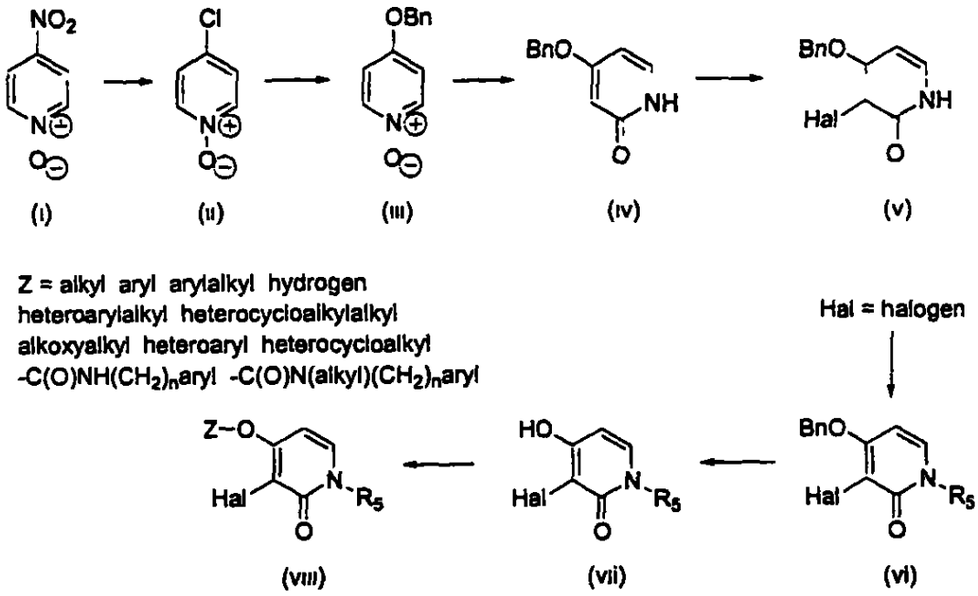
Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredients are dissolved or suspended in suitable carrier, especially an aqueous solvent for the active ingredients The anti-inflammatory active ingredients are preferably present in such formulations in a concentration of 0 5 to 20%, advantageously 0 5 to 10% and particularly about 1 5% w/w For therapeutic purposes, the active compounds of this combination invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration If administered per os, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium

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General Synthetic Procedures

Representative procedures for the preparation of compounds of the invention are outlined below in the Schemes The starting materials can be purchased or prepared using methods known to those skilled in the art Similarly, the preparation of the various intermediates can be achieved using methods known in the art The starting materials may be varied and additional steps employed to produce compounds encompassed by the invention, as demonstrated by the examples below In addition, different solvents and reagents can typically be used to achieve the above transformations Protection of reactive groups may also be necessary to achieve the above transformations In general, the need for protecting groups, as well as the conditions necessary to attach and remove such groups, will be apparent to those skilled in the art of organic synthesis When a protecting group is employed, deprotection will generally be required Suitable protecting groups and methodology for protection and deprotection such as those described in *Protecting Groups in Organic Synthesis* by Greene and Wuts are known and appreciated in the art

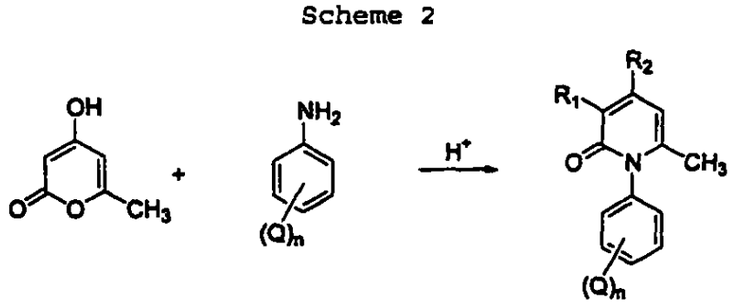
Scheme 1




In this scheme, $R_5$ is as defined above

Alternatively, the compounds of the instant invention can be prepared according to the method outlined in Scheme 2

Scheme 2




In Scheme 2, Q at each occurrence is independently alkyl, halogen, alkoxy, arylalkoxy, thioalkoxy, alkoxycarbonyl, arylalkoxycarbonyl, $CO_2H$, CN, amidinooxime, $NR_6R_7$, $NR_6R_7$alkyl, $-C(O)NR_6R_7$, amidino, haloalkyl, or haloalkoxy, and n is 0, 1, 2, 3, 4, or 5

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oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

The amount of therapeutically active compounds that are administered and the dosage regimen for treating a disease condition with the compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the severity of the inflammation or inflammation related disorder, the route and frequency of administration, and the particular compound employed, and thus may vary widely. The pharmaceutical compositions may contain active ingredients in the range of about 0.1 to 1000 mg, preferably in the range of about 7.0 to 350 mg. A daily dose of about 0.01 to 100 mg/kg body weight, preferably between about 0.1 and about 50 mg/kg body weight and most preferably between about 0.5 to 30 mg/kg body weight, may be appropriate. The daily dose can be administered in one to four doses per day. In the case of skin

conditions, it may be preferable to apply a topical preparation of compounds of this invention to the affected area two to four times a day

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease undergoing therapy

For administration to non-human animals, the composition may also be added to the animal feed or drinking water It may be convenient to formulate the animal feed and drinking water compositions so that the animal takes in a therapeutically appropriate quantity of the composition along with its diet It may also be convenient to present the composition as a premix for addition to the feed or drinking water

The disclosures in this application of all articles and references, including patents, are incorporated herein by reference

The invention is illustrated further by the following examples, which are not to be construed as limiting the invention in scope or spirit to the specific procedures described in them

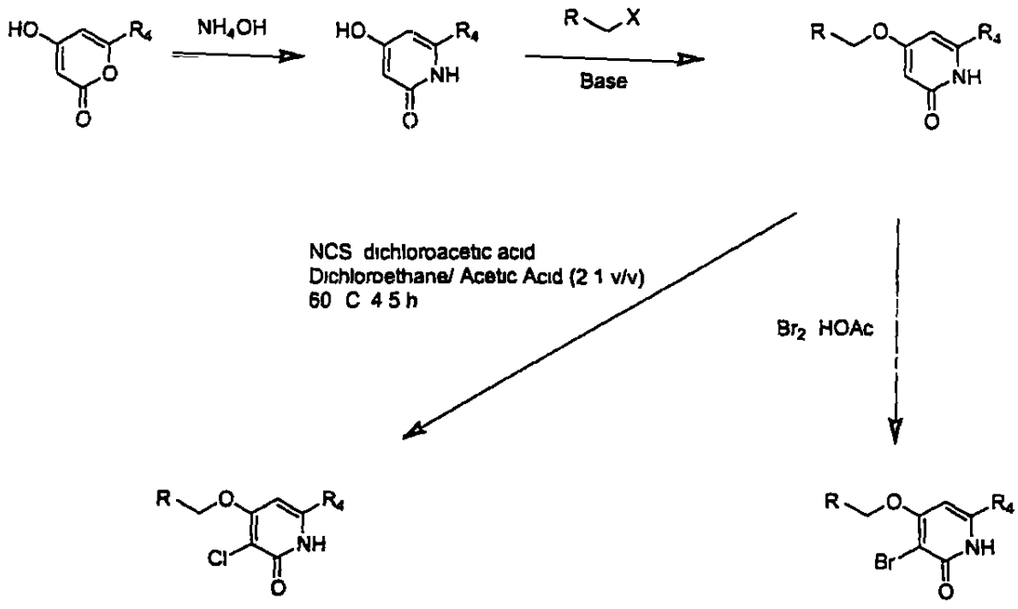
The starting materials and various intermediates may be obtained from commercial sources, prepared from commercially available compounds, or prepared using well-known synthetic methods

The compound names in this application were created using ACD Name Pro version 5 09, or ChemDraw ultra version 6 0 2, software

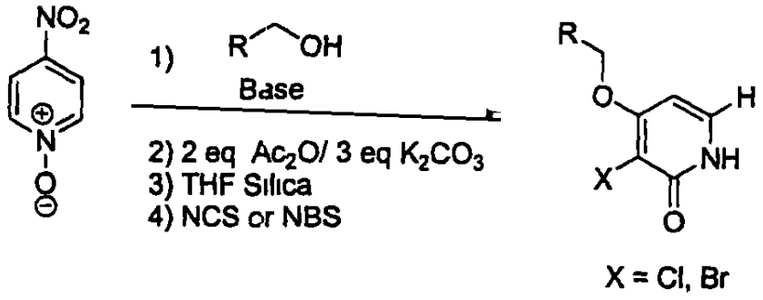
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Alternatively, compounds of the invention can be prepared using the procedures outlined in Schemes 3-25. In Schemes 3-25, the X, X', R, R', and R'' substituents on groups such as aryl, heteroaryl, amine and alkyl, carry the same definition described above for substituents on these groups.

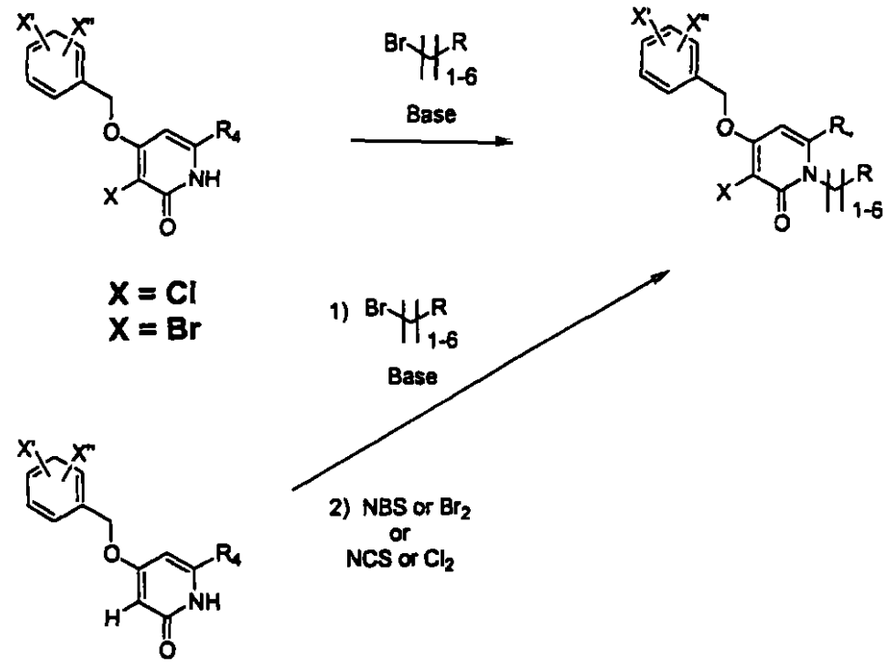
**Scheme 3**



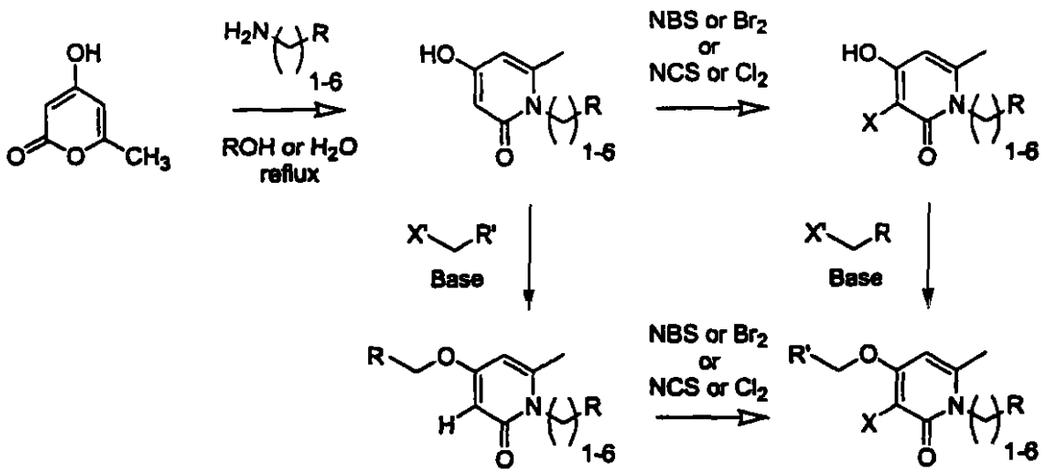

**Scheme 4**



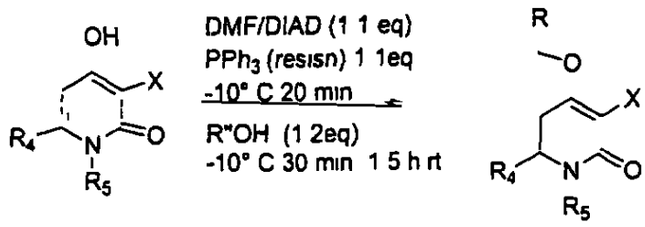
Scheme 5




Scheme 6

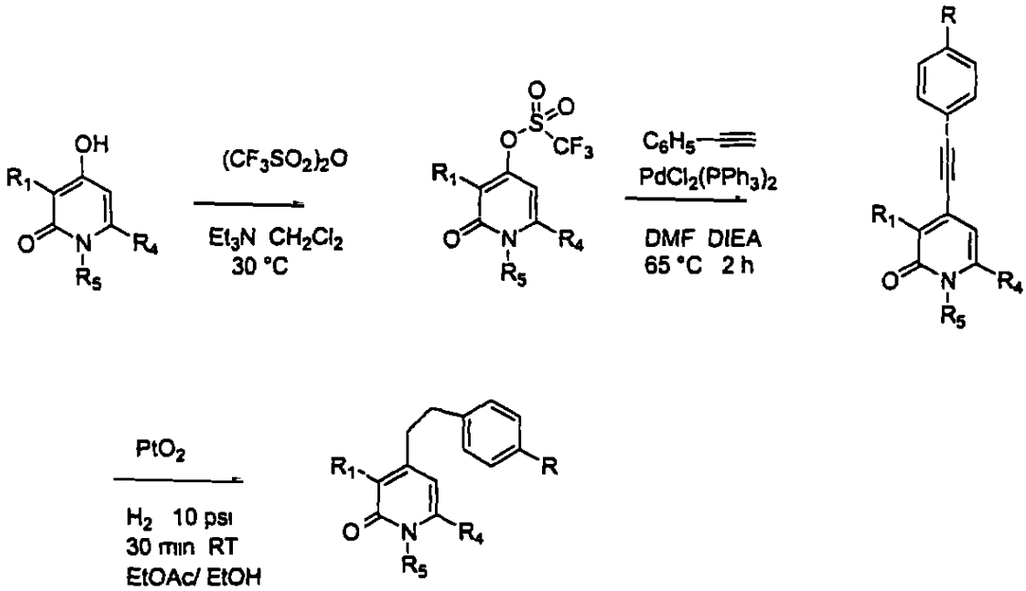



Scheme 7

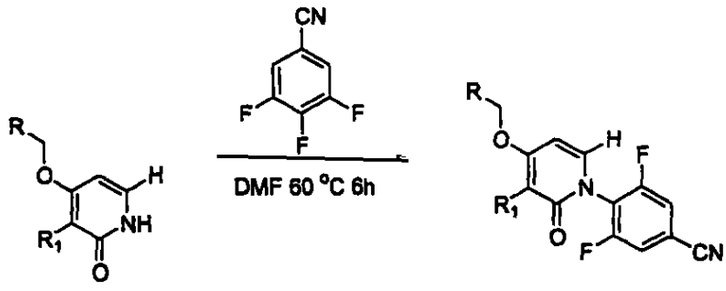



$PPh_3$ resisn 3 mmol=1 g $PPh_3$

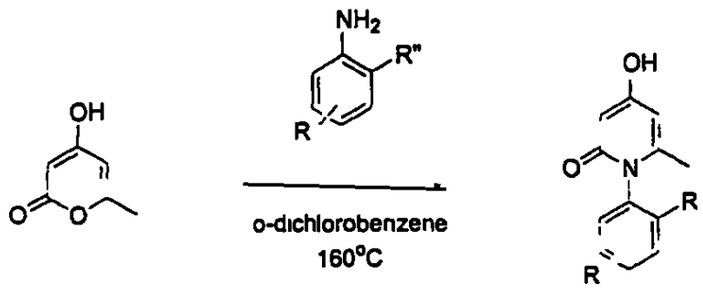
**Scheme 8**



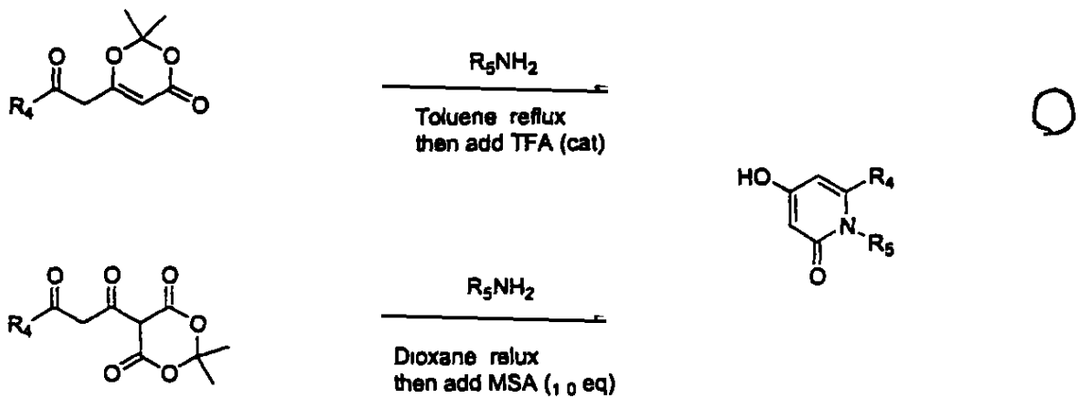

**Scheme 9**



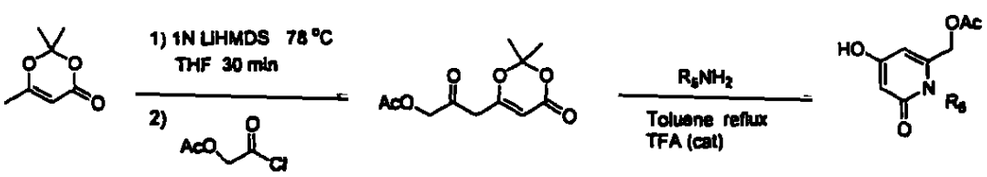
**Scheme 10**



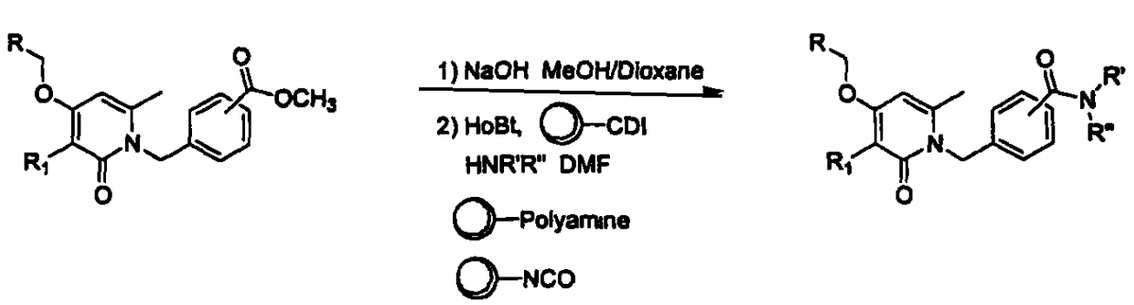

**Scheme 11**




**Scheme 12**

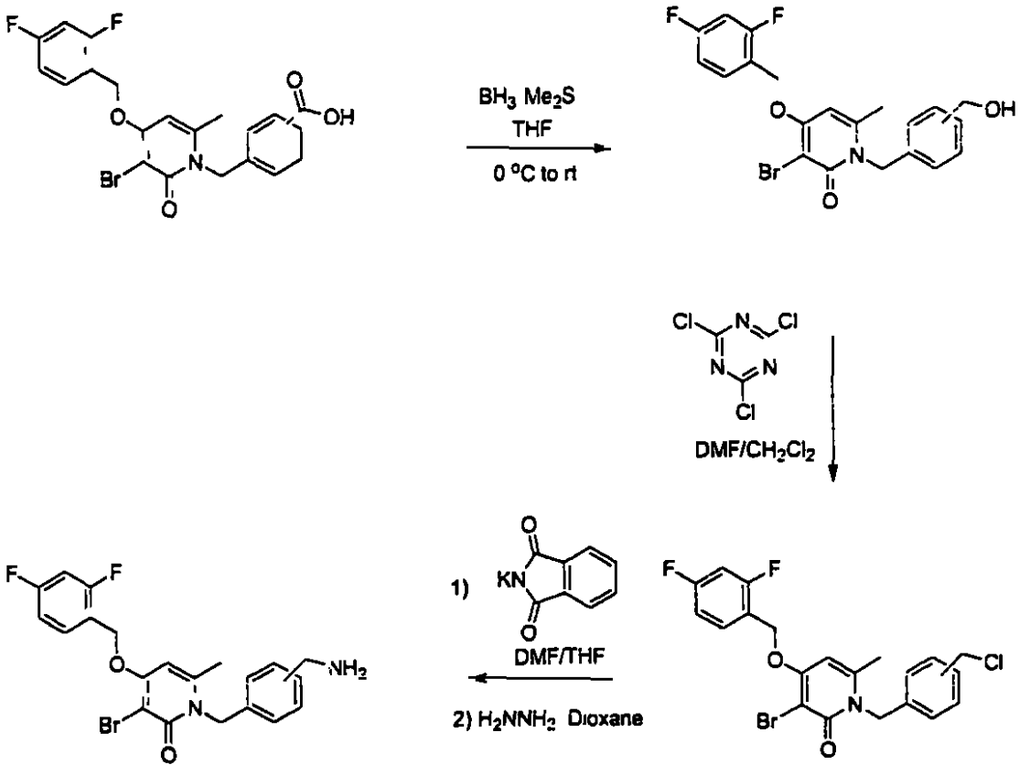



**Scheme 13**

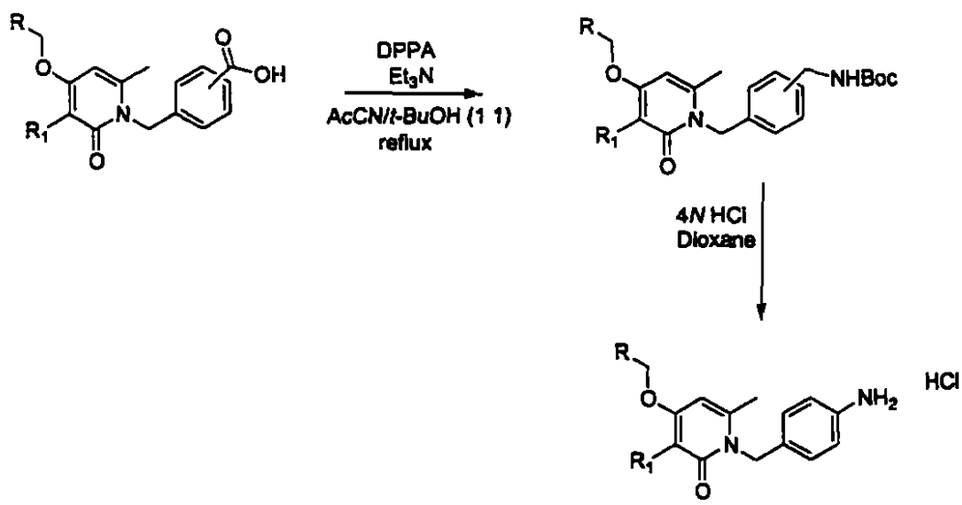


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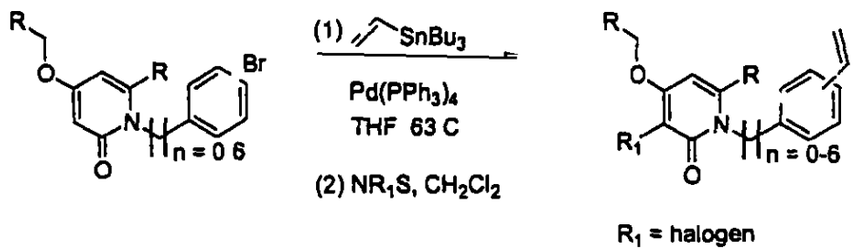
Scheme 14



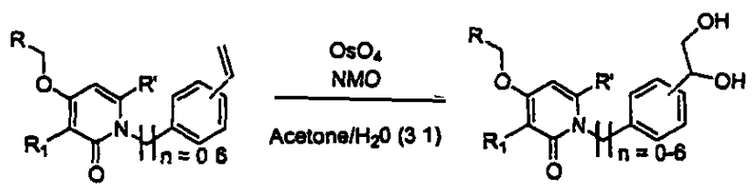

Scheme 15



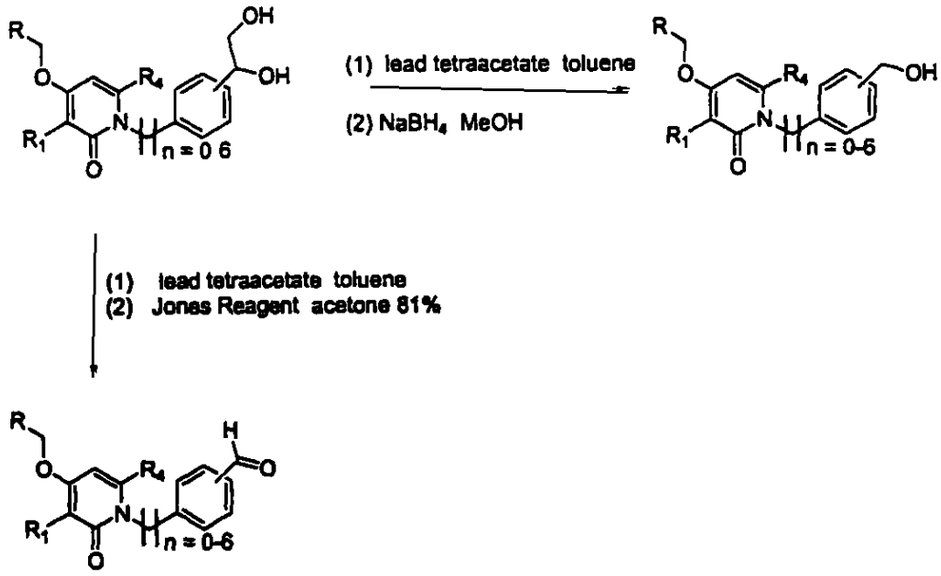
**Scheme 16**




**Scheme 17**

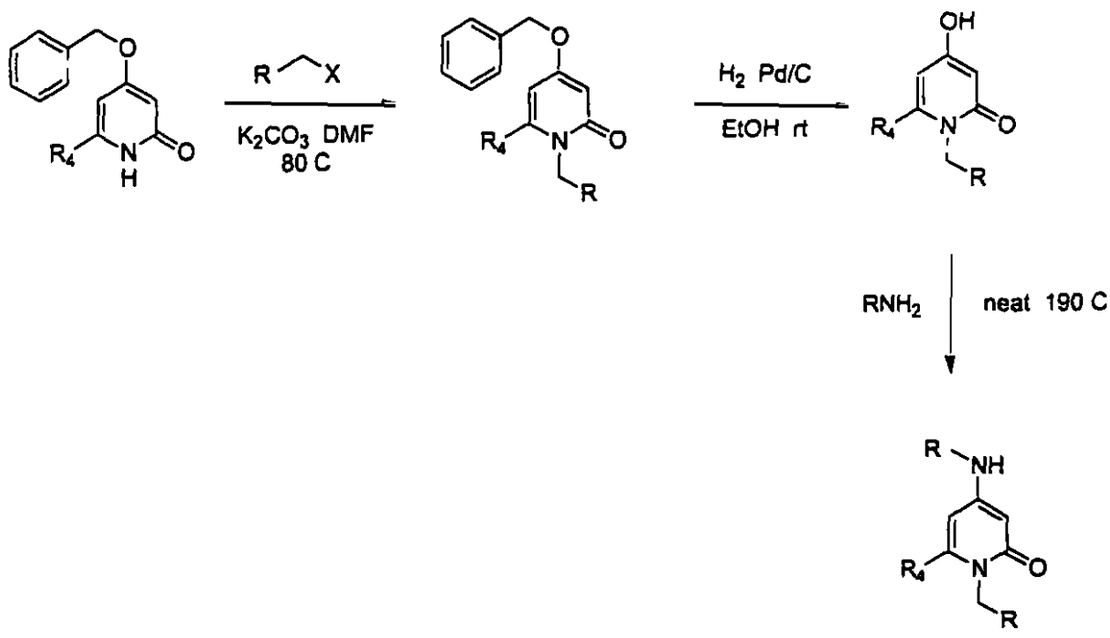



**Scheme 18**

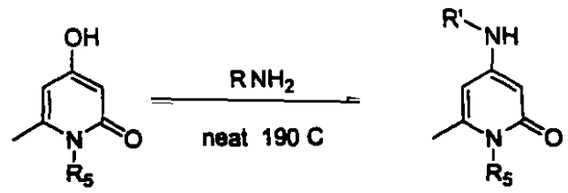


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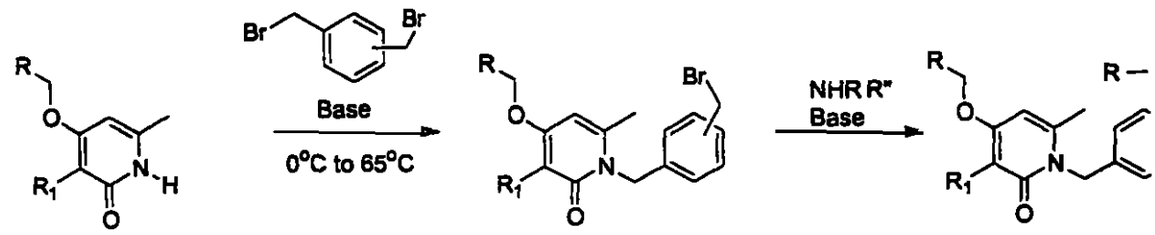
**Scheme 19**



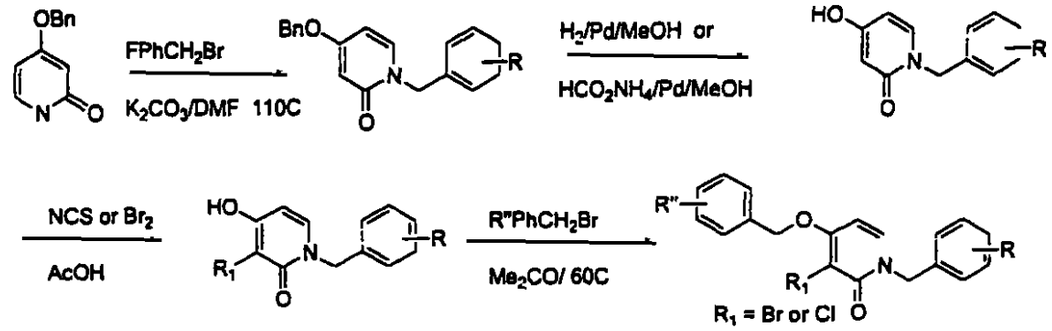

**Scheme 20**



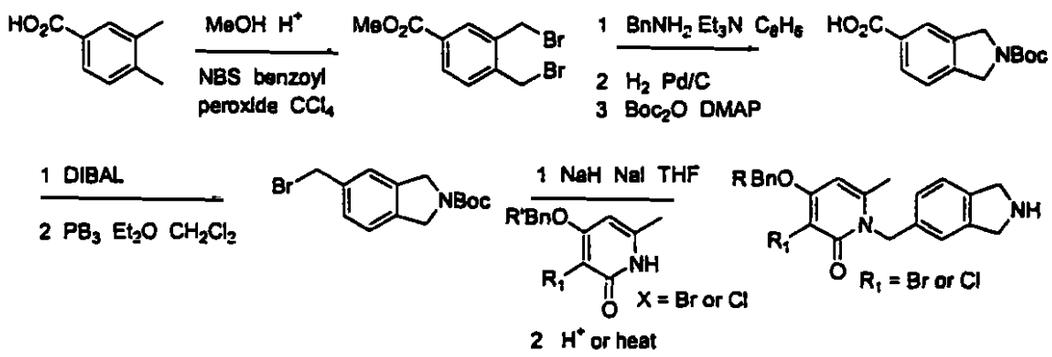

**Scheme 21**



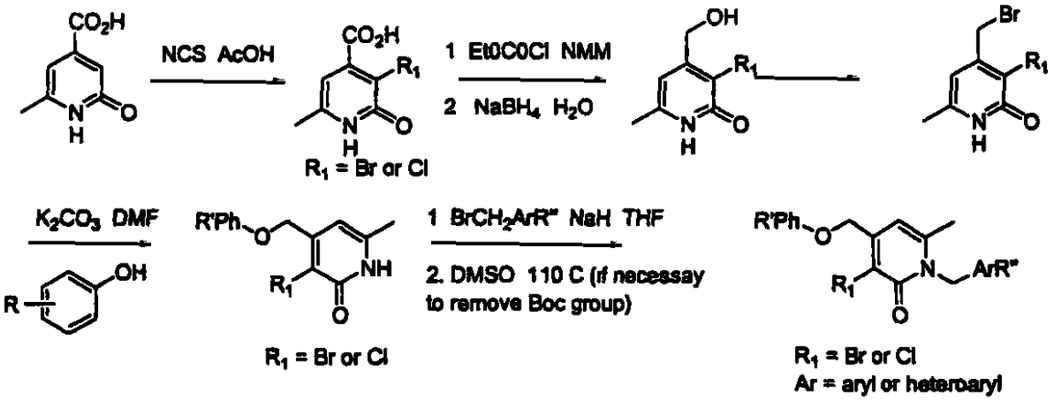
## Scheme 22




## Scheme 23

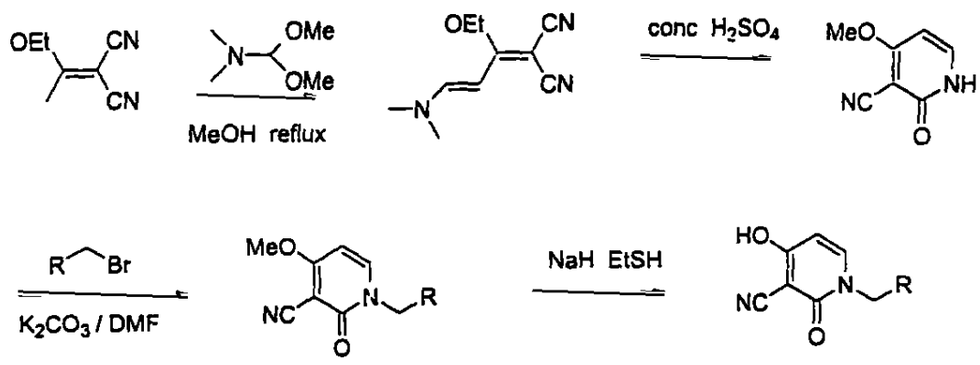



## Scheme 24



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**Scheme 25**




The invention is illustrated further by the following examples, which are not to be construed as limiting the invention in scope or spirit to the specific procedures described in them. Those having skill in the art will recognize that the starting materials may be varied and additional steps employed to produce compounds encompassed by the invention, as demonstrated by the following examples. Those skilled in the art will also recognize that it may be necessary to utilize different solvents or reagents to achieve some of the above transformations. In some cases, protection of reactive functionalities may be necessary to achieve the above transformations. In general, such need for protecting groups, as well as the conditions necessary to attach and remove such groups, will be apparent to those skilled in the art of organic synthesis. When a protecting group is employed, adeprotection step may be required. Suitable protecting groups and methodology for protection and deprotection such as those described in *Protecting Groups in Organic Synthesis* by Greene and Wuts are well known and appreciated in the art.

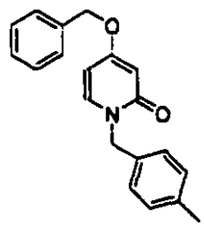
Unless otherwise specified, all reagents and solvents are of standard commercial grade and are used without further

purification The appropriate atmosphere to run the reaction under, for example, air, nitrogen, hydrogen, argon and the like, will be apparent to those skilled in the art

Examples

Example 1

4-(benzyloxy)-1-(4-methylbenzyl)pyridin-2(1*H*)-one

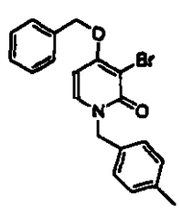


4-Benzyloxy-2(1H)-pyridone (3 0 g, 0 015 mol), 4-methylbenzyl bromide (3 15 g, 0 17 mol), and potassium carbonate (3 0 g, 0 022 mol) were heated at 80 °C for 2 hours Contents were allowed to cool, diluted with water and a solid (5 52 g) was filtered FABHRMS m/z 306 1494 (M+H, $C_{20}H_{20}NO_2$ requires 306 1494) $^1$H NMR ($CDCl_3$ /300 MHz) 7 50-7 40 (m, 5H), 7 20-7 05 (m, 5H), 6 07-6 00 (m, 1H), 5 95-5 90 (m, 1H), 5 05 (s, 2H), 5 00 (s, 2H), 2 32 (s, 3H)

Anal Calcd for $C_{20}H_{19}NO_2$ C, 78 66, H, 6 27, N, 4 59 Found C, 78 54, H, 6 38, N, 4 58

Example 2

4-(benzyloxy)-3-bromo-1-(4-methylbenzyl)pyridin-2(1*H*)-one

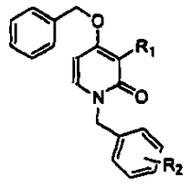


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The material prepared in Example 1 (2.1 g, 0.007 mol) and sodium acetate (738 mg, 0.009 mol) in glacial acetic acid (15 mL) were cooled to 15 °C. Bromine (0.412 mL, 0.008) in glacial acetic acid (5 mL) was added dropwise. Contents were stirred 2 hours, coming to room temperature. Water (200 mL) was added and a light yellow solid was filtered. Mp 150.4 - 151.2°C. FAB-HRMS m/z 384.0599 (M+H, $C_{20}H_{19}BrNO_2$ requires 384.0601). $^1$H-NMR ($CDCl_3$/300 MHz) δ 7.42-7.30 (m, 5H), 7.22-7.08 (m, 5H), 6.02 (d, 1H), 5.20 (s, 2H), 5.12 (s, 2H), 2.32 (s, 3H).

Anal. Calcd for $C_{20}H_{18}BrNO_2$: C, 62.51; H, 4.72; N, 3.65. Found: C, 62.11; H, 4.48; N, 3.54.

Examples 3-10




The compounds of Examples 3-10 are prepared essentially according to the procedure set forth above with respect to Example 1. Compounds wherein $R_1$ = Br are prepared essentially according to the procedure of Example 2.

| Example No | $R_1$ | $R_2$ | MF | M+H m/z Requires | FABHRMS m/z |
|---|---|---|---|---|---|
| Ex 3 | -H | 4-Br | $C_{19}H_{16}BrNO_2$ | 370.0428 | 370.0443 |
| Ex 4 | -Br | 4-Br | $C_{19}H_{15}Br_2NO_2$ | 447.9522 | 447.9548 |
| Ex 5 | -H | 4-Cl | $C_{19}H_{16}ClNO_2$ | 326.0948 | 326.0893 |
| Ex 6 | -Br | 4-Cl | $C_{19}H_{15}BrClNO_2$ | 404.0053 | 404.0035 |
| Ex 7 | -H | 3-F | $C_{19}H_{16}FNO_2$ | 310.1243 | 310.1226 |
| Ex 8 | -Br | 3-F | $C_{19}H_{15}BrFNO_2$ | | |
| Ex 9 | -H | 2-F | $C_{19}H_{16}FNO_2$ | 310.1231 | 310.1243 |

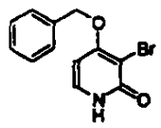
| | | | | | |
|---|---|---|---|---|---|
| Ex 10 | -Br | 2-F | $C_{19}H_{13}BrFNO_2$ | 388 0348 | 388 0373 |

NMR characterization of compounds of Examples 3-10

| Ex No | NMR Data |
|---|---|
| Ex 3 | H NMR ($CDCl_3$/300 MHz) δ 7 43 (d 2H) 7 40-7 33 (m 5H) 7 20-7 07 (m, 3H), 6 04-6 01 (m 1H) 6 00-5 92 (m 1H) 5 03 (s 2H), 4 98 (s, 2H) |
| Ex 4 | $^1$H NMR ($CDCl_3$/300 MHz) δ 7 50-7 15 (m 10H), 6 06 (d 1H) 5 20 (s, 2H), 5 10 (s, 2H) |
| Ex 5 | H NMR ($CDCl_3$/300 MHz) δ 7 40-7 32 (m 5H) 7 24 (AB quartet 4H), 7 10 (d, 1H) 6 03-6 00 (m 1H) 5 98-5 92 (m 1H) 5 03 (s, 2H), 4 99 (s, 2H) |
| Ex 6 | $^1$H NMR ($CDCl_3$/300 MHz) 7 43-7 20 (m 10H), 6 08 (d 1H) 5 20 (s, 2H), 5 10 (s, 2H) |
| Ex 7 | $^1$H NMR ($CDCl_3$/300 MHz) δ 7 45-7 25 (m 5H), 7 12 (d 1H) 7 07-6 93 (m 4H) 6 04-6 02 (m 1H) 6 00-5 94 (m, 1H) 5 08 (s, 2H), 5 00 (s, 2H) |
| Ex 8 | $^1$H NMR ($CDCl_3$/300 MHz) δ 7 43-7 25 (m, 6H) 7 21 (d, 1H), 7 10-6 93 (m, 3H), 6 08 (d 1H) 5 22 (s 2H) 5 12 (s 2H) |
| Ex 9 | $^1$H NMR ($CDCl_3$/300 MHz) δ 7 43-7 00 (m, 10H), 6 01-5 92 (m 2H), 5 10 (s, 2H), 4 99 (s, 2H) |
| Ex 10 | H NMR ($CDCl_3$/300 MHz) 7 52 (d of t 1H) 7 44-7 26 (m 7H) 7 15-7 00 (m, 2H), 6 03 (d, 1H) 5 20 (s, 2H) 5 15 (s, 2H) |

Example 11

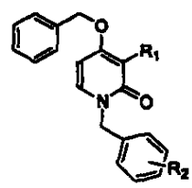
4-(benzyloxy)-3-bromopyridin-2(1*H*)-one



The material of Example 11 was prepared according to the procedure of Example 2 $^1$H NMR ($CDCl_3$/300 MHz) δ 7 50-7 30 (m, 6H), 6 20 (d, 1H), 5 24 (s, 2H)

Anal Calcd for $C_{12}H_{10}BrNO_2$ (0 $3H_2O$) C, 50 48, H, 3 74, N, 4 91 Found C, 50 79, H, 3 41, N, 4 82

Examples 12-19



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The compounds of Examples 12-19 are prepared essentially according to the procedures set forth above for Example 1 Compounds wherein $R_1$ = Br are prepared essentially according to the procedure of Example 2

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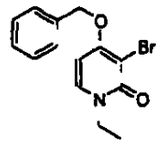
| Example No | $R_1$ | $R_2$ | MF | HRMS Requires | FABHRMS m/z |
|---|---|---|---|---|---|
| Ex 12 | -Br | 4-benzyloxy | $C_{26}H_{22}BrNO_3$ | 476 0861 | 476 0854 |
| Ex 13 | -H | 4-$CO_2$Me | $C_{21}H_{19}NO_4$ | 350 1392 | 350 1391 |
| Ex 14 | -Br | 4-$CO_2$Me | $C_{21}H_{18}BrNO_4$ | 428 0497 | 428 0480 |
| Ex 15 | -Br | 4-$CO_2$H | $C_{20}H_{16}BrNO_4$ | 414 0341 | 414 0360 |
| Ex 16 | -H | 4-CN | $C_{20}H_{16}N_2O_2$ | 317 1290 | 317 1270 |
| Ex 17 | -Br | 4-CN | $C_{20}H_{15}BrN_2O_2$ | 395 0395 | 395 0376 |
| Ex 18 | -H | 4-tButyl | $C_{23}H_{25}NO_2$ | 348 1964 | 348 1949 |
| Ex 19 | -Br | 4-tButyl | $C_{23}H_{24}BrNO_2$ | 426 1069 | 426 1023 |

NMR characterization of compounds of Examples 12-19

| Ex No | NMR Data |
|---|---|
| Ex 12 | $^1$H NMR ($CDCl_3$/300 MHz) 7 45-7 15 (m, 13H), 6 92 (d 2H), 6 01 (d, 1H), 5.20 (s, 2H), 5 08 (s 2H) 5 03 (s 2H) |
| Ex 13 | $^1$H NMR ($CDCl_3$/300 MHz) 8 00 (d 2H) 7 40-7 25 (m 7H) 7 10 (d, 1H), 6 03-6 01 (m, 1H), 6 00-5 93 (m 1H) 5 12, (s, 2H), 5.00 (s, 2H), 3 95 (s, 3H) |
| Ex 14 | $^1$H NMR ($CDCl_3$/300 MHz) 8 00 (d, 2H) 7 42-7 31 (m 7H), 7 23 (d, 1H), 6 08 (d, 1H) 5 22 (d 2H) 5 20 (s 2H), 3 95 (s 3H) |
| Ex 15 | $^1$H NMR (DMSO-$d_6$/300 MHz) 8 00-7 80 (m 3H) 7 53-7 27 (m 7H), 6.50 (d, 1H), 5 32 (s, 2H) 5 20 (s 2H) |
| Ex 16 | $^1$H NMR ($CDCl_3$/300 MHz) δ 7 60 (d 2H), 7 42-7 30 (m, 7H), 7 13 (d, 1H), 6.05-5.98 (m, 2H) 5 11 (s 2H) 5 00 (s 2H) |
| Ex 17 | $^1$H NMR ($CDCl_3$/300 MHz) δ 7 61 (d, 2H) 7 48-7 30 (m 6H), 7 23 (d, 2H), 6.12 (d, 1H), 5 22 (s 2H) 5 20 (s 2H) |
| Ex 18 | $^1$H NMR ($CDCl_3$/300 MHz) 7 40-7 28 (m 7H) 7 20 (d 2H) 7 10 (d 1H) 6 02 (d 1H), 5 97-5 90 (m 1H), 5 02 (d, 2H) 4 98 (d 2H) |
| Ex 19 | $^1$H NMR ($CDCl_3$/300 MHz) δ 7 43-7 20 (m 10H) 6 02 (d 1H), 5 20 (s, 2H), 5 10 (s, 2H), 1 30 (s, 9H) |

Example 20

4-(benzyloxy)-3-bromo-1-ethylpyridin-2(1*H*)-one

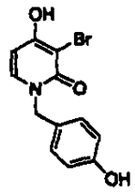


To 4-benzyloxy-2(1H)-pyridone (1 0 g, 0 005 mol) and potassium carbonate (_ 0 g, 0 007 mol) in DMF (10 mL) was added bromoethane (0 82 mL, 0 011 mol) Contents were heated at 75°C overnight Contents were allowed to cool and partitioned between EtOAc and water The EtOAc layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* leaving a waxy solid, which was recrystallized from EtOAc/hexanes to give a white solid (720 mg) To the white solid (700 mg, 0 003 mol) in glacial acetic acid (10 mL), bromine (0 17 mL, 0 00325 mol) in glacial acetic acid (5 mL) was added dropwise at 15°C Contents were stirred one hour at room temperature and a yellow solid (1 1 g) was filtered The solid was partitioned between EtOAc and 2 5N sodium hydroxide The EtOAc layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* leaving a colorless oil (710 mg), which solidified FABHRMS m/z 310 0267 (M+H, $C_{14}H_{15}BrNO_2$ requires 310 0263) $^1H$ NMR ($CDCl_3$/300 MHz) δ 7 45-7 30 (m, 6H), 7 22 (d, 1H), 6 07 (d, 1H), 5 20 (s, 2H), 4 00 (q, 2H), 1 32 (t, 3H)

Anal Calcd for $C_{14}H_{14}BrNO_2$ C, 54 56, H, 4 58, N, 4 55 Found C, 54 21, H, 4 38, N, 4 43

Example 21

3-bromo-4-hydroxy-1-(4-hydroxybenzyl)pyridin-2(1*H*)-one



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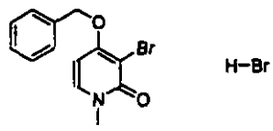
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The material of Example 12 (120 mg, 0 25 mmol) and 10% palladium/carbon (30 mg) in glacial acetic acid (2 mL) were shaken at 55 lbs of hydrogen for 4 hours Contents were filtered and the filtrate was concentrated in vacuo leaving an oil FABHRMS m/z 295 9952 (M+H, $C_{12}H_{11}BrNO_3$ requires 295 9922) $^1$H NMR (DMSO-$d_6$ /300 MHz) δ 11 40 (br s, 1H), 9 40 (br s, 1H), 7 60 (d, 1H), 7 10 (d, 2H), 6 70 (d, 2H), 6 02 (d, 1H), 4 93 (s, 2H)

Anal Calcd for $C_{12}H_{10}BrNO_3$ (1 4 $H_2O$) C, 44 85, H, 4 02 N, 4 36 Found C, 45 07, H, 4 10, N, 4 35

Example 22

4-(benzyloxy)-3-bromo-1-methylpyridin-2(1*H*)-one hydrobromide



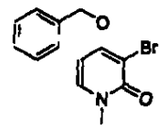

To 4-benzyloxy-2(1H)-pyridone (1 0 g, 0 005 mol) and potassium carbonate (760 mg, 0 0055 mol) in DMF (10 mL) was added methyl iodide (0 342 mL, 0 0055 mol) Contents were stirred overnight Contents were partitioned between EtOAc and water The EtOAc layer was dried over $MgSO_4$, filtered, and concentrated in *vacuo* leaving a white solid (960 mg)

To the white solid (332 mg, 0 0015 mol) in glacial acetic acid (10 mL), bromine (256 mg, 0 0016 mol) in glacial acetic acid (5 mL) was added dropwise at 15°C Contents were stirred one hour at room temperature and the desired was filtered as a white solid, 262 mg (59% yield) mp 105 3-105 6°C FABHRMS m/z 296 0097 (M+H, $C_{13}H_{13}BrNO_2$ requires 296 0110) $^1$H NMR ($CDCl_3$/300 MHz) δ 7 45-7 30 (m, 6H), 7 22 (d, 1H), 6 07 (d, 1H), 5 20 (s, 2H), 4 00 (q, 2H), 1 32 (t, 3H)

Anal Calcd for $C_{13}H_{12}BrNO_2$ (HBr, 0 3$H_2O$) C, 41 04, H, 3 60, N, 3 68 Found C, 41 00, H, 3 87, N, 3 52

Example 23

4-(benzyloxy)-3-bromo-1-methylpyridin-2(1*H*)-one

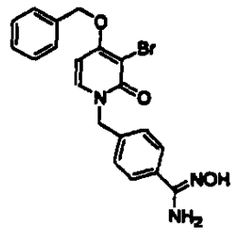


The material of Example 22 was partitioned between EtOAc and 2 5N sodium hydroxide The EtOAc layer was dried over $MgSO_4$, filtered, and concentrated in vacuo leaving a red oil, which solidified FABHRMS m/z 294 0112 (M+H, $C_{13}H_{13}BrNO_2$ requires 294 0130) $^1H$ NMR ($CDCl_3$/300 MHz) 7 45-7 30 (m, 6H), 7 22 (d, 1H), 6 07 (d, 1H), 5 20 (s, 2H), 4 00 (q, 2H), 1 32 (t, 3H)

Anal Calcd for $C_{13}H_{12}BrNO_2$ C, 53 08, H, 4 11, N, 4 76 Found C, 53 06, H, 4 20, N, 4 74

Example 24

4-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]methyl}-*N'*-hydroxybenzenecarboximidamide



The material of Example 17 (500 mg, 0 00127 mol), hydroxylamine hydrochloride (90 mg, 0 0013 mol) and sodium bicarbonate (109 mg) were refluxed in ethanol (15 mL) overnight Contents were allowed to cool and a solid was filtered and washed with water to give the desired as a white solid, 447 mg, (82% yield) mp 210 2-212 2 °C FABHRMS m/z 428 0634 (M+H, $C_{20}H_{19}BrN_3O_3$ requires 428 0610) $^1H$ NMR (DMSO-$d_6$

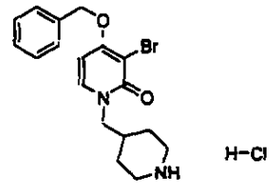
142
140

/ 300 MHz) 9 66 (s, 1H), 7 98 (d, 1H), 7 65 (d, 2H), 7 55-7 35 (m, 5H), 7 30 (d, 1H), 6 54 (d, 1H), 5 82 (s 2H), 5 35 (s, 2H), 5 17 (s, 2H)

Anal Calcd for $C_{20}H_{18}BrNO_3$ C, 56 09 H, 4 24 N 9 81 Found C, 55 92, H, 4 01, N, 9 52

Example 25

4-(benzyloxy)-3-bromo-1-(piperidin-4-ylmethyl)pyridin-2(1*H*)-one hydrochloride

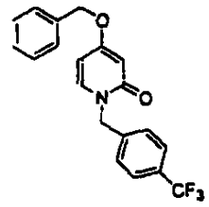



To the material of Example 11 (924 mg, 0 0033 mol) in DMF (5 mL) was added dropwise sodium bis(trimethylsilyl)amide (1M in THF 3 6 mL) Contents were stirred one hour before adding dropwise a solution of 4-methanesulfonyloxymethyl-1-piperidine-1-carboxylic acid tert-butyl ester (*J Labelled Compd, Radiopharm*, 38(7), 1996, 595-606) (1 0 g, 0 0036 mol) in DMF (5 mL) Contents were heated at 75°C overnight Contents were allowed to cool and poured into water (100 mL) A solid was filtered and recrystallized from EtOAc to give white crystals (546 mg) The white crystals were refluxed in 4 N HCl/dioxane (10 mL) for 3 hours, allowed to cool and filtered to give the desired as a white solid, 415 mg (30% yield) mp 207 9°C FABHRMS m/z 377 0852 (M+H, $C_{18}H_{23}BrClN_2O_2$ requires 377 0865) $^1$H NMR (DMSO-$d_6$ /300 MHz) δ 8 90 (br, 1H), 8 64 (br, 1H), 7 80 (d, 1H), 7 50-7 30 (m, 5H), 6 48 (d, 1H), 5 30 (s, 2H), 3 83 (d, 2H), 3 20 (d, 2H), 2 88-2 64 (m, 2H), 2 10-1 90 (m, 1H), 1 60 (d, 2H), 1 50-1 40 (m, 2H)

Anal Calcd for $C_{18}H_{22}BrClN_2O_2$ (0 3 $H_2O$) C, 51 58, H, 5 43, N, 6 68 Found C, 51 59, H, 5 42, N, 6 81

Example 26

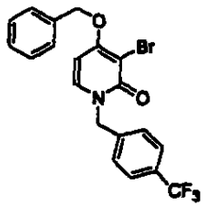
4-(benzyloxy)-1-[4-(trifluoromethyl)benzyl]pyridin-2(1*H*)-one



The material of Example 26 was prepared according to the procedure of Example 1 FABHRMS m/z 360 1213 (M+H, $C_{20}H_{17}F_3NO_2$ requires 360 1211) $^1H$ NMR ($CDCl_3$/300 MHz) δ 7 60 (d, 2H), 7 41-7 30 (m, 7H), 7 13 (d, 1H), 6 05-6 01 (m, 1H) 6 00-5 95 (m, 1H), 5 13 (s, 2H), 5 00 (s, 2H)
Anal Calcd for $C_{20}H_{16}F_3NO_2$ C, 66 85, H, 4 49, N, 3 90
Found C, 66 64, H, 4 26, N, 3 93

Example 27

4-(benzyloxy)-3-bromo-1-[4-(trifluoromethyl) benzyl]pyridin-2(1*H*)-one

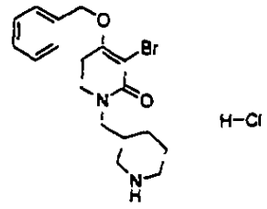


The material of Example 27 was prepared according to the procedure of Example 2 FABHRMS m/z 438 0308 (M+H, $C_{20}H_{16}BrF_3NO_2$ requires 438 0316) $^1H$ NMR ($CDCl_3$/300 MHz) δ 7 65-7 20 (m, 10H), 6 13-6 03 (m, 1H), 5 30-5 13 (m, 4H)
Anal Calcd for $C_{20}H_{15}BrF_3NO_2$ C, 54 81, H, 3 45, N, 3 20
Found C, 54 69, H, 3 34, N, 3 19

Example 28

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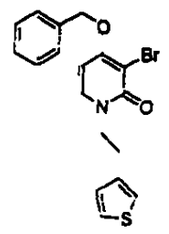
4-(benzyloxy)-3-bromo-1-(piperidin-3-ylmethyl)pyridin-2(1*H*)-one hydrochloride



To the material of Example 11 (3.1 g, 0.011 mol) in DMF (20 mL) was added dropwise sodium bis(trimethylsilyl)amide (1M in THF, 12 mL). Contents were stirred one hour before adding dropwise a solution of 3-methanesulfonyloxymethyl-1-piperidine-1-carboxylic acid tert-butyl ester (*Bioorg Med Chem Lett*, 8(13), 1998, 1595-1600) (4.2 g, 0.015 mol) in DMF (5 mL). Contents were heated at 75°C overnight. Contents were allowed to cool, poured into water (100 mL) and a solid was filtered. The solid was stirred in 4 N HCl/dioxane (15 mL) for 3 hours and filtered to give the desired as a white solid, 752 mg (18% yield). mp 138.1-139.2°C. FABHRMS m/z 377.0859 (M+H, $C_{18}H_{22}BrN_2O_2$ requires 377.0865). $^1$H NMR (DMSO-$d_6$/300 MHz) 9.50-9.10 (br, 2H), 8.00 (d, 1H), 7.50-7.30 (m, 5H), 6.93 (d, 1H), 5.30 (s, 2H), 4.30-3.90 (m, 3H), 3.40-3.10 (m, 3H), 2.80-2.50 (m, 3H), 2.40-2.00 (m, 1H), 1.90-1.60 (m, 4H), 1.40-1.10 (m, 1H). Anal. Calcd for $C_{18}H_{21}BrN_2O_2$ (2HCl, 0.25 $H_2O$): C, 47.55; H, 5.21; N, 6.16. Found: C, 47.48; H, 5.46; N, 6.27.

Example 29

4-(benzyloxy)-3-bromo-1-(2-thien-3-ylethyl)pyridin-2(1*H*)-one



To the material of Example 11 (500 mg 0 0018 mol) in DMF (5 mL) was added dropwise sodium bis(trimethylsilyl)amide (1M in THF, 2 mL) Contents were stirred one hour before adding dropwise a solution of methanesulfonic acid 2-thiophen-3-yl-ethyl ester (*J A C S*, 109(6), 1987, 1858-1859) (412 mg, 0 002 mol) in DMF (5 mL) Contents were heated at 75°C overright Contents were allowed to cool, poured into water (100 mL), and extracted into EtOAc, dried over $MgSO_4$, filtered, and concentrated *in vacuo* leaving a light yellow oil The oil was purified by silica gel chromatography eluting with 50% EtOAc/hexanes to give the desired as a white solid, 199 mg (28% yield) mp 134 0-134 3°C

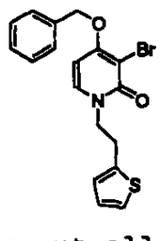
FABHRMS m/z 390 0144 (M+H, $C_{18}H_{17}BrNO_2S$ requires 390 0163) $^1H$ NMR ($CDCl_3$/300 MHz) 7 43-7 20 (m, 6H), 6 92-6 80 (m, 3H), 5 90 (d, 1H), 5 20 (s, 2H), 4 13 (t, 2H), 3 10 (t, 2H)

Anal Calcd for $C_{18}H_{16}BrNO_2S$ C, 55 39, H, 4 13, N, 3 59

Found C, 55 21, H, 3 87, N, 3 52

**Example 30**

**4-(benzyloxy)-3-bromo-1-(2-thien-2-ylethyl)pyridin-2(1*H*)-one**



The title compound was prepared essentially according to the procedure of Example 29 mp 128 0-129 5°C FABHRMS m/z

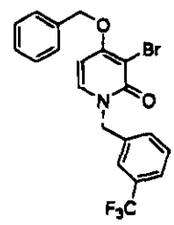
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390 0160 (M+H, $C_{18}H_{17}BrNO_2S$ requires 390 0163) $^1$H NMR ($CDCl_3$/300 MHz) δ 7 48-7 30 (m, 5H), 7 22 (d, 1H), 6 95-6 80 (m, 2H), 6 75-6 68 (m, 1H), 5 95 (d, 1H), 5 20 (s, 2H), 4 56 (t, 2H), 3 30 (t, 2H)

Anal Calcd for $C_{18}H_{16}BrNO_2S$ C, 55 39, H, 4 13, N 3 59 Found C, 55 06, H, 4 02, N 3 56

Example 31

4-(benzyloxy)-3-bromo-1-[3-(trifluoromethyl) benzyl]pyridin-2(1*H*)-one

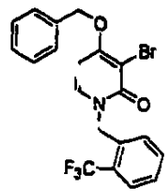



To the material of Example 11 (500 mg, 0 0018 mol) in DMF (5 mL) was added dropwise sodium bis(trimethylsilyl)amide (1M in THF, 2 mL) Contents were stirred one hour before adding dropwise a solution of 3-trifluoromethylbenzyl bromide (478 mg, 0 002 mol) in DMF (5 mL) Contents were heated at 75°C for 2 hours Contents were allowed to cool, poured into water (100 mL), and extracted with EtOAc, which was dried over $MgSO_4$, filtered, and concentrated *in vacuo* leaving a white solid FABHRMS m/z 438 0301 (M+H, $C_{20}H_{16}BrF_3NO_2$ requires 438 0316) $^1$H NMR ($CDCl_3$/300 MHz) 7 60-7 20 (m, 10H), 6 10 (d, 1H), 5 14 (s, 2H), 5 20 (s, 2H)

Anal Calcd for $C_{20}H_{15}BrF_3NO_2$ C, 54 81, H, 3 45, N, 3 20 Found C, 54 81, H, 3 36, N, 3 13

Example 32

4-(benzyloxy)-3-bromo-1-[2-(trifluoromethyl) benzyl]pyridin-2(1*H*)-one



The material of Example 32 was prepared according to the procedure of Example 31

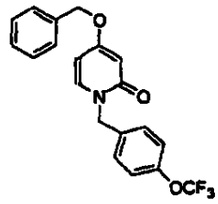
FABHRMS m/z 438 0280 (M+H, $C_{20}H_{16}BrF_3NO_2$ requires 438 0316) $^1H$ NMR ($CDCl_3$/300 MHz) δ 7 68 (d, 1H), 7 55-7 20 (m, 8H), 7 15 (d, 1H), 6 10 (d, 1H), 5 40 (s, 2H), 5 13 (s, 2H)

Anal Calcd for $C_{20}H_{15}BrF_3NO_2$ C, 54 81, H, 3 45, N, 3 20

Found C, 54 48, H, 3 36, N, 3 17

Example 33

4-(benzyloxy)-1-[4-(trifluoromethoxy)benzyl]pyridin-2(1*H*)-one



The material of Example 33 was prepared according to the procedure of Example 1

FABHRMS m/z 376 1158 (M+H, $C_{20}H_{17}F_3NO_3$ requires 376 1161) $^1H$ NMR ($CDCl_3$/300 MHz) δ 7 40-7 05 (m, 10H), 6 05-5 95 (m, 2H), 5 06 (s, 2H), 4 98 (s, 2H)

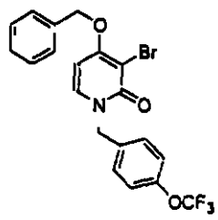
Anal Calcd for $C_{20}H_{16}F_3NO_3$ C, 64 00, H, 4 30, N, 3 73

Found C, 63 97, H, 4 26, N, 3 57

Example 34

4-(benzyloxy)-3-bromo-1-[4-(trifluoromethoxy) benzyl]pyridin-2(1*H*)-one

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The material of Example 34 was prepared according to the procedure of Example 2

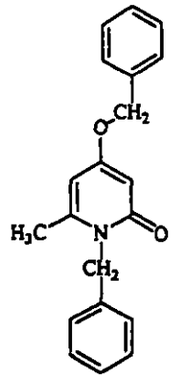
FABHRMS m/z 454 0240 (M+H, $C_{20}H_{16}BrF_3NO_3$ requires 454 0266) $^1$H NMR ($CDCl_3$/300 MHz) δ 7 45-7 10 (m, 10H), 6 08 (d, 1H), 5 20 (s, 2H), 5 12 (s, 2H)

Anal Calcd for $C_{20}H_{15}BrF_3NO_3$ C, 52 88, H, 3 33, N, 3 08

Found C, 52 53, H, 3 09, N, 2 92

Example 35

1-benzyl-4-(benzyloxy)-6-methylpyridin-2(1H)-one



Step 1 Preparation of 1-benzyl-4-hydroxy-6-methylpyridin-2(1H)-one

4-hydroxy-6-methyl-2-pyrone (0 2 mol, 25 2 g) and benzylamine (0 2 mol, 21 4 g) were added to water (800 mL) and heated to reflux with stirring for 2 hours After cooling to room temperature, a light brown solid was collected by filtration (33 4 g, 77%) $^1$H NMR (DMSO-$d_6$/300 MHz) δ 10 5 (s, 1H), 7 4-7 1 (m, 5 H), 5 8-5 6 (m, 2H), 5 2 (s,2H), 5 1

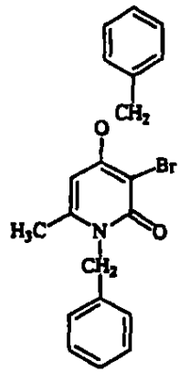
(s, 2H), 2 2 (s, 3H) ESHRMS *m/z* 216 100 (M+H, $C_{12}H_{13}NO_2$ requires 216 102)

Step 2 Preparation of 1-benzyl-4-(benzyloxy)-6-methylpyridin-2(1H)-one

1-benzyl-4-hydroxy-6-methylpyridin-2(1H)-one (10 mmol, 2 15 g), dichloromethane (100 mL) benzylbromide (11 mmol, 1 88 g), sodium hydroxide (2 5 N, 20 mmol, 8 mL), and benzyltriethylammonium chloride (0 5 g) were vigorously stirred at room temperature for 16h Hydrochloric acid (1 N) was added until the mixture produced an acidic reaction to pH paper The mixture was then extracted with ethyl acetate (3 X 50 mL) The combined organic extracts were washed with brine, dried over magnesium sulfate, filtered, and concentrated The product was obtained by flash chromatography eluting with ethyl acetate hexanes (1 2) The appropriate fractions were concentrated to a clear oil (1 3 g, 43%) $^1$H NMR (DMSO-$d_6$/300 MHz) δ 7 4-7 1 (m, 10 H), 6 0-5 9 (m, 2H), 5 2 (s,2H), 5 1 (s, 2H), 2 2 (s, 3H) ESHRMS *m/z* 306 147 (M+H, $C_{20}H_{19}NO_2$ requires 306 149)

Example 36

1-benzyl-4-(benzyloxy)-3-bromo-6-methylpyridin-2(1H)-one



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The product from example 35, 1-benzyl-4-(benzyloxy)-6-methylpyridin-2(1H)-one (4.2 mmol, 1.3 g), acetic acid (50 mL), and sodium acetate (5.0 mmol, 0.41 g) were stirred at room temperature. Bromine (4.2 mmol, 0.67 g) was added dropwise with stirring. After ½ hour, water (100 mL) was added and the mixture was extracted with ethyl acetate (3 X 50 mL). The combined organic extracts were washed with saturated aqueous sodium bicarbonate solution and brine. After drying over magnesium sulfate and concentrating, the mixture was purified by flash column chromatography eluting with ethyl acetate:hexanes (1:2). The appropriate fractions were concentrated to yield a light oil (1.0 g, 62%). $^1$H NMR (DMSO-$d_6$/300 MHz) 7.4-7.0 (m, 10 H), 6.5 (s, 1H), 5.29 (s,2H), 5.27 (s, 2H), 2.2 (s, 3H). ESHRMS *m/z* 384.057 (M+H, $C_{20}H_{18}NO_2Br$ requires 384.060).

Example 37

1-benzyl-4-(benzyloxy)-3,5-dibromo-6-methylpyridin-2(1H)-one

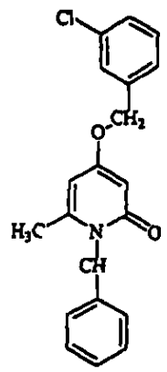



The product from example 35, 1-benzyl-4-(benzyloxy)-6-methylpyridin-2(1H)-one (4.2 mmol, 1.3 g), acetic acid (50 mL), and sodium acetate (5.0 mmol, 0.41 g) were stirred at room temperature. Bromine (4.2 mmol, 0.67 g) was added dropwise with stirring. After ½ hour, water (100 mL) was added and the mixture was extracted with ethyl acetate (3 X 50 mL)

The combined organics were washed with saturated aqueous sodium bicarbonate solution and brine After drying over magnesium sulfate and concentrating, the mixture was purified by flash column chromatography eluting with ethyl acetate hexanes (1 2) The appropriate fractions were concentrated to yield a white solid (0 3 g, 15%) $^1$H NMR (DMSO-$d_6$/300 MHz) 7 5-7 0 (m, 10 H), 5 42 (s,2H), 5 07 (s, 2H), 2 45 (s, 3H) ESHRMS *m/z* 463 966 (M+H, $C_{20}H_{17}NO_2Br_2$ requires 463 968)

Example 38

1-benzyl-4-[(3-chlorobenzyl)oxy]-6-methylpyridin-2(1H)-one



Step 1 Preparation of 1-benzyl-6-methyl-2-oxo-1,2-dihydropyridin-4-yl 4-bromobenzenesulfonate

1-benzyl-4-hydroxy-6-methylpyridin-2(1H)-one (from example 35) (10 mmol, 2 15 g), N,N'-dimethylformamide (30 mL), potassium carbonate (20 mmol, 2 76 g), and 4-bromobenzenesulfonyl chloride (10 mmol, 2 55 g) were stirred at room temperature for 16 hours Hydrochloric acid (1N) was added until the mixture was acidic to pH paper Brine (50 mL) was added and the mixture extracted with ethyl acetate (3 X 50 mL) The combined organic extracts were washed with brine and dried over magnesium sulfate, and filtered After concentrating, the material was purified by flash column

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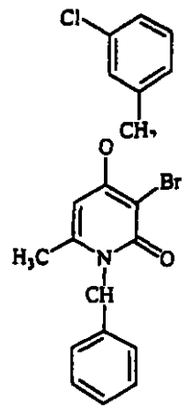
chromatography eluting with ethyl acetate hexanes (1:2). The appropriate fractions were concentrated to a clear oil, which solidified upon standing several days to a white solid (3.3 g, 76%). $^1$H NMR (DMSO-$d_6$/400 MHz) 7.9 (m, 4H), 7.32-7.00 (m, 5H), 7.3 (m, 1H), 6.12 (d, *J* = 2.4 Hz, 1H), 6.02 (d, *J* = 2.6 Hz, 1H), 5.20 (s, 2H), 2.2 (s, 3H). ESHRMS *m/z* 436.002 (M+-, $C_{19}H_{16}NO_4SBr$ requires 436.004).

Step 2. Preparation of 1-benzyl-4-[(3-chlorobenzyl)oxy]-6-methylpyridin-2(1H)-one

1-benzyl-6-methyl-2-oxo-1,2-dihydropyridin-4-yl 4-bromobenzenesulfonate (3.0 mmol, 1.3 g), N,N'-dimethylformamide (30 mL), 3-chlorobenzyl alcohol (3.0 mmol, 0.43 g), and sodium hydroxide (60%, 3.3 mmol, 0.13 g) were stirred at room temperature under nitrogen for 4 hours. Hydrochloric acid (1 N, 10 mL) was added and the mixture extracted with ethyl acetate (3 X 25 mL). The combined organic extracts were washed with saturated aqueous sodium bicarbonate solution and brine. After drying over magnesium sulfate and concentrating, the mixture was purified by flash column chromatography eluting with ethyl acetate hexanes (1:1) to obtain a light yellow oil (1.43 g, 64%). $^1$H NMR (DMSO-$d_6$/300 MHz) δ 7.4-7.0 (m, 10 H), 6.0-5.8 (m, 2H), 5.2 (s,2H), 5.0 (s, 2H), 2.1 (s, 3H). ESHRMS *m/z* 340.110 (M+H, $C_{20}H_{18}NO_2Cl$ requires 340.110).

Example 39

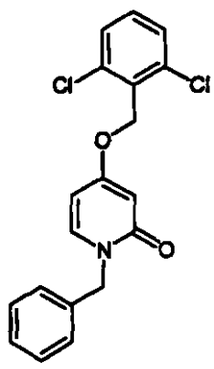
1-benzyl-3-bromo-4-[(3-chlorobenzyl)oxy]-6-methylpyridin-2(1H)-one



The product of example 38 (SC-83316), 1-benzyl-4-[(3-chlorobenzyl)oxy]-6-methylpyridin-2(1H)-one (0 91 mmol, 310 Mg), acetic acid (20 mL), and sodium acetate (0 91 mmol, 80 Mg) were stirred at room temperature when bromine (0 91 mmol, 145 Mg) was added After stirring for one hour, the mixture was concentrated, dissolved in ethyl acetate, and washed successively with saturated aqueous sodium bicarbonate solution, brine, and water After drying over magnesium sulfate and concentrating, the product was recrystallized from tetrahydrofuran / hexanes to yield a white solid (240 Mg, 63%) $^1$H NMR (DMSO-$d_6$/300 MHz) 7 6-7 0 (m, 10 H), 6 5 (s, 1H), 5 33 (s,2H), 5 33 (s, 2H), 2 3 (s, 3H) ESHRMS *m/z* 420 019 (M+H, $C_{20}H_{17}NO_2BrCl$ requires 420 019)

**EXAMPLE 40**

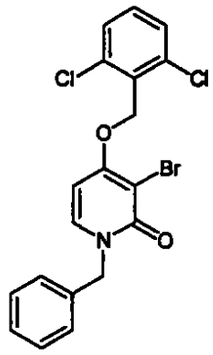
**1-Benzyl-4-[2,6-(dichlorobenzyl)oxy]pyridin-2(1H)-one**



The title compound was prepared essentially as described in claim 1 mp 151 6-152 0 °C $^1$H NMR ($CDCl_3$/300MHz) δ 7 31 (m, 8H), 7 12 (d, 1H, J = 7 45 Hz), 6 13 (d, 1H, J = 2 42 Hz), 5 90 (dd, 1H, J = 2 62 Hz), 5 22 (s, 2H), 5 10 (s, 2H) ESHRMS m/z 360 0551 (M+H $C_{19}H_{15}Cl_2NO_2$ requires 360 0558)

EXAMPLE 41

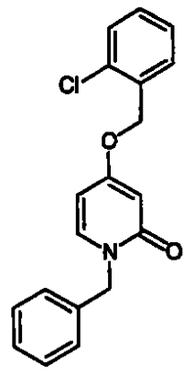
1-Benzyl-3-bromo-4-[2,6-(dichlorobenzyl)oxy]pyridin-2(1H)-one




1-Benzyl-4-[2,6-(dichlorobenzyl)oxy]pyridin-2(1H)-one (0 400 g, 1 11 mmol) was dissolved in acetic acid (10 mL) Sodium acetate (0 091 g, 1 11 mmol was added, and the mixture was cooled to 15 °C Bromine (0 195 g, 1 22 mmol) was added via syringe The reaction stirred at room temperature for 2 hours Water (15 mL) was added, and the mixture transferred to a separatory funnel Ethyl acetate (50 mL) was added and the layers were separated The organic phase was washed with aqueous $NaHCO_3$ (2 x 25 mL), dried over $MgSO_4$, filtered, and evaporated to yield a white solid $^1$HNMR ($CDCl_3$/300MHz) δ 7 34 (m, 9H), 6 24 (d, 1H, J = 7 65 Hz), 5 37 (s, 2H), 5 18 (s, 2H) ESHRMS m/z 439 9646 (M+H $C_{19}H_{14}BrCl_2NO_2$ requires 439 9641)

Example 42

1-Benzyl-4-[(2-chlorobenzyl)oxy]pyridin-2(1H)-one

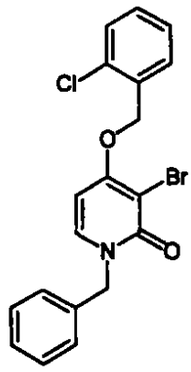


The title compound was prepared by a procedure similar to the one described in Example 1 mp 124 6-125 0 °C $^1$HNMR ($CDCl_3$/300MHz) δ 7 36 (m, 9H), 7 14 (d, 1H, J = 7 65 Hz), 6 04 (d, 1H, J = 2 62 Hz), 5 98 (d, 1H, J = 2 82 Hz), 5 10 (s, 2H), 5 09 (s, 2H) ESHRMS m/z 326 0950 (M+H $C_{19}H_{16}ClNO_2$ requires 326 0948)

Anal Calc'd for $C_{19}H_{16}ClNO_2$ C, 70 05, H, 4 95, N, 4 30, Cl, 10 88 Found C, 69 87, H, 4 74, N, 4 42, Cl, 11 08

EXAMPLE 43

1-Benzyl-3-bromo-4-[(2-chlorobenzyl)oxy]pyridin-2(1H)-one

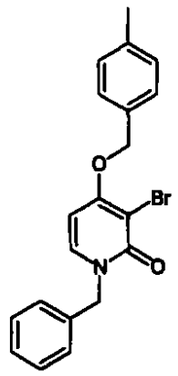


The title compound was prepared by a procedure similar to the one described in Example 2 mp 143 3-145 5 °C $^1$HNMR ($CDCl_3$/300MHz) δ 7 63 (d, 2H, J = 1 81 Hz), 7 44 (m, 9H), 6 06 (d, 1H, J = 7 65 Hz), 5 29 (s, 2H), 5 17 (s, 2H) ESHRMS m/z 406 0036 (M+H $C_{19}H_{15}BrClNO_2$ requires 406 0032)

Anal Calc'd for $C_{19}H_{15}Cl\ BrNO_2$ C, 56 39, H, 3 74, N, 3 46, Cl, 8 76 Found C, 56 01, H, 3 38, N, 3 36, Cl, 9 01

EXAMPLE 44

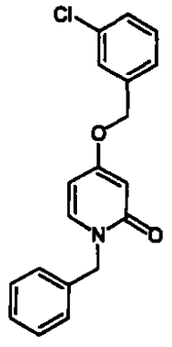
1-Benzyl-3-bromo-4-[(4-methylbenzyl)oxy]pyridin-2(1H)-one



The title compound was prepared by a procedure similar to the one described in Example 2 mp 149 0-149 7 °C $^1$HNMR ($CDCl_3$/300MHz) δ 7 25 (m, 10H), 6 04 (d, 1H, J = 7 65 Hz), 5 17 (s, 2H), 5 15 (s, 2H), 2 34 (s, 3H) ESHRMS m/z 386 0583 (M+H $C_{20}H_{18}BrNO_2$ requires 386 0581)

EXAMPLE 45

1-Benzyl-4-[(3-chlorobenzyl)oxy]pyridin-2(1H)-one

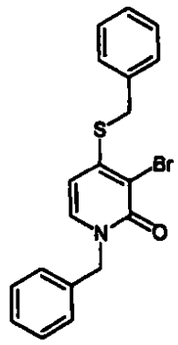


The title compound was prepared by a procedure similar to the one described in Example 1 mp 95 5-95 7 °C $^1$HNMR ($CDCl_3$/300MHz) δ 7 34 (m, 9H), 7 13 (d, 1H, J = 7 45 Hz), 5 96

(m, 1H), 5 95 (d, 1H, J = 7 45 Hz), 5 09 (s, 2H), 4 96 (s, 2H) ESHRMS m/z 326 0977 (M+H $C_{19}H_{16}ClNO_2$ requires 326 0948)

EXAMPLE 46

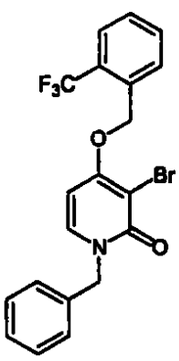
1-Benzyl-4-[benzylthio]-3-bromopyridin-2(1H)-one



The title compound was prepared by a procedure similar to the one described in Example 2 mp 180 6-182 1 °C $^1$HNMR ($CDCl_3$/300MHz) δ 7 33 (m, 10H), 7 14 (d, 1H, J = 7 45 Hz), 6 08 (d, 1H, J = 7 45 Hz), 5 13 (s, 2H), 4 15 (s, 2H) ESHRMS m/z 386 0211 (M+H $C_{19}H_{16}BrNOS$ requires 386 0214)

EXAMPLE 47

1-Benzyl-3-bromo-4-{[2-(trifluoromethyl)benzyl]oxy}pyridin-2(1H)-one

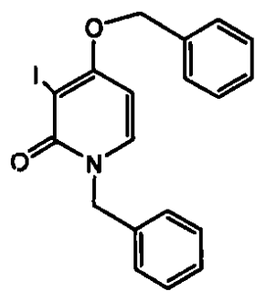


The title compound was prepared by a procedure similar to the one described in Example 2 mp 133 2-133 5 °C $^1$HNMR ($CDCl_3$ / 300MHz) δ 7 81 (d, 1H, J = 7 65 Hz), 7 68 (d, 1H, J = 7 65 Hz), 7 61 (t, 1H, J = 7 65 Hz), 7 38 (m, 7H), 6 01 (d,

1H, J = 7 85 Hz), 5 39 (s, 2H), 5 16 (s, 2H) ESHRMS m/z 438 0313 (M+H $C_{20}H_{15}BrF_3NO_2$ requires 403 0316)

Example 48

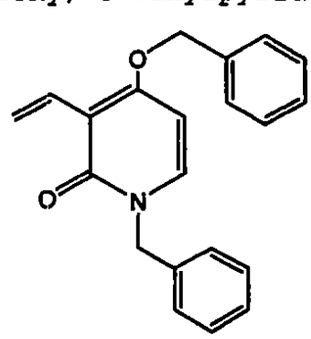
1-benzyl-4-(benzyloxy)-3-iodopyridin-2(1H)-one



A mixture of N,O-dibenzyl-2-pyridone (2 0 g, 6 87 mmol), N-iodosuccinimide (1 7 g) , dichloroacetic acid (0 15 mL) in acetonitrile (40 0 mL) was heated at 65 °C under argon atmosphere for 3 5 h, with constant stirring The reaction mixture was concentrated to dryness, and the residue was purified by silica gel flash chromatography using EtOAc/ hexanes 1 1 v/v to give the title compound 2 3 g (80%) as a flaky white solid $^1$H-NMR ($CDCl_3$) δ 7 4 - 7 2 (m, 10 H), 7 19 (1H, d, J = 7 6 Hz), 5 95 (d, 1H, J = 7 6 Hz), 5 2 (s, 1H), 5 15 (s, 2H), ER-MS m/z = 418 ($MH^+$), HR-MS m/z calcd $C_{19}H_{17}NO_2$ 418 0304, found 418 0277

Example 49

1-benzyl-4-(benzyloxy)-3-vinylpyridin-2(1H)-one

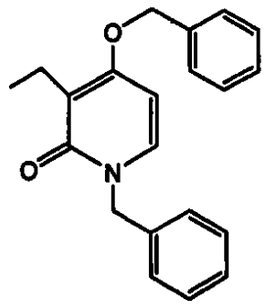


A solution of 1-benzyl-4-(benzyloxy)-3-iodopyridin-2(1H)-one (1 9 g, 4 56 mmol) and vinyl-tri-butyltin (2 5 mL) in acetonitrile (20 0 mL) containing DMF (2 0 mL) was degassed using house vacuum and purged with argon Then added $PdCl_2(PPh_3)_2$ (0 3 g) and the mixture was heated at 65 °C under argon atmosphere for 4 h, with stirring The solvents were distilled in vacuo, and the residue was triturated with EtOAc and filtered through a pad of celite The filtrate was concentrated and the residue was purified by silica gel flash chromatography using 25% EtOAc in hexanes to give the title compound (0 75 g 50%) as an orange colored solid

$^1$H-NMR ($CDCl_3$) δ 7 4 - 7 2 (m, 10 H), 7 14 (d, 1H, J = 7 6 Hz), 7 05 (dd, 1H, J = 12 0 Hz), 6 47 (dd, 1H, J = 2 8 Hz), 6 07 (d, 1H, J = 7 6 Hz), 5 4 (dd, 1H, J = 2 8 Hz), 5 13 (s, 4H), ER-MS m/z = 418 ($MH^+$), ER-MS m/z = 318 ($MH^+$), HR-MS m/z calcd $C_{21}H_{20}NO_2$ 318 1494, found 318 1480

Example 50

1-benzyl-4-(benzyloxy)-3-ethylpyridin-2(1H)-one

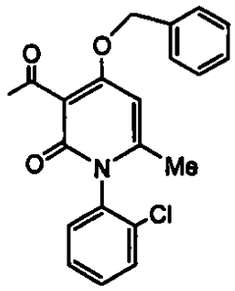


To a solution of 1-benzyl-4-(benzyloxy)-3-vinylpyridin-2(1H)-one (0 5 g, 1 6 mmol) in EtOH (10 0 mL) and EtOAc (10 0 mL) was added Pd/C (10 %, 0 25 g) and stirred in an atmosphere of hydrogen gas at 30 psi for 16 h The catalyst was removed by filtration, the filtrate was concentrated to dryness and the resulting residue was purified by silica gel flash chromatography using EtOAc/hexanes (1:1, v/v) to afford the

title compound (0 32 g 64%) as a pale yellow powder $^1$H-NMR ($CD_3OD$) δ 7 52 (d, 1H, J = 7 6 Hz), 7 39 - 7 2 (m, 10 H), 6 41 (d, 1h, J = 7 6 Hz), 5 18 (s, 2H), 5 15 (s, 2H), 2 58 (q, 2H, J = 7 2 Hz), 1 03 (t, 3H, J = 7 2 Hz), ER-MS m/z = 320 ($MH^+$), HR-MS m/z calcd $C_{21}H_{22}NO_2$ 320 1651, found 320 1648

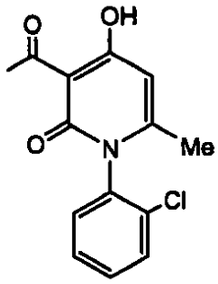
Example 51

3-acetyl-4-(benzyloxy)-1-(2-chlorophenyl)-6-methylpyridin-2(1H)-one




Step A

Preparation of 3-acetyl-1-(2-chlorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one




A mixture of 2-chlorophenylisocyanate (3 0 g, 19 53 mmol), and diketene (3 3 g, 39 28 mmol) in toluene (10 0 mL) containing triethylamine (0 05 mL) was heated to reflux for 6 h, under an atmosphere of argon Toluene was distilled in vacuo and the resulting residue was purified by silica gel flash chromatography using 25 % EtOAc in hexanes as the eluent to afford the title compound (0 85 g, see ref *Heterocycles* 27 (9), 2063, 1988 ) as a pale yellow solid $^1$H-NMR ($CD_3OD$) δ

7 63 (m, 1H), 7 52 (m, 2H), 7 4 (m, 1H), 6 14 (s, 1H), 2 58 (s, 3H), and 1 95 (s, 3H), ES-MS m/z = 278 ( $MH^+$ )

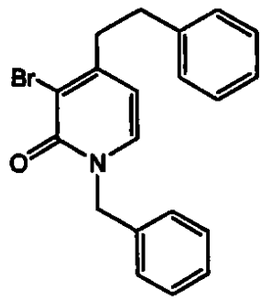
Step B

Preparation of 3-acetyl-4-(benzyloxy)-1-(2-chlorophenyl)-6-methylpyridin-2(1H)-one

To a solution of 3-acetyl-1-(2-chlorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one ( 0 56 g, 2 02 mmol) in DMF (5 0 mL), benzyl bromide (0 3 mL) and potassium carbonate (0 3 g, 2 16 mmol) were added The mixture was stirred at room temperature for 3 h, and at 65 °C for 1 h under argon atmosphere The reaction mixture was concentrated in vacuo and the residue was partitioned between 5% citric acid (25 mL) and EtOAc (50 0 mL) The organic phase was washed with brine, dried ($Na_2SO_4$), filtered, and concentrated to dryness The resulting residue was purified by silica gel flash chromatography using 50% EtOAc in hexanes to afford the title compound (0 58 g, 75%) as a pale yellow amorphous substance $^1$H-NMR ($CD_3OD$) δ 7 65 - 7 3 (m, 9H), 6 5 (s, 1H), 5 31 (s, 2H), 2 42 (s, 3H), and 2 01 (s, 3H), ER-MS m/z = 368 ($MH^+$), HR-MS m/z calcd $C_{21}H_{19}NO_3Cl$ ,368 1060, found 368 1053

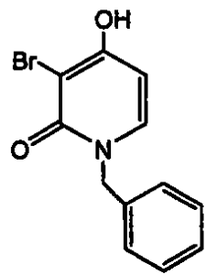
Example 52

1-benzyl-3-bromo-4-(2-phenylethyl)pyridin-2(1H)-one




Step A

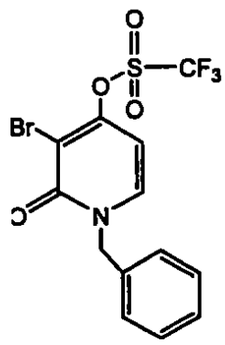
Preparation of 1-benzyl-3-bromo-4-hydroxypyridin-2(1H)-one



A suspension of N-benzyl-4-hydroxy-2-pyridone ((0 75 g, 3 7 mmol), NBS (0 7 g, 1 05 mmol) in dichloromethane was stirred at room temperature for 1 5 h under argon atmosphere It was diluted with dichloromethane (25 mL), cooled and filtered The solids were washed with dichloromethane and dried in vacuo The filtrate and the washings were combined and washed with water, dried ($Na_2SO_4$), filtered, and concentrated to dryness The resulting residue was washed with EtOAc, and dried in vacuo to give a combined mass of 0 65 g of the title compound as a white powder $^1H$ NMR ($CD_3OD$) δ 7 54 (d, 1H, J = 7 6 Hz), 7 27 (m, 5H), 6 12 (d, 1H, J = 7 6 Hz), 5 15 (s, 2H), ES-MS m/z = 280 ($MH^+$)

Step B

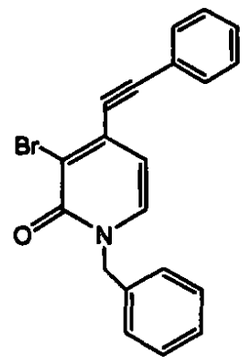
Preparation of 1-benzyl-3-bromo-2-oxo-1,2-dihydropyridin-4-yl trifluoromethanesulfonate



To a cold (-30 °C ) suspension of 1-benzyl-3-bromo-4-hydroxypyridin-2(1H)-one (0 78 g, 2 8 mmol) in dichloromethane (10 0 mL), was added triethylamine (0 6 mL, 4 28 mmol ), followed by the addition of triflic anhydride (0 7 mL, 4 17 mmol) The resulting mixture was stirred at -30 °C under argon atmosphere for 1 h The reaction mixture was then poured into ice/water mixture (50 mL) and the products were extracted with dichloromethane (2 x 25 mL) The combined organic extracts were washed with water (2 x 20 mL), dried ($Na_2SO_4$), filtered, and concentrated to dryness The residue was dried in vacuo to afford the desired trifluorosulfonate (1 0 g) as a pale yellow solid which used as such in the next step $^1$H- NMR ($CDCl_3$) δ 7 35 (m, 6H), 6 26 (d, 1H, J = 8 0 Hz), $^{19}$F- NMR ($CDCl_3$) δ -73 73 ppm, ES-MS m/z = 412 ($MH^+$)

Step C

Preparation of 1-benzyl-3-bromo-4-(phenylethynyl)pyridin-2(1H)-one




To a solution of 1-benzyl-3-bromo-2-oxo-1,2-dihydropyridin-4-yl trifluoromethanesulfonate (1 0 g) in DMF (5 0 mL) was added phenylacetylene (0 4 mL) and degassed using house vacuum The reaction flask was then purged with argon, added diisopropylethylamine (0 53 mL), and $PdCl_2(PPh_3)_2$ (0 35 g) were added The resulting mixture was stirred at room temperature for 15 min and heated at 65 °C under an argon

atmosphere for 3h The dark colored reaction mixture was concentrated in vacuo, and the residue was partitioned between EtOAc (50 mL) and 5% aqueous citric acid (25 mL) The organic extracts were washed with water, dried ($Na_2SO_4$), filtered, and concentrated to dryness The resulting material was purified by silica gel flash chromatography using 25% EtOAc in hexanes as the eluent The appropriate fractions were combined, concentrated under reduced pressure $^1H$ NMR ($CDCl_3$) δ 7 57 (m, 2H), 7 38 (m, 8H), 7 21 (d, 1H, J = 6 8 Hz), 6 25 (d, 1H, J = 6 8 Hz), and 5 16 (d, 2H), ES-MS m/z = 364 ($MH^+$), HR-MS m/z ($MH^+$) calcd $C_{20}H_{15}NOBr$ 364 0337, found 364 0337

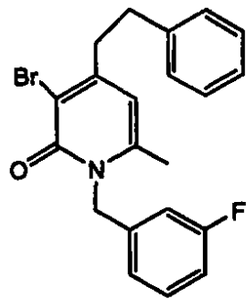
Step D

Preparation of 1-benzyl-3-bromo-4-(2-phenylethyl)pyridin-2(1H)-one

A mixture of 1-benzyl-3-bromo-4-(phenylethynyl)pyridin-2(1H)-one (0 3 g), and platinum oxide (0 05 g) in a solvent mixture of EtOAc (10 0 mL) and EtOH ( 10 0 mL) was stirred in an atmosphere of hydrogen at 15 psi in a Fischer porter bottle for 45 min The catalyst was removed by filtration, and filtrate was concentrated The resulting residue was purified by silica gel flash chromatography using 25% EtOAc in hexanes as the eluent The appropriate fractions (visualized under an UV lamp) were combined and concentrated under reduced pressure $^1H$- NMR ($CD_3OD$) δ 7 56 (d, 1H, J = 6 8 Hz), 7 31 - 7 17 (m, 10 H), 6 24 (d, 1H, J = 6 8 Hz), 5 19 (s, 2H), 2 96 (m, 2H), and 2 91 (m, 2H), ES-MS m/z = 368 ($MH^+$), HR-MS m/z ($MH^+$) calcd $C_{20}H_{19}NOBr$ 368 0650, found 368 0630

Example 53

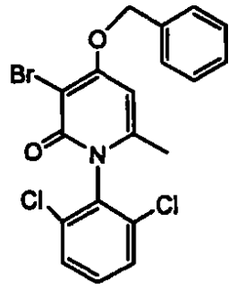
3-bromo-1-(3-fluorobenzyl)-6-methyl-4-(2-phenylethyl)pyridin-2(1H)-one-



The title compound was prepared essentially according to the procedure of Example 52 $^1$H- NMR δ ($CD_3OD$) δ 7 35 (m, 1H), 7 31-7 16 (m, 5H), 6 99(m, 1H), 6 91 (m, 1H), 6 81 (m, 1H), 6 20 (s, 1H), 5 41 (s, 2H), 2 94 (m, 4H), and 2 24 (s, 3H), $^{19}$F-NMR ($CD_3OD$) δ -115 01 (m), ES-MS, m/z = 400 ($MH^+$), HR-MS m/z calcd $C_{21}H_{20}NOBrF$ 400 0712, found 400 0695

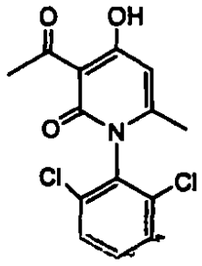
Example 54

4-(benzyloxy)-3-bromo-1-(2,6-dichlorophenyl)-6-methylpyridin-2(1H)-one



Step A

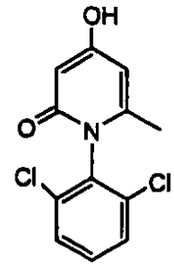
Preparation of 3-acetyl-1-(2,6-dichlorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one



A mixture of 2,6 dichlorophenylisocyanate (4 8 g, 0 025 mol), and diketene (4 3 g, 0 05 mol) in toluene (15 0 mL) was heated to reflux for 4 h under an atmosphere of argon After removal of the solvent in vacuo, the residue was purified by silica gel flash chromatography using EtOAc/hexanes (1 3 v/v) The appropriate fractions, as monitored by ES mass spectrometry ($MH^+$ m/z = 312) were combined and concentrated under reduced pressure The resulting yellow solid (2 3 g) was further purified by reverse-phase HPLC using 10-90% acetonitrile/water gradient (45 min) at a flow rate of 100 mL/min The appropriate fractions, as monitored by ES mass spectrometry ($MH^+$ m/z = 312) were combined and concentrated to half the volume The solid that separated was extracted with EtOAc ( 2 x 25 mL) The combined extracts were washed with water, dried ($Na_2SO_4$), filtered, and concentrated to dryness to give the title compound '0 77 g) as a pale yellow powder $^1H$-NMR ($CD_3OD$) δ 7 62 (m, 2H), 7 52 (m, 1H), 6 19 (s, 1H), 2 59 (s, 3H), and 1 96 (s, 3H), ES-MS m/z = 312 ($MH^+$), HR-MS, m/z calc $C_{14}H_{12}NO_3Cl_2$ 312 0189, found 312 0214

Step B

Preparation of 1-(2,6-dichlorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one

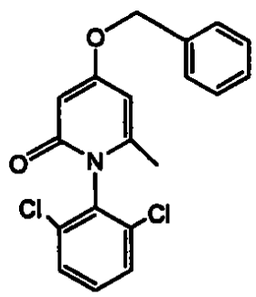



A mixture of 3-acetyl-1-(2,6-dichlorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one 0 7 g (0 002mol) in n-butanol(3 0 mL) containing sulfuric acid (1 5 mL) was heated at 120 °C for 4 h The dark reaction mixture was cooled, added ice/water (25

mL), and extracted with EtOAc (2 x 25 ml) The combined organic extracts were washed with water, dried ($Na_2SO_4$), filtered, concentrated under reduced pressure and the resulting material was purified by silica gel flash chromatography using 25% EtOAc in hexanes as the eluent to afford the title compound (0 14 g) as a pale yellow powder $^1$H-NMR (CD3OD) δ 7 6 (m, 2H), 7 48 (m, 1H), 6 10 (dd, 1H), 5 78 (d, 1H, J = 2 4 Hz), 1 91 (s, 3H), ES-MS m/z = 270 ($MH^+$), HR-MS, m/z calc $C_{12}H_{10}NO_2Cl_2$ 270 0083, found 270 0103

Step C

Preparation of 4-(benzyloxy)-1-(2,6-dichlorophenyl)-6-methylpyridin-2(1H)-one




A mixture of 1-(2,6-dichlorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one (0 125 g, 0 46 mmol) and benzylbromide (0 1 mL) in DMF (2 5 mL) was stirred at room temperature for 16 h The reaction mixture was diluted with water (10 0 mL) and extracted with EtOAc (2 x 20 mL) The combined organic extracts were washed with water, dried ($Na_2SO_4$), filtered, concentrated under reduced pressure and the resulting material was purified by silica gel flash chromatography using 25% EtOAc in hexanes to afford the title compound (0 11 g) as a pale yellow syrup $^1$H- NMR ($CD_3OD$) δ 7 61 (m, 2H), 7 55-7 3 (m, 6H), 6 23 (d, 1H, J = 2 0 Hz), 6 01 (d, 1H, J = 2 0 Hz), 5 12 (s, 2H), and 1 93 (s, 3H), ES-MS

m/z=360 ($MH^+$), HR-MS, m/z calc $C_{19}H_{16}NO_2Cl_2$, 360 0553, found 360 0569

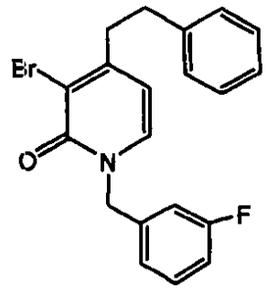
Step D

Preparation of 4-(benzyloxy)-3-bromo-1-(2,6-dichlorophenyl)-6-methylpyridin-2(1H)-one

A mixture of 4-(benzyloxy)-1-(2,6-dichlorophenyl)-6-methylpyridin-2(1H)-one (0 1 g, 0 278 mmol) and N-bromosuccinimide (0 055 g, 0 3 mmol) in dichloroethane (3 0 mL) was stirred at room temperature for 1 h, and heated at 60 °C under argon for 30 min The reaction mixture was then diluted with dichloroethane (15 mL), washed with water, dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure $^1H$ NMR ($CD_3OD$) δ 7 64 (m, 2H), 7 55 (m, 3H), 7 38 (m, 3H), 6 65 (s, 1H), 5 34 (s, 2H), and 2 00(s, 3H), ES-MS m/z = 439 ($MH^+$), HR-MS, m/z calc $C_{19}H_{16}NO_2Cl_2Br$, 439 9635, found 439 9669

Example 55

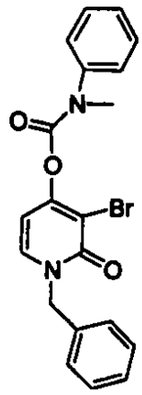
3-bromo-1-(3-fluorobenzyl)-4-(2-phenylethyl)pyridin-2(1H)-one




The title compound was prepared essentially according to the procedure of Example 52 $^1H$- NMR ($CD_3OD$) δ 7 58 (d, 1H, J = 6 8 Hz), 7 4-7 0 (m, 9H), 6 26 (d, 1H J = 6 8 Hz), 5 19 (s, 2H), 2 97 (m, 2H), and 2 90 (m, 2H), ES-MS m/z = 386 ($MH^+$), HR-MS, m/z calc $C_{20}H_{18}NOFBr$, 386 0550, found 386 0585

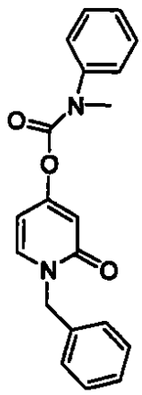
Example 56

1-benzyl-3-bromo-2-oxo-1,2-dihydropyridin-4-yl methyl(phenyl)carbamate



Step A

Preparation of 1-benzyl-2-oxo-1,2-dihydropyridin-4-yl methyl(phenyl)carbamate



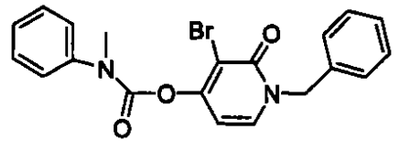
To a chilled solution of 1-benzyl-4-hydroxypyridin-2(1H)-one (0 375 g, 1 86 mmol) in anhydrous acetonitrile (10 mL) was added triethylamine (0 206 g, 2 04 mmol) followed by N-methyl-N-phenylcarbamoyl chloride (0 379 g, 2 24 mmol) The reaction mixture was stirred under nitrogen atmosphere at 0°C for 30 min then at room temperature for 1h The reaction was monitored by TLC (5% methanol in dichloromethane) The solvent was removed under reduced pressure and the residue was washed with 10% citric acid and extracted with EtOAc The

organic extracts were combined, washed with water dried over anhydrous $Na_2SO_4$, and filtered The solvent was removed under reduced pressure to afford a yellow syrup The residue was purified by flash chromatography (silica gel) using 5% MeOH in $CH_2Cl_2$ to give the desired product (0 382g, 61%) as a white semisolid

MS and $^1$H-NMR were consistent with the desired structure $^1$H-NMR ($d_6$-DMSO, 400 MHz) δ 7 8 (d, 1H), 7 39 (m, 10H), 6 19 (s, 2H), 5 03 (s, 2H), 3 29 (s, 3H), HR-MS (ES) m/z calcd for $C_{20}H_{18}N_2O_3$ ($MH^+$) = 335 1396, observed 335 1418

Step B

1-benzyl-3-bromo-2-oxo-1,2-dihydropyridin-4-yl methyl(phenyl)carbamate



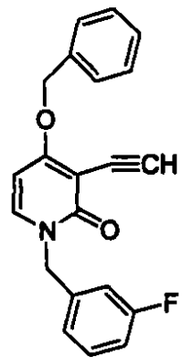

To a solution of 1-benzyl-2-oxo-1,2-dihydropyridin-4-yl methyl(phenyl)carbamate (0 38 g, 1 13 mmol) in anhydrous $CH_2Cl_2$ (7 mL) was added N-Bromosuccinimide (NBS, 0 24 g, 1 34 mmol) The reaction was stirred overnight at room temperature under nitrogen atmosphere The reaction mixture was purified by flash chromatography (silica gel) using EtOAc/hexanes (1 1 v/v) The appropriate fractions were collected according to ES MS (M+H 413) and concentrated The dried product showed about 14% of di-brominated product by analytical HPLC The compounds were separated by reverse phase HPLC using a 10-90% acetonitrile in water, 30 min gradient at a 100 mL/min flow rate, to afford (after lyophilization) the salt of the desired compound The salt was diluted in EtOAc and washed with $NaHCO_3$ The organic extracts were dried over anhydrous $Na_2SO_4$,

filtered, and concentrated to afford the desired compound (0 271 g, 58%) as a beige solid

MS and $^1$H-NMR were consistent with the desired structure $^1$H-NMR ($d_6$-DMSO, 400Hz) δ 7 83 (d, 1H), 7 39 (m, 10H), 6 48 (s, 1H), 5 12 (s,2H), 3 33 (s, 3H), HR-MS (ES) m/z calcd for $C_{20}H_{17}O_3Br$ ($MH^+$) = 413 0495, observed 413 0496

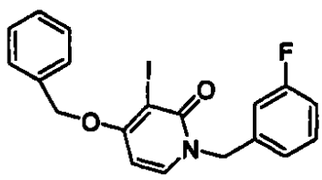
Example 57

4-(benzyloxy)-3-ethynyl-1-(3-fluorobenzyl)pyridin-2(1H)-one




Step A

Preparation of 4-(benzyloxy)-1-(3-fluorobenzyl)-3-iodopyridin-2(1H)-one



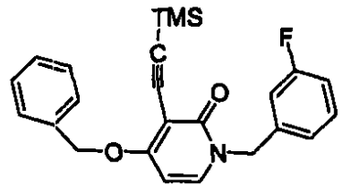

Heated a reaction mixture of 4-(benzyloxy)-1-(3-fluorobenzyl)pyridin-2(1H)-one (4 83 g, 15 6 mmol) in anhydrous acetonitrile (55 mL) and N-iodosuccinimide (NIS, 3 86 g, 17 1 mmol) under nitrogen atmosphere at 65° C for 4 h The reaction mixture was concentrated under reduced pressure and the residue was purified by flash chromatography (silica gel) using EtOAc/hexanes (1 1 v v) The appropriate fractions were collected according to ES MS (M+H 436) and washed with

$Na_2SO_3$ to remove the color impurities The fractions were concentrated under reduced pressure and dried in vacuo to afford the desired product (6 15 g, 90%) as a light yellow solid

MS and $^1$H-NMR were consistent with the desired structure $^1$H-NMR ($CD_3OD$, 400Hz) δ 7 73 (d, 1H), 7 47 (d, 2H), 7 39 (m, 4H), 7 08 (m, 3H), 6 39 (d, 1H), 5 29 (s, 2H), 5 19 (s, 2H), HR-MS (ES) m/z calcd for $C_{19}H_{15}NO_2FI$ ($MH^+$)= 436 0210, observed 436 0196

Step B

Preparation of 4-(benzyloxy)-1-(3-fluorobenzyl)-3-[(trimethylsilyl)ethynyl]pyridin-2(1H)-one



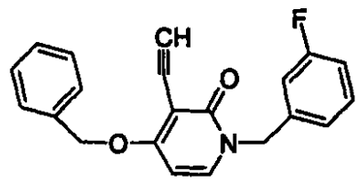

Degassed a solution of 4-(benzyloxy)-1-(3-fluorobenzyl)-3-iodopyridin-2(1H)-one (2 01 g, 4 62 mmol) in anhydrous acetonitrile (25 mL) under argon atmosphere Triethylamine (1 11 g, 11 mmol) was added and quickly degassed The reaction mixture was chilled in an ice bath for 15 minutes before adding bistriphenylphosphine-palladium chloride (0 34 g, 0 48 mmol) and cuprous iodide (0 2 g) The reaction was stirred at room temperature for 30 min before heating at 60° C under an atmosphere of argon for 2 h The reaction mixture was filtered through a bed of celite and the filtrate was concentrated under reduced pressure The dark brown residue was diluted with $CH_2Cl_2$ (100 mL) and washed with water The organic extracts were combined, dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure The dark brown residue was purified by flash chromatography (silica

gel) using 30% EtOAc in hexane The appropriate fractions were combined and concentrated under reduced pressure to afford the desired product (1 34 g, 72%) as a light yellow solid

MS and $^1$H-NMR were consistent with the desired structure $^1$H-NMR ($CD_3OD$, 400Hz) δ 7 74 (d, 1H), 7 47 (d, 2H), 7 35 (m, 4H), 7 09 (m, 3H), 6 46 (d, 1H), 5 26 (s, 2H), 5 13 (s, 2H), 0 18 (s, 9H), HR-MS (ES) m/z calcd for $C_{24}H_{24}NO_2FSi$ ($MH^+$) = 406 1638, observed 406 1610

Step C

Preparation of 4-(benzyloxy)-3-ethynyl-1-(3-fluorobenzyl)pyridin-2(1H)-one

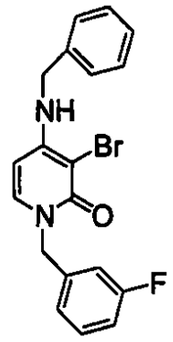



To a solution of 4-(benzyloxy)-1-(3-fluorobenzyl)-3-[(trimethylsilyl)ethynyl]pyridin-2(1H)-one (1 31 g, 3 2 mmol) in anhydrous acetonitrile (25 mL) at 0° C was added tetrabutylammonium fluoride (0 611g, 1 93 mmol) The reaction was stirred at 0° C for 15 min then for 1 h at room temperature The reaction was concentrated under reduced pressure and the residue was diluted with EtOAc and washed with water The organic extracts were combined, dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure The residue was purified by flash chromatography (silica gel) using EtOAc in hexanes (1 1 v/v) The appropriate fractions were combined and concentrated under reduced pressure to afford the desired product (0 779 g, 72%) as a gold solid

MS and $^1$H-NMR were consistent with the desired structure $^1$H-NMR ($CD_3OD$, 400Hz) δ 7 73 (d, 1H), 7 43 (d, 2H), 7 35 (m,4H), 7 09 (m,3H), 6 45 (d, 1H), 5 27 (s, 2H), 5 13 (s,2H), 3 78 (s, 1H), HR-MS (ES) m/z calcd for $C_{21}H_{16}NO_2F$ ($MH^+$)= 334 1243, observed 334 1234

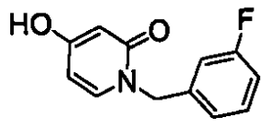
Example 58

4-(benzylamino)-3-bromo-1-(3-fluorobenzyl)pyridin-2(1H)-one




Step A

Preparation of 1-(3-fluorobenzyl)-4-hydroxypyridin-2(1H)-one

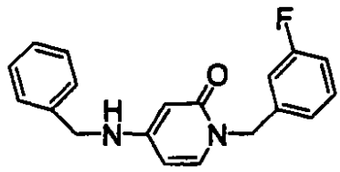



In a Fischer-Porter bottle, added a solution of 4-(benzyloxy)-1-(3-fluorobenzyl)pyridin-2(1H)-one (4 5 g, 14 56 mmol) in absolute ethanol (20 mL) Flushed the solution with nitrogen then added palladium catalyst (1 05 g) Sealed bottle and evacuated system The system was purged with hydrogen gas (2 X 15 psi) to check for leaks The reaction was charged with hydrogen (35 psi) and stirred at room temperature for 45 min The system was evacuated and flushed with nitrogen The reaction was filtered and the catalyst was carefully washed with fresh ethanol The filtrate was concentrated under reduced pressure

MS and $^1$H-NMR were consistent with the desired structure $^1$H-NMR ($CD_3OD$, 400Hz) δ 7 54 (d, 1H), 7 32 (m, 1H), 7 06 (m, 3H), 6 05 (dd, 1H), 5 83 (s, 1H), 5 09 (s, 2H), HR-MS (ES) m/z calcd for $C_{12}H_{10}NO_2F$ ($MH^+$) = 220 0774, observed 220 0787

Step B

Preparation of 4-(benzylamino)-1-(3-fluorobenzyl)pyridin-2(1H)-one

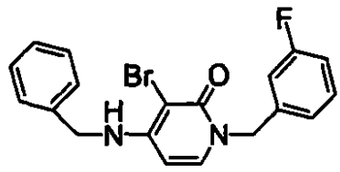



Heated a reaction mixture of 1-(3-fluorobenzyl)-4-hydroxypyridin-2(1H)-one (1 005 g, 4 5 mmol) in benzylamine (15 mL) at reflux (185° C) under nitrogen atmosphere for 24 h The reaction was monitored by ES-MS (MH+ 309) The solvent was removed by vacuum distillation to give a yellow residue

MS and $^1$H-NMR were consistent with the desired structure $^1$H-NMR ($CD_3OD$, 400Hz) δ 7 31 (m, 7H), 7 03 (m, 3H), 5 98 (dd, 1H), 5 45 (s, 1H), 5 00 (s, 2H), 4 30 (s, 2H), HR-MS (ES) m/z calcd for $C_{19}H_{17}N_2OF$ ($MH^+$) = 309 1403, observed 309 1375

Step C

Preparation of 4-(benzylamino)-3-bromo-1-(3-fluorobenzyl)pyridin-2(1H)-one



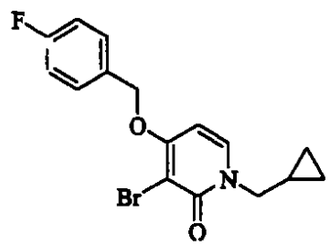

To a solution of 4-(benzylamino)-1-(3-fluorobenzyl)pyridin-2(1H)-one (0 50 g, 1 62 mmol) in anhydrous $CH_2Cl_2$ (10 mL) was added N-bromosuccinimide (NBS, 0 30 g, 1 7 mmol) The reaction was stirred at room

157
159

temperature under a nitrogen atmosphere for 3 h The reaction mixture was purified by flash chromatography (silica gel) using EtOAc in hexanes (1 1 v/v) The appropriate fractions were combined and concentrated

MS and $^1$H-NMR were consistent with the desired structure $^1$H-NMR ($CD_3OD$, 400Hz) δ 7 41 (d, 1H), 7 31 (m, 6H), 7 04 (m, 3H), 5 99 (d, 1H), 5 08 (s, 2H), 4 53 (s, 2H), HR-MS (ES) m/z calcd for $C_{19}H_{16}N_2OFBr$ ($MH^+$)= 387 0508, observed 387 0504

Example 59




3-Bromo-1-cyclopropylmethyl-4-(4-fluorobenzyloxy)-1*H*-pyridin-2-one

Step 1 Preparation of 4-[(4-Fluorobenzyloxy]pyridine-1-oxide

To an ice-cold solution of sodium hydride (1 9 g, of a 60% dispersion in mineral oil, 46 mmol) in DMF (39 mL) was added 4-fluorobenzyl alcohol (5 1 mL, 46 mmol) The reaction mixture was warmed to room temperature, 4-chloropyridine-1-oxide[1] (5 0 g, 39 mmol) was added, and the reaction mixture was stirred for 6 h The reaction mixture was diluted with a 50% aqueous solution of brine, and extracted with $CHCl_3$ (7 x 50 mL) The combined organics were dried ($MgSO_4$), filtered, and concentrated under reduced pressure Trituration with $Et_2O$ afforded 4-[(4-fluorobenzyloxy]pyridine-1-oxide as an off-white solid (9 1 g, 90%), which was used in the next step without further purification or characterization

Step 2 Preparation of 4-(4-Fluorobenzyloxy)-1*H*-pyridin-2-one

A solution of 4-[(4-fluorobenzyloxy]pyridine-1-oxide (6 4 g, 29 mmol) in acetic anhydride (97 mL) was heated at reflux for 3 h The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure The residue was diluted with 1 1 MeOH/water (34 mL), and the mixture was stirred at room temperature for 1 h The solvent was removed under reduced pressure Trituration with $Et_2O$/hexanes afforded 4-(4-fluorobenzyloxy)-1*H*-pyridin-2-one as a brown solid (3 1 g, 48%) $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7 40-7 36 (m, 2H), 7 22 (d, $J$ = 8 Hz, 1H), 7 09 (t, $J$ = 7 Hz, 2H), 6 03 (dd, $J$ = 7, 3 Hz, 1H), 5 94 (d, $J$ = 3 Hz, 1H), 4 98 (s, 2H)

Step 3 Preparation of 3-Bromo-4-(4-fluorobenzyloxy)-1*H*-pyridin-2-one

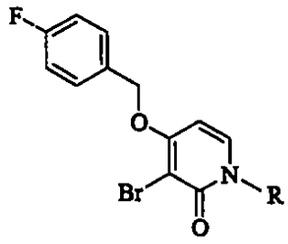
To an ice-cold solution of 4-(4-fluorobenzyloxy)pyridine-2(1H)-one (3 1 g, 14 mmol) in AcOH (26 mL) was added a solution of bromine (0 79 mL, 15 mmol) in AcOH (51 mL), and the reaction mixture was stirred at room temperature for 2 h The solvent was removed under reduced pressure, and purification by flash column chromatography (silica, 1 1 $Et_2O$/hexanes) to afford 3-bromo-4-(4-fluorobenzyloxy)-1*H*-pyridin-2-one as an orange solid (0 78 g, 48%) MS APCI *m/z* 298 $[M + H]^+$

Step 4 Preparation of 3-Bromo-1-cyclopropylmethyl-4-(4-fluorobenzyloxy)-1*H*-pyridin-2-one

To a solution of 3-bromo-4-(4-fluorobenzyloxy)-1*H*-pyridin-2-one (0 25 g, 0 84 mmol) in DMF (13 mL) was added $K_2CO_3$ (0 33 g, 1 7 mmol) and cyclopropylmethyl bromide (0 14 g, 1 0 mmol), and the reaction mixture was stirred at 110 °C for 2 h The reaction mixture was cooled to room temperature, and the

solvent was removed under reduced pressure The residue was diluted with a 50% aqueous solution of brine, and extracted with $CHCl_3$ (3 x 50 mL) The combined organics were washed with water and then brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure Purification by flash column chromatography (silica, 1 1 EtOAc/hexanes) afforded 3-bromo-1-cyclopropyl-methyl-4-(4-fluorobenzyloxy)-1*H*-pyridin-2-one as a yellow solid (0 12 g, 39%) mp 139-141 °C, $^1H$ NMR (300 MHz, $CDCl_3$) δ 7 43-7 34 (m, 3H), 7 07 (t, *J* = 9 Hz, 2H), 6 06 (d, *J* = 6 Hz, 1H), 5 19 (s, 2H), 3 82 (d, *J* = 9 Hz, 2H), 1 26-1 23 (m, 1H), 0 62-0 57 (m, 2H), 0 40-0 36 (m, 2H) ESHRMS m/z 352 0368 (M+H $C_{16}H_{16}BrFNO_2$ requires 352 0343)

Examples 60-69




The compounds of Examples 60-69 are prepared essentially according to the procedures set forth above for Example 59

| Example No | R | MF | M+H Requires | ESHRMS m/z |
|---|---|---|---|---|
| Ex 60 | pyridin-4-ylmethyl | | | |
| Ex 61 | pyridin-3-ylmethyl | $C_{18}H_{14}BrFN_2O_2$ | 489 0296 | 489 0281 |
| Ex 62 | 4-tert-butylbenzyl | $C_{23}H_{23}BrFNO_2$ | 444 0969 | 444 0971 |
| Ex 63 | 3-trifluoromethylbenzyl | $C_{20}H_{14}BrF_4NO_2$ | 456 0217 | 456 0202 |

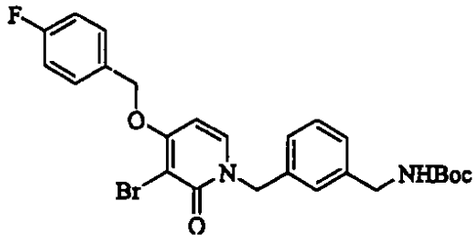
| | | | | |
|---|---|---|---|---|
| Ex 64 | Biphenyl-2-ylmethyl | $C_{25}H_{19}BrFNO_2$ | 464 0656 | 464 0656 |
| Ex 65 | 4-methoxybenzyl | $C_{20}H_{17}BrFNO_3$ | 418 0449 | 418 0457 |
| Ex 66 | 4-cyanobenzyl | $C_{20}H_{14}BrFN_2O_2$ | 413 0295 | 413 0287 |
| Ex 67 | 4-trifluoromethylbenzyl | $C_{20}H_{14}BrF_4NO_2$ | 456 0217 | 456 0192 |
| Ex 68 | Biphenyl-4-ylmethyl | $C_{25}H_{19}BrFNO_2$ | 464 0656 | 464 0653 |
| Ex 69 | cyclohexylmethyl | $C_{19}H_{21}BrFNO_2$ | 394 0812 | 394 0797 |

NMR characterization of compounds of Examples 12-19

| Ex No | NMR Data |
|---|---|
| Ex 60 | $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8 57 (dd, $J$ = 6, 3 Hz, 2H), 7 43-7 38 (m 2H), 7 16 (d $J$ = 6 Hz 2H), 7 09 (t, $J$ = 9 Hz, 2H), 6 12 (d, $J$ = 6 Hz, 1H) 5 20 (s, 2H), 5 16 (s, 2H) |
| Ex 61 | $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8 58-8 55 (m, 2H), 7 75 (d, $J$ = 6 Hz, 1H), 7 41-7 37 (m, 2H), 7 31-7 26 (m, 2H), 7 12-7 04 (m, 2H), 5 17 (d, $J$ = 6 Hz, 1H) 5 18 (s, 2H), 5 16 (s 2H) |
| Ex 62 | $^1$H NMR (300 MHz, MeOD) $\delta$ 7 75 (d, 1H, $J$ = 9 Hz), 7 59 (t, $J$ = 9 Hz 2H), 7 37 (d, $J$ = 9 Hz, 2H), 7 22 (d, $J$ = 9 Hz, 2H), 7 06-6 99 (m, 2H), 6 52 (d, $J$ = 9 Hz, 1H) 5 29 (s, 2H) 5 18 (s, 2H), 1 28 (s, 9H) |
| Ex 63 | $^1$H NMR (300 MHz $CDCl_3$) $\delta$ 7 58-7 37 (m, 5H), 7 29-7 26 (m, 2H) 7 08 (t $J$ = 7 Hz, 2H), 6 10 (d, $J$ = 7 Hz, 1H), 5 20 (s, 2H), 5 18 (s, 2H) |
| Ex 64 | $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7 42-7 27 (m, 11H), 7 07 (t, $J$ = 6 Hz, 2H), 6 72 (d, $J$ = 7 Hz 1H) 5 88 (d, $J$ = 9 Hz, 1H), 5 16 (s, 2H), 5 12 (s, 2H) |
| Ex 65 | $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7 38-7 36 (m, 2H) 7 27-6 84 (m, 3H), 7 08 (s, 2H), 6 86 (d, $J$ = 7 Hz, 2H), 6 01 (d, $J$ = 6 Hz, 1H), 5 15 (s, 2H), 5 09 (s, 2H), 3 78 (s, 3H) |
| Ex 66 | $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7 64-7 61 (m, 2H), 7 42-7 37 (m 4H), 7 27-7 25 (m, 1H), 7 12-7 06 (m, 2H), 6 11 (d, $J$ = 6 Hz, 1H) 5 19 (s, 4H) |
| Ex 67 | $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7 59 (d, $J$ = 6 Hz, 2H), 7 43-7 37 (m, 4H) 7 29-7 25 (m, 1H), 7 08 (t, $J$ = 6 Hz 2H), 6 08 (d, $J$ = 9 Hz, 1H), 5 20 (s 2H), 5 18 (s, 2H) |
| Ex 68 | $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7 57-7 54 (m, 4H), 7 45-7 34 (m, 7H), 7 30-7 26 (m, 1H), 7 08 (t, $J$ = 9 Hz, 2H), 6 06 (d, $J$ = 6 Hz, 1H), 5 20 (s, 2H), 5 17 (s, 2H) |
| Ex 69 | $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7 93 (d, $J$ = 6 Hz, 1H), 7 45-7 40 (m, 2H), 7 29-7 26 (m, 1H), 7 09 (t $J$ = 9 Hz, 2H), 6 50 (d, $J$ = 6 Hz, 1H) 5 17 (s, 2H), 4 14 (d $J$ = 6 Hz, 2H) 1 90-1 74 (m 5H), 1 32-1 05 (m, 5H) |

Example 70

159
161




{3-[3-Bromo-4-(4-fluorobenzyloxy)-2-oxo-2*H*-pyridin-1-ylmethyl]benzyl}carbamic acid *tert*-butyl ester

Step 1 Preparation of 3-Hydroxymethylbenzonitrile
To an ice-cold solution of 3-cyanobenzaldehyde (5 0 g, 38 mmol) in 1 1 MeOH/THF (90 mL) was added $NaBH_4$ (1 6 g, 42 mmol), and the reaction mixture was stirred for 3 h The reaction mixture was diluted with brine, and the solvent was removed under reduced pressure The residue was dissolved in water, and the aqueous layer was extracted with $Et_2O$ (3 x 100 mL) The combined organics were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide 3-hydroxymethyl-benzonitrile (4 95 g, 98%) as a clear oil, which was used in the next step without further purification or characterization

Step 2 Preparation of 3-(*tert*-Butyldimethylsilyloxymethyl)benzonitrile
To an ice-cold solution of 3-hydroxymethyl benzonitrile (4 95 g, 37 mmol) in $CH_2Cl_2$ (47 mL) was added imidazole (5 1 g, 74 mmol), DMAP (0 45 g, 3 7 mmol), and TBSCl (6 2 g, 41 mmol), and the reaction mixture was stirred for 12 h The reaction mixture was diluted with water, and the aqueous layer was extracted with $CH_2Cl_2$ (3 x 150 mL) The combined organics were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide 3-(*tert*-butyldimethylsilyloxymethyl)-benzonitrile (9 1 g, 99%) as a

clear oil $^1$H NMR (300 MHz, $CDCl_3$) δ 7 51 (s, 1H), 7 42 (d, *J* = 6 Hz, 1H), 7 35-7 28 (m, 1H), 4 75 (s, 2H), 0 94 (s, 9H), 0 11 (s, 6H)

Step 3 Preparation of 3-(*tert*-Butyldimethylsilyloxymethyl)benzylamine
To an ice-cold solution of 3-(*tert*-butyldimethylsilyloxymethyl)benzonitrile (4 5 g, 18 mmol) in THF (47 mL) was added $LiAlH_4$ (27 mL, of a 1 M solution in THF, 27 mmol), and the reaction mixture was stirred at reflux for 3 h The reaction mixture was cooled to 0 °C, and the reaction was quenched with water (25 mL) and 15%NaOH in water (75 mL) The reaction mixture was filtered, concentrated under reduced pressure, and the residue was dissolved in EtOAc The organic solution was washed with water and then brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide 3-(*tert*-Butyldimethylsilyloxymethyl)benzylamine (1 4 g, 30%) as a clear oil $^1$H NMR (300 MHz, $CDCl_3$) δ 7 22-7 10 (m, 4H), 4 57 (s, 2H), 3 74 (s, 2H), 0 84 (s, 9H), 0 09 (s, 6H)

Step 4 Preparation of 3-(Hydroxymethyl)benzylcarbamic acid *tert*-butyl ester
To a solution of 3-(*tert*-butyldimethylsilyloxymethyl)benzylamine (1 4 g, 5 5 mmol) and $Et_3N$ (1 5 mL, 11 mmol) in $CH_2Cl_2$ (28 mL) was added di-*tert*-butyl dicarbonate (1 3 g, 5 8 mmol), and the reaction mixture was stirred for 12 h The reaction mixture was diluted with water and extracted with $CH_2Cl_2$ (3 x 100 mL) The combined organics were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure Purification by flash column chromatography (silica, $CH_2Cl_2$) to afford 3-(hydroxymethyl)benzylcarbamic acid *tert*-butyl ester as a yellow oil (1 4 g, 46%) $^1$H NMR (300 MHz, $CDCl_3$) δ 7 32-7 28

160
162

(m, 1H), 7 18 (d, $J$ = 8 Hz, 1H), 7 12 (s, 1H), 7 08-7 01 (m, 1H), 4 60 (s, 2H), 4 04 (d, $J$ = 6 Hz, 2H), 1 36 (s, 9H)

Step 5 Preparation of 3-(Bromomethyl)benzylcarbamic acid tert-butyl ester

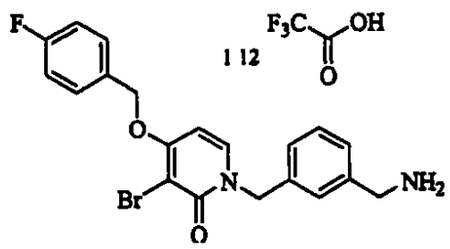
To an ice-cold solution of 3-(hydroxymethylbenzyl)carbamic acid tert-butyl ester (0 7 g, 3 0 mmol) and $CBr_4$ (1 0 g, 3 1 mmol) in THF (14 mL) was added $Ph_3P$ (0 81 g, 3 1 mmol), and the reaction mixture was stirred for 18 h The reaction mixture was filtered, and concentrated under reduced pressure Purification by flash column chromatography (silica, eluent 5 95 to15 85 EtOAc/hexanes) to afford the 3-(bromomethyl)benzyl-carbamic acid tert-butyl ester as a white solid (0 42 g, 51%) $^1$H NMR (300 MHz, MeOD) $\delta$ 7 55 (s, 1H), 7 32-7 27 (m, 2H), 7 21-7 19 (m, 1H), 4 54 (s, 2H), 4 21 (s, 2H), 1 28 (s, 9H)

Step 6 Preparation of 1{3-[3-Bromo-4-(4-fluorobenzyloxy)-2-oxo-2*H*-pyridin-1-ylmethyl]benzyl}carbamic acid tert-butyl ester

To a solution of 3-bromo-4- (4-fluorobenzyloxy)pyridine-2(1*H*)-one (from Step 3, synthesis EXAMPLE 59 ) (0 2 g, 0 67 mmol) in DMF (11 mL) was added $K_2CO_3$ (0 26 g, 1 3 mmol) and 3-(bromomethyl)benzylcarbamic acid tert-butyl ester (0 23 g, 0 80 mmol), and the reaction mixture was stirred at 80 °C for 3 hours The reaction mixture was cooled to room temperature, and concentrated under reduced pressure The residue was diluted with a 50% aqueous solution of brine (24 mL), and extracted with $CHCl_3$ (4 x 50 mL) The combined organics was washed water and then brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure Purification by flash column chromatography (silica, 3 7 EtOAc/hexanes) and recrystallization from MeOH afforded {3-[3-bromo-4-(4-

fluorobenzyloxy)-2-oxo-2*H*-pyridin-1-ylmethyl]benzyl}carbamic acid tert-butyl ester as an off-white solid (0 07 g, 20%) mp 136-138 °C, $^1$H NMR (300 MHz, $CDCl_3$) δ 7 42-7 37 (m, 2H), 7 30-7 20 (m, 5H), 7 08 (t, *J* = 9 Hz, 2H), 6 04 (d, *J* = 9 Hz, 1H), 5 16 (s, 2H), 5 14 (s, 2H), 4 28 (d, *J* = 6 Hz, 1H), 1 44 (s, 9H) ESHRMS m/z 517 1124 (M+H $C_{25}H_{27}BrFN_2O_4$ requires 517 1133)

Example 71

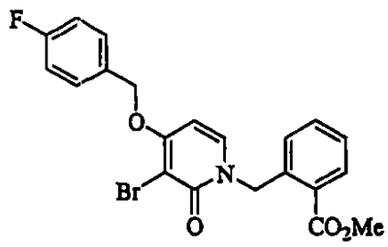



1-(3-Aminomethylbenzyl)-3-bromo-4-(4-fluorobenzyloxy)-1*H*-pyridin-2-one

To an ice-cold solution of 1-[3-{N-*tert*-Butoxycarbonyl}aminomethylbenzyl]-3-bromo-4-(4-fluorobenzyloxy)pyridine-2(1*H*)-one (Example 69) (0 05 g, 0 1 mmol) in $CH_2Cl_2$ (2 mL) was added TFA (2 mL), and the reaction mixture was stirred for 1 h The solvent was removed under reduced pressure to provide 1-(3-aminomethylbenzyl)-3-bromo-4-(4-fluorobenzyloxy)-1*H*-pyridin-2-one as a tan solid (0 049 g, 100%), as the TFA salt mp 127-139 °C, $^1$H NMR (300 MHz, DMSO-$d_6$) δ 8 13 (br s, 2H), 7 94 (d, *J* = 6 Hz, 1H), 7 52-7 47 (m, 2H), 7 44-7 37 (m, 2H), 7 27 (t, *J* = 8 Hz, 3H), 6 53 (d, *J* = 8 Hz, 1H), 5 30 (s, 2H), 5 14 (s, 2H), 4 01 (d, *J* = 6 Hz, 2H), 3 39 (br s, 2H), Anal Calcd for $C_{20}H_{17}BrF_2N_2O_2 \cdot 1\ 125$ TFA C, 48 99, H, 3 53, N, 5 13 Found C, 48 80, H, 3 43, N, 4 75 ESHRMS m/z 417 0608 (M+H $C_{20}H_{19}BrFN_2O_2$ requires 417 0609)

141
163

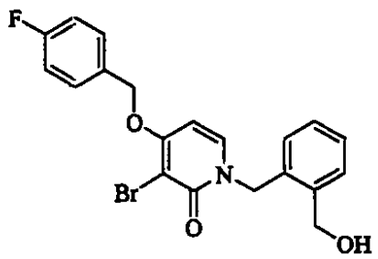
Example 72



Methyl 2-[3-Bromo-4-(4-fluorobenzyloxy)-2-oxo-2*H*-pyridin-1-ylmethyl]benzoate

The title compound was prepared by a procedure similar to the one described for EXAMPLE 59 (0 36 g, 48%) mp 161-165 °C, $^1$H NMR (300 MHz, $CDCl_3$) δ 7 98 (d, *J* = 6 Hz, 1H), 7 51-7 26 (m, 6H), 7 11-7 05 (m, 2H), 6 05 (d, *J* = 8 Hz, 1H), 5 60 (s, 2H), 5 18 (s, 2H), 3 93 (s, 3H) ESHRMS m/z 446 0430 (M+H $C_{21}H_{18}BrFNO_4$ requires 418 0398)

Example 73

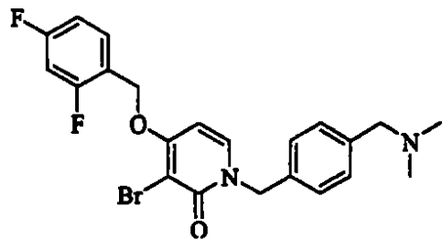


3-Bromo-4-(4-fluorobenzyloxy)-1-(2-hydroxymethylbenzyl)-1*H*-pyridin-2-one

To an ice-cold solution of 3-bromo-4-(4-fluorobenzyloxy)-1-(2-hydroxymethylbenzyl)-1*H*-pyridin-2-one (Example 72) (0 25 g, 0 56 mmol) in THF (1 mL) was added $LiBH_4$ (2 0 M solution in THF, 0 56 mmol), and the reaction mixture was stirred at 40 °C

for 6 hours The reaction mixture was cooled to room temperature, the solvent was removed under reduced pressure, and the residue was dissolved in EtOAc The organic solution was washed with brine, dried ($MgSO_4$), filtered, and concemtrated under reduced pressure $^1H$ NMR (300 MHz, DMSO-$d_6$) δ 7 82 (d, $J$ = 8 Hz, 1H), 7 54-7 49 (m, 2H), 7 41 (d, $J$ = 7 Hz, 1H), 7 29-7 21 (m, 4H), 6 81 (d, $J$ = 7 Hz, 1H), 6 53 (d, $J$ = 8 Hz, 1H), 5 30-5 25 (m, 3H), 5 18 (s, 2H), 4 60 (d, $J$ = 7 Hz, 2H) ESHRMS m/z 418 0437 (M+H $C_{20}H_{18}BrFNO_3$ requires 418 0449)

Example 74



3-Bromo-4-(2,4-difluorobenzyloxy)-1-[(4-dimethylaminomethyl)benzyl]-1*H*-pyridin-2-one

Step 1 Preparation of 4-(2,4-Difluorobenzyloxy)pyridine-1-oxide

To an ice-cold solution of sodium hydride (1 2 g of a 60% dispersion in mineral oil, 51 mmol) in DMF (43 mL) was added 2,4-difluorobenzyl alcohol (5 7 mL, 51 mmol) The reaction mixture was warmed to room temperature, 4-chloropyridine-1-oxide[1] (5 5 g, 43 mmol) was added, and the reaction mixture was stirred for 6 h The reaction mixture was diluted with a 50% aqueous solution of brine, and extracted with $CHCl_3$ (7 x 50 mL) The combined organics were dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure Trituration with $Et_2O$ afforded 4-(2,4-difluorobenzyloxy)pyridine-1-oxide as an off-white solid (9 1 g, 90%) $^1H$ NMR (300 MHz, $CDCl_3$) δ

8 16-8 08 (m, 1H), 7 47-7 36 (m, 1H), 6 97-6 81 (m, 1H), 5 09 (d, *J* = 8 Hz, 1H)

Step 2 Preparation of 4 (2,4-Difluorobenzyloxy)-1*H*-pyridin-2-one

A solution of 4-(2,4-difluorobenzyloxy)pyridine-1-oxide (13 4 g, 57 mmol) in acetic anhydride (30 mL) was stirred at reflux for 4 h The solvent was removed under reduced pressure, the residue was diluted with 1 1 MeOH/water (60 mL), and the mixture was stirred at room temperature for 1 h The solvent was removed under reduced pressure Purification by flash column chromatography (silica, eluent methylene chloride to 9 1 methylene chloride/methanol) provided 4-(2,4-difluorobenzyloxy)-1*H*-pyridin-2-one as a light brown solid (4 2 g, 31%) $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7 43 (q, *J* = 8 Hz, 1H), 7 23 (d, *J* = 7 Hz, 1H), 6 91-6 87 (m, 2H), 6 02 (dd, *J* = 8, 2 Hz, 1H), 5 97 (d, *J* = 2 Hz, 1H), 5 03 (s, 2H)

Step 3 Preparation of 3-Bromo-4-(2,4-difluorobenzyloxy)-1*H*-pyridin-2-one

To an ice-cold solution of 4-(2,4-difluorobenzyloxy)-1*H*-pyridin-2-one (0 75 g, 3 1 mmol) in AcOH (12 mL) was added a solution of bromine (0 2 mL, 3 5 mmol) in AcOH (6 mL), and the reaction mixture was stirred 10 min The solvent was removed under reduced pressure to afford 3-bromo-4-(2,4-difluorobenzyloxy)-1*H*-pyridin-2-one as a white solid (1 0 g, 100%) ESI MS *m/z* 299 $[M + H]^+$

Step 4 Preparation of 3-Bromo-1-(4-chloromethylbenzyl)-4-(2,4-difluorobenzyloxy)-1*H*-pyridin-2-one

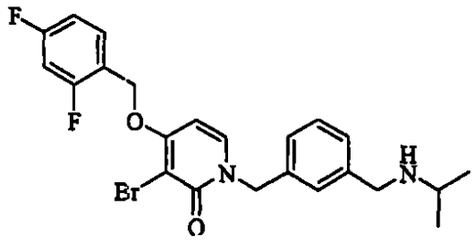
To a solution of 3-bromo-4 (2,4-difluorobenzyloxy)-1*H*-pyridin-2-one (0 60 g, 2 5 mmol) in DMF (40 mL) was added $K_2CO_3$ (0 70 g, 5 1 mmol) and α,α′-dichloro-*p*-xylene (0 53 g, 3 0 mmol), and

the reaction mixture was stirred at 110 °C for 2 h The reaction mixture was cooled to room temperature, diluted with brine, and extracted with $CHCl_3$ (4 x 100 mL) The combined organics were washed water and then brine, dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure to afford 3-bromo-1-(4-chloromethylbenzyl)-4-(2,4-difluorobenzyloxy)-1*H*-pyridin-2-one as an off-white solid (0 49 g, 43%) $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7 54 (app q, $J$ = 8 Hz, 1H), 7 38-7 28 (m, 5H), 6 94 (td, $J$ = 8, 2 Hz, 1H), 6 85 (td, $J$ = 8, 2 Hz, 1H), 6 10 (d, $J$ = 9 Hz, 1H), 5 21 (s, 2H), 5 16 (s, 2H), 4 56 (s, 2H)

Step 5 Preparation of 3-Bromo-4-(2,4-difluorobenzyloxy)-1-[(4-dimethylaminomethyl) benzyl]-1*H*-pyridin-2-one

To a sealed tube containing 3-bromo-1-(4-chloromethylbenzyl)-4-(2,4-difluoro-benzyloxy)-1*H*-pyridin-2-one (0 49 g, 1 1 mmol) was added a solution of dimethylamine (5 5 mL of a 2 0 M solution in THF, 11 mmol), and the reaction mixture was stirred for 15 h The solvent was removed under reduced pressure Purification by flash column chromatography (silica, eluent methylene chloride to 92 7 2 0 8 methylene chloride/methanol/ammonia) provided 3-bromo-4-(2,4-difluorobenzyloxy)-1-(4-dimethylaminomethylbenzyl)-1*H*-pyridin-2-one as a light yellow solid (0 23 g, 46%) mp 111-113 °C, $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7 50-7 49 (m, 1H), 7 26-7 22 (m, 5H), 6 90-6 88 (m, 1H), 6 82-6 78 (m, 1H), 6 04 (d, $J$ = 6 Hz, 1H), 5 16 (s, 2H), 5 11 (s, 2H), 3 37 (s, 2H), 2 19 (s, 6H) ESHRMS m/z 463 0782 (M+H $C_{22}H_{22}BrF_2N_2O_2$ requires 463 0827)

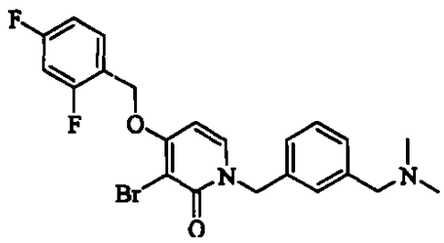
Example 75



3-Bromo-4-(2,4-difluorobenzyloxy)-1-[3-(isopropylaminomethyl)benzyl]-1*H*-pyridin-2-one

The title compound was prepared by a procedure similar to the one described for Example 74 (0 06 g, 35%) mp 109-110 °C, $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7 54 (d, $J$ = 6 Hz, 1H), 7 33-7 20 (m, 5H), 6 94-6 81 (m, 2H), 6 10 (d, $J$ = 6 Hz, 1H), 5 20 (s, 2H), 5 14 (s, 2H), 3 77 (s, 2H), 2 88 (t, $J$ = 6 Hz, 1H), 1 13 (d, $J$ = 6 Hz, 6H) ESHRMS m/z 477 0955 (M+H $C_{23}H_{24}BrF_2N_2O_2$ requires 477 0984)

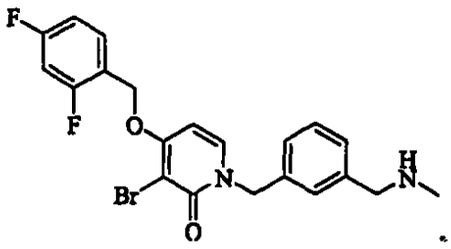
Example 76



3-Bromo-4-(2,4-difluorobenzyloxy)-1-[(3-dimethylaminomethyl)benzyl]-1*H*-pyridin-2-one

The title compound was prepared by a procedure similar to the one described for Example 74 (0 06 g 25%) mp 103-107 °C, $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7 52 (d, $J$ = 8 Hz, 1H), 7 32-7 24 (m, 5H), 6 94 (td, $J$ = 9, 3 Hz, 1H), 6 84 (td, $J$ = 9, 3 Hz, 1H), 6 08 (d, $J$ = 8 Hz, 1H), 5 20 (s, 2H), 5 16 (s, 2H), 3 44 (s, 2H), 2 24 (s, 6H) ESHRMS m/z 463 0801 (M+H $C_{22}H_{22}BrF_2N_2O_2$ requires 463 0827)

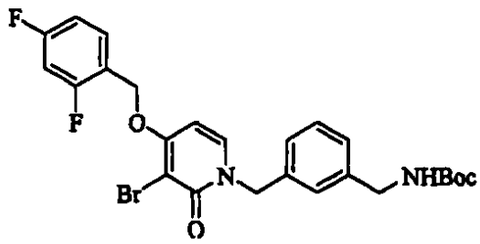
Example 77



3-Bromo-4-(2,4-difluorobenzyloxy)-1-[(3-methylaminomethyl)benzyl]-1*H*-pyridin-2-one

The title compound was prepared by a procedure similar to the one described for Example 74 (0 05 g, 16%) mp 107-111 °C, $^1$H NMR (300 MHz, $CDCl_3$) δ 7 55 (d, *J* = 6 Hz, 1H), 7 31-7 19 (m, 5H), 6 94-6 81 (m, 2H), 6 09 (d, *J* = 6 Hz, 1H), 5 20 (s, 2H), 5 14 (s, 2H), 3 73 (s, 2H), 2 45 (s, 1H) ESHRMS m/z 449 0652 (M+H $C_{21}H_{20}BrF_2N_2O_2$ requires 449 0671)

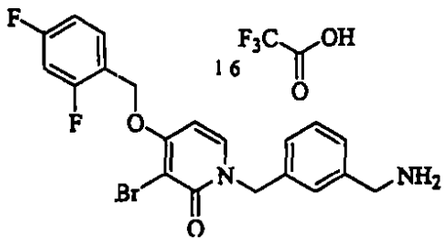
Example 78



{3-[3-Bromo-4-(2,4-difluorobenzyloxy)-2-oxo-2*H*-pyridin-1-ylmethyl]benzyl}carbamic acid tert-butyl ester

The title compound was prepared essentially according to the procedure described in Example 70 mp 80-84 °C, $^1$H NMR (300 MHz, DMSO-$d_6$) δ 7 60-7 50 (m, 1H), 7 33-7 21 (m, 5H), 6 97-6 81 (m, 2H), 6 10 (dd, *J* = 8, 2 Hz, 1H), 5 20 (s, 2H), 5 15 (s, 2H), 4 87 (br s, 2H), 4 30 (s, 2H) 1 45 (s, 9H) ESHRMS m/z 535 1019 (M+H $C_{25}H_{26}BrF_2N_2O_4$ requires 535 1039)

Example 79



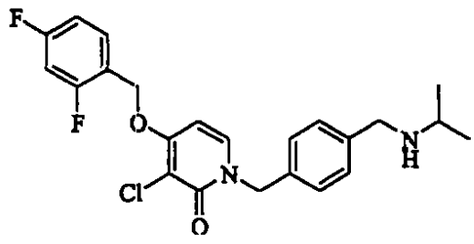
16

1-[(3-Aminomethyl)benzyl]-3-bromo-4-(2,4-difluorobenzyloxy)-1*H*-pyridin-2-one

Step 1 Preparation of 1-[(3-Aminomethyl)benzyl]-3-bromo-4-(2,4-difluorobenzyloxy)-1*H*-pyridin-2-one

To an ice-cold solution of {3-[3-Bromo-4-(2,4-difluorobenzyloxy)-2-oxo-2H-pyridin-1-ylmethyl]benzyl}carbamic acid tert-butyl ester (Example 78) (0 05 g, 0 1 mmol) in $CH_2Cl_2$ (2 mL) was added TFA (2 mL), and the reaction mixture was stirred for 1 hour The solvent was removed under reduced pressure to provide 1-[(3 aminomethyl)benzyl]-3-bromo-4-(2,4-difluorobenzyloxy)-1*H*-pyridin-2-one as a tan solid (0 049 g, 100%), as the TFA salt mp 80-84 °C, $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8 15 (br s, 3H), 7 97 (d, $J$ = 8 Hz, 1H), 7 79-7 60 (m, 1H), 7 44-7 30 (m, 4H), 7 20-7 15 (m, 1H), 6 61 (d, $J$ = 6 Hz, 1H), 5 31 (s, 2H), 5 16 (s, 2H), 4 03 (s, 2H), $^{19}$F NMR (282 MHz, DMSO-$d_6$) $\delta$ -74 56 (4 8F), -109 63 (1F), -113 61 (1F) ESHRMS m/z 435 0540 (M+H $C_{20}H_{18}BrF_2N_2O_2$ requires 435 0515)

Example 80



3-Chloro-4-(2,4-difluorobenzyloxy)-1-[4-(isopropylaminomethyl)benzyl]-1*H*-pyridin-2-one

Step 1 Preparation of 3-Chloro-4-(2,4-difluorobenzyloxy)-1*H*-pyridin-2-one

To a solution of 4-[(4-fluorobenzyl)oxy]pyridine-2(1*H*)-one (from Step 2, Example 74) (1 4 g, 5 9 mmol) in AcOH (25 mL) was added N-chlorosuccinimide (0 95 g, 7 1 mmol) and the reaction mixture was heated at reflux for 2 h The solvent was removed under reduced pressure $^1$H NMR (300 MHz, MeOD) $\delta$ 7 63-7 55 (m, 1H), 7 45(d, $J$ = 8 Hz, 1H), 7 07-7 00 (m, 2H), 6 58 (d, $J$ = 8 Hz, 1H), 5 31 (d, $J$ = 8 Hz, 1H)

Step 2 Preparation of 3-Chloro-1-(4-chloromethylbenzyl)-4-(2,4-difluorobenzyloxy)-1*H*-pyridin-2-one

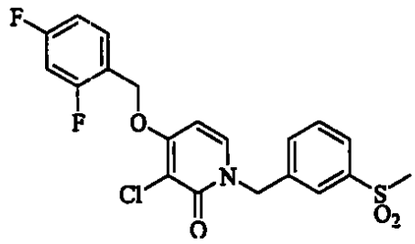
3-Chloro-1-(4-chloromethylbenzyl)-4-(2,4-difluorobenzyloxy)-1*H*-pyridin-2-one was prepared by procedure similar to the one described for 3-bromo-1-(4-chloromethyl-benzyl)-4-(2,4-difluorobenzyloxy)-1*H*-pyridin-2-one (Step 3, ) as white solid (0 24 g, 34%) $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7 53 (app q, $J$ = 9 Hz, 1H), 7 34 (app q, $J$ = 9 Hz, 1H), 7 23 (d, $J$ = 8 Hz, 1H), 6 94 (td, $J$ = 10, 2 Hz, 1H), 6 85 (td, $J$ = 10, 2 Hz, 1H), 6 14 (d, $J$ = 8 Hz, 1H), 5 20 (s, 2H), 5 16 (s, 2H), 4 56 (s, 2H)

Step 3 Preparation of 3-Chloro-4-(2,4-difluorobenzyloxy)-1-[4-(isopropylamino-methyl)benzyl]-1*H*-pyridin-2-one

The title compound was prepared by a procedure similar to the one described for Example 74 (0 17 g, 69 %) mp 146-151 °C, $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7 52 (app q, $J$ = 9 Hz, 1H), 7 35-7 21 (m, 5H), 6 94 (td, $J$ = 8, 2 Hz, 1H), 6 85 (td, $J$ = 8, 2 Hz, 1H), 6 18 (d, $J$ = 8 Hz, 1H), 5 22 (s, 2H), 5 08 (s, 2H),

3 81 (s, 2H), 2 98 (br s 1H), 1 20 (s, 6H) ESHRMS m/z 433 1481 (M+H $C_{23}H_{24}ClF_2N_2O_2$ requires 433 1489)

Example 81



3-Chloro-4-(2,4-difluorobenzyloxy)-1-[(3-methanesulfonyl)benzyl]-1*H*-pyridin-2-one

Step 1 Preparation of (3-Methanesulfonyl)phenyl methanol

To an ice-cold solution of 3-(methylsulfonyl)benzoic acid (1 4 g, 7 1 mmol) in 2 1 $Et_2O$/THF (60 mL) was added $LiAlH_4$ (8 5 mL of 1 0 M solution in THF, 8 5 mmol), and the reaction mixture was heated at reflux for 1 h The reaction mixture was cooled to 0 °C, and the reaction was quenched with water (15 mL) and 15%NaOH in water (35 mL) The reaction mixture was filtered, concentrated under reduced pressure, and the residue was dissolved in EtOAc The organic solution was washed with water and then brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure Purification by flash column chromatography (silica, eluent 1 2 to 3 1 EtOAc/hexanes) provided (3-methanesulfonyl)phenyl methanol as a clear oil (0 56 g, 42%) $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7 93 (s, 1H), 7 83 (d, $J$ = 7 Hz, 1H), 7 64 (d, $J$ = 7 Hz, 1H), 7 53 (t, $J$ = 7 Hz, 1H), 4 78 (d, $J$ = 6 Hz, 2H), 3 05 (s, 3H), 2 61 (br s, 1H)

Step 2 Preparation of 1-Chloromethyl-3-methanesulfonylbenzene

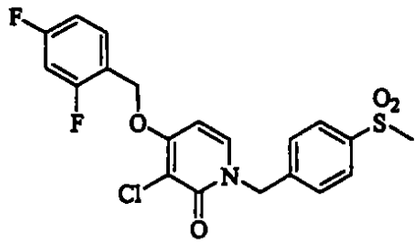
A solution of (3-methanesulfonyl)phenyl methanol (0 21 g, 1 1 mmol) in thionyl chloride (3 mL) was heated at 80 °C for 3 h The reaction mixture was cooled to room temperature, and the

solvent was removed under reduced pressure to provide 1-chloromethyl-3-methanesulfonylbenzene as a yellow oil (0 23 g, 95%) $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7 98 (s, 1H), 7 90 (d, $J$ = 8 Hz, 1H), 7 70 (d, $J$ = 8 Hz, 1H), 7 59 (t, $J$ = 8 Hz, 1H), 4 65 (s, 2H), 3 08 (s, 3H)

Step 3 Preparation of 3-Chloro-4-(2,4-difluorobenzyloxy)-1-[(3-methanesulfonyl)-benzyl]-1*H*-pyridin-2-one

The title compound was prepared by a procedure similar to the one described for Example 80 (0 14 g, 78%) mp 155-157 °C, $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7 88 (d, $J$ = 8 Hz, 1H), 7 83 (m, 1H), 7 67 (d, $J$ = 8 Hz, 1H), 7 58-7 48 (m, 2H), 7 31 (d, $J$ = 8 Hz, 1H), 6 95-6 83 (m, 2H), 6 22 (d, $J$ = 8 Hz, 1H), 5 22 (s, 4H), 3 08 (s, 3H) ESHRMS m/z 440 0525 (M+H $C_{20}H_{17}ClF_2NO_4S$ requires 440 0529)

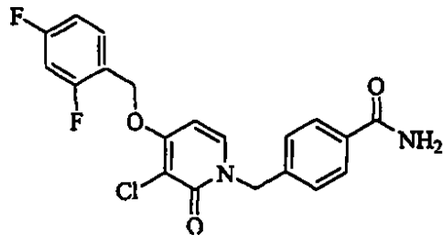
Example 82



3-Chloro-4-(2,4-difluorobenzyloxy)-1-[(4-methanesulfonyl)benzyl]-1*H*-pyridin-2-one

The title compound was prepared by a procedure similar to the one described for Example 81 (0 08 g, 73%) mp 223-225 °C, $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7 91 (d, $J$ = 8 Hz, 2H), 7 53-7 47 (m, 3H), 7 30-7 26 (m, 1H), 6 94-6 86 (m, 2H), 6 22 (d, $J$ = 8 Hz, 1H), 5 23 (s, 4H), 3 03 (s, 3H) ESHRMS m/z 440 0512 (M+H $C_{20}H_{17}ClF_2NO_4S$ requires 440 0529)

Example 83

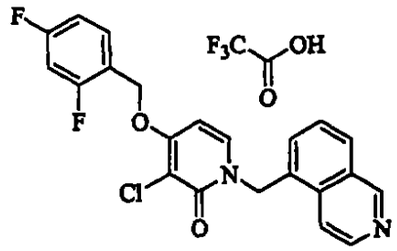


4-[3-Chloro-4-(2,4-difluorobenzyloxy)-2-oxo-2*H*-pyridin-1-ylmethyl]benzamide

Step 1 Preparation of Methyl 4-[3-chloro-4-(2,4-difluorobenzyloxy)-2-oxo-2*H*-pyridin-1-ylmethyl]benzoate
Methyl 4-[3-Chloro-4-(2,4-difluorobenzyloxy)-2-oxo-2*H*-pyridin-1-ylmethyl]benzoate was prepared by a procedure similar to the one described for Example 81 (0 14 g, 60%) $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8 01 (dd, $J$ = 8, 2 Hz, 1H), 7 52 (app q, $J$ = 8 Hz, 1H), 7 36 (d, $J$ = 9 Hz, 2H), 7 26-7 22 (m, 2H), 6 94 (td, $J$ = 8, 2 Hz, 1H), 6 85 (td, $J$ = 8, 2 Hz, 1H), 6 16 (d, $J$ = 9 Hz, 1H), 5 21 (s, 4H), 3 92 (s, 3H)

Step 2 Preparation of 4-[3-Chloro-4-(2,4-difluorobenzyloxy)-2-oxo-2*H*-pyridin-1-ylmethyl]benzamide
A sealed tube containing a solution of 4-[3-Chloro-4-(2,4-difluorobenzyloxy)-2-oxo-2H-pyridin-1-ylmethyl]benzoic acid methyl ester (0 25 g, 0 60 mmol) and $NH_3$ (20 mL of a 7 N solution in MeOH, 140 mmol) was heated at 75 °C for 16 h The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure Trituration with $Et_2O$/MeOH afforded 4-[3-Chloro-4-(2,4-difluorobenzyloxy)-2-oxo-2*H*-pyridin-1-ylmethyl]benzamide as a white solid (0 14 g, 60%) mp 235-238 °C, $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 7 93 (d, $J$ = 8 Hz, 2H), 7 79 (d, $J$ = 8 Hz, 2H), 7 60 (app q, $J$ = 8 Hz, 1H), 7 35-7 27 (m, 4H), 7 20-7 10 (m, 1H), 6 61 (d, $J$ = 8 Hz, 1H), 5 28 (s, 2H), 5 14 (s, 2H) ESHRMS m/z 405 0788 (M+H $C_{20}H_{16}ClF_2N_2O_3$ requires 405 0812)

Example 84



3-Chloro-4-(2,4-difluorobenzyloxy)-1-isoquinolin-5-ylmethyl-1H-pyridin-2-one

Step 1 Preparation of Isoquinolin-5-ylmethanol

To an ice-cold solution of isoquinoline-5-carbaldehyde[2] (0 68 g, 4 3 mmol) in MeOH (15 mL) was added $NaBH_4$ (0 17 g, 4 6 mmol), and the reaction mixture was stirred for 15 min The reaction was quenched with brine, the solvent was removed under reduced pressure, and the residue was dissolved in EtOAc The organic solution was washed with water and then brine, dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure to afford isoquinolin-5-ylmethanol as a brown solid (0 63 g, 93%) $^1H$ NMR (300 MHz, DMSO-$d_6$) $\delta$ 9 87(s, 1H), 8 82 (d, $J$ = 6 Hz, 1H), 8 57 (d, $J$= 6 Hz, 1H), 8 47 (d, $J$ = 9 Hz, 1H), 8 30 (d, $J$ = 6 Hz, 1H), 7 95 (t, $J$ = 9 Hz, 1H), 5 34 (s, 2H)

Step 2 Preparation of 5-Bromomethylisoquinoline

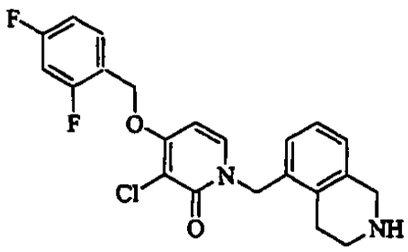
To a solution of isoquinolin-5-ylmethanol (0 63 g, 3 9 mmol) in AcOH (3 3 mL) was added HBr (6 6 mL, a 30% w/w solution in AcOH, 24 mmol), and the reaction mixture was stirred at 75 °C for 45 min The reaction mixture was cooled to room temperature, and the precipitate was collected to provide the

5-bromomethylisoquinoline hydrobromide acid salt as a brown solid (1 1 g, 87%) $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 9 22 (s, 1H), 8 58 (d, $J$ = 6 Hz, 1H), 7 95-7 89 (m, 2H), 7 76 (d, $J$ =9 Hz, 1H), 7 59 (dd, $J$ = 9, 6 Hz, 1H), 5 16 (s, 2H)

Step 3 Preparation of 3-Chloro-4-(2,4-difluorobenzyloxy)-1-isoquinolin-5-ylmethyl-1*H*-pyridin-2-one

The title compound was prepared by a procedure similar to the one described for Example 81, as the TFA salt (0 13 g, 33%) mp 235-238 °C, $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 9 55 (s, 1H), 8 66 (d, $J$ = 6 Hz, 1H), 8 29 (d, $J$ = 6 Hz, 1H), 8 22 (d, $J$ = 8 Hz, 1H), 7 91 (d, $J$ = 8 Hz, 1H), 7 77 (t, $J$ = 8 Hz, 1H), 7 65-7 63 (m, 1H), 7 53 (d, $J$ = 7 Hz, 1H), 7 35-7 25 (m, 1H), 7 20-7 10 (m, 1H), 6 68 (d, $J$ = 8 Hz, 1H), 5 67 (s, 2H), 5 32 (s, 2H), $^{19}$F NMR (282 MHz, DMSO-$d_6$) $\delta$ -74 79 (3F), -109 43 (1F), -113 62 (1F) ESHRMS m/z 413 0868 (M+H $C_{22}H_{16}ClF_2N_2O_3$ requires 413 0863)

Example 85



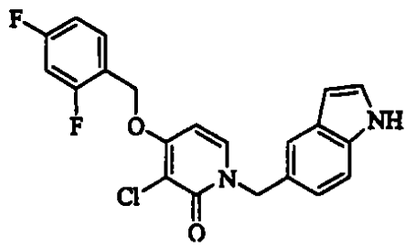

3-Chloro-4-(2,4-difluorobenzyloxy)-1-(1,2,3,4-tetrahydroisoquinolin-5-ylmethyl)-1*H*-pyridin-2-one

Step 1 Preparation of 3-Chloro-4-(2,4-difluorobenzyloxy)-1-(1,2,3,4-tetrahydro-isoquinolin-5-ylmethyl)-1*H*-pyridin-2-one

To a solution of 3-chloro-4-(2,4-difluorobenzyloxy)-1-isoquinolin-5-ylmethyl-1*H*-pyridin-2-one (Example 84) (0 14 g, 0 34 mmol) in AcOH (1 3 mL) was added $NaCNBH_3$ (0 09 g, 1 4 mmol), and the reaction mixture was stirred for 2 h The

reaction mixture was cooled to 0 °C, and diluted with water(10 mL) and 40% aqueous NaOH (10 mL), and the aqueous layer was washed with EtOAc (3 x 50 mL) The combined organics were washed with brine, dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure Purification by flash column chromatography (silica, eluent 98 1 8 0 2 to 88 10 8 1 2 $CH_2Cl_2$/MeOH/$NH_3$) provided 3-chloro-4-(2,4-difluoro-benzyloxy)-1-(1,2,3,4-tetrahydroisoquinolin-5-ylmethyl)-1*H*-pyridin-2-one as a white solid (0 13 g, 92%) mp 180-184 °C, $^1$H NMR (300 MHz, MeOD) δ 7 65-7 55 (m, 2H), 7 16-7 00 (m, 4H), 6 90-6 80 (m, 1H), 6 60 (d, *J* = 8 Hz, 1H), 5 31 (s, 2H), 5 20 (s, 2H), 4 06 (s, 2H), 3 21 (t, *J* = 6 Hz, 2H), 2 82 (t, *J* = 6 Hz, 2H) ESHRMS m/z 417 1173 (M+H $C_{22}H_{20}ClF_2N_2O_2$ requires 417 1176)

Example 86




3-Chloro-4-(2,4-difluorobenzyloxy)-1-(1*H*-indol-5-ylmethyl)-1*H*-pyridin-2-one

Step 1 Preparation of 5-(Carboxymethyl)-indole-1-carbamic acid tert-butyl ester

To a solution of methyl indole-5-carboxylate (6 9 g, 39 mmol) and $Et_3N$ (6 0 mL, 43 mmol) in $CH_2Cl_2$ (150 mL) was added di-tert-butyl dicarbonate (19 g, 86 mmol), and the reaction mixture was stirred for 14 h The reaction mixture was diluted with $CH_2Cl_2$, washed with water and then brine, dried ($Na_2SO_4$), filtered, and the solvent was removed under reduced pressure Purification by flash column chromatography (silica, 3:7 EtOAc/hexanes) provided 5-(carboxymethyl)-indole-

1-carbamic acid tert-butyl ester as a light yellow oil (11 g, 100%) $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8 29 (s, 1H), 8 15 (d, $J$ = 9 Hz, 1H), 7 93 (d, $J$ = 9 Hz, 1H), 7 78 (d, $J$ = 3 Hz, 1H), 6 85 (d, $J$ = 3 Hz, 1H), 3 91 (s, 3H), 1 68 (s, 9H)

Step 2 Preparation of 5-Hydroxymethylindole-1-carbamic acid tert-butyl ester

To a -78 °C solution of 5-(carboxymethyl)-indole-1-carbamic acid tert-butyl ester (10 8 g, 39 mmol) in THF (180 mL) was added DIBAL (127 mL of a 1 M solution in THF, 127 mmol), and the reaction mixture was stirred for 2 5 h The reaction was quenched with 1 1 1 N HCl/MeOH (100 mL), the reaction mixture was warmed to room temperature, diluted with $CH_2Cl_2$ (100 mL), and separated The organic solution was washed with saturated Rochelle salt, dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure Purification by flash column chromatography (silica, 1 1 EtOAc/hexanes) provided 5-hydroxymethylindole-1-carbamic acid tert-butyl ester as a yellow oil (6 5 g, 68%) $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8 07 (d, $J$ = 9 Hz, 1H), 7 59 (d, $J$ = 6 Hz, 1H), 7 54 (s, 1H), 7 28 (d, $J$ = 9 Hz, 1H), 6 58 (d, $J$ = 6 Hz, 1H), 4 73 (s, 2H), 1 97 (s, 9H)

Step 3 Preparation of 5-Bromomethylindole-1-carbamic acid tert-butyl ester

To an ice-cold solution of 5-hydroxymethylindole-1-carbamic acid tert-butyl ester (0 51 g, 2 1 mmol) in 4 1 $Et_2O/CH_2Cl_2$ (4 mL) was added $PBr_3$ (0 2 mL, 2 2 mmol), and the reaction mixture was stirred for 40 min The reaction mixture was diluted with $CH_2Cl_2$, washed a saturated solution of $NaHCO_3$ (3 x 10 mL), dried ($Na_2SO_4$), filtered, and the solvent was removed under reduced pressure to provide 5-bromomethyl-indole-1-carbamic acid tert-butyl ester as a yellow solid (0 59 g, 93%) $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8 07 (d, $J$ = 9 Hz, 1H), 7 68-7 62 (m, 2H),

7 33 (d, $J$ = 9 Hz, 1H), 6 60 (s, 1H), 4 68 (s, 2H), 1 67 (s, 9H)

Step 4 Preparation of 5-[3-Chloro-4-(2,4-difluorobenzyloxy)-2-oxo-2*H*-pyridin-1-ylmethyl]indole-1-carbamic acid tert-butyl ester

5-[3-Chloro-4-(2,4-difluorobenzyloxy)-2-oxo-2*H*-pyridin-1-ylmethyl]indole-1-carbamic acid tert-butyl ester was prepared by a procedure similar to the one described for Example 81 as an off-white solid (0 54 g, 67%) $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8 10 (d, $J$ = 8 Hz, 1H), 7 60 (d, $J$ = 3 Hz, 2H), 7 52 (m, 1H), 7 26 (m, 1H), 6 94 (td, $J$ = 9, 2 Hz, 1H), 6 84 (td, $J$ = 9, 2 Hz, 1H) 6 53 (d, $J$ = 2 Hz, 1H), 6 08 (d, $J$ = 8 Hz, 1H), 5 25 (s, 2H), 5 18 (s, 2H), 1 66 (s, 9H)

Step 5 Preparation of 3-Chloro-4-(2,4-difluorobenzyloxy)-1-(1*H*-indol-5-ylmethyl)-1*H*-pyridin-2-one

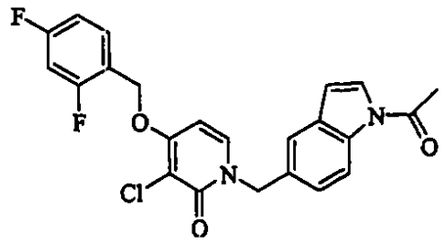
A flask containing 5-[3-chloro-4-(2,4-difluorobenzyloxy)-2-oxo-2*H*-pyridin-1-ylmethyl]indole-1-carbamic acid tert-butyl ester (0 48 g, 0 96 mmol) was heated at 150 °C for 4 h The reaction mixture was cooled to room temperature, and purification by preparatory HPLC (Phenomenex Luna C18(2) column, 250 x 21 20 mm, 10 µ

Solvent A 0 05% TFA in 95 5 $H_2O/CH_3CN$, Solvent B 0 05% TFA in 95 5 $CH_3CN/H_2O$

Eluent 30-95% B over 20 min, flow 20 0 mL/min, UV Detector 254 nm, Retention Time 15 6 min) provided 3-chloro-4-(2,4-difluorobenzyloxy)-1-(1*H*-indol-5-ylmethyl)-1*H*-pyridin-2-one as an off-white solid (0 14 g, 36%) mp 152-153 °C, $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 11 11 (br s, 1H), 7 91 (d, $J$ = 8 Hz, 1H), 7 61 (app q, $J$ = 8 Hz, 1H, 7 51 (s, 1H), 7 36-7 33 (m, 3H), 7 16 (td, $J$ = 8, 2 Hz, 1H), 7 09 (dd, $J$ = 8, 2 Hz, 1H), 6 57 (d, $J$

= 8 Hz, 1H), 6 40 (br s, 1H), 5 28 (s, 2H), 5 16 (s, 2H) ESHRMS m/z 401 0845 (M+H $C_{21}H_{16}ClF_2N_2O_2$ requires 401 0863)

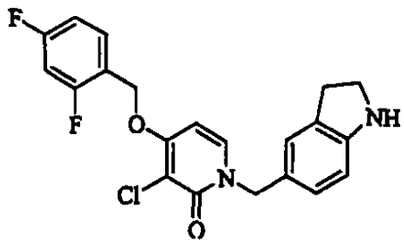
Example 87



1-(1-Acetyl-1*H*-indol-5-ylmethyl)-3-chloro-4-(2,4-difluorobenzyloxy)-1*H*-pyridin-2-one

To a solution of 3-chloro-4-(2,4-difluorobenzyloxy)-1-(1*H*-indol-5-ylmethyl)-1*H*-pyridin-2-one (Step 5, synthesis of Example 86 ) (0 22 g, 0 57 mmol) in $CH_3CN$ (10 mL) was added acetic anhydride (0 06 mL, 0 58 mmol) and $Et_3N$ (2 mL) , and the reaction mixture was stirred at 86 °C for 6 h The reaction mixture was cooled to room temperature, and partitioned between 1 N HCl and EtOAc The organic solution was separated, washed with brine, dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure $^1H$ NMR (300 MHz, MeOD) δ 8 35 (d, *J* = 9 Hz, 1H), 7 77 (d, *J* = 9 Hz, 1H), 7 70 (d, *J* = 3 Hz, 1H), 7 54 (s, 2H), 7 31 (d, *J* = 9 Hz, 1H), 7 01-6 99 (m, 2H), 6 66 (d, *J* = 3 Hz, 1H), 6 59 (d, *J* = 9 Hz, 1H), 5 29 (s, 4H), 2 63 (s, 3H) ESHRMS m/z 443 0965 (M+H $C_{23}H_{18}ClF_2N_2O_3$ requires 443 0969)

Example 88

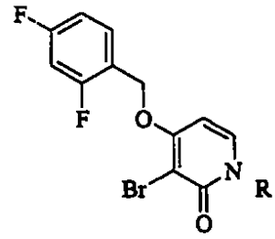


3-Chloro-4-(2,4-difluorobenzyloxy)-1-(2,3-dihydro-1*H*-indol-5-ylmethyl)-1*H*-pyridin-2-one

To a solution of 3-chloro-4-(2,4-difluorobenzyloxy)-1-(1*H*-indol-5-ylmethyl)-1*H*-pyridin-2-one (Step 5, synthesis of Example 86 ) (0 24 g, 0 60 mmol) in AcOH (5 mL) was added $NaCNBH_3$ (0 06 g, 1 0 mmol), and the reaction mixture was stirred for 1 h The reaction mixture was partitioned between water and EtOAc, and the precipitate was collected by filtration Trituration with $CH_2Cl_2$ afforded 3-Chloro-4-(2,4-difluorobenzyl-oxy)-1-(2,3-dihydro-1*H*-indol-5-ylmethyl)-1*H*-pyridin-2-one as a white solid (0 2 g, 81%) mp 137-139 °C, $^1H$ NMR (300 MHz, $CDCl_3$) δ 7 51 (app q, *J* = 9 Hz, 1H), 7 21 (d, *J* = 6 Hz, 1H), 7 11 (s, 1H), 6 99-6 80 (m, 3H), 6 57 (d, *J* = 9 Hz, 1H), 6 08 (d, *J* = 9 Hz, 1H), 5 18 (s, 2H), 5 02 (s, 2H), 3 83 (br s, 1H), 3 55 (t, *J* = 9 Hz, 2H), 2 99 (t, *J* = 9 Hz, 2H) ESHRMS m/z 403 1022 (M+H $C_{21}H_{18}ClF_2N_2O_2$ requires 403 1019)

The following example compounds were prepared by procedures similar to that described for Example 74 The yields and the analytical data of the title compounds are reported below

Examples 89-101

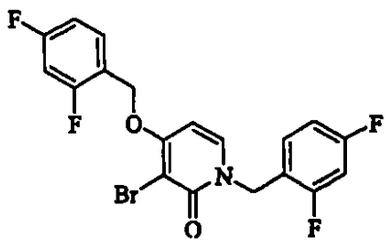


The compounds of Examples 89-101 are prepared essentially according to the procedures set forth above for Example 74 The yield (Y), molecular formula (MF) and analytical data for these compounds are shown below

| Example No | R | Y | MF | M+H Requires | ESHRMS m/z |
|---|---|---|---|---|---|
| Ex 89 | pyridin-3-ylmethyl | 25 | $C_{18}H_{13}BrF_2N_2O_2$ | 407 0202 | 407 0197 |
| Ex 90 | pyridin-4-ylmethyl | 6 | $C_{18}H_{13}BrF_2N_2O_2$ | 407 0202 | 407 0189 |
| Ex 91 | pyridin-2-ylmethyl | 56 | $C_{18}H_{13}BrF_2N_2O_2$ | 407 0201 | 407 0184 |
| Ex 92 | 4-tert-butyl)benzyl | 32 | $C_{23}H_{22}BrF_2NO_2$ | 462 0875 | 462 0863 |
| Ex 93 | 3-methoxybenzyl | 50 | $C_{20}H_{16}BrF_2NO_3$ | 436 0354 | 436 0353 |
| Ex 94 | Benzo[1,3]dioxol-5-ylmethyl | 35 | $C_{20}H_{14}BrF_2NO_4$ | 450 0147 | 450 0136 |
| Ex 95 | 2-fluorobenzyl | 42 | $C_{19}H_{14}BrF_3NO_2$ | 424 0155 | 424 0143 |

%) mp 179-182 °C, $^1$H NMR (300 MHz, $CDCl_3$) δ 7 58-7 53 (m, 3H), 7 33-7 26 (m, 1H), 7 14-7 02 (m, 2H), 6 96-6 82 (m, 2H), 6 11 (d, $J$ = 9 Hz, 1H), 5 20 (s, 2H), 5 18 (s, 2H) ESHRMS m/z (M+H requires)

Example 96



3-Bromo-4-(2,4-difluorobenzyloxy)-1-(2,4-difluorobenzyl)-1*H*-pyridin-2-one

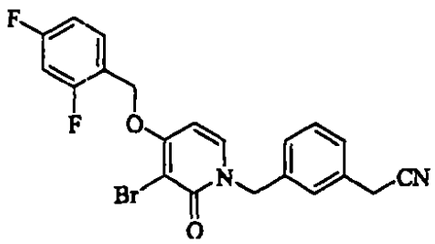
Step 1 Preparation of 4-(2,4-Difluorobenzyloxy)-1-(2,4-difluorobenzyl)-1*H*-pyridin-2-one

To a solution of 2,4-dihydroxypyridine (0 35 g, 3 2 mmol) in DMF (50 mL) was added $K_2CO_3$ (2 5 g, 13 mmol) and 2,4-difluorobenzyl bromide (1 0 mL, 7 6 mmol), and the reaction mixture was stirred at 110 °C for 4 h The reaction mixture was cooled to room temperature, diluted with brine, and extracted with $CHCl_3$ (4 x 100 mL) The combined organics were washed with water and then brine, dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure $^1H$ NMR (300 MHz, $CDCl_3$) δ 7 54 (app q, *J* = 8 Hz, 1H), 7 38-7 28 (m, 5H), 6 94 (td, *J* = 8, 2 Hz, 1H), 6 85 (td, *J* = 8, 2 Hz, 1H), 6 10 (d, *J* = 9 Hz, 1H), 5 21 (s, 2H), 5 16 (s, 2H), 4 56 (s, 2H)

Step 2 Preparation of 3-Bromo-4-(2,4-difluorobenzyloxy)-1-(2,4-fluorobenzyl)-1*H*-pyridin-2-one

To an ice-cold solution of 4-(2,4-difluorobenzyloxy)-1-(2,4-difluorobenzyl)-1*H*-pyridin-2-one (0 72 g, 2 0 mmol) in AcOH (4 0 mL) was added a solution of bromine (0 11 mL, 2 2 mmol) in AcOH (7 2 mL), and the reaction mixture was stirred for 40 min The solvent was removed under reduced pressure $^1H$ NMR (300 MHz, $CDCl_3$) δ 7 63-7 45 (m, 2H), 7 42 (d, *J* = 6 Hz, 1H), 6 93-6 77 (m, 4H), 6 12 (d, *J* = 6 Hz, 1H), 5 20 (s, 2H), 5 12 (s, 2H) ERMS m/z M+H 442

Example 97



{3-[3-Bromo-4-(2,4-difluorobenzyloxy)-2-oxo-2*H*-pyridin-1-ylmethyl]-phenyl}acetonitrile

Step 1 Preparation of Methyl 3-cyanomethylbenzoate

To an ice-cold solution of methyl 3-bromomethylbenzoate (9 1 g, 40 mmol) in $CH_3CN$ (108 mL) was added tetrabutylammonium fluoride (17 3 mL, 60 mmol) and trimethylsilylcyanide (8 0 mL, 60 mmol), and the reaction mixture was heated at reflux for 20 h The reaction mixture was cooled to room temperature, and the solvent was removed under reduced pressure Purification by flash column chromatography (silica, 1 1 EtOAc/hexanes) provided methyl 3-cyanomethylbenzoate as a clear oil (3 0 g, 43%) $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 7 97 (s, 1H), 7 92 (d, $J$ = 8 Hz, 1H), 7 64 (d, $J$ = 8 Hz, 1H), 7 56 (t, $J$ = 8 Hz, 1H), 4 16 (s, 2H), 3 87 (s, 3H)

Step 2 Preparation of (3-Hydroxymethylphenyl)acetonitrile

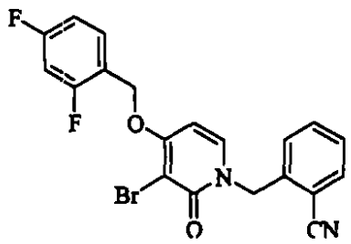
To an ice-cold solution of methyl 3-cyanomethylbenzoate (2 8 g, 18 mmol) in THF (23 mL) was added $LiBH_4$ (8 8 mL of a 2 M solution in THF, 18 mmol), and the reaction mixture was heated at reflux for 4 h The reaction mixture was cooled to room temperature, the reaction was quenched with 1 1 water/1 N HCl, and the aqueous layer was washed with EtOAc (3 x 150 mL) The combined organics were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure

Purification by flash column chromatography (silica, 2 1 EtOAc/hexanes) provided (3-hydroxymethylphenyl)-acetonitrile as a clear oil (0 97 g, 41%) $^1$H NMR (300 MHz, MeOD) $\delta$ 8 15-8 08 (m, 1H), 7 47-7 34 (m, 1H), 7 27 (s, 1H), 6 97-6 82 (m, 1H), 4 87 (s, 2H), 3 91 (s, 2H)

Step 3 Preparation of (3-Bromomethylphenyl)acetonitrile
To an ice-cold solution of (3-hydroxymethylphenyl)acetonitrile (0 97 g, 7 3 mmol) in THF (35 mL) was added $CBr_4$ (2 5 g, 7 7 mmol) and $Ph_3P$ (2 0 g, 7 7 mmol), and the reaction mixture was stirred for 3 h The reaction mixture was filtered, and concentrated under reduced pressure Purification by flash column chromatography (silica, eluent 1 9 to 1 4 EtOAc/hexanes) provided (3-bromomethylphenyl)acetonitrile as a clear oil (0 89 g, 58%) $^1$H NMR (300 MHz, MeOD) $\delta$ 7 47-7 29 (m, 1H), 7 27 (s, 1H), 6 97-6 82 (m, 1H), 4 87 (s, 2H), 3 91 (s, 2H)

Step 4 Preparation of {3-[3-Bromo-4-(2,4-difluorobenzyloxy)-2-oxo-2*H*-pyridin-1-ylmethyl]phenyl}acetonitrile
The title compound was prepared by a procedure similar to the one described for Example 74 (0 07 g, 10%) mp 120-121 °C, $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7 60-7 50 (m, 1H), 7 37-7 27 (m, 5H), 6 96 (td, $J$ = 9, 3 Hz, 1H), 6 82 (td, $J$ = 9, 3 Hz, 1H), 6 13 (d, $J$ = 8 Hz, 1H), 5 21 (s, 2H), 5 16 (s, 2H) ESHRMS m/z 445 0381 (M+H $C_{21}H_{16}BrF_2N_2O_2$ requires 445 0358)

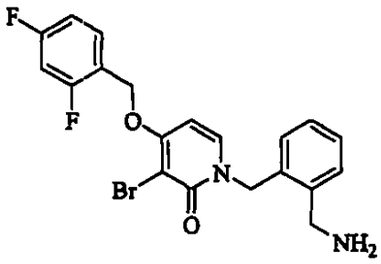
Example 98



2-[3-Bromo-4-(2,4-difluorobenzyloxy)-2-oxo-2*H*-pyridin-1-ylmethyl]benzonitrile

The title compound was prepared by a procedure similar to the one described for Example 74 (0 13 g, 47%) mp 194-197 °C, $^1$H NMR (300 MHz, $CDCl_3$) δ 7 75 (d, *J* = 9 Hz, 1H), 7 69-7 49 (m, 4H), 7 42 (t, *J* = 8 Hz, 1H), 6 96-6 73 (m, 2H), 6 18 (d, *J* = 8 Hz, H), 6 17 (s, 2H), 5 30 (s, 2H) ESHRMS m/z 431 0210 (M+H $C_{20}H_{14}BrF_2N_2O_2$ requires 431 0201

Example 99

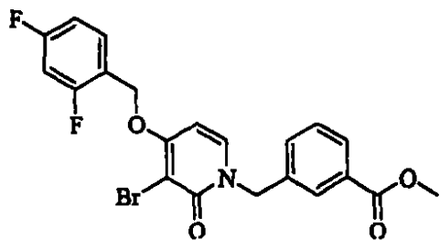


1-[(2-Aminomethyl)benzyl)]-3-bromo-4-(2,4-difluorobenzyloxy)-1*H*-pyridin-2-one

To a solution of 2-[3-bromo-4-(2,4-difluorobenzyloxy)-2-oxo-2*H*-pyridin-1-ylmethyl]-benzonitrile (0 11 g, 0 25 mmol) in THF (3 mL) was added $BH_3$ DMS (0 25 mL of a 2 0 M solution in THF, 0 5 mmol), and the reaction mixture was stirred at 70 °C for 1 h The reaction mixture was cooled to 0 °C, and the reaction was quenched with MeOH The solvent was removed under reduced

pressure, and the residue was partitioned between 2N NaOH and EtOAc The organic solution was washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure Purification by flash column chromatography (silica, eluent methylene chloride to 90 9 1 methylene chloride/methanol/ammonia) provided 1-[(2-aminomethyl)benzyl]-3-bromo-4-(2,4-difluorobenzyloxy)-1*H*-pyridin-2-one as a white solid (0 15 g, 48%) $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7 55 (app q, $J$ = 8 Hz, 1H), 7 40-7 26 (m, 4H), 7 14 (d, $J$ = 8 Hz, 1H), 6 94 (td, $J$ = 8, 2 Hz, 1H), 6 85 (td, $J$ = 8, 2 Hz, 1H), 6 08 (d, $J$ = 8 Hz, 1H), 5 31 (s, 2H), 5 21 (s, 2H) 4 03 (s, 2H) ESHRMS m/z 435 0517 (M+H $C_{20}H_{18}BrF_2N_2O_2$ requires 435 0514)

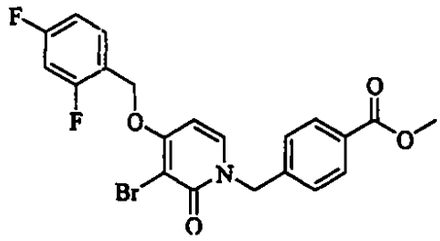
Example 100




Methyl 3-[3-Bromo-4-(2,4-difluorobenzyloxy)-2-oxo-2*H*-pyridin-1-ylmethyl] benzoate

The title compound was prepared by a procedure similar to the one described for Example 74 (0 05 g, 11%) mp 115-117 °C, $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8 15-7 95 (m, 2H), 7 65-7 50 (m, 2H), 7 45-7 40 (m, 1H), 7 32 (d, $J$ = 6 Hz, 1H), 7 00-6 80 (m, 2H), 6 12 (d, $J$ = 9 Hz, 1H), 5 21 (s, 2H), 5 20 (s, 2H), 3 92 (s, 3H) ESHRMS m/z 464 0292 (M+H $C_{21}H_{17}BrF_2NO_4$ requires 464 0303)

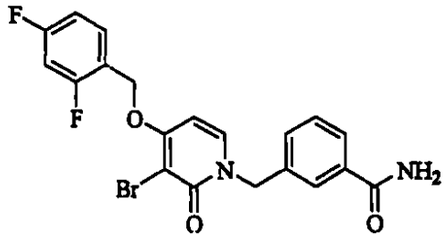
Example 101



Methyl 4-[3-Bromo-4-(2,4-difluorobenzyloxy)-2-oxo-2*H*-pyridin-1-ylmethyl]-benzoate

The title compound was prepared by a procedure similar to the one described for Example 74 (0 17 g, 46%) mp136-139 °C, $^1$H NMR (300 MHz, $CDCl_3$) δ 8 01 (d, $J$ = 8 Hz, 2H), 7 60-7 51 (m, 1H), 7 37 (d, $J$ = 8 Hz, 2H), 7 29-7 26 (m, 1H), 6 93 (td, $J$ = 9, 2 Hz, 1H), 6 84 (td, $J$ = 9, 2 Hz, 1H), 6 13 (d, $J$ = 8 Hz, 1H), 5 23 (s, 4H), 3 91 (s, 3H) ESHRMS m/z 464 0306 (M+H $C_{21}H_{17}BrF_2NO_2$ requires 464 0304)

Example 102

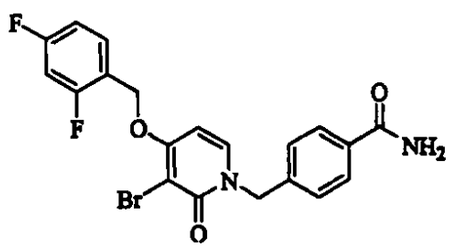


3-[3-Bromo-4-(2,4-difluorobenzyloxy)-2-oxo-2*H*-pyridin-1-ylmethyl]benzamide

A sealed tube containing a solution of methyl 3-[3-bromo-4-(2,4-difluorobenzyloxy)-2-oxo-2*H*-pyridin-1-ylmethyl]benzoate (0 1 g, 0 21 mmol) and $NH_3$ (3 mL of a 7 N solution in MeOH, 21 mmol) was heated at 75 °C for 16 h The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure Trituration with $Et_2O$/MeOH afforded a white

solid (0 06 g, 64%) mp 198-201 °C, $^1$H NMR (300 MHz, DMSO-$d_6$) δ 8 02-8 00 (m, 2H), 7 85-7 75 (m, 2H), 7 70-7 60 (m, 1H), 7 45-7 30 (m, 4H), 7 17 (t, $J$ = 3 Hz, 1H), 6 60 (d, $J$ = 9 Hz, 1H), 5 32 (s, 2H), 5 18 (s, 2H) ESHRMS m/z 449 0295 (M+H $C_{20}H_{16}BrF_2N_2O_3$ requires 449 0307)

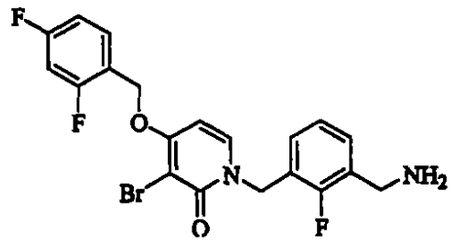
Example 103



4-[3-Bromo-4-(2,4-difluorobenzyloxy)-2-oxo-2H-pyridin-1-ylmethyl]benzamide

The title compound was prepared by a procedure similar to the one described for Example 102 from Example 101 (0 04 g, 12%) mp 235-238 °C, $^1$H NMR (300 MHz, DMSO-$d_6$) δ 8 00 (d, $J$ = 8 Hz, 1H), 7 94 (br s, 1H), 7 78 (d, $J$ = 8 Hz, 1H), 7 64 (app q, $J$ = 8 Hz, 1H), 7 38-7 30(m, 4H), 7 17 (td, $J$ = 6, 2 Hz, 1H), 6 60 (d, $J$ = 9 Hz, 1H), 5 27 (s, 2H), 5 14 (s, 2H) ESHRMS m/z 449 0291 (M+H $C_{20}H_{16}BrF_2N_2O_3$ requires 449 0307)

Example 104



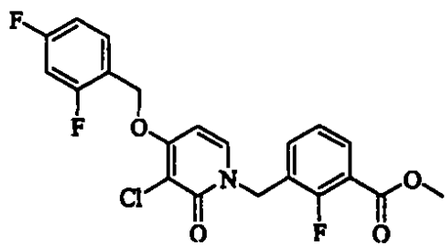
1-(3-Aminomethyl-2-fluorobenzyl)-3-bromo-4-(2,4-difluorobenzyloxy)-1H-pyridin-2-one

Step 1 Preparation of 1-Bromo-1-(3-bromomethyl-2-fluorobenzyl)-4-(2,4-difluoro-benzyloxy)-1*H*-pyridin-2-one
To a solution of 3-bromo 4-(2,4-difluorobenzyloxy)-1*H*-pyridin-2-one (from Step 3, Example 74) (0 3 g, 0 95 mmol) in DMF (26 mL) was added $K_2CO_3$ (0 26 g, 1 9 mmol) and 2,6-bis(bromomethyl)fluorobenzene (1 6 g, 5 7 mmol), and the reaction mixture was stirred at 110 °C for 3 h The reaction mixture was cooled to room temperature, and the solvent was removed under reduced pressure The residue was diluted with a 50% aqueous solution of brine, and the aqueous layer was extracted with EtOAc (3 x 50 mL) The combined organics were washed with water, dried ($Na_2SO_4$), filtered, and the solvent was removed under reduced pressure Purification by flash column chromatography (silica, eluent 99 1 to 95 5 methylene chloride/methanol) afforded 3-bromo-1-(3-bromomethyl-2-fluorobenzyl)-4-(2,4-difluorobenzyloxy)-1*H*-pyridin-2-one as an off-white solid (0 24 g, 49%) $^1$H NMR (300 MHz, $CDCl_3$) δ 7 55-7 40 (m, 3H), 7 35-7 25 (m, 1H), 7 10-7 05 (m, 1H), 7 00-6 80 (m, 2H), 6 14 (d, *J* = 6 Hz, 1H), 5 22 (s, 2H), 5 19 (s, 2H), 4 50 (s, 2H)

Step 2 Preparation of 1-(3-Aminomethyl-2-fluorobenzyl)-3-bromo-4-(2,4-difluoro-benzyloxy)-1*H*-pyridin-2-one
A sealed tube containing a solution of 3-bromo-1-(3-bromomethyl-2-fluorobenzyl)-4-(2,4-difluorobenzyloxy)-1*H*-pyridin-2-one (0 24 g, 0 45 mmol) and $NH_3$ (24 mL of a 7 N solution in MeOH, 168 mmol) was heated at 80 °C for 1 h The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure Purification by flash column chromatography (silica, eluent 99 5 0 5 to 96 4 methylene chloride/methanol) afforded a white solid (0 12 g, 60% ) mp 160-163 °C, $^1$H NMR (300 MHz, $CDCl_3$) δ 7 46-7 45 (m, 1H), 7 44-7 35 (m, 2H), 7 34-7 26 (m, 1 H), 7 15-7 05 (m, 1H),

6 95-6 80 (m, 2H), 6 11 (d, $J$ = 9 Hz, 1H), 5 21 (s, 2H), 5 19 (s, 2H), 3 90 (s, 2H) ESHRMS m/z 453 0442 (M+H $C_{20}H_{17}BrF_3N_2O_2$ requires 453 0420)

Example 105



Methyl 3-[3-chloro-4-(2,4-difluorobenzyloxy)-2-oxo-2*H*-pyridin-1-ylmethyl]-2-fluoro-benzoate

Step 1 Preparation of Methyl 2-fluoro-3-methylbenzoate
To a solution of 2-fluoro-3-methyl benzoic acid (3 57 g, 23 mmol) in MeOH (40 mL) was added concentrated sulfuric acid (2 3 mL), and the reaction mixture was heated at reflux for 12 h The reaction mixture was cooled, the solvent was removed under reduced pressure, and the residue was dissolved in EtOAc The organic solution was washed with a saturated solution of $NaHCO_3$ and then brine, dried ($Na_2SO_4$), filtered and concentrated under reduced pressure to afford methyl 2-fluoro-3-methylbenzoate as a yellow oil (3 2 g, 82%) $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7 76-7 71 (m, 1H), 7 39-7 34 (m, 1H), 7 08 (t, $J$ = 8 Hz, 1H), 3 98 (s, 3H), 2 31 (d, $J$ = 3 Hz, 3H)

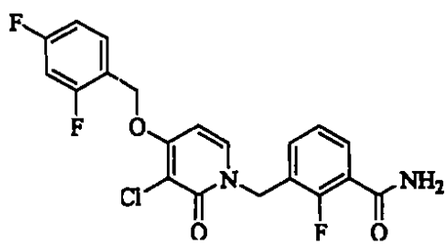
Step 2 Preparation of Methyl 3-bromomethyl-2-fluorobenzoate
To a mixture of methyl 2-fluoro-3-methylbenzoate (1 5 g, 8 9 mmol) and N-bromosuccinimide (1 67 g, 9 4 mmol) was added carbon tetrachloride (24 mL) and benzoyl peroxide (5 mg), and the mixture was heated at reflux for 16 h The reaction mixture was cooled, filtered, and concentrated under reduced

pressure Purification by flash column chromatography (silica, eluent 5 95 to 60 40 EtOAc/hexanes) afforded methyl 3-bromomethyl-2-fluorobenzoate as a light yellow solid (0 91 g, 41% ) $^1$H NMR (300 MHz, $CDCl_3$) δ 7 93-7 88 (m, 1H), 7 61-7 56 (m, 1H), 7 20 (t, *J* = 8 Hz, 1H), 4 53 (d, *J* = 3 Hz, 2H), 3 94 (s, 3H)

Step 3 Preparation of Methyl 3-[3-chloro-4-(2,4-difluorobenzyloxy)-2-oxo-2*H*-pyridin-1-ylmethyl]-2-fluorobenzoate

Methyl 3-[3-chloro-4-(2,4-difluorobenzyloxy)-2-oxo-2*H*-pyridin-1-ylmethyl]-2-fluorobenzcate was prepared by a procedure similar to the one described for Example 81 (0 33 g, 69%) mp 171-174 °C, $^1$H NMR (300 MHz, $CDCl_3$) δ 7 89-7 84 (m, 2H), 7 60-7 45 (m, 2H), 7 25-7 15 (m, 1H), 7 00-6 80 (m, 2H), 6 17 (d, *J* = 6 0 Hz, 1H), 5 21 (s, 2H), 5 19 (s, 2H), 3 93 (s, 3H) ESHRMS m/z 438 0747 (M+H $C_{21}H_{16}ClF_3NO_4$ requires 438 0714)

Example 106

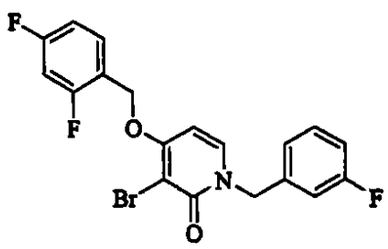



3-[3-Chloro-4-(2,4-difluorobenzyloxy)-2-oxo-2*H*-pyridin-1-ylmethyl]-2-fluoro-benzamide

The title compound was prepared by a procedure similar to the one described for Example 99 (0 15 g, 62%) mp 252-254 °C, $^1$H NMR (300 MHz, DMSO-$d_6$) δ 8 04 (d, *J* = 8 Hz, 1H), 7 92 (br s, 1H), 7 79-7 65 (m, 3H), 7 49-7 48 (m, 1H), 7 37-7 31 (m, 3H),

6 80 (d, $J$ = 8 Hz, 1H), 5 46 (s, 2H), 5 33 (s, 2H) ESHRMS m/z 423 0710 (M+H $C_{20}H_{15}ClF_3N_2O_3$ requires 423 0718)

Example 107



3-Bromo-4-(2,4-difluorobenzyloxy)-1-(3-fluorobenzyl)-1*H*-pyridin-2-one

Step 1 Preparation of 4-Benzyloxy-1-(3-fluorobenzyl)-1*H*-pyridin-2-one

To a solution of 4-benzyloxy-1*H*-pyridin-2-one (1 0 g, 5 mmol) and $K_2CO_3$ (2 0 g, 9 9 mmol) in DMF (30 mL) was added 3-fluorobenzyl bromide (1 4 g, 7 5 mmol), and the reaction mixture was heated to 110 °C for 3 h The reaction mixture was cooled to room temperature, and partitioned between EtOAc and water The organic solution was washed with water and then brine, dried ($Na_2SO_4$), filtered and concentrated under reduced pressure Purification by flash column chromatography (silica, eluent 97 3 to 93 7 methylene chloride /methanol) afforded 4-benzyloxy-1-(3-fluorobenzyl)-1*H*-pyridin-2-one (1 04 g, 67% ) $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7 45-7 25 (m, 5H), 7 13 (d, $J$ = 8 Hz, 1H), 7 10-6 90 (m, 3H), 6 10-5 95 (m, 2H), 5 07 (s, 2H), 5 00 (s, 2H)

Step 2 Preparation of 1-(3-Fluorobenzyl)-4-hydroxy-1*H*-pyridin-2-one

To a solution of 4-benzyloxy-1-(3-fluorobenzyl)-1*H*-pyridin-2-one (1 79 g, 5 8 mmol) in EtOH (50 mL) was added 10% Pd/C (0 4 g), and reaction mixture was stirred under a hydrogen atmosphere for 1 5 h The reaction mixture was filtered through diatomaceous earth and concentrated under reduced pressure to give 1-(3-fluorobenzyl)-4-hydroxy-1*H*-pyridin-2-one (0 92 g, 72% ) $^1$H NMR (300 MHz, $CDCl_3$) δ 7 55 (d, *J* = 6 Hz, 1H), 7 40-7 30 (m, 1H), 7 10-6 95 (m, 3H), 6 07 (dd *J* = 6, 3 Hz, 1H), 5 85 (d, *J* = 3 Hz, 1H), 5 11 (s, 2H)

Step 3 Preparation of 3-Bromo-1-(3-fluorobenzyl)-4-hydroxy-1*H*-pyridin-2-one

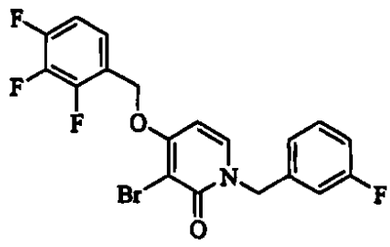
To an ice-cold solution of 1-(3-fluorobenzyl)-4-hydroxy-1*H*-pyridin-2-one (0 67 g, 3 1 mmol) in AcOH (5 7 mL) was added a solution of bromine (0 52 g, 3 24 mmol) in AcOH (10 8 mL), and the reaction mixture was stirred for 5 min The reaction mixture was warmed to room temperature and concentrated under reduced pressure to afford 3-bromo-1-(3-fluorobenzyl)-4-hydroxy-1*H*-pyridin-2-one as a yellow solid (1 07 g, crude) $^1$H NMR (500 MHz, MeOD) δ 7 64 (d, *J* = 8 Hz, 1H), 7 35-7 30 (m, 1H), 7 05-6 90 (m, 3H), 6 20 (d, *J* = 8 Hz, 1H), 5 18 (s, 2H)

Step 4 Preparation of 3-Bromo-4-(2,4-difluorobenzyloxy)-1-(3-fluorobenzyl)-1*H*-pyridin-2-one

To a solution of 3-bromo-1-(3-fluorobenzyl)-4-hydroxy-1*H*-pyridin-2-one (0 20 g, 0 67) and $K_2CO_3$ (0 27 g, 1 34 mmol) in acetone (10 mL) was added 2,4-difluorobenzyl bromide (0 16 g, 0 8 mmol), and the reaction mixture was heated at reflux for 1 h The reaction mixture was cooled to room temperature, concentrated under reduced pressure, and the residue was dissolved in EtOAc The organic solution was washed with water and then brine, dried ($Na_2SO_4$), filtered and concentrated under reduced pressure $^1$H NMR (300 MHz, $CDCl_3$) δ 7 65-7 55

(m, 1H), 7 40-7 25 (m, 2H), 7 15-6 80 (m, 5H), 6 14 (d, $J$ = 8 Hz, 1H), 5 22 (s, 2H), 5 16 (s, 2H) ESHRMS m/z 424 0159 (M+H $C_{19}H_{14}BrF_3NO_2$ requires 424 0155)

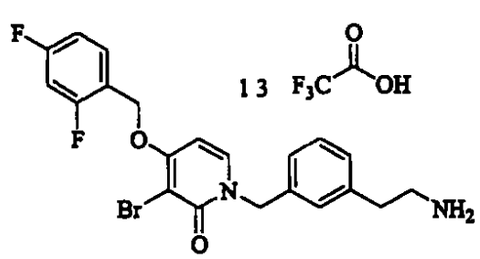
Example 108



3-Bromo-1-(3-fluorobenzyl)-4-(2,3,4-trifluorobenzyloxy)-1*H*-pyridin-2-one

The title compound was prepared by a procedure similar to the one described for Example 107 (0 09 g, 39%) mp 176-178 °C, $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7 40-7 25 (m, 4H), 7 11-6 98 (m, 4H), 6 11 (d, $J$ = 9 Hz, 1H), 5 23 (s, 2H), 5 16 (s, 2H) ESHRMS m/z 442 0060 (M+H $C_{19}H_{13}BrF_4NO_2$ requires 442 0061)

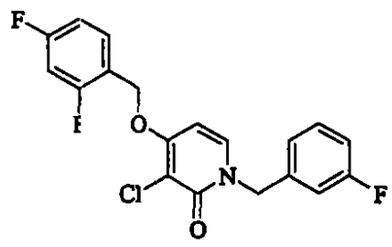
Example 109



1-[3-(2-Aminoethyl) benzyl]-3-bromo-4-(2,4-difluorobenzyloxy)-1*H*-pyridin-2-one

The title compound was prepared from compound of Example 97 by a procedure similar to the one described for Example 99, as the TFA salt (0 13 g, 33%) mp 70-74 °C, $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8 21 (br s, 1H), 6 60-6 50 (m, 1H), 7 52 (d, $J$ = 6 Hz, 1H), 7 30-7 10 (m, 3H), 7 01 (d, $J$ = 9 Hz, 1H), 6 94-6 85 (m, 2H), 6 20 (d, $J$ = 6 Hz, 1H), 5 20 (s, 2H), 5 05 (s, 2H), 3 23 (br s, 2H), 2 97 (t, $J$ = 8 Hz, 2H), 2 05 (br s, 2H) ESHRMS m/z 449 0698 (M+H $C_{21}H_{20}BrF_2N_2O_2$ requires 449 0671)

Example 110



3-Chloro-4-(2,4-diflucrobenzyloxy)-1-(3-fluorobenzyl)-1*H*-pyridin-2-one

Step 1 Preparation of 4-(2,4-difluorobenzyloxy)-1-(3-fluorobenzyl)-1*H*-pyridin-2-one

To a solution of 1-(3-fluorobenzyl)-4-hydroxy-1*H*-pyridin-2-one (from Step 2 EXAMPLE 107) (0 92 g, 4 2 mmol) and $K_2CO_3$ (1 2 g, 8 4 mmol) in acetone (62 mL) was added 2,4-difluorobenzyl bromide (1 3 g, 6 3 mmol), and the reaction mixture was heated at reflux for 3 h The reaction mixture was cooled room temperature, concentrated under reduced pressure, and the residue was partitioned between water and EtOAc The organic solution was washed with brine, dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure Purrfication by flash

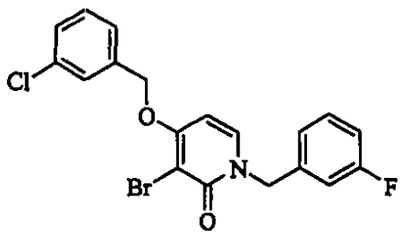
column chromatography (silica, eluent methylene chloride to 95 5 methylene chloride/methanol) to provide 4-(2,4-difluorobenzyloxy)-1-(3-fluorobenzyl)-1*H*-pyridin-2-one as a white solid (1 21 g, 84%) $^1$H NMR (300 MHz, $CDCl_3$) δ 7 45-7 20 (m, 2H), 7 14 (d, *J* = 8 Hz, 1H), 7 05-6 75 (m, 5H), 6 05 (d, *J* = 3 Hz, 1H), 5 95 (dd, *J* = 5, 3 Hz, 1H), 5 08 (s, 2H), 5 00 (s, 2H)

Step 2 Preparation of 3-Chloro-4-(2,4-difluorobenzyloxy)-1-(3-fluorobenzyl)-1*H*-pyridin-2-one
To a solution of 4-(2,4-difluorobenzyloxy)-1-(3-fluorobenzyl)-1*H*-pyridin-2-one (0 15 g, 0 4 mmol) in AcOH (3 mL) was added N-chlorosuccinimide (70 mg, 0 5 mmol), and the reaction mixture was heated at reflux for 10 min The reaction mixture was cooled room temperature and the solvent was removed under reduced pressure $^1$H NMR (300 MHz, $CDCl_3$) δ 7 60-7 50 (m, 1H), 7 45-7 20 (m, 2H), 7 10-6 80 (m, 5H), 6 16 (d, *J* = 8 Hz, 1H), 5 21 (s, 2H), 5 15 (s, 2H) ESHRMS m/z 380 0641 (M+H $C_{19}H_{14}ClF_3NO_2$ requires 480 0660)

Examples 111-123

The following example compounds were prepared by procedures similar to that described for Example 107 The yields and the analytical data are described below

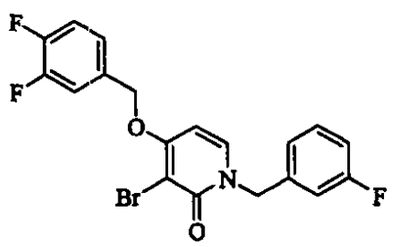
Example 111



3-Bromo-4-(3-chlorobenzyloxy)-1-(3-fluorobenzyl)-1*H*-pyridin-2-one

The title compound was prepared by a procedure similar to the one described for EXAMPLE 107 (0 12 g, 42%) mp 149-153 °C, $^1$H NMR (300 MHz, $CDCl_3$) δ 7 40-7 23 (m, 6H), 7 09 (d, *J* = 8 Hz, 1H), 7 05-6 95 (m, 2H), 6 05 (d, *J* = 8 Hz, 1H), 5 19 (s, 2H), 5 14 (s, 2H) ESMS m/z M+H 442

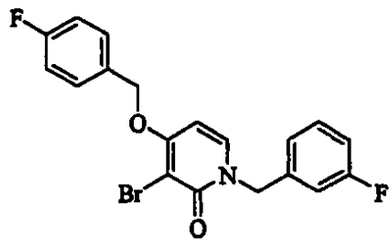
Example 112



3-Bromo-4-(3,4-difluorobenzyloxy)-1-(3-fluorobenzyl)-1*H*-pyridin-2-one

The title compound was prepared by a procedure similar to the one described for EXAMPLE 107 (0 08 g, 48%) mp 172-174 °C, $^1$H NMR (300 MHz, $CDCl_3$) δ 7 40-6 95 (m, 8H), 6 05 (d, *J* = 6 Hz, 1H), 5 16 (s, 4H) ESHRMS m/z 424 0111 (M+H $C_{19}H_{14}BrF_3NO_2$ requires 424 0155)

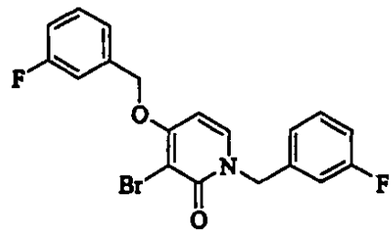
Example 113



3-Bromo-1-(3-fluorobenzyl)-4-(4-fluorobenzyloxy)-1*H*-pyridin-2-one

The title compound was prepared by a procedure similar to the one described for EXAMPLE 107 (0 07 g, 35%) mp 180-183 °C, $^1$H NMR (300 MHz, $CDCl_3$) δ 7 50-7 25 (m, 5H), 7 15-7 00 (m, 4H), 6 07 (d, *J* = 8 Hz, 1H), 5 18 (s, 2H), 5 14 (s, 2H) ESHRMS m/z 406 0258 (M+H $C_{19}H_{15}BrF_2NO_2$ requires 406 0249)

Example 114



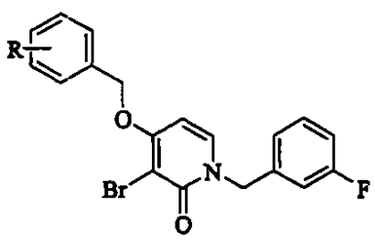
3-Bromo-1-(3-fluorobenzyl)-4-(3-fluorobenzyloxy)-1*H*-pyridin-2-one

To an ice-cold solution of 1-(3-fluorobenzyl)-4-(3-fluorobenzyloxy)-1*H*-pyridin-2-one (0 14 g, 0 43 mmol) in AcOH (2 mL) was added a solution of bromine (72 mg, 0 45 mmol) in

AcOH (1 mL), and the reaction mixture was stirred for 5 min The reaction mixture was warmed to room temperature and the solvent was removed under reduced pressure $^1$H NMR (300 MHz, $CDCl_3$) δ 7 45-6 95 (m, 9H), 6 05 (d, $J$ = 8 Hz, 1H), 5 21 (s, 2H), 5 14 (s, 2H) ESHRMS m/z 406 0254 (M+H $C_{19}H_{15}BrF_2NO_2$ requires 406 0249)

Examples 115-123

The compounds of Examples 115-123 are prepared essentially according to the procedures set forth above for Example 107



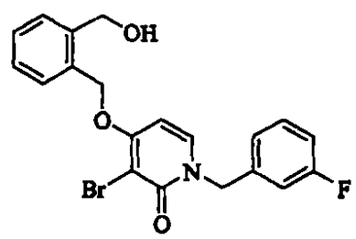

| Example No | R | MF | M+H Requires | ESHRMS m/z |
|---|---|---|---|---|
| Ex 115 | 3-methoxy | $C_{20}H_{17}BrFNO_3$ | 418 0449 | 418 0427 |
| Ex 116 | 4-tert-butyl | $C_{23}H_{23}BrFNO_2$ | 444 0969 | 444 0977 |
| Ex 117 | 3-methyl | $C_{20}H_{17}BrFNO_2$ | 402 0499 | 402 0513 |
| Ex 118 | 4-trifluoromethyl | $C_{20}H_{14}BrF_4NO_2$ | 456 0217 | 456 0210 |
| Ex 119 | 4-cyano | $C_{20}H_{14}BrFN_2O_2$ | 413 0295 | 413 0313 |
| Ex 120 | 2-methyl | $C_{20}H_{17}BrFNO_2$ | 402 0499 | 402 0502 |
| Ex 121 | 2-phenyl | $C_{25}H_{19}BrFNO_2$ | 464 0656 | 464 0654 |
| Ex 122 | 4-methoxy | $C_{20}H_{17}BrFNO_3$ | 418 0449 | 418 0455 |
| Ex 123 | 2-$CO_2CH_3$ | $C_{21}H_{17}BrFNO_4$ | 446 0398 | 446 0403 |

NMR characterization of compounds of Examples 115-123

| Example | NMR Data |
|---|---|

| No | |
|---|---|
| Ex 115 | $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7 35-7 20 (m, 4H), 7 15-6 85 (m, 5H) 6 07 (d, $J$ = 8 Hz 1H) 5 21 (s, 2H), 5 13 (s, 2H), 3 82 (s, 3H) |
| Ex 116 | $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7 45-7 20 (m, 4H), 7 10-6 95 (m, 3H) 6 11 (d $J$ = 8 Hz, 1H), 5 19 (s, 2H), 5 14 (s, 2H), 1 32 (s, 9H) |
| Ex 117 | $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7 40-6 90 (m, 9H), 6 08 (d, $J$ = 8 Hz, 1H), 5 19 (s 2H), 5 14 (s, 2H), 2 37 (s, 3H) |
| Ex 118 | $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7 67-7 53 (m, 4H) 7 31-724 (m, 2H) 7 09-6 98 (m, 3H), 6 04 (d, $J$ = 8 Hz 1H), 5 26 (s 2H) 5 14 (s, 2H) |
| Ex 119 | $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7 71 (dd, $J$ = 8, 2 Hz, 2H), 7 58-7 55 (m 2H) 7 29-7 25 (m 2H), 7 09 (d, $J$ = 8 Hz, 1H), 7 03-6 98 (m, 2H), 6 03 (dd $J$ = 8 2 Hz 1H) 5 26 (s, 2H), 5 15 (s, 2H) |
| Ex 120 | $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7 45-6 90 (m 9H), 6 15-6 10 (m, 1H), 5 18 (s, 2H), 5 15 (s, 2H), 2 38 (s, 3H) |
| Ex 121 | $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7 70-7 65 (m, 1H), 7 55-7 25 (m 9H) 7 14 (d, $J$ = 8 Hz, 1H), 7 10-6 95 (m, 3H), 5 81 (d, $J$ = 8 Hz, 1H), 5 12 (s, 2H), 5 08 (s, 2H) |
| Ex 122 | $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7 40-7 25 (m 3H), 7 15-6 90 (m, 6H), 6 15-6 10 (m, 1H), 5 16 (s 2H) 5 14 (s, 2H), 3 82 (s, 3H) |
| Ex 123 | $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8 06 (dd, $J$ = 8 1 Hz, 1H), 7 87 (d $J$ = 8 Hz 1H), 7 70-7 60- (m, 1H), 7 50-7 25 (m, 3H), 7 09 (d, $J$ = 8 Hz, 1H), 7 05-6 95 (m, 2H), 6 19 (d, $J$ = 8 Hz, 1H), 5 65 (s 2H), 5 16 (s, 2H), 3 91 (s 3H) |

Example 124



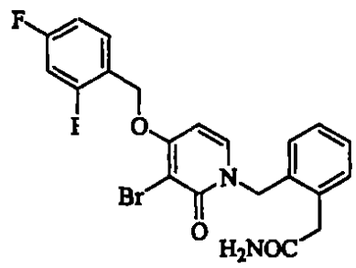

3-Bromo-1-(3-fluorobenzyl)-4-(2-hydroxymethylbenzyloxy)-1*H*-pyridin-2-one

Step 1 Preparation of 3-Bromo-1-(3-fluorobenzyl)-4-(2-hydroxymethylbenzyloxy)-1*H*-pyridin-2-one

To an ice-cold solution of methyl 2-[3-bromo-1-(3-fluorobenzyl)-2-oxo-1,2-dihydro-pyridin-4-yloxymethyl]benzoate

(0 12 g, 0 28 mmol) in THF (5 mL) was added $LiBH_4$ (0 15 mL of a 2 0 M solution in THF, 0 30 mmol), and the reaction mixture heated at reflux for 5 hours The reaction mixture was cooled to room temperature, the solvent was removed under reduced pressure, and the residue dissolved in EtOAc The organic solution was washed with brine, dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure $^1H$ NMR (300 MHz, DMSO-$d_6$) δ 7 98 (d, $J$ = 8 Hz, 1H), 7 46-7 28 (m, 5H), 7 15-7 10 (m, 3H), 6 56 (d, $J$ = 8 Hz, 1H), 5 35 (s, 2H), 5 25 (br s, 1H), 5 14 (s, 2H) ESHRMS m/z 418 0453 (M+H $C_{20}H_{18}BrFNO_3$ requires 418 0449)

Example 126




2-{2-[3-Bromo-4-(2,4-difluorobenzyloxy)-2-oxo-2*H*-pyridin-1-ylmethyl]-phenyl}acetamide

Step 1 Preparation of (2-Bromomethylphenyl)acetic acid
A solution of isochroman-3-one (1 5 g, 10 mmol) in 30% HBr in acetic acid (13 mL) was stirred at room temperature for 2 h, and 70 °C for 1 h The reaction mixture was cooled to room temperature, and poured into ice-water The precipitate was collected to afford (2-bromomethylphenyl)acetic acid as an off-white solid (2 15 g, 93%) $^1H$ NMR (300 MHz, DMSO-$d_6$) δ 7 45-7 23 (m, 4H), 4 73 (s, 2H), 3 73 (s, 2H)

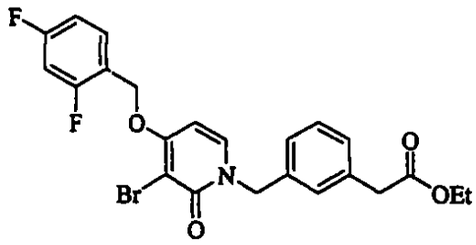
Step 2 Preparation of Methyl (2-Bromomethylphenyl)acetate

To an ice-cold solution of (2-bromomethylphenyl)acetic acid (1 g, 4 4 mmol) in THF (2 4 mL) was added trimethylsilyldiazomethane (3 mL of a 2 M solution in hexanes, 6 mmol), and the reaction mixture was stirred for 14 h The reaction was quenched with AcOH, and the solvent was removed under reduced pressure Purification by flash column chromatography (silica, eluent 98 2 to 94 6 methylene chloride/hexanes) afforded methyl (2-bromomethylphenyl)acetate as a light yellow solid (0 34 g, 32%) $^1$H NMR (300 MHz, $CDCl_3$) δ 7 40-7 20 (m, 4H), 4 59 (s, 2H), 3 81 (s 2H), 3 71 (s, 3H)

Step 3 Preparation of Methyl {2-[3-bromo-4-(2,4-difluorobenzyloxy)-2-oxo-2*H*-pyridin-1-ylmethyl]phenyl}acetate Methyl {2-[3-bromo-4-(2,4-difluorobenzyloxy)-2-oxo-2*H*-pyridin-1-ylmethyl]-phenyl}acetate was prepared by a procedure similar to the one described for EXAMPLE 74 (0 41 g, 68%) $^1$H NMR (300 MHz, $CDCl_3$) δ 7 55-6 81 (m, 8 H), 6 10 (d, $J$ = 6 Hz, 1H), 5 20 (s, 4 H), 3 78 (s, 2H), 3 60 (s, 3H)

Step 4 Preparation of 2-{2-[3-Bromo-4-(2,4-difluorobenzyloxy)-2-oxo-2*H*-pyridin-1-ylmethyl]phenyl}acetamide 2-{2-[3-Bromo-4-(2,4-difluorobenzyloxy)-2-oxo-2*H*-pyridin-1-ylmethyl]phenyl}-acetamide was prepared by a procedure similar to the one described for Example 102 (0 07 g, 72%) mp 178-183 °C, $^1$H NMR (300 MHz, DMSO-$d_6$) δ 7 89 (d, $J$ = 8 Hz, 1H), 7 66 (d, $J$ = 9 Hz, 1 H), 7 54 (br s, 1H), 7 35 (br s, 1H), 7 30-7 15 (m, 4H), 6 98 (br s, 1H), 6 85 (d, $J$ = 7 Hz, 1H), 6 60 (d, $J$ = 8 Hz, 1H), 5 32 (s, 2H), 5 19 (s, 2H), 3 62 (s, 2H) ESHRMS m/z 463 0442 (M+H $C_{21}H_{18}BrF_2N_2O_3$ requires 463 0463)

Example 127



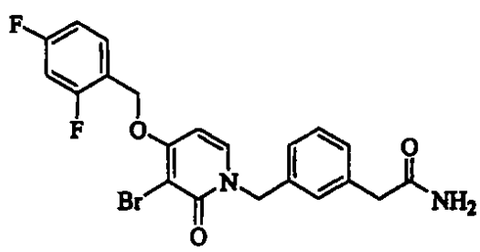
Ethyl {3-[3-Bromo-4-(2,4-difluorobenzyloxy)-2-oxo-2*H*-pyridin-1-ylmethyl]-phenyl}acetate

Step 1 Preparation of Ethyl (3-bromomethylphenyl) acetate
To a mixture of *m*-tolylacetic acid ethyl ester (3 0 g, 16 8 mmol) and N-bromosuccinimide (3 0 g, 16 8 mmol) was added carbon tetrachloride (45 mL), followed by benzoyl peroxide (5 mg), and the reaction mixture was heated at reflux for 16 h The reaction mixture was cooled to room temperature, filtered, and concentrated under reduced pressure Purification by flash column chromatography (silica, eluent 5 95 to 2 3 EtOAc/hexanes) afforded ethyl (3-bromomethylphenyl) acetate as an off-white solid (0 89 g, 21% ) $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7 32-7 21 (m, 4H), 4 48 (s, 2H), 4 16 (q, $J$ = 6 Hz, 2H), 3 63, (s, 2H), 1 27 (t, $J$ = 6 Hz, 3H)

Step 2 Preparation of Ethyl {3-[3-Bromo-4-(2,4-difluorobenzyloxy)-2-oxo-2*H*-pyridin-1-ylmethyl]phenyl}acetate
Ethyl {3-[3-Bromo-4-(2,4-difluorobenzyloxy)-2-oxo-2*H*-pyridin-1-ylmethyl]phenyl}-acetate was prepared by a procedure similar to the one described for EXAMPLE 74 (0 27 g, 69%) mp 95-98 °C, $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7 65-7 55 (m, 1H), 7 40-7 20 (m, 5H), 7 00-6 80 (m, 2H), 6 09 (d, $J$ = 9 Hz, 1H), 5 21 (s, 2H), 5 16 (s, 2H), 4 14 (q, $J$ = 6 Hz, 2H), 3 60 (s, 2H), 1 25 (t, $J$

= 6 Hz, 3H) ESHRMS m/z 492 0655 (M+H $C_{23}H_{21}BrF_2NO_4$ requires 435 0617)

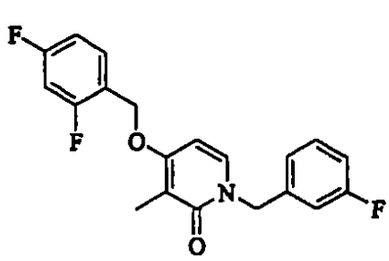
Example 128



2-{3-[3-Bromo-4-(2,4-difluorobenzyloxy)-2-oxo-2*H*-pyridin-1-ylmethyl] phenyl} acetamide

The title compound was prepared by a procedure similar to the one described for EXAMPLE 102 (0 07 g, 28%) mp 164-167 °C, $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 7 96 (d, $J$ = 9 Hz, 1H), 7 70-7 60 (m, 1H), 7 60 (br s, 1H), 7 50-7 10 (m, 6H), 6 89 (br s, 1H), 6 58 (d, $J$ = 9 Hz, 1H), 5 31 (s, 2H), 5 12 (s, 2H), 3 32 (s, 2H) ESHRMS m/z 463 0485 (M+H $C_{21}H_{18}BrF_2N_2O_3$ requires 463 0464)

Example 129



4-(2,4-Difluorobenzyloxy)-1-(3-fluorobenzyl)-3-methyl-1*H*-pyridin-2-one

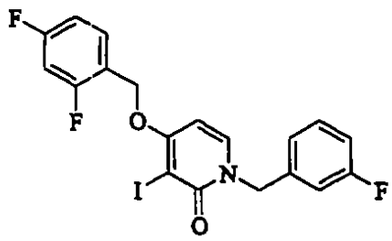
184

182

Step 1 Preparation of 4-(2,4-Difluorobenzyloxy)-1-(3-fluorobenzyl)-3-methyl-1*H*-pyridin-2-one

To a solution of 3-bromo-4-(2,4-difluorobenzyloxy)-1-(3-fluorobenzyl)-1*H*-pyridin-2-one (EXAMPLE 107) (0 14 g, 0 32 mmol), $K_2CO_3$ (88 mg, 0 64 mmol) and $Cs_2CO_3$ (0 10 g, 0 32 mmol) in dioxane (2 mL) was added $Pd(PPh_3)_4$ (18 mg, 0 12 mmol), followed by trimethylboroxine (40 mg, 0 32 mmol) The reaction mixture was degassed, purged with argon, and heated at reflux for 4 h The reaction mixture was cooled to room temperature, and partitioned between water and EtOAc The organic solution was washed with brine, dried ($Na_2SO_4$), filtered and concentrated under reduced pressure Purification by flash column chromatography (silica, eluent methylene chloride to 97 3 methylene chloride/MeOH) afforded 4-(2,4-difluorobenzyloxy)-1-(3-fluorobenzyl)-3-methyl-1*H*-pyridin-2-one as a white solid (0 09 g, 79% ) mp 127-129 °C, $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7 50-7 40 (m, 1H), 7 35-7 25 (m, 1H), 7 17 (d, $J$ = 9 Hz, 1H), 7 06 (d, $J$ = 6 Hz, 1H), 7 00-6 80 (m, 4H), 6 12 (d, $J$ = 9 Hz, 1H), 5 12 (s, 4H), 2 07 (s, 3H) ESHRMS m/z 360 1180 (M+H $C_{20}H_{16}F_3NO_2$ requires 360 1206)

Example 130



4-(2,4-Difluorobenzyloxy)-1-(3-fluorobenzyl)-3-iodo-1*H*-pyridin-2-one

Step 1 Preparation of 4-(2,4-Difluorobenzyloxy)-1-(3-fluorobenzyl)-1*H*-pyridin-2-one

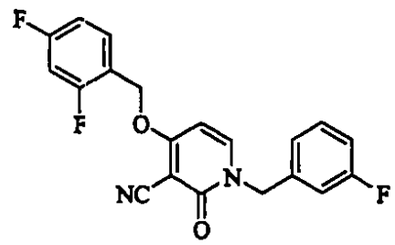
To a mixture of 1-(3-fluorobenzyl)-4-hydroxy-1*H*-pyridin-2-one (from Step 1, EXAMPLE 110) (0 92 g, 4 2 mmol) and $K_2CO_3$ (1 15 g, 8 4 mmol) in acetone (62 mL) was added 2,4-difluorobenzyl bromide (1 3 g, 6 3 mmol), and the reaction mixture was heated at reflux for 3 h The reaction mixture was cooled to room temperature, concentrated under reduced pressure, and the residue was dissolved in EtOAc The organic solution was washed with water and then brine, dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure Purification by flash column chromatography (silica, eluent methylene chloride to 95 5 methylene chloride/methanol) provided 4-(2,4-difluorobenzyloxy)-1-(3-fluorobenzyl)-1*H*-pyridin-2-one as a white solid (1 21 g, 84%) $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7 45-7 20 (m, 2H), 7 14 (d, $J$ = 8 Hz, 1H), 7 05-6 75 (m, 5H), 6 05 (d, $J$ = 3 Hz, 1H), 5 95 (dd, $J$ = 5, 3 Hz, 1H), 5 08 (s, 2H), 5 00 (s, 2H)

Step 2 Preparation of 4-(2,4-Difluorobenzyloxy)-1-(3-fluorobenzyl)-3-iodo-1*H*-pyridin-2-one

To a mixture of 4-(2,4-difluorobenzyloxy)-1-(3-fluorobenzyl)-1*H*-pyridin-2-one (0 15 g, 0 43 mmol) and N-iodosuccinimide (0 10 g, 0 46 mmol) in $CH_3CN$ (3 mL) was added dichloroacetic acid (13 mg, 0 10 mmol), and the reaction mixture was heated to 60 °C for 4 h The reaction mixture was cooled to room temperature, concentrated under reduced pressure, and the residue was dissolved in methylene chloride The organic solution was washed with a saturated solution of $NaHCO_3$ and then brine, dried ($Na_2SO_4$), filtered and concentrated under reduced pressure Purification by flash column chromatography (silica, eluent 90 10 methylene chloride/hexanes to 99 1 methylene chloride/methanol) provided 4-(2,4-difluorobenzyloxy)-1-(3-fluorobenzyl)-3-iodo-1*H*-pyridin-2-one as a white solid (0 15 g, 77%) mp 164-167 °C, $^1$H NMR (300 MHz,

$CDCl_3$) δ 7 65-7 55 (m 1H), 7 35-7 26 (m, 2H) 7 15-6 80 (m, 5H), 6 05 (d, $J$ = 6 Hz, 1H), 5 22 (s, 2H), 5 16 (s, 2H)
ESHRMS m/z 472 0033 (M+H $C_{19}H_{14}F_3INO_2$ requires 472 0018)

Example 131



4-(2,4-Difluorobenzyloxy)-1-(3-fluorobenzyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile

Step 1 Preparation of 4-Methoxy-2-oxo-1,2-dihydropyridine-3-carbonitrile
A solution of 2-(dimethylaminoethoxymethylene)malononitrile (1 97 g) in concentrated sulfuric acid (7 0 mL) was stirred at room temperature for 6 5 h The reaction mixture was poured into water, and the precipitate was collected by filtration $^1$H NMR (300 MHz, DMSO-$d_6$) δ 12 14 (br s, 1H), 7 79 (d, $J$ = 9 Hz, 1H), 6 35 (d, $J$ = 9 Hz, 1H), 3 98 (s, 3H)

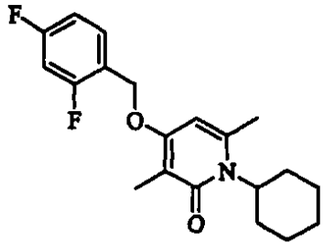
Step 2 Preparation of 1-(3-Fluorobenzyl)-4-methoxy-2-oxo-1,2-dihydro-pyridine-3-carbonitrile
1-(3-Fluorobenzyl)-4-methoxy-2-oxo-1,2-dihydro-pyridine-3-carbonitrile was prepared by a procedure similar to the one described for EXAMPLE 74 (0 56 g, 93%) $^1$H NMR (300 MHz, $CDCl_3$) δ 7 48 (d, $J$ = 9 Hz, 1H), 7 40-7 27 (m, 1H), 7 00-6 95 (m, 2H), 6 08 (d, $J$ = 9 Hz, 1H), 5 10 (s, 2H), 4 00 (s, 3H)

Step 3 Preparation of 1-(3-Fluorobenzyl)-4-hydroxy-2-oxo-1,2-dihydropyridine-3-carbonitrile

To a solution of sodium hydride (92 mg of a 60% dispersion in mineral oil, 2 3 mmol) in DMF (7 mL) was added ethanethiol (0 14 g, 2 2 mmol), followed by a solution of 1-(3-fluorobenzyl)-4-methoxy-2-oxo-1,2-dihydropyridine-3-carbonitrile (0 23 g, 0 89 mmol) in DMF (2 mL), and the reaction mixture was heated to 100 °C The reaction mixture was cooled to room temperature, acidified with 3 N HCl, and washed with EtOAc The organic solution was washed with brine, dried ($Na_2SO_4$), filtered and concentrated under reduced pressure to give 1-(3-fluorobenzyl)-4-hydroxy-2-oxo-1,2-dihydro-pyridine-3-carbonitrile as an off-white solid (0 20 g, 91%) $^1$H NMR (300 MHz, MeOD) $\delta$ 8 00 (s, 1H), 7 82 (d, $J$ = 8 Hz, 1H), 7 40-7 30 (m, 1H), 7 15-7 00 (m, 2H), 6 13 (d, $J$ = 8 Hz, 1H), 5 11 (s, 2H)

Step 4 Preparation of 4-(2,4-Difluorobenzyloxy)-1-(3-fluorobenzyl)-2-oxo-1,2-dihydro-pyridine-3-carbonitrile 4-(2,4-Difluorobenzyloxy)-1-(3-fluorobenzyl)-2-oxo-1,2-dihydro-pyridine-3-carbonitrile was prepared by a procedure similar to the one described for EXAMPLE 107 (0 09 g, 30%) mp 187-190 °C, $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7 60-7 45 (m, 2H), 7 40-7 30 (m, 1H), 7 10-6 50 (m, 5H), 6 13 (d, $J$ = 9 Hz, 1H), 5 27 (s, 2H), 5 10 (s, 2H)

Example 132



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1-Cyclohexyl-4-(2,4-difluorobenzyloxy)-3,6-dimethyl-1H-pyridin-2-one

Step 1 Preparation of Methyl 1-cyclohexyl-4-hydroxy-2,5-dimethyl-6-oxo-1,6-dihydro-pyridine-3-carboxylate

To a solution of 3-cyclohexylaminobut-2-enoic acid methyl ester (1 12 g, 5 72 mmol) in bromobenzene (20 mL) was added 2-methylmalonic acid bis-(2,4,6-trichloro-phenyl) ester (2 71 g, 5 72 mmol)and the reaction mixture was heated at 170 °C for 3 h The reaction mixture was cooled to room temperature, and concentrated under reduced pressure Purification by flash column chromatography (silica, eluent methylene chloride to 94 6 methylene chloride/MeOH) and recrystallization from hot MeOH provided methyl 1-cyclohexyl-4-hydroxy-2,5-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxylate as pale yellow crystals (0 34 g, 21%) $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 9 82 (s, 1H), 4 00-3 90 (m, 1H), 3 76 (s, 3H), 2 75-2 60 (m, 2H), 2 31 (s, 3H), 1 81 (s, 3H), 1 80-1 70 (m, 2H), 1 65-1 50 (m, 3H), 1 40-1 20 (m, 2H), 1 15-1 05 (m, 1H)

Step 2 Preparation of 1-Cyclohexyl-4-hydroxy-2,5-dimethyl-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid

A solution of methyl 1-cyclohexyl-4-hydroxy-2,5-dimethyl-6-oxo-1,6-dihydro-pyridine-3-carboxylate (0 35 g, 1 25 mmol) in 2 N NaOH (5 mL) was heated at reflux for 3 5 h The reaction mixture was cooled room temperature, acidified to pH 1-2 with 1 N HCl, and washed with EtOAc The organic solution was washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford 1-cyclohexyl-4-hydroxy-2,5-dimethyl-6-oxo-1,6-dihydrcpyridine-3-carboxylic acid as a white solid (0 31 g, 94%) $^1$H NMR (300 MHz, MeOD) $\delta$ 4 30-4 00 (br s, 1H), 2 76 (br s, 5H), 1 90 (s, 3H), 1 90-1 80 (m, 2H), 1 75-1 60 (m, 3 H), 1 50-1 15 (m, 3H)

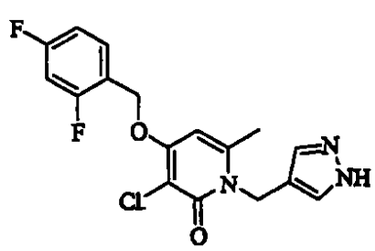
Step 3 Preparation of 1-Cyclohexyl-4-hydroxy-3,6-dimethyl-1*H*-pyridin-2-one

A solution of 1-cyclohexyl-4-hydroxy-2,5-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxylic acid (0 15 g, 0 57 mmol) in concentrated HCl (5 mL) was heated at reflux for 4 h The reaction mixture was cooled to room temperature, diluted with water and washed with EtOAc The organic solution was washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give 1-cyclohexyl-4-hydroxy-3,6-dimethyl-1*H*-pyridin-2-one as a white solid (0 2 g, 77%) $^1H$ NMR (300 MHz, DMSO-$d_6$) $\delta$ 9 81 (s, 1H), 5 73 (s, 1H), 3 95-3 75 (m, 1H), 2 80-2 55 (m, 2H), 2 25 (s, 3H), 1 85-1 40 (m, 5H), 1 72 (s, 3H), 1 38-1 05 (m, 3H)

Step 4 Preparation of 1-Cyclohexyl-4-(2,4-difluorobenzyloxy)-3,6-dimethyl-1*H*-pyridin-2-one

1-Cyclohexyl-4-(2,4-difluorobenzyloxy)-3,6-dimethyl-1*H*-pyridin-2-one was prepared by a procedure similar to the one described for EXAMPLE 107 (0 05 g, 16%) mp 118-120 °C, $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7 48-7 41 (m, 1H), 6 95-6 81 (m, 2H), 5 87 (s, 1H), 5 07 (s, 2H), 4 05-3 85 (m, 1H), 3 00-2 80 (m, 2H), 2 35 (s, 3H), 1 98 (s, 3H), 1 95-1 80 (m, 2H), 1 70-1 55 (m, 3H), 1 40-1 20 (m, 3H)

Example 133



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3-Chloro-4-(2,4-difluorobenzyloxy)-6-methyl-1-(1*H*-pyrazol-4-ylmethyl)-1*H*-pyridin-2-one

Step 1 Preparation of 4-Methylpyrazole-1-carboxylic acid *tert*-butyl ester

To a solution of 4-methyl-1H-pyrazole (1 g, 12 mmol) and DMAP (0 15 g, 1 2 mmol) in $CH_3CN$ (20 mL) was added di-*tert*-butyl dicarbonate (2 8 g, 13 mmol), and the reaction mixture was stirred for 1 h The reaction mixture was concentrated under reduced pressure, and the residue dissolved in EtOAc The organic solution was washed with 1 N HCl, water and then brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide 4-methyl-pyrazole-1-carboxylic acid *tert*-butyl ester as a light yellow oil (2 2 g, 100%) $^1$H NMR (300 MHz, $CDCl_3$) δ 7 83 (s, 1H), 7 53 (s, 1H), 2 09 (s, 3H), 1 64 (s, 9H)

Step 2 Preparation of 4-Bromomethylpyrazole-1-carboxylic acid *tert*-butyl ester

To a solution of 4-methylpyrazole-1-carboxylic acid *tert*-butyl ester (1 0 g, 5 5 mmol) in carbon tetrachloride (20 mL) was added N-bromosuccinimide (1 0 g, 5 6 mmol) and benzoyl peroxide (50 mg), and the reaction mixture was heated at reflux for 16 h The reaction mixture was cooled to room temperature, filtered, and concentrated under reduced pressure Purification by flash column chromatography (silica, 1 4 EtOAc/hexanes) provided 4-bromomethylpyrazole-1-carboxylic acid *tert*-butyl ester as a light yellow oil (0 42 g, 30%) $^1$H NMR (300 MHz, $CDCl_3$) δ 8 10 (s, 1H), 7 74 (s, 1H), 4 39 (s, 2H), 1 65 (s, 9H)

Step 3 Preparation of 4-[3-Chloro-4-(2,4-difluorobenzyloxy)-6-methyl-2-oxo-2*H*-pyridin-1-ylmethyl]pyrazole-1-carboxylic acid *tert*-butyl ester

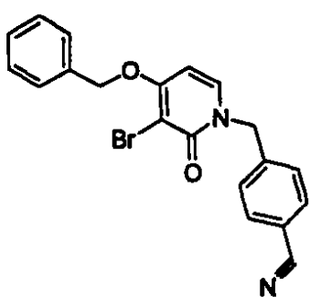
4-[3-Chloro-4-(2,4-difluorobenzyloxy)-6-methyl-2-oxo-2*H*-pyridin-1-ylmethyl]pyrazole-1-carboxylic acid *tert*-butyl ester was prepared by a procedure similar to the one described for EXAMPLE 632 $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8 09 (s, 1H), 7 72 (s, 1H), 7 53 (app q, $J$ = 6 Hz, 1H), 6 97-6 82 (m, 2H), 6 00 (s, 1H), 5 19 (s, 2H), 5 13 (s, 2H), 2 43 (s, 3H), 1 63 (s, 9H)

Step 4 Preparation of 3-Chloro-4-(2,4-difluorobenzyloxy)-6-methyl-1-(1*H*-pyrazol-4-ylmethyl)-1*H*-pyridin-2-one

4-[3-Chloro-4-(2,4-difluorobenzyloxy)-6-methyl-2-oxo-2*H*-pyridin-1-ylmethyl]pyrazole-1-carboxylic acid *tert*-butyl ester (0 16 g, 0 34 mmol) was heated to 140 °C for 16 h The reaction mixture was cooled to room temperature $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8 33 (s, 2H), 7 68 (d, $J$ = 6 Hz, 1H), 7 52 (app q, $J$ = 6 Hz, 1H), 6 93-6 83 (m, 2H), 6 47 68 (d, $J$ = 9 Hz, 1H), 5 19 (s, 2H), 5 24 (s, 2H), 5 20(s, 2H)

Example 134

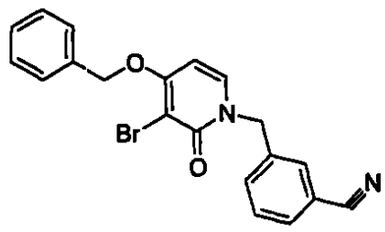
4-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]methyl}benzonitrile



Preparation of 4-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]methyl}benzonitrile 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one(1 0 g, 3 6 mmol) was dissolved in *N,N*-dimethylformamide (5 mL) α-Bromo-*p*-tolunitrile (0 85g, 4 3 mmol) was added followed by $K_2CO_3$ (0 59 g, 4 3 mmol) The resulting mixture was heated to 80 °C for 16 h The reaction was concentrated to an oil that was partitioned between water and ethyl acetate and extracted with ethyl acetate (3 x 100 ml) The organic extracts were combined, washed with brine, dried over $Na_2SO_4$, and filtered The filtrate was concentrated to an oil, and purified by chromatography (silica gel, hexane/ethyl acetate) to yield a white solid (0 65 g, 46%) $^1$H NMR (400 MHz, $CDCl_3$) δ 7 52 (d, *J* = 8 4 Hz, 2H), 7 41-7 31 (m, 7H), 7 23 (d, *J* = 7 6 Hz, 1H), 6 11 (d, *J* = 8 0 Hz, 1H), 5 24 (s, 2H), 5 18 (s, 2H) ES HRMS m/z 395 0404 (M+H $C_{20}H_{15}BrN_2O_2$ requires 395 0390)

Example 135

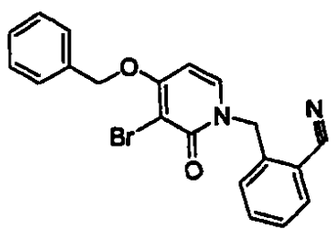
3-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]methyl}benzonitrile




The title compound was prepared by a procedure essentially as described in example 134 $^1$H NMR (400 MHz, $CDCl_3$) δ 7 62-7 54 (m, 3H), 7 45 (d, *J* = 7 6Hz, 1H), 7 43-7 31 (m, 5H), 7 26 (d, *J* = 1 6 Hz, 1H), 6 12 (d, *J* = 1 6 Hz, 1H), 5 24 (s, 2H), 5 15 (s, 2H) ES HRMS m/z 395 0420 (M+H $C_{20}H_{15}BrN_2O_2$ requires 395 0390)

Example 136

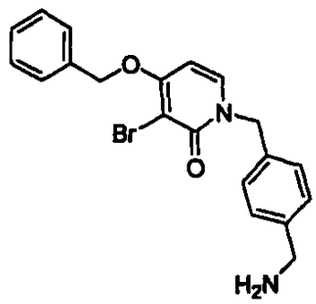
2-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]methyl}benzonitrile



The title compound was prepared by a procedure essentially as described in example 134 $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7 74 (d, $J$ = 8 4 Hz, 1H), 7 63 (dd, $J$ = 1 2, 8 0 Hz, 1H), 7 57 (dt, $J$ = 1 2, 8 4 Hz, 1H), 7 55 (d, $J$ = 8 0 Hz, 1H), 7 43-7 30 (m, 6H), 6 13 (d, $J$ = 8 0 Hz, 1H,), 5 33 (s, 2H), 5 23 (s, 2H) ES HRMS m/z 395 0398 (M+H $C_{20}H_{15}BrN_2O_2$ requires 395 0390)

Example 137

1-[4-(aminomethyl)benzyl]-4-(benzyloxy)-3-bromopyridin-2(1H)-one

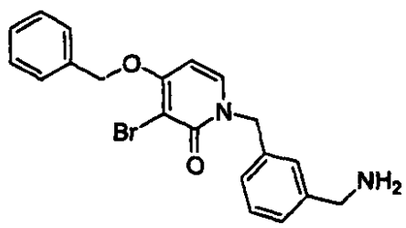


Preparation of 1-[4-(aminomethyl)benzyl]-4-(benzyloxy)-3-bromopyridin-2(1H)-one EXAMPLE 134 (100 mg, 0 25 mmol) was dissolved in tetrahydrofuran (2 mL) under $N_2$ Borane

dimethylsulfide complex (0 25 mL, 0 5mmol, 2M in tetrahydrofuran) was added The reaction was then heated to 70 C and shaken overnight The mixture was cooled and all the solvent was distilled under vacuum The resulting residue was partitioned between ethyl acetate and 0 2 N NaOH, and extracted with ethyl acetate (3 x 10 mL) The organic extracts were combined, washed with brine, dried over $Na_2SO_4$, and filtered The filtrate was concentrated to an oil, and triturated with dichloromethane and hexane to give an off-white solid (80 mg, 80%) $^1$H NMR (400 MHz, $d_6$DMSO) $\delta$ 7 90 (d, $J$ = 7 6 Hz, 1H), 7 43-7 21 (m, 9H), 6 70 (d, $J$=7 6 Hz, 1H), 5 29 (s, 2H), 5 08 (s, 2H), 3 71 (s, 2H) ES HRMS m/z 399 0721 (M+H $C_{20}H_{19}BrN_2O_2$ requires 399 0703)

Example 138

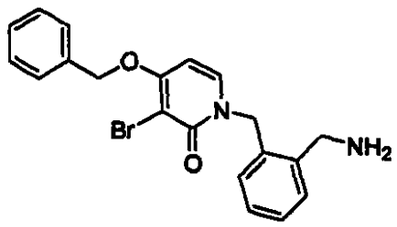
1-[3-(aminomethyl)benzyl]-4-(benzyloxy)-3-bromopyridin-2(1H)-one




The title compound was prepared by a procedure essentially as described in Example 137 using the title compound of Example 135 as starting material $^1$H NMR (400 MHz, $d_6$DMSO) $\delta$ 7 90 (d, $J$ = 7 6 Hz, 1H), 7 44-7 22 (m, 9H), 6 50 (d, $J$=7 6 Hz, 1H), 5 30 (s, 2H), 5 12 (s, 2H), 3 88 (s, 2H) ES HRMS m/z 399 0730 (M+H $C_{20}H_{19}BrN_2O_2$ requires 399 0703)

Example 139

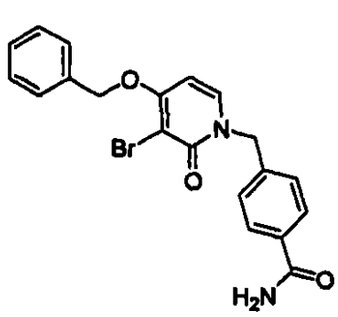
1-[2-(aminomethyl)benzyl]-4-(benzyloxy)-3-bromopyridin-2(1H)-one



The title compound was prepared by a procedure essentially as described in Example 137 using the title compound of Example 136 as starting material $^1$H NMR (400 MHz, $d_6$DMSO) $\delta$ 7 88 (d, $J$ = 8 0 Hz, 1H), 7 45-7 34 (m, 5H), 7 26- 7 21 (m, 3H), 6 85 (d, $J$=7 2 Hz, 1H), 6 53 (d, $J$=7 6 Hz, 1H), 5 32 (s, 2H), 5 12 (s, 2H), 3 90 (s, 2H) ES HRMS m/z 399 0699 (M+H $C_{20}H_{19}BrN_2O_2$ requires 399 0703)

Example 140

4-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]methyl}benzamide

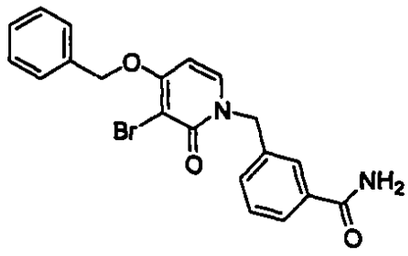


Preparation of 4-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]methyl}benzamide EXAMPLE 134 (100 mg, 0 25 mmol) was added to a suspension of potassium fluoride (40% on alumina) in t-butyl alcohol, heated to 85 C, and stirred for 20h The

alumina was removed by filtration and washed with dichloromethane and water The resulting filtrate was separated and the aqueous layer was extracted with dichloromethane (2 x 20 mL) The organic extracts were combined, dried over $Na_2SO_4$, and filtered The filtrate was concentrated to an oil Trituration with dichloromethane and hexane gave a solid (11 5 mg, 11%) $^1$H NMR (400 MHz, $d_6$DMSO) $\delta$ 7 94 (d, $J$ = 8 0 Hz, 1H), 7 80 (d, $J$ = 8 4 Hz, 2H), 7 43-7 29 (m, 7H), 6 51 (d, $J$=7 6 Hz, 1H), 5 31 (s, 2H), 5 16 (s, 2H) ES HRMS m/z 413 0541 (M+H $C_{20}H_{17}BrN_2O_3$ requires 413 0495)

Example 141

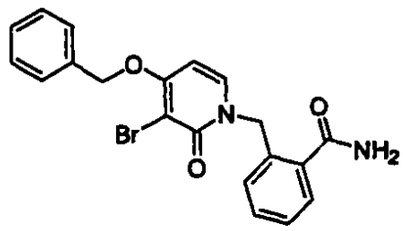
3-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]methyl}benzamide




The title compound was prepared by a procedure essentially as described in Example 140 using the title compound of Example 135 as starting material $^1$H NMR (400 MHz, $d_6$DMSO) $\delta$ 7 95 (d, $J$ = 7 6 Hz, 2H), 7 76 (m, 2H), 7 43-7 26 (m, 8H), 6 51 (d, $J$=7 6 Hz, 1H), 5 31 (s, 2H), 5 15 (s, 2H) ESHRMS m/z 413 0497 (M+H $C_{20}H_{17}BrN_2O_3$ requires 413 0495)

Example 142

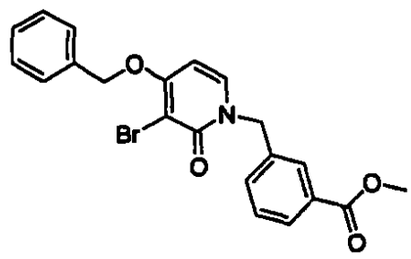
2-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]methyl}benzamide



The title compound was prepared by a procedure essentially as described in Example 140 using the title compound of Example 136 as starting material $^1$H NMR (400 MHz, $d_6$DMSO) $\delta$ 7 78 (d, $J$ = 7 6 Hz, 1H), 7 54 (dd, $J$ = 1 6, 7 6 Hz, 1H), 7 45 (d, $J$=7 6 Hz, 2H), 7 44-7 32 (m, 5H), 7 15 (d, $J$=7 6 Hz, 1H), 6 49 (d, $J$=7 6 Hz, 1H), 5 39 (s, 2H), 5 30 (s, 2H) ES HRMS m/z 4413 0506 (M+H $C_{20}H_{17}BrN_2O_3$ requires 413 0495)

Example 143

Methyl 3-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]methyl}benzoate

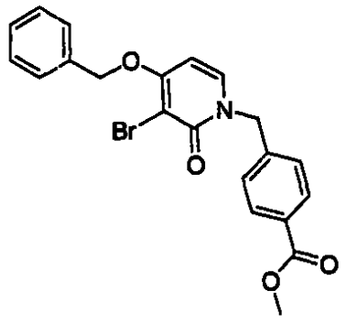


Preparation of Methyl 3-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]methyl}benzoate EXAMPLE 134 (100 mg, 0 25 mmol) was suspended in methanol and cooled to 0 C HCl (g) was bubbled through the mixture until saturated (~30 minutes) The reaction was warmed to ambient temperature and stirred for 4 hours HCl and methanol were removed *in vacuo*, yielding an oil, that was purified by chromatography (silica gel, hexane/ethyl acetate) to yield a white solid (3 mg, 3%) $^1$H NMR

(400 MHz, $CD_3OD$) $\delta$ 7 98 (*app* d, $J$ = 8 0 Hz, 2H), 7 77 (*app* d, $J$ = 8 0 Hz, 1H), 7 55 (*app* d, $J$ = 8 0 Hz, 2H), 7 41-7 35 (m, 5H), 6 52 (d, $J$ = 7 6 Hz, 1H), 5 31 (s, 2H), 5 27 (s, 2H), 3 88, (s, 3H) API-ES MS m/z 429 0 (M+H $C_{21}H_{18}BrNO_4$ requires 428 0492)

Example 144

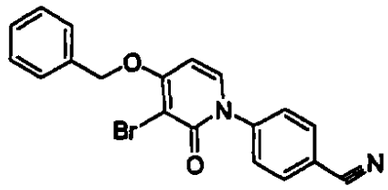
Methyl 4-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]methyl}benzoate




The title compound was prepared by a procedure essentially as described in Example 143 using the title compound of Example 134 as starting material $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ 7 94 (*app* d, $J$ = 8 4 Hz, 2H), 7 76 (*app* d, $J$ = 7 6 Hz, 1H), 7 46 (*app* d, $J$ = 8 0 Hz, 2H), 7 39-7 35 (m, 5H), 6 51 (d, $J$=7 6 Hz, 1H), 5 31 (s, 2H), 5 26 (s, 2H), 3 88, (s, 3H) ES HRMS m/z 428 0492 (M+H $C_{21}H_{18}BrNO_4$ requires 428 0492)

Example 145

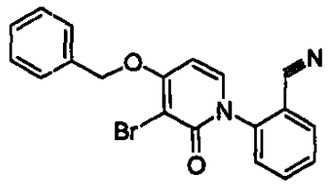
4-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]benzonitrile



Preparation of 4-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]benzonitrile 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one(100 mg, 0 36 mmol) was suspended in dimethylsulfoxide (5 mL), cesium carbonate (375 mg, 1 15 mmol) was added and the reaction was shaken for 5 minutes 4-Fluorobenzonitrile (52 mg, 0 43 mmol was then added, the reaction was heated to 80 C, and stirred Reaction was monitored by LC/MS, and after 4h was heated to 100 C and stirred for 16 hours Reaction mixture was partitioned between water and ethyl acetate and extracted with ethyl acetate (5 x 50 mL) The organic extracts were combined, washed with brine, dried over $Na_2SO_4$, and filtered The filtrate was concentrated to an oil, and purified by chromatography (silica gel, hexane/ethyl acetate) to yield a white solid (40 mg, 29%) $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7 77 (d, $J$ = 8 4 Hz, 2H), 7 52 (d, $J$ = 8 8 Hz, 2H), 7 44-7 42 (m, 4H), 7 28 (d, $J$ = 7 6 Hz, 1H), 7 26 (s, 1H), 6 24 (d, $J$ = 7 6 Hz, 1H), 5 31, (s, 2H) ES HRMS m/z 381 0230 (M+H $C_{19}H_{13}BrN_2O_2$ requires 381 0233)

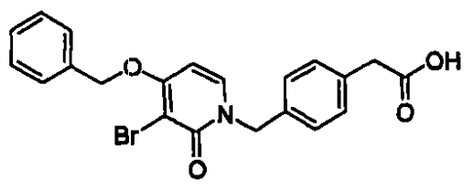
Example 146

2-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]benzonitrile



Preparation of 2-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]benzonitrile 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one(100 mg, 0 36 mmol) was suspended in dimethylsulfoxide (5 mL), cesium carbonate (375 mg, 1 15 mmol) was added and the reaction was shaken for 5 minutes 4-Fluorobenzonitrile (52 mg, 0 43 mmol) was then added and the reaction was heated to 80 C with stirring Reaction was monitored by LC/MS, and after 4h was heated to 100 C and stirred for 16 hours The reaction mixture was partitioned between water and ethyl acetate and extracted with ethyl acetate (5 x 50 mL) The organic extracts were combined, washed with brine, dried over $Na_2SO_4$, and filtered The filtrate was concentrated to an oil, and purified by chromatography (silica gel, hexane/ethyl acetate) to yield a white solid (18 mg, 13%) $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7 81 (dd, $J$ = 1 2, 8 4 Hz, 1H), 7 73 (dt, $J$ = 1 2, 8 0 Hz, 1H), 7 57 (dt, $J$ = 0 8, 8 0 Hz, 1H), 7 50-7 36 (m, 6H), 7 27 (d, $J$ = 8 0 Hz, 1H), 6 28 (d, $J$ = 8 0 Hz, 1H), 5 31 (s, 2H) ES HRMS m/z 381 0249 (M+H $C_{19}H_{13}BrN_2O_2$ requires 381 0233) Example 147

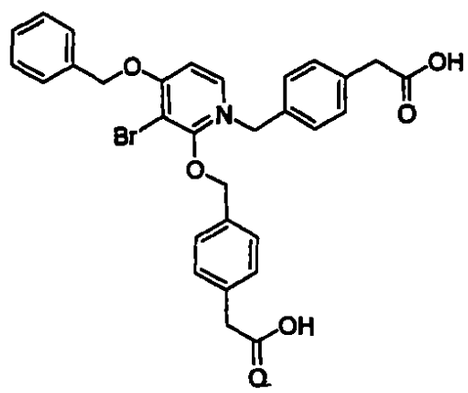
(4-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]methyl}phenyl)acetic acid



3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one(0 5g, 1 78 mmol) was dissolved in *N,N*-dimethylformamide (5 mL) 4-(Bromomethyl)phenylacetic acid (0 5 g, 2 14 mmol) was added followed by $K_2CO_3$ (0 3 g, 2 14 mmol) The reaction was heated to 80 C and shaken for 16 hours, then heated to 100 C and shaken for 16 hours more The reaction mixture was partitioned between water and ethyl acetate and extracted with ethyl acetate (2 x 50 mL) The aqueous layer was acidified (pH 2) with 1N HCl and extracted with ethyl acetate (3 x 50 ml) The organic extracts were combined, washed with brine, dried over $Na_2SO_4$, and filtered The filtrate was concentrated to an oil, and purified by chromatography (silica gel, hexane/ethyl acetate) followed by reversed phase chromatography ($C_{18}$, 0 1% aqueous trifluoroacetic acid /acetonitrile) to yield a white solid (25 mg, 3%) $^1$H NMR (400 MHz, $CDCl_3$) δ 7 40-7 38 (m, 3H), 7 25-7 20 (m, 7H), 6 05 (d, *J* = 8 0 Hz, 1H), 5 21 (s, 2H), 5 13, (s, 2H), 3 62, (s, 2H) ES HRMS m/z 428 0510 (M+H $C_{21}H_{18}BrNO_4$ requires 428 0492)

Example 148

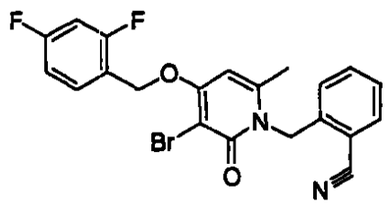
{4-[(4-(benzyloxy)-3-bromo-2-{[4-(carboxymethyl)benzyl]oxy}-1lambda$^5$-pyridin-1-yl)methyl]phenyl}acetic acid



Preparation of {4-[(4-(benzyloxy)-3-bromo-2-{[4-(carboxymethyl)benzyl]oxy}-1lambda$^5$-pyridin-1-yl)methyl]phenyl}acetic acid The desired product was isolated by reversed phase chromatography ($C_{18}$, 0 1% aqueous trifluoroacetic acid/acetonitrile) using the preparation of Example 147 yielding a white solid (53 mg, 5%) $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7 40-7 38 (m, 3H), 7 27-7 24 (m, 6H), 7 20 (d, $J$ = 7 6 Hz, 1H), 7 14 (d, $J$ = 8 0 Hz, 2H), 7 08 (d, $J$ = 8 4 Hz, 1H), 6 06 (d, $J$ = 7 6 Hz, 1H), 5 21 (s, 2H), 5 11 (s, 2H), 5 11 (s, 2H), 3 63 (s, 2H), 3 58 (s, 2H) ES HRMS m/z 576 1009(M+H $C_{30}H_{28}BrNO_6$ requires 576 1016)

Example 149

2-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzonitrile

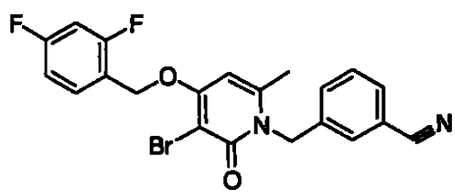



Preparation of 2-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzonitrile 3-bromo-4-(2,4-difluorophenoxy)-6-methylpyridin-2(1*H*)-one (50 mg, 0 15 mmol) was dissolved in tetrahydrofuran (2 mL) α-Bromo-*o*-tolunitrile (44 mg, 0 23 mmol) was added followed by sodium hydride (7 2 mg, 0 18 mmol, 60% in mineral oil) and sodium iodide (56 mg, 0 38 mmol) The reaction was heated to 50 C and stirred for 16 hours The reaction was filtered through Celite® and the filtrate was concentrated to an oil that was partitioned between water and ethyl acetate and extracted with

ethyl acetate (4 x 10 mL) The organic extracts were combined, washed with brine, dried over $MgSO_4$, and filtered The filtrate was concentrated to an oil, and purified by chromatography (silica gel, hexane/ethyl acetate) to yield a white solid (25 mg, 37%) $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7 68 (dd, *J* = 8 0, 1 2 Hz, 1H), 7 58 (*app* q, *J* = 8 8 Hz, 1H), 7 52 (dt, *J* = 8 0 & 1 2 Hz, 1H), 7 38 (t, *J* = 7 6 Hz, 1H), 7 08 (d, *J* = 8 8 Hz, 1H), 7 00-6 93 (m, 1H), 6 89-6 84 (m, 1H), 6 05 (s, 1H), 5 57 (s, 2H), 5 22 (s, 2H), 2 28, (s, 3H) ES HRMS m/z 445 0335 (M+H $C_{21}H_{15}BrF_2N_2O_2$ requires 445 0358)

Example 150

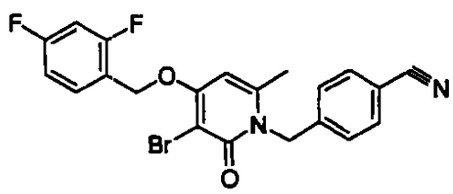
3-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzonitrile




The title compound was prepared by a procedure essentially as described in Example 149 using 3-bromo-4-(2,4-difluorophenoxy)-6-methylpyridin-2(1H)-one (1 g, 3 0 mmol) as starting material $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 7 61-7 55 (m, 2H), 7 45-7 41 (m, 3H), 6 98-6 94 (m, 1H), 6 89-6 84 (m, 1H), 6 03 (s, 1H), 5 36 (s, 2H), 5 22 (s, 2H), 2 30, (s, 3H) ES HRMS m/z 445 0349 (M+H $C_{21}H_{15}BrF_2N_2O_2$ requires 445 0358)

Example 151

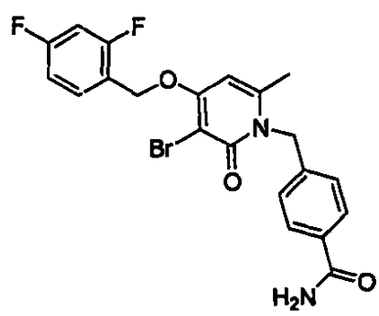
4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzonitrile



The title compound was prepared by a procedure essentially as described in Example 149 using 3-bromo-4-(2,4-difluorophenoxy)-6-methylpyridin-2(1H)-one (1 g, 3 0 mmol) as starting material $^1$H NMR (400 MHz, $CDCl_3$) δ 7 61 (d, *J* = 8 4 Hz, 2H), 7 62-7 56 (m, 1H), 7 27 (d, *J* = 8 8 Hz, 2H), 6 95 (*app* t, *J* = 8 4 Hz, 1H), 6 88-6 83 (m, 1H), 6 03 (s, 1H), 5 39 (s, 2H), 5 21 (s, 2H), 2 28 (s, 3H) ES HRMS m/z 445 0359 (M+H $C_{21}H_{15}BrF_2N_2O_2$ requires 445 0358)

Example 152

4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzamide

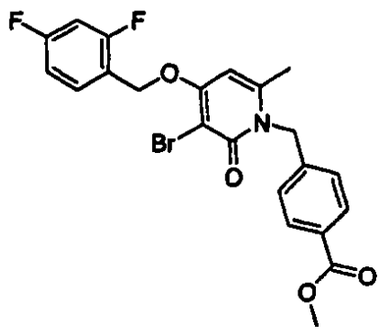


EXAMPLE 151 (50 mg, 0 11 mmol) was added to a suspension or potassium fluoride (40% on alumina) in t-butyl alcohol The

reaction was heated to 90 C and stirred for 20 hours Alumina was removed by filtration and washed with dichloromethane and water The resulting filtrate was separated and the aqueous layer was extracted with dichloromethane (2 x 20 mL) The organic extracts were combined, dried over $Na_2SO_4$ and filtered The filtrate was concentrated to an oil which was purified by chromatography (silica gel, hexane/ethyl acetate) to yield a white solid, yielding the product (13 mg, 25%) $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7 75 (*app* d, $J$ = 8 4 Hz, 2H), 7 58 (*app* q, $J$ = 8 4 Hz, 1H), 7 24 (d, $J$ = 8 4 Hz, 2H), 6 98-6 94 (m, 1H), 6 89-6 83 (m, 1H) 6 01 (s, 1H), 5 40 (s, 2H), 5 21 (s, 2H), 2 28 (s, 3H) ES HRMS m/z 463 0486 (M+H $C_{21}H_{17}BrF_2N_2O_3$ requires 463 0463)

Example 153

Methyl 4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzoate

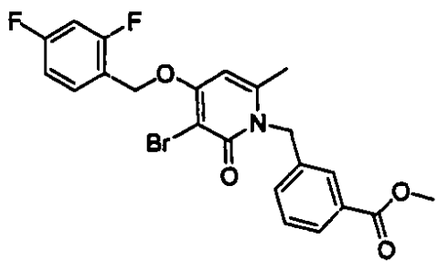


EXAMPLE 151 (50 mg, 0 11 mmol) was suspended in methanol and cooled to 0 C HCl (g) was bubbled through the mixture until saturated (~30 minutes) Reaction was sealed, warmed to ambient temperature, and stirred for 2 hours HCl and methanol were removed *in vacuo*, yielding an oil, that was purified by chromatography (silica gel, hexane/ethyl acetate)

to yield a white solid (19 mg, 36%) $^1$H NMR (400 MHz, $CDCl_3$) δ 7 97 (*app* d, *J* = 8 4 Hz, 2H), 7 58 (*app* q, *J* = 8 0 Hz, 1H), 7 22 (d, *J* = 8 4 Hz, 2H), 6 95 (*app* dt, *J* = 1 5, 9 6 Hz, 1H), 6 89-6 83 (m, 1H), 6 00 (s, 1H), 5 41 (s, 2H), 5 21 (s, 2H), 3 90, (s, 3H), 2 27 (s, 3H) ES HRMS m/z 478 0461 (M+H $C_{22}H_{18}BrNO_4$ requires 478 0460)

Example 154

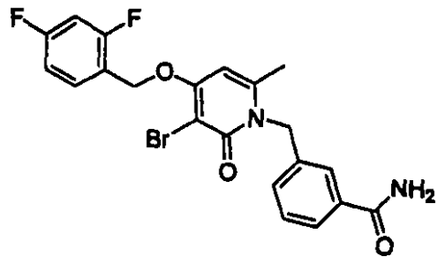
Methyl 3-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzoate



The title compound was prepared by a procedure essentially as described in Example 149 using the title compound of Example 150 as starting material $^1$H NMR (400 MHz, $CDCl_3$) δ 7 95-7 92 (m, 1H), 7 84 (bs, 1H), 7 58 (*app* q, *J* = 8 0 Hz, 1H), 7 39-7 37 (m, 2H), 6 95 (*app* dt, *J* = 1 6, 8 4 Hz, 1H), 6 88-6 83 (m, 1H), 6 00 (s, 1H), 5 40 (s, 2H), 5 21 (s, 2H), 3 90, (s, 3H), 2 30 (s, 3H) ES HRMS m/z 478 0449 (M+H $C_{22}H_{18}BrNO_4$ requires 478 0460)

Example 155

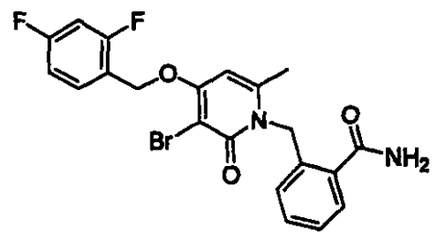
3-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzamide



The title compound was prepared by a procedure essentially as described in Example 152 using the title compound of Example 150 as starting material $^1$H NMR (400 MHz, $CDCl_3$) δ 7 68-7 66 (m, 2H), 7 57 (*app* q, *J* = 8 4 Hz, 1H), 7 42-7 34 (m, 2H), 6 98-6 92 (m, 1H), 6 89-6 83 (m, 1H) 6 01 (s, 1H), 5 39 (s, 2H), 5 21 (s, 2H), 2 28 (s, 3H) ES HRMS m/z 463 0461 (M+H $C_{21}H_{17}BrF_2N_2O_3$ requires 463 0463)

Example 156

2-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzamide

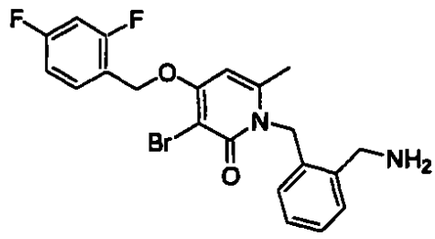


The title compound was prepared by a procedure essentially as described in Example 152 using the title compound of Example 149 as starting material $^1$H NMR (400 MHz, $CDCl_3$) δ 7 68-7 66 (m, 2H), 7 57 (*app* q, *J* = 8 4 Hz, 1H), 7 42-7 34 (m, 2H), 6 98-6 92 (m, 1H), 6 89-6 83 (m, 1H) 6 01 (s, 1H), 5 39 (s, 2H), 5 21 (s, 2H), 2 28 (s, 3H) ES HRMS m/z 463 0461 (M+H $C_{21}H_{17}BrF_2N_2O_3$ requires 463 0463) $^1$H NMR (400 MHz, $CDCl_3$) δ

7 56-7 55 (m, 2H), 7 32-7 25 (m, 2H), 7 00-6 94 (m, 1H), 6 88-6 84 (m, 1H), 6 81-6 79 (m, 1H) 6 11 (s, 1H), 5 51 (s, 2H), 5 24 (s, 2H), 2 43 (s, 3H) ESHRMS m/z 463 0467 (M+H $C_{21}H_{17}BrF_2N_2O_3$ requires 463 0463)

Example 157

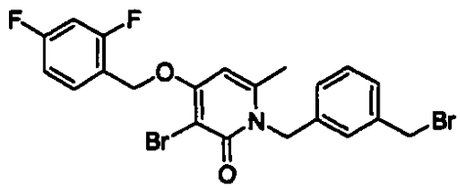
1-[2-(aminomethyl)benzyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one



EXAMPLE 149 (50 mg, 0 11 mmol) was dissolved in tetrahydrofuran (2 mL) under $N_2$ Borane-methyl sulfide complex (0 11 mL, 0 22 mmol, 2M in tetrahydrofuran) was added The reaction was then heated to 70 C and shaken overnight After cooling to ambient temperature, all the solvent was distilled under vacuum The resulting residue was partitioned between ethyl acetate and 0 2 N NaOH, and extracted with ethyl acetate (3 x 20 mL) The organic extracts were combined, washed with brine, and dried over $Na_2SO_4$, and filtered The filtrate was concentrated to an oil, and purified by chromatography (silica gel, hexane/ethyl acetate) to yield a white solid, to give product (19 mg, 39%) $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7 56-7 55 (m, 2H), 7 32-7 25 (m, 2H), 7 00-6 94 (m, 1H), 6 88-6 84 (m, 1H), 6 81-6 79 (m, 1H), 6 11 (s, 1H), 5 44 (s, 2H), 5 17 (s, 2H), 4 59 (s, 2H), 2 18 (s, 3H) ESHRMS m/z 449 0692 (M+H $C_{21}H_{19}BrF_2N_2O_2$ requires 449 0671)

Example 158

3-bromo-1-[3-(bromomethyl)benzyl]-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one

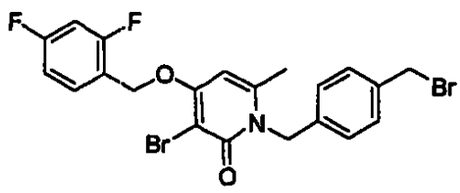


Preparation of 3-bromo-1-[3-(bromomethyl)benzyl]-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (2 g, 6 06 mmol) was suspended in 1,4-dioxane (250 mL) α,α'-Dibromo-*m*-xylene (8 g, 30 3 mmol) was added followed by sodium hydride (0 3 g, 7 5 mmol, 60% in mineral oil) The reaction was heated to 60 C and stirred for 16 hours The reaction was filtered through Celite® and the filtrate was concentrated to an oil that was partitioned between water and dichloromethane and extracted with dichloromethane (4 x 250 mL) The organic extracts were combined, washed with brine, dried over $Na_2SO_4$, and filtered The filtrate was concentrated to an oil, and purified by chromatography (silica gel, hexane/ethyl acetate) to yield a white solid (1 2g, 38%) $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7 57 (*app* q, $J$ = 7 6 Hz, 1H), 7 28-7 25 (m, 2H), 7 17 (s, 1H), 7 08 (m,1H), 6 94 (*app* dt, $J$ = 1 2, 9 6 Hz, 1H), 6 87-6 82 (m, 1H), 5 99 (s, 1H), 5 34 (s, 2H), 5 20 (s, 2H), 4 43 (s, 2H), 2 29 (s, 3H) ES HRMS m/z 511 9672 (M+H $C_{21}H_{17}Br_2F_2NO_2$ requires 511 9667)

Example 159

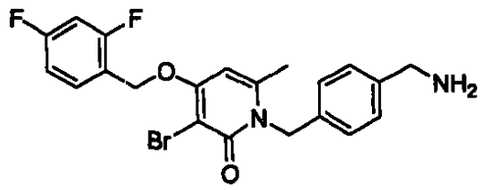
3-bromo-1-[4-(bromomethyl)benzyl]-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one



The title compound was prepared by a procedure essentially as described in Example 158 $^1$H NMR (400 MHz, $CDCl_3$) δ 7 68-7 66 (m, 2H), 7 57 (*app* q, *J* = 8 4 Hz, 1H), 7 42-7 34 (m, 2H), 6 98-6 92 (m, 1H), 6 89-6 83 (m, 1H) 6 01 (s, 1H), 5 39 (s, 2H), 5 21 (s, 2H), 2 28 (s, 3H) ES HRMS m/z 463 0461 (M+H $C_{21}H_{17}BrF_2N_2O_3$ requires 463 0463) $^1$H NMR (400 MHz, $CDCl_3$) δ 7 56 (*app* q, *J* = 7 6 Hz, 1H), 7 32(d, *J* = 8 0 Hz, 2H), 7 14 (d, *J* = 8 0 Hz, 2H), 6 94 (*app* t, *J* = 8 4 Hz, 1H), 6 87-6 82 (m, 1H), 5 98 (s, 1H), 5 33 (s, 2H), 5 19 (s, 2H), 4 44 (s, 2H), 2 29 (s, 3H) ES HRMS m/z 511 9683 (M+H $C_{21}H_{17}Br_2F_2NO_2$ requires 511 9667)

Example 160

1-[4-(aminomethyl)benzyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one

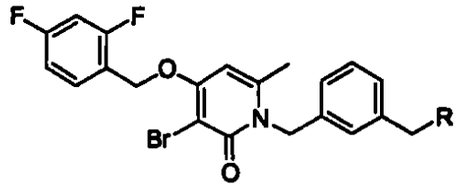


Example 159 (200 mg, 0 39 mmol) was suspended in methanol (3 mL) and cooled to -78 C Ammonia (g) was bubbled through the mixture for 30 minutes The reaction vessel was sealed

allowed to reach ambient temperature, and stirred for 4 hours The solvent and ammonia were removed from the reaction *in vacuo* with stirring and the resulting oil was triturated with ether to yield a solid (174 mg, 99%) $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 7 61 (q, $J$ = 7 6 Hz, 1H), 7 40 (d, $J$ = 8 0 Hz, 2H), 7 20 (d, $J$ = 8 0 Hz, 2H), 7 03 (*app* t, $J$ = 8 8 Hz, 2H), 6 51 (s, 1H), 5 43 (s, 2H), 5 29 (s, 2H), 4 07 (s, 2H), 2 36 (s, 3H) ES HRMS m/z 449 0673 ($C_{21}H_{19}BrF_2N_2O_2$ requires 449 0671)

Examples 161-168

The compounds of Examples 161-168 are prepared essentially according to the procedures set forth above for Examples 158-160 or by using the compound of Example 158




| Example No | R | MF | M+H Requires | ESHRMS m/z |
|---|---|---|---|---|
| Ex 161 | -$NH_2$ | $C_{21}H_{19}BrF_2N_2O_2$ | 449 0671 | 449 0694 |
| Ex 162 | morpholin-4-yl | $C_{25}H_{25}BrF_2N_2O_3$ | 519 1089 | 519 1132 |
| Ex 163 | dimethylamino | $C_{23}H_{23}BrF_2N_2O_2$ | 477 0984 | 477 0991 |
| Ex 164 | isopropylamino | $C_{24}H_{25}BrF_2N_2O_2$ | 491 1140 | 491 1121 |
| Ex 165 | piperidin-1-yl | $C_{26}H_{27}BrF_2N_2O_2$ | 517 1297 | 517 1341 |
| Ex 166 | (2-hydroxyethyl)amino | $C_{23}H_{23}BrF_2N_2O_3$ | 493 0933 | 493 0961 |
| Ex 167 | bis(2-hydroxyethyl)amino | $C_{25}H_{27}BrF_2N_2O_4$ | 537 1195 | 537 1171 |
| Ex 168 | piperazin-1-yl | $C_{25}H_{26}BrF_2N_3O_2$ | 518 1249 | 518 1280 |

NMR characterization of compounds of Examples 161-168

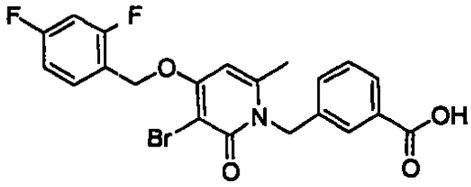
| Ex. No. | NMR Data |
|---|---|

196

| | |
|---|---|
| Ex 161 | $^1$H NMR (400 MHz, $CD_3OD$) δ 7 61 (q, *J* = 7 6 Hz 1H), 7 42-7 35 (m, 2H), 7 24-7 20 (m 2H), 7 03 (*app* t, *J* = 8 4 Hz, 2H), 6 51 (s 1H) 5 43 (s, 2H), 5 29 (s 2H) 4 07 (s, 2H) 2 04 (s, 3H) |
| Ex 162 | $^1$H NMR (400 MHz $CD_3OD$) δ 7 58 (*app* q, *J* = 7 6 Hz, 1H), 7 26-7 22 (m, 2H), 7 15 (s 2H) 7 01 (*app* d *J* = 6 4 Hz, 2H), 6 95 (*app* dt, *J* = 1 2 8 0 Hz, 1H), 6 88-6 82 (m, 1H) 5 98 (s, 1H), 5 35 (s 2H) 5 20 (s 2H) 3 69 (t *J* = 8 4 Hz 4H) 3 46 (s, 2H) 2 41 (m, 4H), 2 29 (s 3H) |
| Ex 163 | $^1$H NMR (400 MHz $CD_3OD$) δ 7 61 (*app* q *J* = 7 6 Hz 1H), 7 25-7 14 (m, 3H), 7 01-6 92 (m, 2H) 6 85 (m 1H) 5 97 (s, 1H) 5 36 (s, 2H) 5 20 (s 2H) 3 38 (s 2H) 2 28 (s, 3H) 2 21 (s 6H) |
| Ex 164 | $^1$H NMR (400 MHz $CDCl_3$) δ 7 61 (*app* q, *J* = 8 0 Hz 1H) 7 25-7 22 (m 2H), 7 14 (s 1H), 6 99 (*app* d, 6 8 Hz, 1H), 6 94 (*app* dt, *J* = 2 0 8 0 Hz, 1H) 6 88-6 80 (m, 1H), 5 97 (s, 1H) 5 34 (s 2H) 5 19 (s 2H), 3 73 (s 2H) 2 28 (s, 3H), 2 82 (*app* heptet *J* = 6 0 Hz, 1H) 1 07 (d *J* = 6 0 Hz 6H) |
| Ex 165 | $^1$H NMR (400 MHz, $CD_3OD$) δ 7 61 (*app* q *J* = 8 0 Hz, 1H) 7 27 (*app* t *J* = 8 0 Hz 1H) 7 20 (*app* d *J* = 7 6 Hz 1H) 7 08 (bs, 1H) 7 01 (*app* t, *J* = 8 0 Hz 2H) 6 48 (s 1H), 5 41 (s 2H) 5 28 (s, 2H), 3 44 (s, 2H) 2 35 (s, 3H) 2 40-2 30 (m, 4H), 1 57-1 53 (m, 4H) 1 48-1 38 (m, 2H) |
| Ex 166 | $^1$H NMR (400 MHz $CDCl_3$) δ 7 51 (*app* q *J* = 8 0 Hz 1H) 7 22-7 14 (m, 3H) 7 09 (bs 1H), 6 98 (*app* d, *J* = 7 2 Hz 1H) 6 89 (*app* dt *J* = 1 6, 8 0 Hz 1H), 6 81-6 76 (m 1H), 5 92 (s 1H) 5 28 (s, 2H) 5 14 (s, 2H), 3 73 (s 2H), 3 59 (*app* t, *J* = 4 8 Hz 2H) 2 73 (*app* t *J* = 4 8 Hz, 2H) 2 24 (s, 3H) |
| Ex 167 | $^1$H NMR (400 MHz, $CD_3OD$) δ 7 61 (*app* q, *J* = 8 0 Hz, 1H), 7 46 (*app* d, *J* = 8 8 Hz, 2H), 7 31 (bs, 1H), 7 27 (*app* t, *J* = 8 0 Hz, 1H), 7 03 (*app* t, *J* = 8 8 Hz, 2H), 6 54 (s, 1H), 5 44 (s, 2H), 5 30 (s, 2H), 4 47 (s, 2H), 3 90-3 84 (m, 4H), 3 40-3 25 (m, 4H), 2 40 (s, 3H) |
| Ex 168 | $^1$H NMR (400 MHz $CD_3OD$) δ 7 62 (*app* q, *J* = 8 0 Hz 1H) 7 53-7 46 (m 2H) 7 36 (bs 1H) 7 30 (*app* d *J* = 7 6 Hz 1H) 7 05-7 01 (m, 2H) 6 55 (s 1H), 5 44 (s 2H) 5 30 (s 2H) 4 47 (s 2H), 3 58-3 53 (m 8H) 2 42 (s 3H) |

Example 169

3-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzoic acid

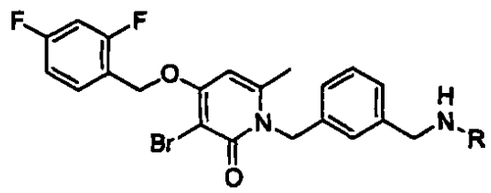



Preparation of 3-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzoic acid EXAMPLE 154 (150 mg, 0 31 mmol) was dissolved in tetrahydrofuran (5 mL)

Potassium trimethylsilanolate (80 mg, 0 62 mmol) was added and the reaction was stirred at ambient temperature for 4 hours The reaction mixture was concentrated to an oil that was partitioned between water and ethyl acetate and extracted with ethyl acetate The organic extracts were combined, washed with brine, dried over $Na_2SO_4$, and filtered The filtrate was concentrated to an oil and purified by reversed phase chromatography ($C_{18}$, 0 1% aqueous trifluoroacetic acid/acetonitrile) to yield the product (64 mg, 44%) $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 7 92 (*app* d, $J$ = 8 0 Hz, 1H), 7 78 (s, 1H), 7 62 (*app* q, $J$ = 8 0 Hz, 1H), 7 44 (t, $J$ = 7 6 Hz, 1H), 7 36 (*app* d, $J$ = 8 0 Hz, 1H), 7 02 (*app* t, $J$ = 7 6 Hz, 2H), 6 51 (s, 1H), 5 48 (s, 2H), 5 30 (s, 2H), 2 37 (s, 3H) ES HRMS m/z 464 0328 ($C_{21}H_{16}BrF_2NO_4$ requires 464 0304)

Examples 170-174

The compounds of Examples 170-174 are prepared using the compound of Example 159 or 161



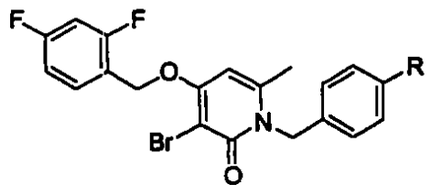
| Example No | R | MF | M+H Requires | ESHRMS m/z |
|---|---|---|---|---|
| Ex 170 | -C(O)$CH_3$ | $C_{23}H_{21}BrF_2N_2O_3$ | 491 0776 | 491 0772 |
| Ex 171 | -C(O)$OCH_3$ | $C_{23}H_{21}BrF_2N_2O_4$ | 507 0726 | 507 0731 |
| Ex 172 | -$SO_2CH_3$ | $C_{22}H_{21}BrF_2N_2O_4S$ | 527 0446 | 527 0430 |
| Ex 173 | -C(O)$CH_2OH$ | $C_{23}H_{21}BrF_2N_2O_4$ | 507 0726 | 507 0712 |
| Ex 174 | -C(O)$NH_2$ | $C_{22}H_{20}BrF_2N_3O_3$ | 492 0729 | 492 0751 |

NMR characterization of compounds of Examples 170-174

| Ex No | NMR Data |
|---|---|
| Ex 170 | $^1$H NMR (400 MHz, $CD_3OD$) δ 7 61 (*app* q, *J* = 8 0 Hz, 1H) 7 28 (*app* t, *J* = 8 0, 1H) 7 18 (*app* d, *J* = 8 0 Hz, 1H), 7 05-7 00 (m, 4H), 6 49 (s 1H) 5 41 (s 2H), 5 29 (s, 2H) 2 37 (s 3H) 1 94 (s 3H) |
| Ex 171 | $^1$H NMR (400 MHz, $CDCl_3$) δ 7 57 (*app* q, *J* = 7 6 Hz 1H) 7 25 (*app* t, *J* = 8 0, 1H) 7 17 (*app* d, *J* = 8 0 Hz 1H), 7 06-7 02 (m 2H) 6 97-6 91 (m 1H), 6 87-6 82 (m 1H), 5 98 (s 1H), 5 33 (s 2H), 5 19 (s 2H), 4 30 (d, *J* = 6 0 Hz 2H) 3 67 (s, 3H) 2 28 (s 3H) |
| Ex 172 | $^1$H NMR (400 MHz, $CD_3CN$) δ 7 58 (*app* q, *J* = 7 6 Hz, 1H) 7 31 (*app* t *J* = 8 0 1H) 7 24 (*app* d, *J* = 8 0 Hz 1H) 7 11 (s, 1H) 7 05-7 00 (m, 3H) 6 32 (s, 1H), 6 06 (bs, 1H) 5 31 (s, 2H) 5 23 (s, 2H), 4 17 (d, *J* = 6 4 Hz 2H), 2 78 (s, 3H), 2 28 (s, 3H) |
| Ex 173 | $^1$H NMR (400 MHz, $CDCl_3$) δ 7 55 (*app* q, *J* = 8 0 Hz 1H) 7 23 (*app* t *J* = 7 6 1H), 7 15 (*app* d, *J* = 7 2 Hz 1H), 7 05-7 00 (m, 3H), 6 94 (*app* dt, *J* = 1 2, 8 8 Hz 1H), 6 88-6 81 (m, 1H), 6 03 (s, 1H) 5 27 (s 2H) 5 19 (s, 2H) 4 39 (d, *J* = 6 4 Hz, 2H) 4 05 (s, 2H), 2 31 (s 3H) |
| Ex 174 | $^1$H NMR (400 MHz $CD_3OD$) δ 7 62 (*app* q, *J* = 8 0 Hz, 1H) 7 28 (*app* t, *J* = 8 0 1H), 7 19 (*app* d *J* = 8 0 Hz, 1H) 7 05-6 96 (m, 4H), 6 49 (s 1H) 5 41 (s, 2H), 5 29 (s, 2H), 4 25 (s 2H) 2 35 (s, 3H) |

Examples 175-185

The compounds of Examples 175-175 are prepared using the compounds of Examples 159 or 160




| Example No | R | MF | M+H Requires | ESHRMS m/z |
|---|---|---|---|---|
| Ex 175 | -$CH_2NHCH(CH_3)_2$ | $C_{24}H_{25}BrF_2N_2O_2$ | 491 1140 | 491 1143 |
| Ex 176 | morpholin-4-ylmethyl | $C_{25}H_{25}BrF_2N_2O_3$ | 519 1089 | 519 1062 |
| Ex 177 | -$CH_2N(CH_3)_2$ | $C_{23}H_{23}BrF_2N_2O_2$ | 477 0984 | 477 0931 |
| Ex 178 | piperidin-1-ylmethyl | $C_{26}H_{27}BrF_2N_2O_2$ | 517 1297 | 517 1258 |

| | | | | |
|---|---|---|---|---|
| Ex 179 | [bis(2-hydroxyethyl)amino]methtyl | $C_{25}H_{27}BrF_2N_2O_4$ | 537 1195 | 537 1181 |
| Ex 180 | $-CH_2NHCH_2CH_2OH$ | $C_{23}H_{23}BrF_2N_2O_3$ | 493 0933 | 493 0907 |
| Ex 181 | piperazin-1-ylmethyl | $C_{25}H_{26}BrF_2N_3O_2$ | 518 1249 | 518 1213 |
| Ex 182 | $-CH_2NHC(O)OCH_3$ | $C_{23}H_{21}BrF_2N_2O_4$ | 507 0726 | 507 0752 |
| Ex 183 | $-CH_2NHC(O)CH_3$ | $C_{23}H_{21}BrF_2N_2O_3$ | 491 0776 | 491 0793 |
| Ex 184 | $-CH_2NHSO_2CH_3$ | $C_{22}H_{21}BrF_2N_2O_4S$ | 527 0446 | 527 0431 |
| Ex 185 | $-CH_2NHC(O)NH_2$ | $C_{22}H_{20}BrF_2N_3O_3$ | 492 0729 | 492 0720 |

NMR characterization of compounds of Examples 175-185

| Ex No | NMR Data |
|---|---|
| Ex 175 | $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7 56 (q, $J$ = 8 0 Hz, 1H), 7 25 (d, $J$ = 8 0 Hz 2H) 7 10 (d $J$ = 8 0 Hz, 2H), 6 94 (app t $J$ = 8 0 Hz, 1H), 6 88-6 80 (m 1H) 5 97 (s, 1H), 5 31 (s 2H), 5 19 (s, 2H), 3 74 (s, 2H), 2 82 (app heptet, $J$ = 6 0 Hz, 1H), 2 28 (s, 3H), 1 09 (d $J$ = 6 4 Hz, 6H) |
| Ex 176 | $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7 56 (q, $J$ = 8 0 Hz, 1H) 7 25 (d, $J$ = 8 0 Hz, 2H), 7 11 (d, $J$ = 8 0 Hz, 2H), 6 94 (app dt $J$ = 2 0, 8 0 Hz, 1H) 6 87-6 81 (m 1H), 5 97 (s, 1H) 5 33 (s, 2H) 5 19 (s, 2H) 3 67 (app t $J$ = 4 8 Hz, 4H), 3 44 (s 2H), 2 44-2 38 (m, 4H), 2 29 (s, 3H) |
| Ex 177 | $^1$H NMR (400 MHz $CDCl_3$) $\delta$ 7 56 (q, $J$ = 8 0 Hz, 1H), 7 23 (d, $J$ = 8 0 Hz, 2H), 7 11 (d $J$ = 8 0 Hz, 2H), 6 93 (app dt $J$ = 2 0, 8 0 Hz, 1H), 6 86-6 81 (m 1H), 5 96 (s, 1H), 5 33 (s, 2H), 5 18 (s, 2H), 3 38 (s 2H), 2 29 (s, 3H), 2 20 (s 6H) |
| Ex 178 | $^1$H NMR (400 MHz $CDCl_3$) $\delta$ 7 56 (q, $J$ = 8 0 Hz, 1H), 7 24-7 20 (m, 2H), 7 10-7 07 (m, 2H) 6 96-6 90 (m,1H), 6 86-6 81 (m, 1H), 5 96 (s, 1H), 5 32 (s, 2H), 5 18 (s, 2H), 3 34 (s, 2H), 2 31 (s, 3H), 2 31-2 28 (m, 4H), 1 53-1 51 (m 4H), 1 39 (m, 2H) |
| Ex 179 | $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7 57 (q, $J$ = 8 0 Hz, 1H) 7 25 (d $J$ = 8 0 Hz, 2H), 7 12 (d, $J$ = 8 0 Hz, 2H), 6 94 (dt, $J$ = 8 8 Hz, 2H), 6 87-6 82 (m, 1H), 5 98 (s, 1H), 5 33 (s, 2H), 5 19 (s, 2H), 3 68 (s, 2H) 3 61 (t, $J$ = 5 2 Hz 4H), 2 70 (t, $J$ = 5 2 Hz, 4H), 2 29 (s, 3H) |
| Ex 180 | $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7 57 (q, $J$ = 8 0 Hz, 1H), 7 25 (d, $J$ = 8 0 Hz, 2H), 7 12 (d, $J$ = 8 0 Hz, 2H), 6 94 (app dt, $J$ = 8 8 Hz 2H), 6 87-6 82 (m 1H), 5 98 (s, 1H) 5 33 (s, 2H) 5 19 (s, 2H) 3 68 (s, 2H) 3 61 (t $J$ = 5 2 Hz, 4H), 2 70 (t, $J$ = 5 2 Hz, 4H), 2 29 (s, 3H) |
| Ex 181 | $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7 61 (q, $J$ = 8 0 Hz, 1H), 7 52 (d, $J$ = 8 0 Hz, 2H), 7 25 (d, $J$ = 8 0 Hz, 2H), 7 03 (app t, $J$ = 8 0 Hz 2H), 6 53 (s 1H), 5 44 (s, 2H) 5 30 (s, 2H) 4 32 (bs, 2H), 3 55-3 35 (m, 8H), 2 39 (s, 3H) |

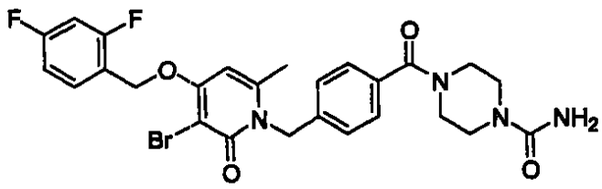
200

198

| | |
|---|---|
| Ex 182 | $^1$H NMR (400 MHz $CDCl_3$) δ 7 56 (*app* q, *J* = 8 0 Hz 1H) 7 20 (d, *J* = 8 0 Hz, 1H) 7 13 (d *J* = 8 0 Hz 2H), 6 94 (*app* dt *J* = 1 2, 8 0 Hz 1H) 6 87-6 81 (m, 2H), 5 97 (s, 1H), 5 32 (s, 2H), 5 19 (s 2H) 4 31 (d, *J* = 6 0 Hz, 2H) 3 68 (s, 3H), 2 28 (s 3H) |
| Ex 183 | $^1$H NMR (400 MHz, $CDCl_3$) δ 7 61 (*app* q *J* = 8 0 Hz 1H), 7 23 (d, *J* = 8 0 Hz, 2H), 7 08 (d, *J* = 8 0 Hz, 2H) 7 04-6 99 (m 2H) 6 47 (s, 1H) 5 39 (s 2H) 5 28 (s, 2H), 4 30 (s, 2H), 2 34 (s, 3H) 1 95 (s, 3H) |
| Ex 184 | $^1$H NMR (400 MHz, $CD_3OD$) δ 7 62 (*app* q *J* = 8 0 Hz 1H), 7 34 (d, *J* = 8 4 Hz 2H), 7 11 (d, *J* = 8 4 Hz, 2H) 7 02 (*app* t, *J* = 8 8 Hz 2H), 6 48 (s 1H) 5 42 (s, 2H) 5 28 (s 2H), 4 21 (s, 2H) 2 82 (s, 3H), 2 35 (s 3H) |
| Ex 185 | $^1$H NMR (400 MHz $d_7$DMF) δ 7 76 (*app* q, *J* = 8 0 Hz, 1H) 7 28 (d *J* = 8 0 Hz ) 7 14 (d, *J* = 8 0 Hz 2H), 7 34-7 26 (m 1H) 7 22-7 14 (m 1H), 6 62 (s 1H), 5 65 (s, 2H), 5 39 (s, 2H) 5 37 (s 2H), 4 26 (d *J* = 6 0 Hz, 2H), 2 40 (s 3H) |

Example 186

4-(4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzoyl)piperazine-1-carboxamide

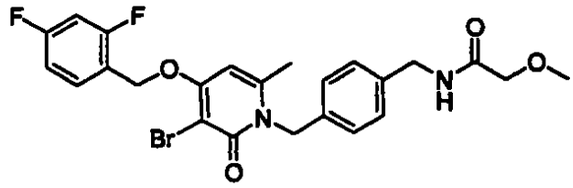



3-bromo-4-(2,4-difluorophenoxy)-6-methyl-1-[4-(piperazin-1-ylcarbonyl)benzyl]pyridin-2(1*H*)-one (300 mg, 0 54 mmol) was dissolved in *N,N*-dimethylacetamide (5 mL) Trimethylsilyl isocyanate (0 15 mL, 1 08 mmol) was added followed by *N,N*-diisopropylethylamine (0 23 mL, 1 3 mmol) and the reaction was stirred for 1 hour at ambient temperature The reaction was then diluted with tetrahydrofuran (40 mL) and polyamine resin (1 3 g, 2 81 mmol/g) and methylisocyanate functionalized polystyrene (1 g, 1 38 mmol/g) were added The mixture was shaken for 6 hours, filtered, and the resulting filtrate was concentrated to a white solid (279 mg, 90%) $^1$H NMR (400 MHz, $CD_3OD$) δ 7 61 (*app* q, *J* = 8 0 Hz, 1H), 7 41 (d, *J* = 8 0 Hz, 2H), 7 23 (d, *J* = 8 0 Hz, 2H), 7 03 (*app* t, *J* = 8 8 Hz, 2H), 6 51 (s, 1H), 5 46 (s, 2H), 5 30 (s, 2H), 3 75-3 35 (m, 8H),

2 37 (s, 3H) ES HRMS m/z 575 1104 ($C_{26}H_{25}BrF_2N_4O_4$ requires 575 1100)

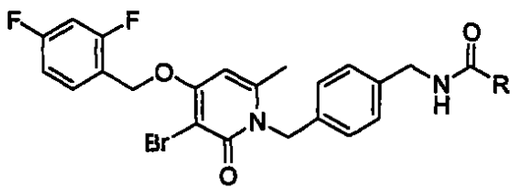
Example 187

N-(4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzyl)-2-methoxyacetamide



Polymer bound carbodiimide resin (2 3 g, 1 18 meq/g, 2 7 mmol) was suspended in *N,N*-dimethylformamide Acetoxyacetic acid (120 mg, 1 33 mmol) was added, followed by 1-hydroxybenzotriazole (1M in *N,N*-dimethylformamide, 0 165 mL) and *N,N*-diisopropylethylamine (0 3 mL, 2 0 mmol) The reaction was shaken for 1 hour when EXAMPLE 159 (300 mg, 0 67 mmol) was added The reaction was shaken for 16 hours and then diluted with tetrahydrofuran Polyamine resin (1 g, 2 81 mmol/g) and methylisocyanate functionalized polystyrene (2 g, 1 38 mmol/g) were added and the mixture was shaken for 72 hours, filtered and the resulting filtrate concentrated Trituration with water followed by trituration with ether yielded a white solid (125 mg, 36%) $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7 56 (*app* q, $J$ = 8 0 Hz, 1H), 7 21 (d, $J$ = 8 0 Hz, 2H), 7 13 (d, $J$ = 8 0 Hz, 2H), 6 94 (*app* t, $J$ = 8 8 Hz, 1H), 6 88-6 81 (m, 1H), 5 97(s, 1H), 5 33 (s, 2H), 5 19 (s, 2H), 4 43 (d, $J$ = 6 0 Hz, 2H), 3 92 (s, 2H), 3 39 (s, 3H), 2 29 (s, 3H) ES HRMS m/z 521 0882 ($C_{24}H_{22}BrF_2N_2O_4$ requires 521 0882)

Examples 188-193

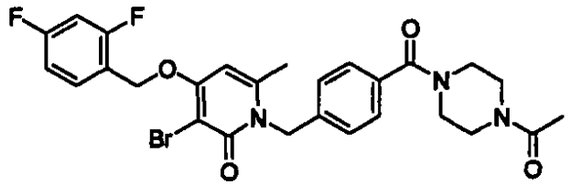


By following the general method for the preparation of Example 187 and substituting the appropriate carboxylic acid for acetoxyacetic acid, the compounds of Examples 188-193 are prepared These compounds were triturated with water and again with ether and purified by chromatography (silica gel, hexane/ethyl acetate) as appropriate to yield off-white solids Example 191 was prepared from its *N*-t-butoxycarbonyl protected intermediate Deprotection was accomplished with 4N HCl in dioxane to afford the title compound as its hydrochloride salt (86 mg, 24%) Deprotection of the methyl ester from Ex 188 was accomplished with $K_2CO_3$ in methanol/water to yield Ex 192 as a white solid The yields and analytical data are shown below

| Compound No | R | % Yield | MF | M+H Requires | ESHRMS m/z |
|---|---|---|---|---|---|
| Ex 188 | $CH_2OCOCH_3$ | 49 | $C_{25}H_{23}BrF_2N_2O_5$ | 549 0831 | 549 0849 |
| Ex 189 | $C(CH_3)_2OH$ | 13 | $C_{25}H_{25}BrF_2N_2O_4$ | 535 1039 | 535 1035 |
| Ex 190 | $C(-CH_2CH_2-)OH$ | 33 | $C_{25}H_{23}BrF_2N_2O_4$ | 535 0865 | 535 0876 |
| Ex 191 | $CH_2NH_2$ | 24 | $C_{23}H_{22}BrF_2N_3O_3$ | 533 0882 | 533 0899 |
| Ex 192 | $CH_2OH$ | 25 | $C_{23}H_{21}BrF_2N_2O_4$ | 507 0726 | 507 0730 |
| Ex 193 | $CH_2NHCOCH_3$ | 81 | $C_{25}H_{24}BrF_2N_3O_3$ | 548 0991 | 548 1000 |

Example 194

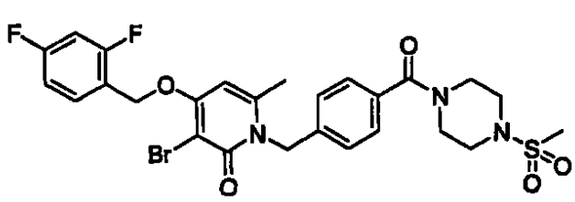
1-{4-[(4-acetylpiperazin-1-yl)carbonyl]benzyl}-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one



3-bromo-4-(2,4-difluorophenoxy)-6-methyl-1-[4-(piperazin-1-ylcarbonyl)benzyl]pyridin-2(1*H*)-one (200 mg, 0 36 mmol) was dissolved in *N,N*-dimethylformamide (5 mL) *N,N*-Diisopropylethylamine (0 25 mL, 1 44 mmol) was added followed by acetic anhydride (0 10 mL, 1 06 mmol) The reaction was stirred for 2 hours at ambient temperature and concentrated to an oil that was triturated in ether and again in water to yield an off-white solid (131 mg, 63%) $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 7 62 (*app* q, *J* = 8 0 Hz, 1H), 7 42 (d, *J* = 8 0 Hz, 2H), 7 23 (d, *J* = 8 0 Hz, 2H), 7 62-7 02 (m, 1H), 7 02 (*app* t, *J* = 8 0 Hz, 1 H), 6 52 (s, 1H), 5 46 (s, 2H), 5 30 (s, 2H), 3 80-3 65 (m, 8H), 2 37 (s, 3H), 2 11 (s, 3H) ES HRMS m/z 574 1150 ($C_{27}H_{26}BrF_2N_3O_4$ requires 574 1148)

Example 195

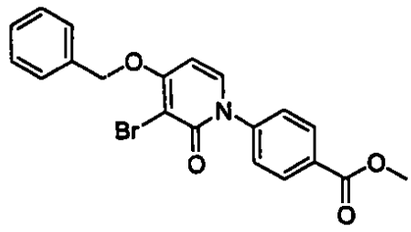
3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(4-{[4-(methylsulfonyl)piperazin-1-yl]carbonyl}benzyl)pyridin-2(1H)-one



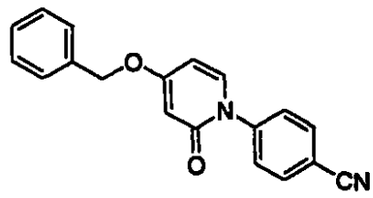
3-bromo-4-(2,4-difluorophenoxy)-6-methyl-1-[4-(piperazin-1-ylcarbonyl)benzyl]pyridin-2(1H)-one (300 mg, 0 54 mmol) was dissolved in *N,N*-dimethylformamide (5 mL) 4-Methylmorpholine (0 23 mL, 2 2 mmol) was added followed by methanesulfonyl chloride (0 10 mL, 1 33 mmol) and the reaction was stirred for 2 h The reaction was then diluted with tetrahydrofuran (40 mL) and polyamine resin (1 3 g, 2 81 mmol/g) and methylisocyanate functionalized polystyrene (1 g, 1 38 mmol/g) were added The mixture was shaken for 16 hours, filtered, and the resulting filtrate concentrated to an oil that was triturated with water The resulting white solid was collected, washed with ether and dried (172 mg, 52%) $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7 57 (*app* q, $J$ = 8 2 Hz, 1H), 7 34 (d, $J$ = 8 0 Hz, 2H), 7 20 (d, $J$ = 8 0 Hz, 2H), 7 02 (*app* dt, $J$ = 1 2, 8 8 Hz, 1H), 6 88-6 82 (m, 1H), 6 02 (s, 1H), 5 37 (s, 2H), 5 21 (s, 2H), 3 80-3 20 (m, 8H), 2 79 (s, 3H), 2 30 (s, 3H) ES HRMS m/z 610 0851 ($C_{26}H_{26}BrF_2N_3O_5S$ requires 610 0817)

Example 196

Methyl-4-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]benzoate

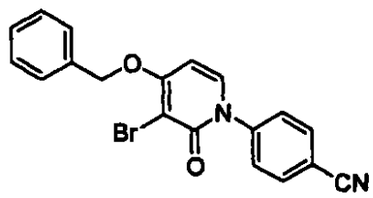



Step 1 Preparation of 4 [4-(benzyloxy)-2-oxopyridin-1(2H)-yl]benzonitrile



4-benzyloxy-2(1H)-pyridone (12 00 g, 59 63 mmol) was dissolved in dimethyl sulfoxide (100 mL) Potassium carbonate (10 99 g, 79 50 mmol) was added, followed by 4-fluorobenzonitrile (4 81 g, 39 75 mmol) The reaction was stirred at 100 °C for 18 hours After cooling to room temperature the reaction was diluted with $H_2O$ (150 mL) and the solids were collected by filtration washing with diethyl ether Chromatography (silica gel, hexanes/ethyl acetate) provided an off-white solid (7 78 g, 65%) $^1$H NMR (300 MHz, $CDCl_3$) δ 7 79 (d, *J* = 8 3 Hz, 2H), 7 54 (d, *J* = 8 5 Hz, 2H), 7 44-7 41 (m, 5H), 7 22 (d, *J* = 13 3, 1H), 6 13 (dd, *J* = 2 6, 7 7 Hz, 1H), 6 06 (d, *J* = 2 6 Hz, 1H), 5 07 (s, 2H)

Step 2 Preparation of 4-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]benzonitrile



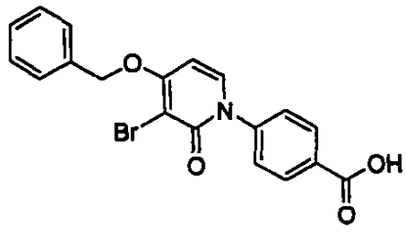
4-[4-(benzyloxy)-2-oxopyridin-1(2H)-yl]benzonitrile (Step 1) (2 76 g, 9 13 mmol) was suspended in acetonitrile (50 mL) and cooled in an ice-bath *N*-bromosuccinimide (1 71 g, 9 54 mmol) was added Once the addition was complete the cooling bath was removed After stirring for 45 minutes the reaction was diluted with acetonitrile and solids were collected by

filtration to give a white solid (3 13 g, 90%) $^1$H NMR (300 MHz, DMSO-$d_6$) δ 8 00 (d, $J$ = 8 5 Hz, 2H), 7 84 (d, $J$ = 7 9 Hz, 1H), 7 66 (d, $J$ = 8 5, 2H), 7 50-7 37 (m, 5H), 6 63 (d, $J$ = 7 9 Hz, 1H), 5 41 (s, 2H)

Step 3 Preparation of methyl-4-[4-(benzyl)oxy-3-bromo-2-oxopyridin-1(2H)-yl]benzoate 4-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]benzonitrile (Step 2) (1 50 g, 3 93 mmol) suspended in methanol (50 mL) was cooled in an ice-bath HCl (g) was then bubbled through the mixture for 5 minutes The reaction was then stirred at room temperature overnight, at which time the reaction mixture was concentrated The residue was suspended in 6$N$ HCl (60 mL) and heated at reflux for 1 5 hours After cooling to room temperature the solids were collected by filtration Chromatography (silica gel, hexanes/ethyl acetate) provided an off-white shiny solid (0 540 g, 61%) $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8 04 (d, $J$ = 8 5 Hz, 2H), 7 81 (d, $J$ = 7 8 Hz, 1H), 7 55 (d, $J$ = 8 6 Hz, 2H), 7 47-7 39 (m, 5H), 6 57 (d, $J$ = 7 9 Hz, 1H), 5 38 (s, 2H), 3 86 (s, 3H) ES-HRMS m/z 416 0355 (M+H caldc for $C_{20}H_{16}BrNO_4$ requires 414 0341)

Example 197

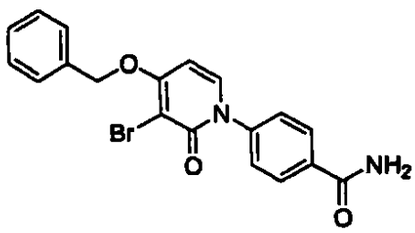
4-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]benzoic acid



Preparation of 4-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]benzoic acid EXAMPLE 196 (0 460 g, 1 11 mmol) was dissolved in tetrahydrofuran (5 0 mL) Potassium trimethylsilanolate (0 285 g, 2 22 mmol) was added The reaction was stirred at room temperature for 3 hours at which time $H_2O$ (10 mL) was added The aqueous reaction mixture was acidified (pH-3) with 1*N* HCl The tetrahydrofuran was evaporated, additional $H_2O$ (50 mL) was added and the aqueous layer was extracted with ethyl acetate (2 x 50 mL) The combined organic layers were washed with brine (50 mL), dried over $Na_2SO_4$, filtered and evaporated to provide a rust colored solid (0 444 g, 100%) $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 8 02 (d, *J* = 8 6 Hz, 2H), 7 80 (d, *J* = 7 8 Hz, 1H), 7 55 (d, *J* = 8 6 Hz, 2H), 7 50-7 34 (m, 5H), 6 57 (d, *J* = 7 9 Hz, 1H), 5 38 (s, 2H) ES-HRMS m/z 400 0191 (M+H calcd for $C_{19}H_{14}BrNO_4$ requires 400 0184)

Example 198

4-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]benzamide

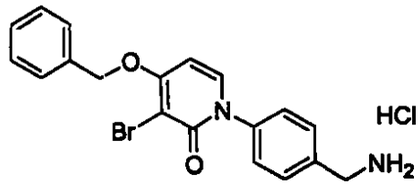



Preparation of 4-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]benzamide STEP 2, EXAMPLE 196 (0 238 g, 0 624 mmol) was suspended in tert-butyl alcohol (3 0 mL) KF on 40 wt % $Al_2O_3$ (0 453 g, 3 12 mmol) was added The reaction mixture was heated at reflux for 5 days Additional KF on 40 wt % $Al_2O_3$ (0 453 g, 3 12 mmol) was added and heating was continued at reflux overnight After cooling to room temperature

chloroform and methanol were added and the solids were collected by filtration Chromatography (reverse-phase, acetonitrile/$H_2O$) provided a tan solid (0 073 g, 30%) $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 8 07 (s, 1H), 7 95 (d, $J$ = 8 6 Hz, 2H), 7 79 (d, $J$ = 7 8 Hz, 1H), 7 47-7 34 (m, 7H), 6 56 (d, $J$ = 7 9 Hz, 1H), 5 38 (s, 2H) ES-HRMS m/z 399 0372 (M+H calcd for $C_{19}H_{15}BrN_2O_3$ requires 399 0344)

Example 199

1-[4-(aminomethyl)phenyl -4-(benzyloxy)-3-bromopyridin-2(1H)-one

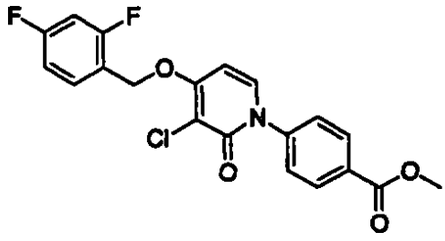



Preparation of 1-[4-(aminomethyl)phenyl]-4-(benzyloxy)-3-bromopyridin-2(1H)-one STEP 2, EXAMPLE 196 (1 25 g, 3 28 mmol) was dissolved in tetrahydrofuran (15 mL) Borane-dimethylsulfide (3 44 mL, 6 89 mmol, 2 0 M in tetrahydrofuran) was added and the mixture heated at reflux After 14 5 hours the solvent was evaporated 0 5$M$ NaOH (50 mL) was added followed by ethyl acetate The aqueous layer was neutralized with 1$N$ HCl Methanol saturated with HCl was added and the mixture was heated at reflux for 5 hours After cooling to room temperature, diethyl ether was added and the solids were collected by filtration The solids were treated with 4$N$ HCl in dixoane (5 mL) and methanol (1 mL) at room temperature for 1 hour, at which time diethyl ether was added and the solids were collected by filtration to give a tan solid (0 920 g,

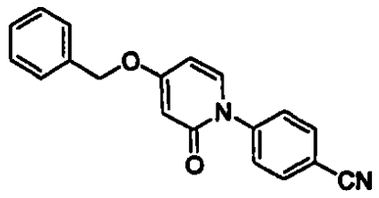
67%) $^1$H NMR (300 MHz, DMSO-$d_6$) δ 8 67 (br s, 2H), 7 76 (d, $J$ = 7 6 Hz, 1H), 7 64 (d, $J$ = 8 3 Hz, 2H), 7 50-7 37 (m, 7H), 6 56 (d, $J$ = 7 6 Hz, 1H), 5 41 (s, 2H), 4 09 (br s, 2H) ES-HRMS m/z 385 0555 (M+H calcd for $C_{19}H_{17}BrN_2O_2$ requires 385 0552)

Example 200

Methyl-4-[3-chloro-4-[(2,4-diflurobenzyl)oxy]-2-oxypyridin-1(2H)-yl]benzoate



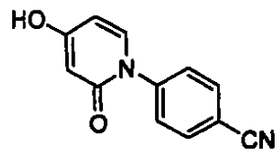
Step 1 Preparation of 4-[4-(benzyloxy)-2-oxopyridin-1(2H)-yl]benzonitrile



4-benzyloxy-2(1H)-pyridone (50 0 g, 248 47 mmol) was dissolved in dimethyl sulfoxide (300 mL) Potassium carbonate (68 68 g, 496 94 mmol) was added, followed by 4-fluorobenzonitrile (31 60 g, 260 89 mmol) The reaction was stirred at 100 °C for 20 hours After cooling to room temperature the reaction was diluted with $H_2O$ (600 mL) and the solids were collected by filtration washing with diethyl ether The solids were then washed with hot methanol to provide a tan solid (55 6 g, 74%) $^1$H NMR (300 MHz, $CDCl_3$) δ 7 79 (d, $J$ = 8 3 Hz, 2H), 7 54 (d, $J$

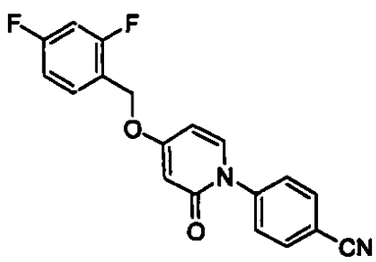
= 8 5 Hz, 2H), 7 44-7 41 (m, 5H), 7 22 (d, *J* = 13 3, 1H), 6 13 (dd, *J* = 2 6, 7 7 Hz, 1H), 6 06 (d, *J* = 2 6 Hz, 1H), 5 07 (s, 2H)

Step 2 Preparation of 1-[4-nitrilephenyl]-4-hydroxy-2(1H)-pyridinone



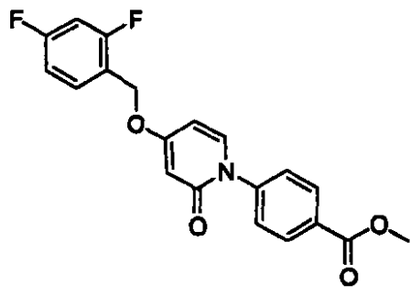

4-[4-(benzyloxy)-2-oxopyridin-1(2H)-yl]benzonitrile (Step 1) (20 0 g, 66 15 mmol) was dissolved in methanol (300 mL) Ammonium formate (8 34 g, 132 3 mmol) was added followed by 5% Pd/C (6 62 g) The resulting mixture was heated at reflux for 20 minutes at which time the reaction began to exotherm The reaction was allowed to cool to room temperature at which time it was filtered through a pad of Celite® washing with methanol The filtrate was evaporated to provide a pale yellow solid (16 2 g, >100%) $^1$H NMR (300 MHz, $CDCl_3$) δ 8 46 (s, 1H), 7,95 (d, *J* = 8 5 Hz, 2H), 7 62 (d, *J* = 8 5 Hz, 2H), 7 47 (d, *J* = 7 7 Hz, 1H), 5 98 (dd, *J* = 2 6, 7 7 Hz, 1H), 5 54 (d, *J* = 2 4 Hz, 1H)

Step 3 Preparation of 4-[4-[(2,4-difluorobenzyloxy)]-2-oxopyridin-1(2H)-yl]benzonitrile



1-[4-Nitrilephenyl]-4-hydroxy-2(1H)-pyridinone (Step 2) (16 2 g) was dissolved in *N,N*-dimethylformamide (100 mL) Potassium carbonate (10 06 g, 72 77 mmol) was added followed by α-bromo-2,4-difluorotoluene (8 91 mL, 69 46 mmol) The resulting mixture was heated to 65°C for 1 hour Additional α-bromo-2,4-difluorotoluene (4 25 mL, 33 08 mmol) was added The resulting mixture was heated to 65°C for 5 hours Additional α-bromo-2,4-difluorotoluene (2 12 mL, 16 54 mmol) was added After stirring at 65°C overnight the reaction was allowed to cool to room temperature $H_2O$ (300 mL) was added and the solid was collected by filtration A portion (8 0 g) of the solids were washed with hot methanol to give a pale yellow solid (6 22 g, 78%) $^1H$ NMR (300 MHz, $CDCl_3$) δ 8 00 (d, *J* = 8 5 Hz, 2H), 7 72-7 64 (m, 2H), 7 66 (d, *J* = 8 5 Hz, 2H), 7 40-7 32 (m, 1H), 7 22-7 16 (m, 1H), 6 17-6 11 (m, 2H), 5 17 (s, 2H)

Step 4 Preparation of methyl-4-[4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]benzoate



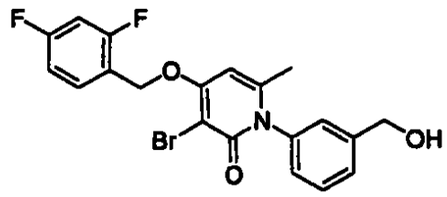
4-[4-[(2,4-difluorobenzyloxy)]-2-oxopyridin-1(2H)-yl]benzonitrile (Step 3) (2 00 g, 5 91 mmol) suspended in methanol (20 mL) and $H_2O$ (5 mL) was cooled in an ice-bath HCl (g) was bubbled through the mixture until most of the solids dissolved The resulting mixture was then heated at reflux for 3 hours The reaction was then recooled in an ice-bath

and HCl was bubbled through the mixture for 5 minutes The mixture was heated at reflux for 2 hours and then the methanol was evaporated Additional $H_2O$ (50 mL) was added and the aqueous reaction mixture was extracted with ethyl acetate (50 mL) and tetrahydrofuran (50 mL) The combined organic layers were washed with brine (50 mL), dried over $Na_2SO_4$, filtered and evaporated Chromatography (silica gel, hexanes/ethyl acetate with 10% methanol) gave an off-white solid (0 630 g, 29%) $^1H$ NMR (300 MHz, DMF-$d_6$) δ 8 15 (d, $J$ = 8 5 Hz, 2H), 7 80 (*app* q, $J$ = 7 9 Hz, 1H), 7 74-7 67 (m, 1H), 7 68 (d, $J$ = 8 5 Hz, 2H), 7 42-7 34 (*app* dt, $J$ = 2 4, 9 0 Hz, 1H), 7 28-7 22 (m, 1H), 6 20 (dd, $J$ = 2 6, 7 6 Hz, 1H), 6 15 (d, $J$ = 2 4 Hz, 1H), 5 28 (s, 2H), 3 98 (s, 3H)

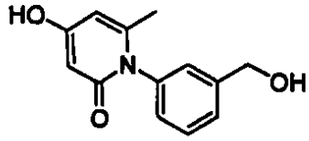
Step 5 Preparation of methyl-4-[3-chloro-4-[(2,4-diflurobenzyl)oxy]-2-oxypyridin-1(2H)-yl]benzoate Methyl-4-[4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]benzoate (Step 4) (0 520 g, 1 40 mmol) was suspended in acetonitrile (10 0 mL) *N*-chlorosuccinimide (0 196 g, 1 47 mmol) was added followed by several drops of dichloroacetic acid The resulting mixture was heated at reflux overnight After cooling to room temperature additional acetonitrile was added and the precipitate was collected by filtration to give an off-white solid (0 331 g, 58%) $^1H$ NMR (300 MHz, DMF-$d_6$) δ 8 34 (d, $J$ = 8 5 Hz, 2H), 8 12 (d, $J$ = 7 9 Hz, 1H), 8 04-7 96 (m, 1H), 7 88 (d, $J$ = 8 5 Hz, 2H), 7 59-7 53 (m, 1H), 7 52-7 41 (m, 1H), 7 05 (d, $J$ = 7 9 Hz, 1H), 5 70 (s, 2H), 4 15 (s, 3H) ES-HRMS m/z 406 0644 (M+H calcd for $C_{20}H_{14}ClF_2NO_4$ requires 406 0652)

Example 201

3-Bromo-4-[(2,4-diflurorbenzyl)oxy]-1-[3-(hydroxymethyl)phenyl]-6-methylpyridin-2(1H)-one

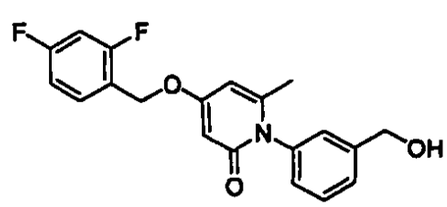


Step 1 Preparation of 4-Hydroxy-1-[3-(hydroxymethyl)phenyl]6-methylpyridin-2(1H)-one



4-hydroxy-6-methyl-2-pyrone (10 0 g, 79 3 mmol) and 3-aminobenzyl alcohol (9 77g, 79 3 mmol) were combined in $H_2O$ (100 mL) and heat at reflux After 48 hours at reflux the reaction mixture was concentrated The residue was treated with methanol and the precipitate was collected by filtration to give a pale yellow solid (3 04 g, 17%) $^1$H NMR (300 MHz, DMSO-$d_6$) d 10 6 (br s, 1H), 7 46-7 35 (m, 2H), 7 09-7 03 (m, 2H), 5 88 (d, $J$ = 1 6 Hz, 1H), 5 55 (d, $J$ = 2 6 Hz, 1H), 4 54 (d, $J$ = 4 2 Hz, 2H), 1 83 (s, 3H)

Step 2 Preparation of 1-[3-(hydroxymethyl)phenyl]-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one

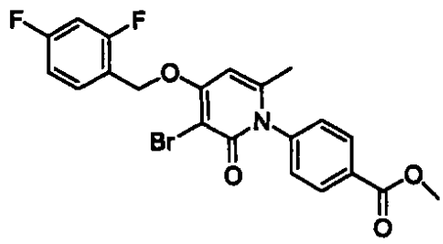


4-Hydroxy-1-[3-(hydroxymethyl)phenyl]6-methylpyridin-2(1H)-one (Step 1) (0 674 g, 2 91 mmol) was suspended in acetone (10 mL) Cesium carbonate (1 04 g, 3 21 mmol) was added followed by α-bromo-2,4-difluorotoluene (0 392 mL, 3 06 mmol) After stirring at room temperature for 2 days the reaction was concentrated The residue was portioned between $H_2O$ (30 mL) and ethyl acetate (30 mL) The aqueous layer was further extracted with ethyl acetate (30 mL) The combined organic layers were washed with brine (30 mL), dried over $Na_2SO_4$, filtered and concentrated Chromatography (on silica, hexanes/ethyl acetate with 10% methanol) provided a white solid (0 531 g, 51%) $^1$H NMR (300 MHz, $CDCl_3$) δ 7 51-7 39 (m, 3H), 7 82 (s, 1H), 7 16 (d, $J$ = 26 8 Hz, 1H), 7 08-6 86 (m, 2H), 6 00 (d, $J$ = 2 6 Hz, 1H), 5 92 (d, $J$ = 2 6 Hz, 1H), 5 05 (s, 2H), 4 68 (s, 2H), 1 93 (s, 3H) ES-HRMS m/z 358 1256 (M+H calcd for $C_{20}H_{17}F_2NO_3$ requires 358 1249)

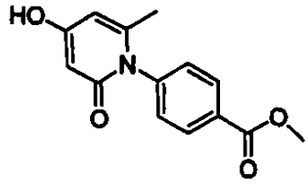
Step 3 Preparation of 3-bromo-4-[(2,4-diflurorbenzyl)oxy]-1-[3-(hydroxymethyl)phenyl]-6-methylpyridin-2(1H)-one 1-[3-(hydroxymethyl)phenyl]-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (Step 2) (0 460 g, 1 29 mmol) was suspended in acetonitrile (5 0 mL) and cooled in an ice-bath *N*-bromosuccinimide (0 241 g, 1 35 mmol) was added Once the addition was complete the cooling bath was removed After stirring for 1 5 hours the reaction was diluted with acetonitrile and solids were collected by filtration to give a white solid (0 385 g, 68%) $^1$H NMR (300 MHz, DMSO-$d_6$) d 7 70 (app q, J = 7 9 Hz, 1H), 7 49-7 32 (m, 3H), 7 24-7 10 (m, 3H), 6 66 (s, 1H), 5 35 (s, 2H), 4 56 (d, J = 5 6 Hz, 2H), 1 95 (s, 3H) ES-HRMS m/z 436 0384 (M+H calcd for $C_{20}H_{16}BrF_2NO_3$ requires 436 0354)

Example 202

Methyl-4-[3-bromo-4-[(difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoate



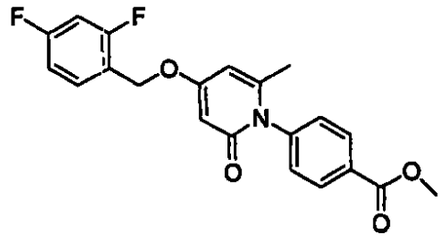
Step 1 Preparation of Methyl 4-(4-hydroxy-6-methyl-2-oxypyridin-1(2H)-yl)benzoate



4-hydroxy-6-methyl-2-pyrone (21 00 g, 166 70 mmol) and 4-methylaminobenzoate (25 20 g, 166 70 mmol) were combined in 1,2-dichlorobenzene (50 mL) and rapidly heated to 160 °C After 15 minutes at 160 °C the reaction was allowed to cool to room temperature The reaction was diluted with dichloromethane (50 mL) and extracted with saturated $Na_2CO_3$ (2 x 100 mL) The combined aqueous layers were acidified (pH-2) with concentrated HCl The precipitate was collected by filtration and washed with diethyl ether to give a yellow/orange solid (10 9 g, 25%) $^1H$ NMR (300 MHz, DMSO-$d_6$) δ 10 8 ( s, 1H), 8 07 (d, $J$ = 8 5 Hz, 2H), 7 40 (d, $J$ = 8 5 Hz,

2H), 5 95 (d, $J$ = 2 4 Hz, 1H), 5 61 (d, $J$ = 2 4, 1H), 3 91 (s, 3H), 1 85 (s, 3H)

Step 2 Preparation of Methyl-4-[4-[(difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoate



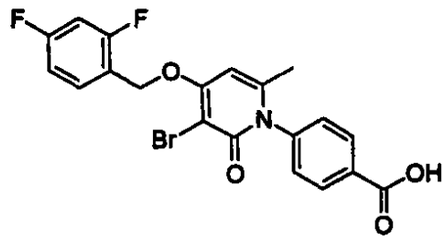
Methyl 4-(4-hydroxy-6-methyl-2-oxypyridin-1(2H)-yl)benzoate (Step 1) (10 90 g, 42 04 mmol) was dissolved in *N,N*-dimethylformamide (100 mL) Potassium carbonate (6 97 g, 50 45 mmol) was added, followed by 2,4-difluorobenzyl bromide (5 66 mL, 44 14 mmol) The reaction was stirred at room temperature for 3 days then diluted with $H_2O$ (100 mL) The reaction mixture was extracted into ethyl acetate and tetrahydrofuran (2 x 100 mL) The precipitate was collected by filtration and the crganic filtrate was washed with brine (50 mL), dried over $Na_2SO_4$, filtered and evaporated The resulting solid was combined with the precipitate to provide a pale pink solid (6 77 g, 42%) $^1$H NMR (300 MHz, DMSO-$d_6$) δ 8 01 (d, $J$ = 8 3 Hz, 2H), 7 67 (q, $J$ = 7 9 Hz, 1H), 7 43 (d, $J$ = 8 3 Hz, 2H), 7 35 (m, 1H), 7 18 (*app* dt, $J$ = 1 6, 8 5 Hz, 1H), 6 08 (d, $J$ = 1 8 Hz, 1H), 5 98 (d, $J$ = 2 4 Hz, 1H), 5 14 (s, 2H), 3 91 (s, 3H), 1 87 (s, 3H)

Step 3 Preparation cf methyl-4-[3-bromo-4-[(difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoate Methyl-4-[4-[(difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-

yl]benzoate (Step 2) (6 74 g, 17 49 mmol) suspended in acetonitrile (100 mL) was cooled in an ice-bath *N*-bromosuccinimide (3 27 g, 18 36 mmol) was added After 1 hour the ice-bath was removed and after an additional 30 minutes the reaction was diluted with acetonitrile (20 mL) The precipitate was collected by filtration to provide the title compound as an off-white solid (6 94 g, 85%) $^1$H NMR (300 MHz, $CDCl_3$) δ 8 20 (d, *J* = 8 7 Hz, 2H), 7 61 (q, *J* = 7 9 Hz, 1H), 7 30 (d, *J* = 8 7 Hz, 2H), 7 02-6 96 (m, 1H), 6 90 (*app* dt, *J* = 2 4, 9 5 Hz, 1H), 6 14 (s, 1H), 5 28 (s, 2H), 3 98 (s, 3H), 2 00 (s, 3H) ES-HRMS m/z 464 0304 (M+H calcd for $C_{21}H_{16}BrF_2NO_4$ requires 464 0301)

Example 203

4-[3-bromo-4-[(difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoic acid

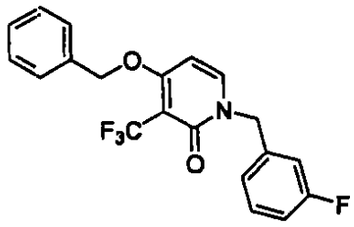



EXAMPLE 202 (7 43 g, 16 00 mmol) was dissolved in tetrahydrofuran (40 mL) Potassium trimethylsilanolate (4 10 g, 32 00 mmol) was added and the reaction mixture was stirred at room temperature for 22 hours The tetrahydrofuran was evaporated and $H_2O$ (50 mL) was added The aqueous reaction mixture was acidified with 1*N* HCl and the precipitate was collected by filtration The solids were washed with boiling methanol to give an off-white solid (5 05 g, 70%) $^1$H NMR

(300 MHz, DMSO-$d_6$) δ 13,2 (br s, 1H), 8 10 (d, $J$ = 8 5 Hz, 2H), 7 72 (q, $J$ = 7 9 Hz, 1H), 7 45 (d, $J$ = 8 3 Hz, 2H), 7 38 (*app* dt, $J$ = 2 4, 9 9 Hz, 1H), 7 23 (*app* dt, $J$ = 1 8, 8 5 Hz, 1H), 6 72 (s, 1H), 5 37 (s, 2H), 1 97 (s, 3H) ES-HRMS m/z 450 0154 (M+H calcd for $C_{20}H_{14}BrF_2NO_4$ requires 450 0147)

Example 204

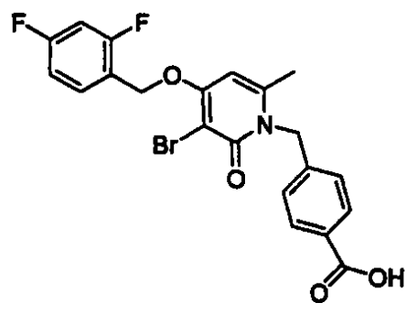
4-(Benzyloxy)-1-(3-fluorobenzyl)-3-(trifluoromethyl)pyridin-2(1H)-one




The starting material (0 250 g, 0 591 mmol) was dissolved in 1-methyl-2-pyrrolidinone (5 0 mL) Trifluoroacetic acid, sodium salt (0 322 g, 2 36 mmol) was added, followed by copper(I)iodide (0 225 g, 1 18 mmol) The resulting mixture was heated to 180°C for 5 hours and then allowed to cool to room temperature The reaction was diluted with $H_2O$ (50 mL) and brine (50 mL), then extracted into ethyl acetate (2 x 50 mL) The combined organic layers were washed with brine (50 mL), dried over $Na_2SO_4$, filtered and evaporated Chromatography (reverse-phase, acetonitrile/$H_2O$) provided an off-white solid (0 050 g, 22%) $^1$H NMR (400 MHz, $CDCl_3$) δ 7 40-7 27 (m, 8H), 7 06 (d, $J$ = 7 7 Hz, 1H), 6 97 (d, $J$ = 9 0 Hz, 1H), 6 07 (d, $J$ = 7 7 Hz, 1H), 5 20 (s, 2H), 5 06 (s, 2H) ES-HRMS m/z 378 1097 (M+H calcd for $C_{20}H_{15}F_4NO_2$ requires 378 1112)

Example 205

4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzoic acid

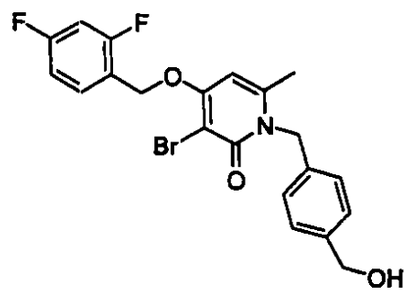


EXAMPLE 153 (50 0 g, 104 54 mmol) was dissolved in methanol (500 mL) and dioxane (100 mL) 1*N* NaOH (130 mL, 130 mmol) was added The resulting mixture was heated to 50 °C for 5 5 hours The reaction was partially concentrated and the heterogenous mixture was acidified (pH 2) with 1*N* HCl The precipitate was collected by filtration to afford a white solid (49 2 g, >100 %) $^1$H NMR (300 MHz, DMSO-$d_6$) δ 7 94 (d, *J* = 8 3 Hz, 2H), 7 70 (*app* q, *J* = 7 9 Hz, 1H), 7 35 (dt, *J* = 2 2, 9 9 Hz, 1H), 7 18 (*app* d, *J* = 8 3 Hz, 2H), 7 17-7 12 (m, 1H), 6 64 (s, 1H), 5 41 (s, 2H), 5 33 (s, 2H), 2 32 (s, 3H) ES-HRMS m/z 464 0327 (M+H calcd for $C_{21}H_{16}BrF_2NO_4$ requires 464 0304)

Example 206

3-Bromo-4-[(2,4-diflurobenzyl)oxy]-1-[4-(hydroxymethyl)benzyl]-6-methylpyridin-2(1H)-one

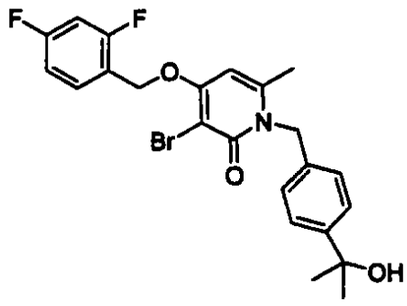
210
208




Example 205 (40 0 g, 86 16 mmol) suspended in tetrahydrofuran (300 mL) was cooled in an ice-bath Borane dimethylsulfide (129 2 mL, 258 48 mmol, 2 0 *M* in tetrahydrofuran) was slowly added The resulting mixture was slowly allowed to warm to room temperature overnight The mixture was recooled in an ice-bath and quenched by the addition of small pieces of ice After the evolution of gas ceased additional ice-water was added The flask was fitted with a distillation apparatus and the dimethylsulfide was removed After the reaction was cooled to room temperature, $H_2O$ (300 mL), ethyl acetate (200 mL) and tetrahydrofuran (300 mL) were added The precipitate that formed was collected by filtration and the filtrate was placed in a separatory funnel The aqueous layer was further extracted with ethyl acetate (300 mL) The combined organic layers were washed with brine (300 mL) The organic phase was dried over $Na_2SO_4$ and evaporated which was combined with the precipitate to yield an off-white solid (37 8 g, 97%) $^1H$ NMR (400 MHz, $CDCl_3$) δ 7 47 (*app* q, *J* = 7 7 Hz, 1H), 7 23 (d, *J* = 7 9 Hz, 2H), 7 05 (d, *J* 7 9 Hz, 2H), 6 86 (*app* dt, *J* = 2 3, 8 6 Hz, 1H), 6 79 (*app* dt, *J* = 2 4, 8 4 Hz, 1H), 6 00 (s, 1H), 5 28 (s, 2H), 5 16 (s, 2H), 4 57 (s, 2H), 2 25 (s, 3H) ES-HRMS m/z 450 0512 (M+H calcd for $C_{21}H_{18}BrF_2NO_3$ requires 450 0511)

Example 207

3-Bromo-4-[(2,4-dıflurobenzyl)oxy]-1-[4-(1-hydroxy-1-methylethyl)benzyl]-6-methylpyrıdın-2(1H)-one



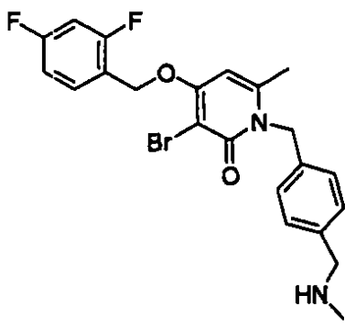
Preparatıon of 3-bromo-4-[(2,4-dıflurobenzyl)oxy]-1-[4-(1-hydroxy-1-methylethyl)benzyl]-6-methylpyrıdın-2(1H)-one

EXAMPLE 153 (2 00 g, 4 18 mmol) suspended ın tetrahydrofuran (20 mL) was cooled ın the dry ıce/acetone bath Methyl magnesıum bromıde (4 32 mL, 12 96 mmol, 3 0 *M* ın dıethyl ether) was slowly added The reactıon was slowly allowed to warm to room temperature overnight The reactıon was then cooled ın an ıce bath and quenched by the addıtıon of saturated $NH_4Cl$ (50 mL) $H_2O$ was added and the reactıon was extracted wıth ethyl acetate The combıned organıc layers were washed wıth brıne, drıed over $Na_2SO_4$, fılerted and evaporated The resıdue was subjected to chromatography (sılıca gel, hexanes/ethyl acetate wıth 10% methanol) to provıde an off-whıte foam The foam was dıssolved ın acetonitrıle and cooled ın an ıce bath *N*-bromosuccınımıde (0 057 g, 0 320 mmol) was added Once the addıtıon was complete the coolıng bath was removed After 2 5 hours at room temperature the reactıon was concentrated Purıfıcatıon by chromatography (sılıca gel, hexanes/ethyl acetate wıth 10% methanol) provıded a whıte foam $^1H$ NMR (400 MHz, $CDCl_3$) δ 7 56 (*app* q, *J* = 7 7 Hz, 1H ), 7 39 (d, *J* = 78 3 Hz, 2H), 7 11 (d, *J* = 8 2 Hz, 2H), 6 92 (*app* dt, *J* = 1 7, 8 4 Hz, 1H), 6 86-6 81 (m, 1H), 5 97 (s, 1H), 5 31 (s, 2H), 5 18 (s, 2H), 2 29

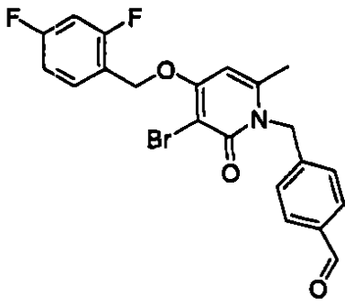
(s, 3H), 1 52 (s, 6H) ES-HRMS m/z 478 0811 (M+H $C_{23}H_{22}BrF_2NO_3$ requires 478 0824)

Example 208

3-bromo-4-[(2,4-diflurobenzyl)oxy]- 6-methyl-1-{4-[(methylamino)methyl]benzyl}pyridin-2(1H)-one



Step 1 Preparation of 4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzaldehyde



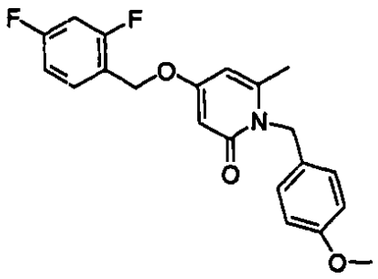
EXAMPLE 206 (1 30 g, 2 89 mmol) was suspended in acetonitrile (10 mL) and cooled in an ice-bath 1-hydroxy-1,3-dihydro-3,3-bis(trifluoromethyl)-1,2-benziodoxole 1-oxide (0 580 g, 1 44 mmol) was added and the reaction mixture was stirred at room temperature overnight Diethyl ether was added and the solid was collected by filtration to give a white solid (1 14 g,

88%) $^1$H NMR (400 MHz, $CDCl_3$) δ 9 96 (s, 1H), 7 80 (d, *J* = 8 2 Hz, 2H), 7 56 (*app* q, *J* = 7 7 Hz, 1H), 7 30 (d, *J* = 8 2 Hz, 2H), 6 93 (*app* dt, *J* = 1 6, 8 3 Hz, 1H), 6 87-6 82 (m, 1H), 6 02 (s, 1H), 5 41 (s, 2H), 5 20 (s, 2H), 2 27 (s, 3H)

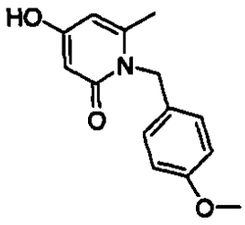
Step 2 3-bromo-4-[(2,4-dıflurobenzyl)oxy]- 6-methyl-1-{4-[(methylamıno)methyl]benzyl}pyrıdın-2(1H)-one 4-{[3-Bromo-4-[(2,4-dıfluorobenzyl)oxy]-6-methyl-2-oxopyrıdın-1(2H)-yl]methyl}benzaldehyde (Step 1) (1 53 g, 3 41 mmol) of step 1 was dıssolved ın *N,N*-dımethylformamıe (5 0 mL) Methylamıne (3 41 mL, 6 83 mmol, 2 0 M ın tetrahydrofuran) was added followed by NaHB(OAc) $_3$ (2 17 g, 10 23 mmol) ın *N,N*-dımethylformamıde (8 0 mL) and acetıc acıd (2 0 mL) The reactıon was stırred at room temperature overnight at whıch tıme 1N NaOH (50 mL) was added and then extracted wıth ethyl acetate (2 x 50 mL) The organıc layers were washed wıth brıne (25 mL), drıed over $Na_2SO4$ and evaporated Chromatography ( on sılıca, ethyl acetate wıth 5% methanolıc ammonıa/hexanes) afforded a tan solıd (0 810 g, 53%) $^1$H NMR (400 MHz, $CDCl_3$) δ 7 55 (*app* q, *J* = 7 8 Hz, 1H), 7 22 (d, *J* = 8 1 Hz, 2H), 7 11 (d, *J* = 8 1 Hz, 2H), 6 92 (*app* dt, *J* = 2 4, 8 3 Hz, 1H), 6 90-6 80 (m, 1H), 5 95 (s, 1H), 5 32 (s, 2H), 5 17 (s, 2H), 3 68 (s, 2H), 2 40 (s, 3H), 2 27 (s, 3H) ES-HRMS m/z 463 0838 (M+H calcd for $C_{22}H_{21}BrF_2N_2O_4$ requıres 463 0827)

Example 209

4-[(2,4-dıflurobenzyl)oxy]-1-(4-methoxybenzyl)-6-methylpyrıdın-2-(1H)-one



Step 1 Preparation of _-(4-methoxybenzyl)-4-hydroxy-6-methylpyridin-2(1H)-one



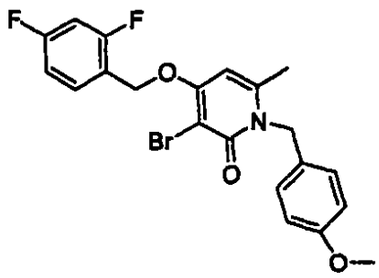
4-Hydroxy-6-methyl-2-pyrone (4 60 g, 36 45 mmol) and 4-methoxybenzylamine (5 00 g, 36 45 mmol) in $H_2O$ (100 mL) were heated to reflux After 15 hours at reflux the reaction was allowed to cool to room temperature The precipitate was collected by filtration washing with $H_2O$ to give a pale yellow solid (8 00 g, 89 %) $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7 2 (d, $J$ = 8 7 Hz, 2H), 6 85 (d, $J$ = 8 7 Hz, 2H), 5 74 (d, $J$ = 2 0 Hz, 1H), 5 56 (d, $J$ = 2 5 Hz, 1H), 5 08 (s, 2H), 3 68 (s, 3H), 2 14 (s, 3H)

Step 2 Preparation of 4-[(2,4-diflurobenzyl)oxy]-1-(4-methoxybenzyl)-6-methylpyridin-2(1H)-one 1-(4-methoxybenzyl)-4-hydroxy-6-methylpyridin-2(1H)-one (Step 1) (7 97 g, 32 49 mmol) was dissolved in *N*,*N*-dimethylformamide (60 mL) Potassium carbonate (4 94 g, 35 74 mmol) was added, followed by α-bromo-2,4-difluorotoluene (4 38 mL, 34 11 mmol) The reaction was stirred at room temperature for 20 hours at which time the mixture was filtered through a pad of Celite®

washing with acetonitrile and the filtrate was evaporated The residue was dissolved in $H_2O$ (150 mL) and extracted into ethyl acetate (2 x 100 mL) The organic phase was washed with brine (100 mL), dried over $Na_2SO_4$, filtered and evaporated Chromatography (on silica, hexanes/ethyl acetate with 10% methanol) yielded an off-white solid (3 64 g, 30%) $^1$H NMR (300 MHz $CDCl_3$) δ 7 42 (*app* q, *J* = 7 7 Hz, 1H), 7 13 (d, *J* = 8 5 Hz, 2H), 6 96-6 84 (m 2H), 6 85 (*app* d, *J* = 8 7 Hz, 2H), 6 01 (d, *J* = 2 6 Hz, 1H), 5 82 (d, *J* = 2 8 Hz, 1H), 5 23 (s, 2H), 5 02 (s, 2H), 3 79 (s, 3H), 2 25 (s, 3H) ES-HRMS m/z 372 1412 (M+H $C_{21}H_{19}F_2NO_3$ requires 372 1417)

Example 210

3-bromo-4-[(2,4-diflurobenzyl)oxy]-1-(4-methoxybenzyl)-6-methylpyridin-2(1H)-one



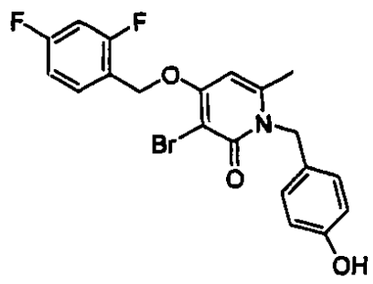

Preparation of 3-bromo-4-[(2,4-diflurobenzyl)oxy]-1-(4-methoxybenzyl)-6-methylpyridin-2(1H)-one EXAMPLE 209 (0 200 g, 0 538 mmol) suspended in acetonitrile (3 mL) was cooled in an ice-bath *N*-bromosuccinimide (0 101 g, 0 565 mmol) was added Once the addition was complete the cooling bath was removed After 1 hour the reaction was concentrated Purification by chromatography (silica gel, hexanes/ethyl acetate) provided a white solid (0 240 g, 99%) $^1$H NMR (300 MHz, $CDCl_3$) δ 7 59 (*app* q, *J* = 7 8 Hz, 1H), 7 16 (d, *J* = 8 7 Hz, 2H), 6 97 (app dt, *J* = 2 4, 8 6 Hz, 1H), 6 91-6 83 (m,

213
211

1H), 6 85 (*app* d, *J* = 8 7 Hz, 2H), 5 98 (s, 1H), 5 31 (s, 2H), 5 21 (s, 2H), 3 79 (s, 3H), 2 34 (s, 3H) ES-HRMS m/z 450 0491 (M+H $C_{21}H_{18}BrF_2NO_3$ requires 450 0511)

Example 211

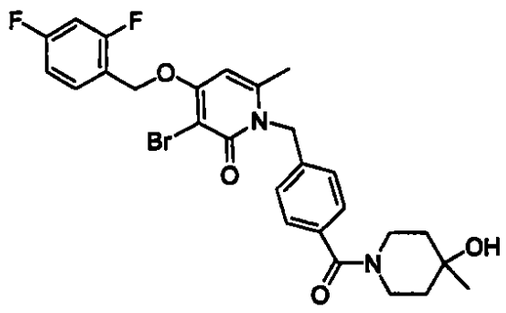
3-bromo-4-[(2,4-diflurobenzyl)oxy]-1-(4-hydroxybenzyl)-6-methylpyridin-2(1H)-one



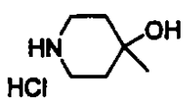

Preparation of 3-bromo-4-[(2,4-diflurobenzyl)oxy]-1-(4-hydroxybenzyl)-6-methylpyridin-2(1H)-one EXAMPLE 210 (0 235 g, 0 522 mmol) was suspended in acetonitrile (3 mL) Cerric ammonium nitrate (1 14 g, 2 09 mmol) dissolved in $H_2O$ (1 mL) was added The reaction was stirred at room temperature for 1 hour and then diluted with dichloromethane (25 mL) The reaction was then washed with $H_2O$ (10 mL) The aqueous phase was back extracted with dichloromethane (20 mL) The combined organic layers were dried over $Na_2SO_4$, filtered and evaporated The residue was washed with hot ethyl acetate to give an off-white solid (0 134 g, 59%) $^1H$ NMR (300 MHz, DMSO-$d_6$) δ 7 75 (*app* q, *J* = 7 9 Hz, 1H), 7 65 (s, 1H), 7 45-7 36 (m, 1H), 7 36 (d, *J* = 10 1Hz, 2H), 7 27-7 20 (m, 1H), 6 49 (d, *J* = 10 1 Hz, 2H), 5 60 (s, 2H), 5 07 (s, 2H), 2 63 (s, 3H) ES-HRMS m/z 436 0187 (M+H $C_{20}H_{16}BrF_2NO_3$ requires 436 0354)

Example 212

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1{4-[(4-hydroxy-4-methylpiperidin-1-yl)carbonyl]benzyl}-6-methylpyridin-2(1H)-one



Step 1 Preparation of 4-hydroxy-4-methylpiperidine hydrochloride

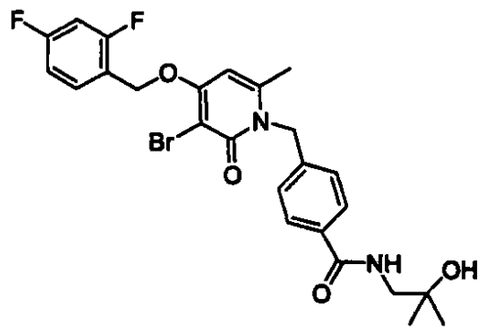


tert-Butyl-4-oxo-1-piperidine (10 0 g, 50 19 mmol) dissolved in diethyl ether (100 mL) was cooled in an ice-bath Methyl magnesium bromide (18 40 mL, 55 21 mmol, 3 0 *M* in diethyl ether) was added After slowly warming to room temperature the reaction was recooled in an ice-bath and quenched by the addition of saturated $NH_4Cl$ (75 mL) Additional $H_2O$ was added and the organic layer was removed The aqueous layer was further extracted with diethyl ether (50 mL) The combined organic layers were washed with brine, dried over $Na_2SO_4$, filtered and concentrated Chromatography ( silica gel, hexanes/ethyl acetate) provided a clear oil The resulting oil was dissolved in diethyl ether (10 mL) and treated with 4*N* HCl/dioxane (32 61 mL, 130 43 mmol) After stirring at room temperature for 1 hour the reaction mixture was concentrated to give a pale yellow solid (5 05 g, >100%)

Step 2 Preparation of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1{4-[(4-hydroxy-4-methylpiperidin-1-yl)carbonyl]benzyl}-6-methylpyridin-2(1H)-one THE ACID (0 300 g, 0 646 mmol) was suspended in dichloromethane (6 0 mL) 1-hydroxybenzotriazole (0 044 g, 0 323 mmol) was added followed by 3-(1-cyclohexylcarbodiimide)propyl-functionalized silica gel (2 02 g, 1 29 mmol, loading = 0 64 mmol/g), 3-(1-morpholine)propyl functionalized silica gel (1 84 g, 1 29 mmol, loading = 0 7 mmol/g) and dichloromethane (2 mL) After stirring at room temperature for 15 minutes, 4-hydroxy-4-methylpiperidine hydrochloride (0 147 g, 0 969 mmol) was added The resulting mixture was stirred at room temperature overnight, at which time dimethylamine-3-functionalized silica gel (1 7 g, 2 58 mmol, loading = 1 5 mmol/g) was added followed by isocyanate-3-functionalized silica gel (1 3 g, 1 62 mmol, loading = 1 22 mmol/g) The resulting mixture was stirred at room temperature for 3 hours The reaction mixture was then filtered and concentrated Chromatography (silica gel, hexanes/ethyl acetate with 10% methanol) provided a white foam (0 200 g, 55%) $^1$H NMR (300 MHz, $CDCl_3$) δ 7 58 (*app* q, *J* = 7 7 Hz, 1H), 7 33 (d, *J* = 8 1 Hz, 2H), 7 18 (d, *J* = 8 1 Hz, 2H), 6 96 (*app* t, *J* = 8 3 Hz, 1H), 6 87 (*app* dt, *J* = 2 0, 9 5 Hz, 1H), 6 06 (s, 1H), 5 38 (s, 2H), 5 22 (s, 2H), 4 27 (*br* m, 1H), 3 41 (*br* m, 3H), 2 30 (s, 3H), 2 06 (s, 1H), 1 60 (*br* m, 4H), 1 28 (s, 3H) ES-HRMS m/z 561 1173 (M+H $C_{27}H_{27}BrF_2N_2O_4$ requires 561 1195)

Example 213

4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]- 6-methyl-2-oxypyridin-1(2H)-yl]methyl}-N-(2-hydroxy-2-methylpropyl)benzamide

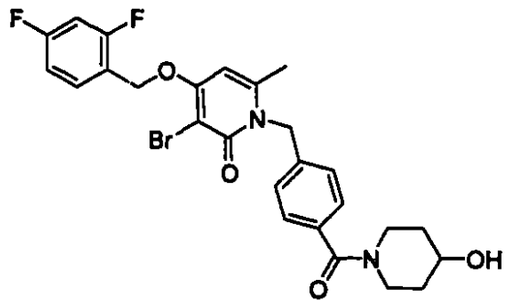


The title compound was by a procedure essentially as in Example 212 using 1-amino-2-methyl-2-propanol hydrochloride as starting material

$^1$H NMR (400 MHz, $CDCl_3$) δ 7 70 (d, *J* = 8 3 Hz, 2H), 7 53 (*app* q, *J* = 7 8 Hz, 1H), 7 33 (t, *J* = 5 8 Hz, 1H), 7 06 (d, *J* = 8 3 Hz, 2H), 6 95-6 90 (m, 1H), 6 86-6 81 (m, 1H), 6 04 (s, 1H), 5 30 (s, 2H), 5 19 (s, 2H), 3 40 (d, J = 5 9 Hz, 2H), 2 98 (*br* s, 1H), 2 24 (s, 3H), 1 21 (s, 6H) ES-HRMS m/z 535 1012 (M+H $C_{25}H_{25}BrF_2N_2O_4$ requires 535 1039)

Example 214

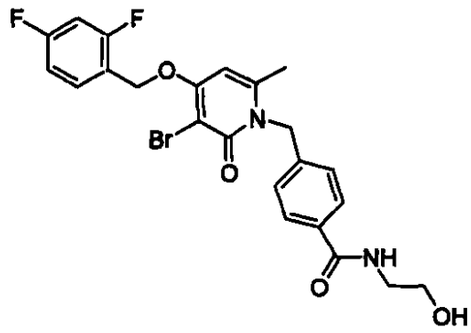
3-bromo-4-[(2,4-difluorobenzyl)oxy]-1{4-[(4-hydroxypiperidin-1-yl)carbonyl]benzyl}-6-methylpyridin-2(1H)-one



The title compound was produced essentially as in Example 212 using 4-hydroxypiperidine as starting material $^1$H NMR (400 MHz, $CDCl_3$) δ 7 55 (*app* q, *J* = 7 7 Hz, 1H), 7 30 (d, *J* = 8 2 Hz, 2H), 7 15 (d, *J* = 8 3 Hz, 2H), 6 94 (*app* dt, *J* = 2 4, 8 4 Hz, 1H), 6 84 (*app* ddd, *J* = 2 6, 8 9, 10 3 Hz, 1H), 6 01 (s, 1H), 5 36 (s, 2H), 5 19 (s, 2H), 4 12-4 07 (m, 1H), 3 96-3 90 (m, 1H), 3 60 (*br* s, 1H), 3 33 (*br* s, 1H), 3 13 (*br* s, 1H), 2 27 (s, 3H), 1 91 (*br* s, 3H), 1 77 (*br* s, 1H), 1 57 (*br* s, 1H), 1 44 (*br* s, 1H) ES-HRMS m/z 547 1006 (M+H $C_{26}H_{25}BrF_2N_2O_4$ requires 547 1039)

Example 215

4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-N-(2-hydroxyethyl)benzamide

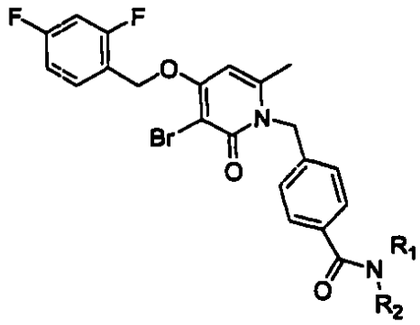


Preparation of 4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-*N*-(2-hydroxyethyl)benzamide To a reaction vessel (borosilicate culture tube) was added EXAMPLE 205 (0 300 g, 0 646 mmol) A stock solution of 1-hydroxybenzotriazole in *N,N*-dimethylformamide (3 mL, 0 11 M) was added to the reaction vessel followed by approximately 1 10 g of the polymer bound carbodiimide resin (1 8 mmol/g) Additional *N,N*-dimethylformamide (2 mL) was then added to the reaction vessel The parallel reaction apparatus was then orbitally shaken (Labline Benchtop Orbital Shaker) at approximately 200 RPM at room temperature for 15 minutes Ethanolamine (0 06 mL, 0 994 mmol) was then added to the reaction vessel and the reaction apparatus was orbitally shaken at room temperature overnight At this time the reaction was diluted with tetrahydrofuran (20 mL) and treated with approximately 2 0 g of polyamine resin (2 63 mmol/g) and approximately 2 6 g of methylisocyanate functionalized polystyrene (1 10 mmol/g) and the orbital shaking was continued at 200 RPM at room temperature for 3 hours The reaction vessel was then opened and the solution phase product was separated from the insoluble quenched byproducts by filtration and collection into a vial After partially evaporation the insoluble byproducts were rinsed further with tetrahydrofuran (2 x 10 mL) and combined with the partially reduced filtrate The resulting filtrate was concentrated by blowing $N_2$ over the vial while heating (60 °C) in a reaction block (KEM-Lab Parallel Reactor) to give an off-white solid (0 111 g, 34%) $^1$H NMR (400 MHz, DMF-$d_6$) δ 8 45 (t, *J* = 5 4 Hz, 1H), 7 94 (d, *J* = 8 2 Hz, 2H), 7 76 (*app* q, *J* = 7 9 Hz, 1H), 7 33-7 27 (m, 1H), 7 27 (*app* d, *J* = 7 9 Hz, 2H), 7 20 (*app* dt, *J* = 2 4, 8 6 Hz, 1H), 6 65 (s, 1H), 5 47 (s, 2H), 5 38 (s, 2H), 4 83 (*br* s, 1H),

3 64-3 60 (m, 2H), 2 47-3 42 (m, 2H), 2 40 (s, 3H) ES-HRMS m/z 507 0742 (M+H $C_{23}H_{21}BrF_2N_2O_4$ requires 507 0726)

Example 216-231

Preparation of 3-bromc-4-(2,4-difluorophenoxy)-6-methyl-1-[4-(aminocarbonyl)benzyl]pyridin-2(1H)-one compounds



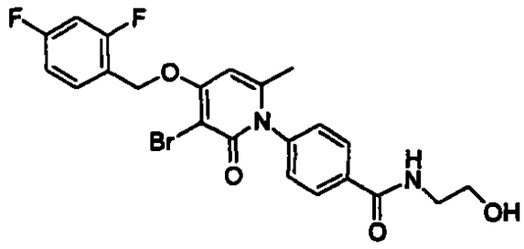
By following the method of Example 215 and substituting the appropriate amine, the compounds of Examples 216-231 are prepared The deprotection of the protected intermediates was accomplished with 4*N* HCl in dioxane to afford the compounds as hydrochloride salts

| Compound No | $R_1$ | $R_2$ | % Yield | MF | M+H Requires | ESHRMS m/z |
|---|---|---|---|---|---|---|
| Ex 216 | $CH_2CH_2NH$- | $CH_2CH_2NH$- | 73 | $C_{25}H_{24}BrF_2N_3O_4$ | 532 1042 | 532 102 |
| Ex 217 | H | $CH_2CH_2NH_2$ | 49 | $C_{23}H_{22}BrF_2N_3O_3$ | 506 0885 | 506 088 |
| Ex 218 | H | $CH_2CH_2CH_2NH_2$ | 31 | $C_{24}H_{24}BrF_2N_3O_3$ | 520 1042 | 520 104 |
| Ex 219 | H | OH | 53 | $C_{21}H_{17}BrF_2N_2O_4$ | 479 0413 | 479 042 |
| Ex 220 | H | $CH_3$ | 59 | $C_{22}H_{19}BrF_2N_2O_4$ | 477 0620 | 477 060 |
| Ex 221 | $CH_3$ | $CH_3$ | 51 | $C_{23}H_{21}BrF_2N_2O_3$ | 491 0776 | 491 079 |
| Ex 222 | $CH_2CH_2O$- | $CH_2CH_2O$- | 61 | $C_{25}H_{23}BrF_2N_2O_4$ | 533 0882 | 533 090 |
| Ex 223 | $CH_2CH_2OH$ | $CH_2CH_2OH$ | 69 | $C_{25}H_{25}BrF_2N_2O_5$ | 551 0988 | 551 097 |
| Ex 224 | $CH_2CH_2CH_2$- | $CH_2CH_2CH_2$- | 66 | $C_{26}H_{25}BrF_2N_2O_3$ | 531 1084 | 531 108 |
| Ex 225 | H | $CH(CH_3)_2$ | 50 | $C_{24}H_{23}BrF_2N_2O_3$ | 505 0933 | 505 090 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Ex 226 | $CH_2CH_2$- | $CH_2CH_2$- | 71 | $C_{25}H_{23}BrF_2N_2O_3$ | 517 0933 | 517 0908 |
| Ex 227 | $CH_2CH_2N(CH_3)$- | $CH_2CH_2N(CH_3)$- | 83 | $C_{26}H_{26}BrF_2N_3O_3$ | 546 1198 | 546 1215 |
| Ex 228 | H | $CH_2CH_2N(CH_3)_2$ | 81 | $C_{25}H_{26}BrF_2N_3O_3$ | 534 1198 | 534 1197 |
| Ex 229 | H | $CH_2CH_2OCH_3$ | 79 | $C_{24}H_{23}BrF_2N_2O_4$ | 521 0882 | 521 0861 |
| Ex 230 | $CH_3$ | $CH_2CH_2OH$ | 36 | $C_{24}H_{23}BrF_2N_2O_4$ | 521 0882 | 521 0893 |
| Ex 231 | $CH_3$ | $CH_2CH_2OCH_3$ | 82 | $C_{25}H_{25}BrF_2N_2O_4$ | 535 1039 | 535 1028 |

Example 232

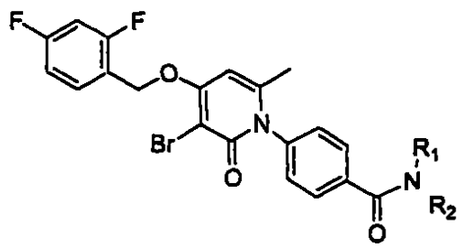
4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]- N-(2-hydroxyethyl)benzamide



Preparation of 4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]- N-(2-hydroxyethyl)benzamide To a reaction vessel (borosilicate culture tube) was added EXAMPLE 203 (0 300 g, 0 666 mmol) A stock solution of 1-hydroxybenzotriazole in *N,N*-dimethylformamide (3 mL, 0 11 M) was added to the reaction vessel followed by approximately 1 13 g of the polymer bound carbodiimide resin (1 8 mmol/g) Additional *N,N*-dimethylformamide (2 mL) was then added to the reaction vessel The parallel reaction apparatus was then orbitally shaken (Labline Benchtop Orbital Shaker) at approximately 200 RPM at room temperature for 15 minutes Ethanolamine (0 06 mL, 0 994 mmol) was then added to the reaction vessel and the reaction apparatus was orbitally shaken at room temperature overnight At this time the reaction was diluted with tetrahydrofuran (20 mL) and treated

with approximately 2 0 g of polyamine resin (2 63 mmol/g) and approximately 2 7 g of methylisocyanate functionalized polystyrene (1 10 mmol/g) and the orbital shaking was continued at 200 RPM at room temperature for 3 hours The reaction vessel was ther opened and the solution phase products were separated from the insoluble quenched byproducts by filtration and collection into a vial After partially evaporation the insoluble byproducts were rinsed further with tetrahydrofuran (2 x 10 mL) and combined with the partially reduced filtrate The resulting filtrate was concentrated by blowing $N_2$ over the vial while heating (60 °C) in a reaction block (KEM-Lab Parallel Reactor) Purification by chromatography (silica gel) provided an off-white solid (0 155 g, 47%) $^1$H NMR (400 MHz, DMF-$d_6$) δ 8 58 (t, *J* = 5 5 Hz, 1H), 8 10 (d, *J* = 8 3 Hz, 2H), 7 79 (*app* q, *J* = 7 9 Hz, 1H), 7 47 (d, *J* = 8 3 Hz, 2H), 7 36-7 30 (m, 1H), 7 21 (*app* dt, *J* = 2 4, 8 5 Hz, 1H), 6 73 (s, 1H), 5 43 (s, 2H), 3 68 (*app* t, *J* = 5 9 Hz, 2H), 3 52-3 49 (m, 2H), 2 03 (s, 3H) ES-HRMS m/z 493 0597 (M+H $C_{22}H_{19}BrF_2N_2O_4$ requires 493 0569)

Examples 233-243

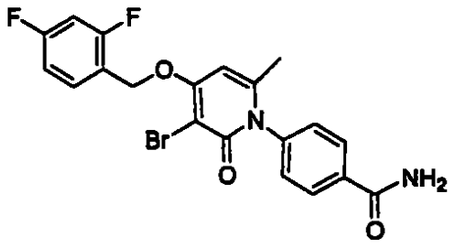



By following the method of Example 232 and substituting ethanolamine for the appropriate amine, the compounds of Examples 233-243 are prepared The deprotection of the protected intermediates was accomplished with 4*N* HCl in dioxane to afford the compounds as hydrochloride salts

| Compound No | $R_1$ | $R_2$ | % Yield | MF | M+H Requires | ESHRMS m/z |
|---|---|---|---|---|---|---|
| Ex 233 | $CH_2CH_2NH$- | $CH_2CH_2NH$- | 40 3 | $C_{24}H_{22}BrF_2N_3O_3$ | 518 0885 | 518 0866 |
| Ex 234 | H | $CH_2CH_2NH_2$ | 57 1 | $C_{22}H_{20}BrF_2N_3O_3$ | 492 0729 | 492 0748 |
| Ex 235 | H | $CH_2CH_2CH_2NH_2$ | 21 5 | $C_{23}H_{22}BrF_2N_3O_3$ | 506 0885 | 506 0915 |
| Ex 236 | H | OH | 33 9 | $C_{20}H_{15}BrF_2N_2O_4$ | 465 0256 | 465 0259 |
| Ex 237 | H | $CH_3$ | 20 7 | $C_{21}H_{17}BrF_2N_2O_3$ | 463 0463 | 463 0479 |
| Ex 238 | $CH_3$ | $CH_3$ | 22 3 | $C_{22}H_{19}BrF_2N_2O_3$ | 477 0620 | 477 0643 |
| Ex 239 | $CH_2CH_2O$- | $CH_2CH_2O$- | 84 4 | $C_{24}H_{21}BrF_2N_2O_4$ | 519 0726 | 519 0723 |
| Ex 240 | $CH_2CH_2OH$ | $CH_2CH_2OH$ | 46 6 | $C_{24}H_{23}BrF_2N_2O_5$ | 537 0831 | 537 0854 |
| Ex 241 | $CH_2CH_2CH_2$- | $CH_2CH_2CH_2$- | 76 5 | $C_{25}H_{23}BrF_2N_2O_3$ | 517 0933 | 517 0892 |
| Ex 242 | H | $CH(CH_3)_2$ | 52 6 | $C_{23}H_{21}BrF_2N_2O_3$ | 491 0776 | 491 0781 |
| Ex 243 | $CH_2CH_2$- | $CH_2CH_2$- | 47 2 | $C_{24}H_{21}BrF_2N_2O_4$ | 503 0776 | 503 0791 |

Ex 244

4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzamide

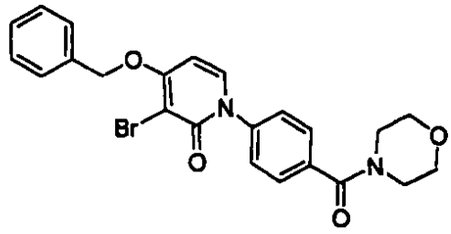



Preparation of 4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzamide EXAMPLE 203 (0 500 g, 1 11 mmol) was suspended in tetrahydrofuran (5 0 mL) 2-Chloro-4,6-dimethoxy-1,3,5-triazine (0 234 g, 1 33 mmol) was added followed by 4-methylmorpholine (0 366 mL, 3 33 mmol) The resulting mixture was stirred at room temperature for 1 5

hours at which time $NH_4OH$ (2 5 mL) was added The resulting mixture was stirred at room temperature overnight $H_2O$ (25 mL) and tetrahydrofuran (25 mL) was added The aqueous layer was further extracted with ethyl acetate (25 mL) The combined organic layers were washed with saturated sodium carbonate solution (25 mL), 1*N* HCl (25 mL), brine (25 mL), dried over $Na_2SO4$, filtered and concentrated to provide a pale yellow solid (0 500 g, 100 %) $^1H$ NMR (400 MHz, DMF-$d_6$) δ 8 13 (s, 1H), 8 02 (d, *J* = 8 5 Hz, 2H), 7 70 (*app* q, *J* = 7 9 Hz, 1H), 7 40 (d, *J* = 8 5 Hz, 2H), 7 41-7 34 (m, 1H), 7 22 (*app* dt, *J* = 1 8, 8 5 Hz, 1H), 6 71 (s, 1H), 5 37 (s, 2H), 1 97 (s, 3H) ES-HRMS m/z 449 0281 (M+H $C_{20}H_{15}BrF_2N_2O_3$ requires 449 0307)

Ex 245

4-(Benzyloxy)-3-bromo-1-[4-(morpholin-4-ylcarbonyl)phenyl]pyridin-2(1H)-one



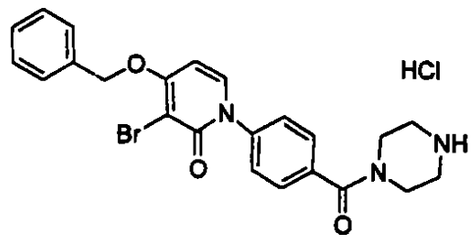

Preparation of 4-(Benzyloxy)-3-bromo-1-[4-(morpholin-4-ylcarbonyl)phenyl]pyridin-2(1H)-one To a reaction vessel (borosilicate culture tube) was added EXAMPLE 197 (0 100 g, 0 250 mmol) which was dissolved in *N,N*-dimethylformamide (2 0 mL) 1-Hydroxybenzotriazole (0 017 g, 0 125 mmol) was added to the reaction vessel followed by approximately 0 423 g of the polymer bound carbodiimide resin (1 8 mmol/g) Additional *N,N*-dimethylformamide (2 mL) was then added to the reaction

vessel The parallel reaction apparatus was then orbitally shaken (Labline Benchtop Orbital Shaker) at approximately 200 RPM at room temperature for 15 minutes Morpholine (0 033 g, 0 0 375 mmol) dissolved in *N,N*-dimethlyformamide (0 5 mL) was then added to the reaction vessel and the reaction apparatus was orbitally shaken at room temperature overnight At this time the reaction was diluted with *N,N*-dimethylformamide (2 0 mL) and dichloromethane (4 0 mL) and treated with approximately 0 770 g of polyamine resin (2 63 mmol/g) and approximately 1 0 g of methylisocyanate functionalized polystyrene (1 10 mmol/g) and the orbital shaking was continued at 200 RPM at room temperature for 3 hours The reaction vessel was then opened and the solution phase product was separated from the insoluble quenched byproducts by filtration and collection into a vial After partially evaporation the insoluble byproducts were rinsed with dichloromethane (2 x 10 mL) The filtrate was evaporated by blowing $N_2$ over the vial while heating (60 °C) in a reaction block (KEM-Lab Parallel Reactor) to give an off-white solid (0 092 g, 79%)

$^1$H NMR (400 MHz, $CDCl_3$) δ 7 50 (d, *J* = 8 5 Hz, 2H), 7 48-7 33 (m, 7H), 7 27 (d, *J* = 7 8 Hz, 1H), 6 19 (d, *J* = 7 8 Hz, 1H), 5 29 (s, 2H), 3 76-3 47 (*br* m, 8H) ES-HRMS m/z 469 0733 (M+H $C_{23}H_{21}BrN_2O_4$ requires 469 0757)

Ex 246

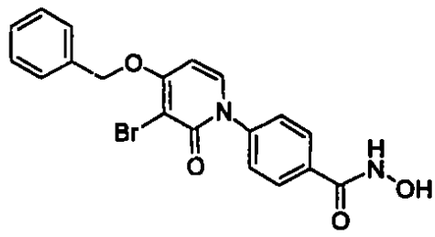
4-(Benzyloxy)-3-bromo-1-[4-(piperazin-1-ylcarbonyl)phenyl]pyridin-2(1H)-one hydrochloride




Preparation of 4-(benzyloxy)-3-bromo-1-[4-(piperazin-1-ylcarbonyl)phenyl]pyrid·n-2(1H)-one hydrochloride By following the method of Ex 245 and substituting *N*-tert-butyl carboxylate piperazine ·0 070 g, 0 375 mmol) for morpholine the title compound was prepared as the *N*-t-butoxycarbonyl protected compound The deprotection of the N-t-butoxycarbonyl intermediate was accomplished with 4*N* HCl in dioxane to afford the title compound as its hydrochloride salt (0 112 g, >100%) $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9 55 (*br* s, 2H), 7 78 (d, *J* = 7 8 Hz, 1H), 7 58 (d, *J* = 8 5 Hz, 2H), 7 48-7 33 (m, 7H), 6 57 (d, *J* = 7 8 Hz, 1H), 5 38 (s, 2H), 3 79-3 36 (*br* m, 4H), 3 30-3 14 (*br* s, 4H) ES-HRMS m/z 468 0940 (M+H $C_{23}H_{22}BrN_3O_3$ requires 468 0917)

Ex 247

4-[4-(Benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]-N-hydoxybenzamide

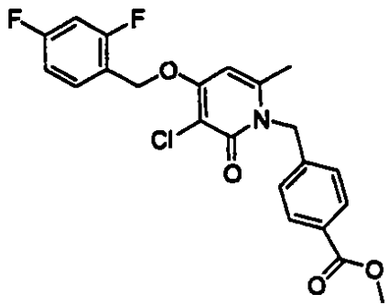



Preparation of 4-[4-(Benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]-N-hydoxybenzamide By following the method of EXAMPLE 245

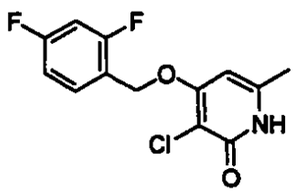
and substituting O-(tetrahydro-2H-pyranyl-2yl) hydroxylamine (0 044 g, 0 375 mmol) for morpholine the title compound was prepared as the tetrahydropyranly protected compound The deprotection of the tetrahydropyranly intermediate was accomplished with 4*N* HCl in dioxane to afford the title compound (0 056 g, >71%) $^1$H NMR (400 MHz, DMSO-$d_6$) δ 11 03 (*br* s,1H), 7 83 (d, *J* = 8 6 Hz, 2H), 7 78 (d, *J* = 7 8 Hz, 1H), 7 48-7 35 (m, 7H), 6 55 (d, *J* = 7 8 Hz, 1H), 5 37 (s, 2H) ES-HRMS m/z 415 0278 (M+H $C_{19}H_{15}BrN_2O_4$ requires 415 0288)

Ex 248

Methyl-4-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzoate



Step 1 Preparation of 3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpridin-2(1H)-one

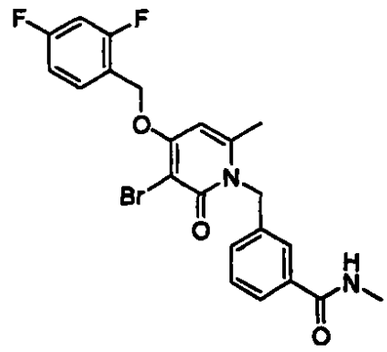


(5 00 g, 19 90 mmol) was suspended in 1,2-dichloroethane (100 mL) Dichloroacetic acid (0 082 mL, 0 995 mmol) was added, followed by *N*-chlorosuccinimide (3 19 g, 23 88 mmol) The reaction mixture was heated at 80 °C for 15 5 hours The 1,2-

dichloroethane was evaporated and the remaining solids were washed with acetonitrile to provide a tan solid (4 97 g, 88%)

Step 2 Preparation of methyl-4-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzoate 3-Chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpridin-2(1H)-one (Step 1) (4 97 g, 17 40 mmol) suspended in tetrahydrofuran (50 mL) was cooled in an ice-bath Methyl 4-(bromomethyl)benzoate (5 98 g, 26 10 mmol) was added, followed by sodium hydride (0 835 g, 20 88 mmol, 60% dispersion in mineral oil) Once the addition was complete the cooling bath was removed in the mixture was heated to 50 °C for 19 hours After cooling to room temperature saturated $NH_4Cl$ (50 mL) was added Ethyl acetate was added and the precipitate was collected by filtration The filtrate was further extracted with ethyl acetate The combined organic layers were washed with brine (50 mL), dried over $Na_2SO_4$, filtered and evaporated The resulting solid was combined with the precipitate and washed with hot ethyl acetate to give an off-white solid (5 24 g, 69%) $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 7 90 (d, J = 8 5 Hz, 2H), 7 63 (app q, J = 7 9 Hz, 1H), 7 31 (app dt, J = 2 4, 9 9 Hz, 1H), 7 21 (d, J = 8 3 Hz, 2H), 7 17-7 13 (m, 1H), 6 60 (s, 1H), 5 36 (s, 2H), 5 27 (s, 2H), 3 81 (s, 3H), 2 27 (s, 3H) ES-HRMS m/z 434 0931 (M+H $C_{22}H_{18}BrF_2NO_4$ requires 434 0965)

Example 249

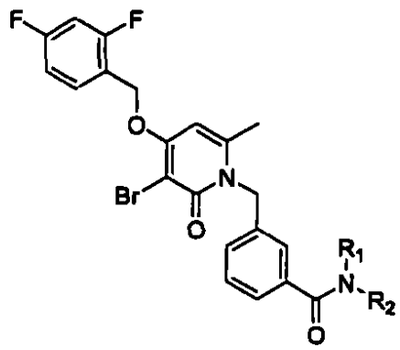


3-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-*N*-methylbenzamide

To a reaction vessel (borosilicate culture tube) was added EXAMPLE 169 (0 300 g, 0 646 mmol) A stock solution of 1-hydroxybenzotriazole in *N,N*-dimethylformamide (3 mL, 0 11 M) was added followed by approximately 1 10 g of the polymer bound carbodiimide resin (1 8 mmol/g) Additional *N,N*-dimethylformamide (2 mL) was then added to the reaction vessel The parallel reaction apparatus was then orbitally shaken (Labline Benchtop Orbital Shaker) at approximately 200 RPM at room temperature for 15 minutes *N*-Methylamine (0 50 mL, 0 999 mmol) was then added to the reaction vessel and the reaction apparatus was orbitally shaken at room temperature overnight At this time the reaction was diluted with tetrahydrofuran (35 mL) and treated with approximately 2 0 g of polyamine resin (2 63 mmol/g) and approximately 2 6 g of methylisocyanate functionalized polystyrene (1 50 mmol/g) and the orbital shaking was continued at 200 RPM at room temperature for 4 hours The reaction vessel was then opened and the solution phase products were separated from the insoluble quenched byproducts by filtration and collection into a vial After partial evaporation the insoluble byproducts were rinsed with tetrahydrofuran (2 x 10 mL) The

filtrate was evaporated by blowing $N_2$ over the vial while heating (60 °C) in a reaction block (KEM-Lab Parallel Reactor) Chromatography (C-18, acetonitrile/$H_2O$ with 0 1% trifluoroacetic acid) afforded a white solid (0 178 g, 58%) $^1H$ NMR (400 MHz, DMF-$d_6$) δ 7 65-7 53 (m, 3H), 7 37-7 28 (m, 2H), 6 97-6 82 (m, 2H), 6 00 (s, 1H), 5 36 (s, 2H), 5 19 (s, 3H), 2 96 (t, *J* = 4 83 Hz, 3H), 2 29 (s, 3H) ES-HRMS *m/z* 477 0635 (M+H $C_{22}H_{19}BrF_2N_2O_3$ requires 477 0620)

Preparation of Examples 250- 261

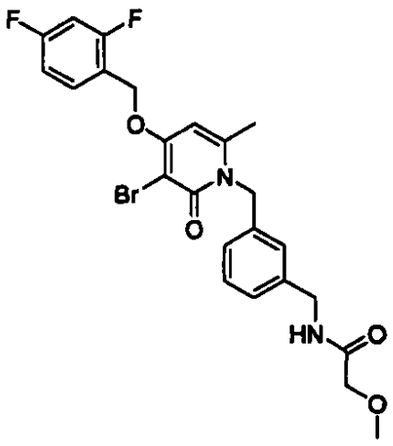


By following the methcd of Example 249 and replacing *N*-methylamine with the appropriate amine, the compounds of Examples 250-261 are prepared The deprotection of the protected intermediates was accomplished with 4*N* HCl in dioxane to afford the compounds as hydrochloride salts

| Compound No | $R_1$ | $R_2$ | % Yield | MF | M+H Requires | ES-HRMS *m/z* |
|---|---|---|---|---|---|---|
| Ex 250 | $CH_2CH_2NH$- | $CH_2CH_2NH$- | 89 | $C_{25}H_{24}BrF_2N_3O_4$ | 532 1042 | 532 1067 |
| Ex 251 | H | $CH_2CH_2NH_2$ | 75 | $C_{23}H_{22}BrF_2N_3O_3$ | 506 0885 | 506 0900 |
| Ex 252 | H | $CH_2CH_2CH_2NH_2$ | 84 | $C_{24}H_{24}BrF_2N_3O_3$ | 520 1042 | 520 1000 |
| Ex 253 | H | OH | 45 | $C_{21}H_{17}BrF_2N_2O_4$ | 479 0413 | 479 0394 |
| Ex 254 | $CH_3$ | $CH_3$ | 69 | $C_{23}H_{21}BrF_2N_2O_3$ | 491 0776 | 491 0731 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Ex 255 | H | $CH_3$ | 58 | $C_{22}H_{19}BrF_2N_2O_3$ | 479 0602 | 479 0598 |
| Ex 256 | $CH_2CH_2O$- | $CH_2CH_2O$- | 69 | $C_{25}H_{23}BrF_2N_2O_4$ | 533 0882 | 533 0857 |
| Ex 257 | H | $CH_2CH_2OH$ | 51 | $C_{23}H_{21}BrF_2N_2O_4$ | 507 0726 | 507 0698 |
| Ex 258 | $CH_2CH_2OH$ | $CH_2CH_2OH$ | 25 | $C_{25}H_{25}BrF_2N_2O_5$ | 551 0988 | 551 0972 |
| Ex 259 | $CH_2CH_2CH_2$- | $CH_2CH_2CH_2$- | 62 | $C_{26}H_{25}BrF_2N_2O_3$ | 531 1089 | 531 1088 |
| Ex 260 | H | $CH(CH_3)_2$ | 46 | $C_{24}H_{23}BrF_2N_2O_3$ | 505 0933 | 505 0918 |
| Ex 261 | $CH_2CH_2$- | $CH_2CH_2$- | 60 | $C_{25}H_{23}BrF_2N_2O_3$ | 517 0933 | 517 0950 |

Example 262

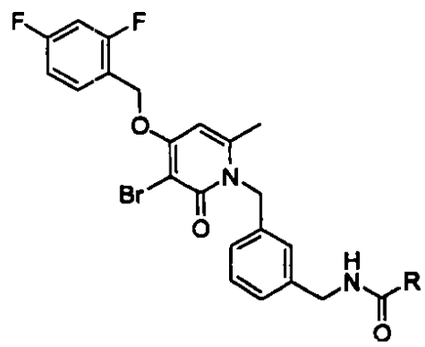



N-(3-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzyl)-2-methoxyacetamide

To a reaction vessel (borosilicate culture tube) was added methoxyacetic acid (0 09 g, 1 00 mmol) A stock solution of 1-hydroxybenzotriazole (3 mL, 0 16 M) and *N*-methylmorpholine (3 mL, 0 43 M) in *N,N*-dimethylformamide were added to the reaction vessel followed by approximately 0 97 g of the polymer bound carbodiimide resin (1 38 mmol/g) Additional *N,N*-dimethylformamide (3 mL) was then added to the reaction vessel The parallel reaction apparatus was then orbitally shaken (Labline Benchtop Orbital Shaker) at approximately 200 RPM at room temperature for 4 hours 1-[3-

(aminomethyl)benzyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (EXAMPLE 61) (0 30 g, 0 668 mmol) was then added to the reaction vessel followed by additional *N,N*-dimethylformamide (5 0 mL) and the reaction apparatus was orbitally shaken at room temperature overnight At this time the reaction was diluted with tetrahydrofuran (20 mL) and treated with approximately 2 06 g of polyamine resin (2 63 mmol/g) and approximately 2 67 g of methylisocyanate functionalized polystyrene (1 10 mmol/g) and the orbital shaking was continued at 200 RPM at room temperature for 4 hours The reaction vessel was then opened and the solution phase products were separated from the insoluble quenched byproducts by filtration and collection into a vial After partial evaporation the insoluble byproducts were rinsed with tetrahydrofuran (2 x 10 mL) The filtrate was evaporated by blowing $N_2$ over the vial while heating (60 °C) in a reaction block (KEM-Lab Parallel Reactor) afforded a tan solid (0 321 g, 89 4%) $^1$H NMR (400 MHz, DMF-$d_6$) δ 8 33 (br s, 1H), 7 81 (*app* q, *J* = 7 85 Hz, 1H), 7 40-7 23 (m, 5H), 7 09 (d, *J* = 7 25 Hz, 1H), 6 68 (s, 1H), 5 46 (s, 2H), 5 42 (s, 2H), 4 45 (d, *J* = 6 24 Hz, 2H), 3 93 (s, 2H), 3 39 (s, 3H), 2 44 (s, 3H) ES-HRMS *m/z* 521 0891 (M+H $C_{24}H_{23}BrF_2N_2O_4$ requires 521 0882)

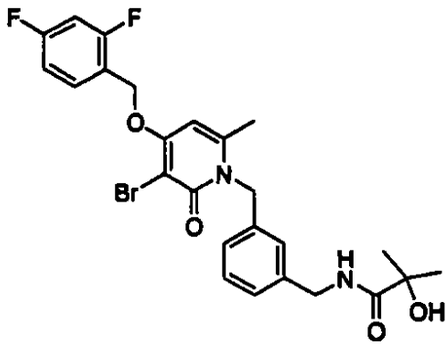
Preparation of Example 263-265



By following the method of Example 262 and replacing methoxyacetic acid with the appropriate acid, the compounds of Examples 263-265 are prepared The deprotection of the protected intermediates was accomplished with 4*N* HCl in dioxane to afford the compounds as hydrochloride salts

| Compound No | R | % Yield | MF | M+H Requires | ES-HRMS *m/z* |
|---|---|---|---|---|---|
| Ex 263 | $CH_2NH_2$ | 46 1 | $C_{23}H_{23}BrF_2N_3O_3$ | 506 0885 | 506 0870 |
| Ex 264 | $CH_2NHCOCH_3$ | 70 4 | $C_{25}H_{24}BrF_2N_3O_4$ | 548 0991 | 548 1007 |
| Ex 265 | $CH_2OCOCH_3$ | 42 7 | $C_{23}H_{21}BrF_2N_2O_4$ | 549 0831 | 549 0837 |

Example 266

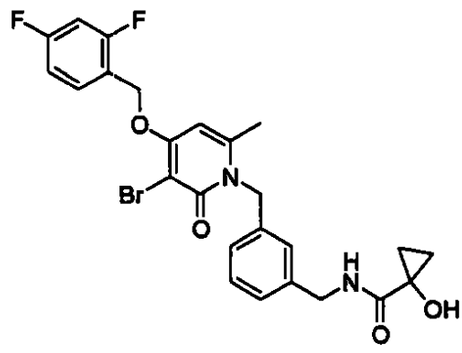


N-(3-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzyl)-2-hydroxy-2-methylpropanamide

1-[3-(aminomethyl)benzyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (EXAMPLE 161) (0 300 g, 0 668 mmol), 1-hydroxyisobutyric acid (0 215 g, 2 064 mmol), 1-hydroxybenzotriazole (0 112 g, 0 826 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0 185 g, 0 963 mmol) were dissolved in *N,N*-dimethylacetamide (3 mL).

*N*-methylmorpholine (0 209 g, 2 064 mmol) was added, and the reaction stirred for 1 hour at room temperature The reaction was diluted with $H_2O$ (50 mL) and the aqueous layer extracted with ethyl acetate (3 x 25 mL) The combined organics were then washed with 1*N* HCl (25 mL), saturated $Na_2CO_3$ (25 mL), brine (25 mL), dried over $Na_2SO_4$, and concentrated to yield an off-white solid (0 235 g, 64%) $^1$H NMR (400 MHz, DMF-$d_6$) δ 8 25 (br s, 1H), 7 81 (*app* q, *J* = 7 92 Hz, 1H), 7 40-7 21 (m, 5H), 7 09 (d, *J* = 6 84 Hz, 1H), 6 67 (s, 1H), 5 46 (s, 2H), 5 42 (s, 2H), 4 42 (d, *J* = 6 24 Hz, 2H), 2 44 (s, 3H), 1 38 (s, 6H) ES-HRMS *m/z* 535 1024 (M+H $C_{25}H_{25}BrF_2N_2O_4$ requires 535 1039)

Example 267

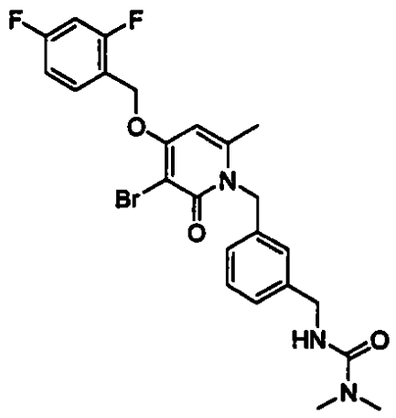


N-(3-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzyl)-1-hydroxycyclopropanecarboxamide

By following the method of Example 266 and substituting 1-hydroxy-1-cyclopropane-carboxylic acid for 1-hydroxyisobutyric acid, the title compound was prepared (0 352 g, 96%) $^1$H NMR (400 MHz, DMF-$d_6$) δ 8 46 (*app* t, *J* = 6 24 Hz, 1H), 7 81 (*app* q,

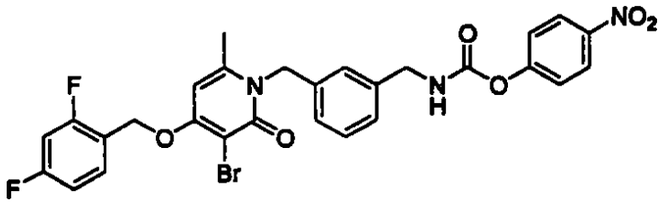
*J* = 7 92 Hz, 1H), 7 40-7 22 (m, 5H), 7 06 (d, *J* = 7 05 Hz, 1H), 6 67 (s, 1H), 5 45 (s, 2H), 5 42 (s, 2H), 4 46 (d, *J* = 6 44 Hz, 2H), 2 45 (s, 3H), 1 17-1 12 (m, 2H), 0 93 (app q, *J* = 3 82 Hz, 2H) ES-HRMS *m/z* 533 0861 (M+H $C_{25}H_{23}BrF_2N_2O_4$ requires 533 0882)

Example 267



N'-(3-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzyl)-N,N-dimethylurea

Step 1 Preparation of 4-nitrophenyl 3-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzylcarbamate



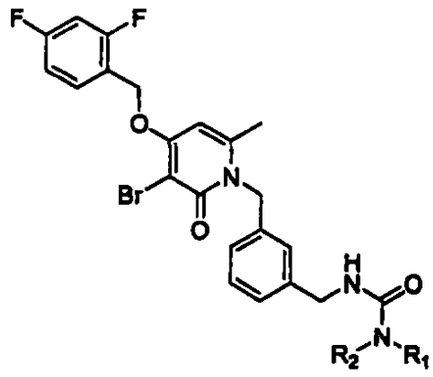
1-[3-(aminomethyl)benzyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (EXAMPLE 161) (2.00 g, 4.45 mmol)

was suspended in dichloromethane (15 mL) Pyridine was added (0 43 mL, 5 34 mmol) After stirring for 10 minutes at room temperature, a stock solution of 4-nitrophenyl chloroformate (10 0 mL, 0 50 M) in dichloromethane was added dropwise After stirring for 4 5 hours at room temperature, a stock solution of 4-nitrophenyl chloroformate (2 5 mL, 0 50 M) in dichloromethane was again added dropwise and stirring continued at 40 °C overnight The reaction mixture was concentrated and subjected to chromatography (silica gel, ethyl acetate with 10% methanol/hexanes) to afford a yellow solid (1 11 g, 66%) $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8 56 (*app* t, $J$ = 6 10 Hz, 1H), 8 24-8 21 (m, 2H), 7 62 (*app* q, $J$ = 7 88 Hz, 1H), 7 40-7 27 (m, 7H), 6 98 (d, $J$ = 7 52 Hz, 1H), 6 54 (s, 1H), 5 30 (s, 2H), 5 2[illegible] (s, 2H), 4 25 (d, $J$ = 6 18 Hz, 2H), 2 30 (s, 3H) ES-HRMS $m/z$ 614 0753 (M+H $C_{28}H_{22}BrF_2N_3O_6$ requires 614 0733)

Step 2 Preparation of N'-(3-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzyl)-N,N-dimethylurea To a reaction vessel (borosilicate culture tube) was added 4-nitrophenyl 3-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzylcarbamate (from step 1) (0 350 g, 0 570 mmol) dissolved in dichloromethane (6 0 mL) The parallel reaction apparatus was then orbitally shaken (Labline Benchtop Orbital Shaker) at approximately 200 RPM at room temperature for 15 minutes A stock solution of *N,N*-dimethylamine in tetrahydorfuran (0 427 mL, 2 0 M) was then added to the reaction vessel and the reaction apparatus was orbitally shaken at room temperature overnight The reaction mixture was concentrated and subjected to chromatography (silica gel, ethyl acetate with 10% methanol/hexanes) which afforded an off

white solid (0 226 g, 63 3%) $^1$H NMR (400 MHz, DMF-$d_6$) δ 7 81 (*app* q, *J* = 7 92 Hz, 1H), 7 40-7 19 (m, 5H), 7 06 (d, *J* = 7 45 Hz, 1H), 6 88 (*app* t, *J* = 5 84 Hz, 1H), 6 68 (s, 1H), 5 45 (s, 2H), 5 42 (s, 1H), 4 35 (d, *J* = 5 84 Hz, 1H), 2 92 (s, 6H), 2 44 (s, 3H) ES-HRMS *m/z* 520 1065 (M+H $C_{24}H_{24}BrF_2N_3O_3$ requires 520 1042)

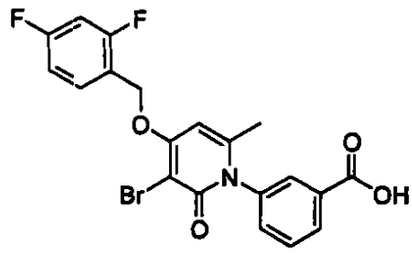
Preparation of Example 268-270



By following the method of Example 267 and replacing *N,N*-dimethylamine with the appropriate amine, the compounds of Examples 268-270 are prepared The deprotection of the protected intermediates was accomplished with 4*N* HCl in dioxane to afford the compounds as hydrochloride salts

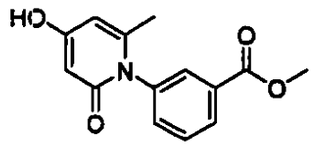
| Compound No | $R_1$ | $R_2$ | % Yield | MF | M+H Requires | ES-HRMS *m/z* |
|---|---|---|---|---|---|---|
| Ex 268 | $CH_2CH_2N$- | $CH_2CH_2N$- | 66 6 | $C_{26}H_{27}BrF_2N_4O_3$ | 561 1307 | 561 1309 |
| Ex 269 | H | $CH_3$ | 27 0 | $C_{23}H_{22}BrF_2N_3O_3$ | 506 0885 | 506 0898 |
| Ex 270 | $CH_2CH_2O$- | $CH_2CH_2O$- | 64 4 | $C_{26}H_{26}BrF_2N_3O_4$ | 562 1148 | 562 1137 |

Example 271



3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoic acid

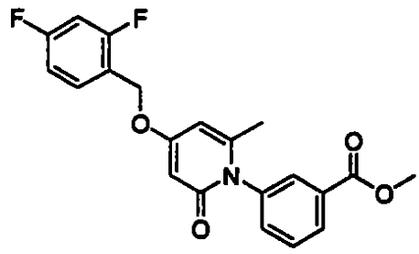
Step 1 Preparation of methyl 3-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)benzoate



Methyl 3-aminobenzoate (75 00 g, 496 13 mmol) and 4-hydroxy-6-methyl-2-pyrone (62 57 g, 496 13 mmol) were suspended in 1,2-dichlorobenzene (150 mL) and heated to 165 °C for 15 minutes The reaction was cooled to room temperature and extracted with 0 54M $K_2CO_3$ (4 x 250 mL) The aqueous layers were acidified (pH 2) with 4*N* HCl The precipitate was collected by filtration to afford a yellow-orange solid (20 24 g, 16%) The resulting filtrate was extracted with ethyl acetate (3 x 1 L) The organic layers were washed with brine (500 mL), dried over $MgSO_4$ and evaporated The resulting solid was washed with hot $H_2O$ to afford a yellow-orange solid (3 84 g, 3%) The two solids were then combined $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 7 98 (dt, *J* = 1 31, 7 79 Hz, 1H), 7 69 (*app* t, *J* = 1 78 Hz, 1H), 7 62 (t, *J* = 7 78 Hz, 1H) 7 49 (ddd, *J* = 1 07, 1 07, 7 85 Hz, 1H), 5 89 (dd, *J* = 0 87, 2 48 Hz, 1H), 5 55 (*app* d, *J* = 0 94

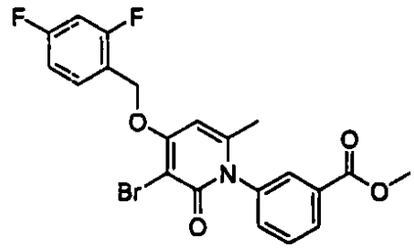
Hz, 1H), 3 83 (s, 3H), 1 80 (s, 3H) ES-HRMS *m/z* 260 0895 (M+H $C_{14}H_{13}NO_4$ requires 260 0917)

Step 2 Preparation of methyl 3-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoate



Methyl 3-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)benzoate ( from step 1) (24 00 g, 92 57 mmol) and $K_2CO_3$ (15 35 g, 111 08 mmol) were dissolved in *N,N*-dimethylformamide (220 mL) 2,4-Difluorobenzyl bromide (20 12 g, 97 20 mmol) was then added and the reaction mixture stirred for 48 hours at room temperature The reaction mixture was diluted with $H_2O$ (1 L) and the precipitate collected by filtration to afford a white solid (4 08 g, 11%) The resulting oil was purified by chromatography (silica gel, ethyl acetate with 10% methanol/hexanes) to afford an off white solid (11 88 g, 33%) The two solids were combined $^1H$ NMR (400 MHz, $CDCl_3$) δ 8 11 (dt, *J* = 1 41, 7 79 Hz, 1H), 7 87 (*app* t, *J* = 1 78 Hz, 1H), 7 58 (*app* t, *J* = 7 69 Hz, 1H) 7 45-7 38 (m, 2H), 6 94-6 84 (m, 2H), 5 97 (d, *J* = 2 68 Hz, 1H), 5 90 (ddd, *J* = 0 94, 1 74, 1 74 Hz, 1H), 5 97 (s, 1H), 3 90 (s, 3H), 1 89 (s, 3H) ES-HRMS *m/z* 386 1179 (M+H $C_{21}H_{17}F_2NO_4$ requires 386 1198)

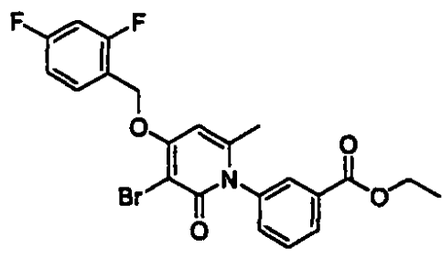
Step 3 Preparation of methyl 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoate



Methyl 3-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoate ( from step 2) (15 85 g, 41 130 mmol) suspended in acetonitrile (165 mL) was cooled in an ice-bath *N*-bromosuccinimide (7 687 g, 43 186 mmol) was added and the ice-bath was removed The reaction mixture was stirred for 1 5 hours at room temperature Reaction was concentrated and subjected to chromatography (silica gel, ethyl acetate with 10% methanol/hexanes) afforded an off white solid (17 63 g, 92%) $^1$H NMR (400 MHz, $CDCl_3$) δ 8 17 (dt, *J* = 1 41, 7 85 Hz, 1H), 7 90 (t, *J* = 1 81 Hz, 1H), 7 67-7 41 (m, 3H), 7 05-6 88 (m, 2H), 6 13 (s, 1H), 5 30 (s, 2H), 3 95 (s, 1H), 2 01 (s, 3H) ES-HRMS *m/z* 464 0286 (M+H $C_{21}H_{16}BrF_2NO_4$ requires 464 0304)

Step 4 Preparation of the title compound Methyl 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoate ( from step 3) (10 0 g, 21 539 mmol) was dissolved in methanol (36 mL) and tetrahydrofuran (14 mL) 4*N* NaOH (13 5 mL, 53 847 mmol) was added The resulting mixture was stirred for 1 5 hours at room temperature The reaction was acidified (pH 2) with 4*N* HCl The precipitate was collected by filtration to afford an off white solid (7 83 g, 81%) $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8 01 (dt, *J* = 1 41, 7 65 Hz, 1H), 7 76 (*app* t, *J* = 1 78 Hz, 1H), 7 76-7 15 (m, 5H), 6 66 (s, 1H), 5 32 (s, 2H), 1 92 (s, 3H) ES-HRMS *m/z* 450 0134 (M+H $C_{20}H_{14}BrF_2NO_4$ requires 450 0147)

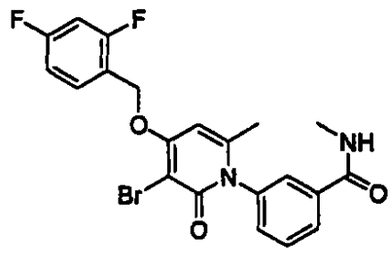
Example 272



Ethyl 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoate

By following the method of Example 271 and substituting ethyl 3-aminobenzoate for methyl 3-aminobenzoate, the title compound was prepared (2 66 g, 79%) $^1$H NMR (400 MHz, $CDCl_3$) δ 8 13 (dt, *J* = 1 41, 7 85 Hz, 1H), 7 84 (t, *J* = 1 88 Hz, 1H), 7 62-7 55 (m, 2H), 7 36 (*app* dq, *J* = 1 07, 7 85 Hz, 1H), 6 96 (*app* dt, *J* = 2 55, 8 35 Hz, 1H), 6 88-6 84 (m, 1H), 6 08 (s, 1H), 5 25 (s, 2H), 4 42-4 30 (m, 2H), 1 96 (s, 3H), 1 36 (t, *J* = 7 12 Hz, 3H) ES-HRMS *m/z* 478 0482 (M+H $C_{22}H_{18}BrF_2NO_4$ requires 478 0460)

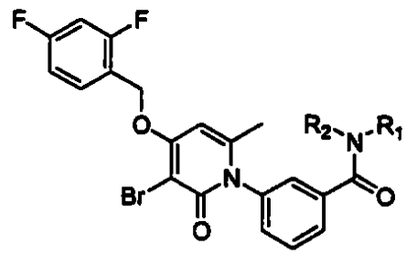
Example 273



3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-*N*-methylbenzamide

To a reaction vessel (borosilicate culture tube) was added EXAMPLE 271 (0 300 g, 0 666 mmol) A stock solution of 1-hydroxybenzotriazole in *N,N*-dimethylformamide (3 mL, 0 11 M) was added to the reaction vessel followed by approximately 0 97 g of the polymer bound carbodiimide resin (1 38 mmol/g) Additional *N,N*-dimetnylformamide (2 mL) was then added to the reaction vessel The parallel reaction apparatus was then orbitally shaken (Labline Benchtop Orbital Shaker) at approximately 200 RPM at room temperature for 15 minutes *N*-Methylamine in tetrahydrofuran (0 50 mL, 0 999 mmol) was then added to the reaction vessel and the reaction apparatus was orbitally shaken at room temperature overnight At this time the reaction was diluted with tetrahydrofuran (30 mL) and treated with approximately 2 0 g of polyamine resin (2 63 mmol/g) and approximately 3 6 g of methylisocyanate functionalized polystyrene (1 10 mmol/g) and the orbital shaking was continued at 200 RPM at room temperature for 4 hours The reaction vessel was then opened and the solution phase products were separated from the insoluble quenched byproducts by filtration and collection into a vial After partial evaporation the insoluble byproducts were rinsed with tetrahydrofuran (2 x 10 mL) The filtrate was evaporated by blowing $N_2$ over the vial while heating (60 °C) in a reaction block (KEM-Lab Parallel Reactor) to give an off-white solid (0 189 g, 61%) $^1$H NMR (400 MHz, DMF-$d_6$) δ 8 56 (br d, *J* = 4 16 Hz, 1H), 8 05-7 76 (m, 3H), 7 66 (t, *J* = 7 79 Hz, 1H), 7 56-7 19 (m, 3H), 6 74 (s, 1H), 5 43 (s, 2H), 3 46 (s, 3H), 2 03 (s, 3H) ES-HRMS *m/z* 463 0476 (M+H $C_{21}H_{17}BrF_2N_2O_3$ requires 463 0463)

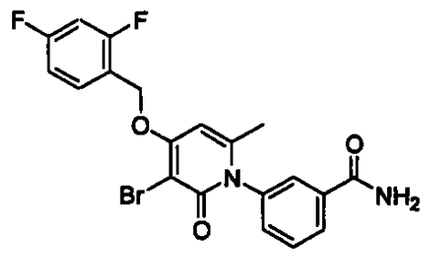
Preparation of Example 274-289



By following the method of Example 273 and replacing *N*-methylamine with the appropriate amine, the compounds of Examples 274-289 are prepared The deprotection of the protected intermediates was accomplished with 4*N* HCl in dioxane to afford the compounds as their hydrochloride salts

| Compound No | R1 | R2 | % Yield | MF | M+H Requires | ES-HRMS *m/z* |
|---|---|---|---|---|---|---|
| Ex 274 | CH2CH2NH- | CH2CH2NH- | 92 8 | $C_{24}H_{22}BrF_2N_3O_3$ | 518 0885 | 518 0865 |
| Ex 275 | H | CH2CH2NH2 | 95 7 | $C_{22}H_{20}BrF_2N_3O_3$ | 492 0729 | 492 0711 |
| Ex 276 | H | CH2CH2CH2NH2 | 97 8 | $C_{23}H_{22}BrF_2N_3O_3$ | 506 0885 | 506 0889 |
| Ex 277 | H | OH | 91 0 | $C_{20}H_{15}BrF_2N_2O_4$ | 465 0256 | 465 0278 |
| Ex 278 | CH3 | CH3 | 67 7 | $C_{22}H_{19}BrF_2N_2O_3$ | 477 0620 | 477 0626 |
| Ex 279 | CH2CH2O- | CH2CH2O- | 86 7 | $C_{24}H_{21}BrF_2N_2O_4$ | 519 0726 | 519 0696 |
| Ex 280 | H | CH2CH2OH | 78 3 | $C_{22}H_{19}BrF_2N_2O_4$ | 493 0569 | 493 0575 |
| Ex 281 | CH2CH2CH2- | CH2CH2CH2- | 87 9 | $C_{25}H_{23}BrF_2N_2O_3$ | 517 0933 | 517 0918 |
| Ex 282 | H | CH(CH3)2 | 80 6 | $C_{23}H_{21}BrF_2N_2O_3$ | 491 0776 | 491 0797 |
| Ex 283 | CH2CH2- | CH2CH2- | 87 9 | $C_{24}H_{21}BrF_2N_2O_4$ | 503 0776 | 503 0732 |
| Ex 284 | CH2CH2N(CH3)- | CH2CH2N(CH3)- | 75 8 | $C_{25}H_{24}BrF_2N_3O_3$ | 532 1042 | 532 1038 |
| Ex 285 | H | CH2CH2N(CH3)2 | 86 1 | $C_{24}H_{24}BrF_2N_3O_3$ | 520 1042 | 520 1030 |
| Ex 286 | H | CH2CH2OCH3 | 90 2 | $C_{23}H_{21}BrF_2N_2O_4$ | 507 0726 | 507 0680 |
| Ex 287 | CH3 | CH2CH2N(CH3)2 | 60 0 | $C_{25}H_{26}BrF_2N_3O_3$ | 534 1198 | 534 1155 |
| Ex 288 | CH3 | CH2CH2OH | 81 6 | $C_{23}H_{21}BrF_2N_2O_4$ | 507 0726 | 507 0694 |
| Ex 289 | CH3 | CH2CH2OCH3 | 94 4 | $C_{24}H_{23}BrF_2N_2O_4$ | 521 0882 | 521 0862 |

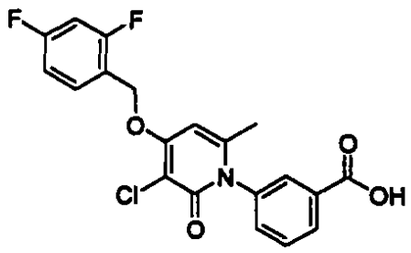
Example 290



3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzamide

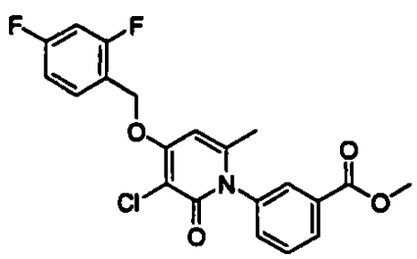
EXAMPLE 271 (2 00 g, 4 44 mmol) and 2-chloro-4,6-dimethoxy-1,3,5-triazine (0 94 g, 5 33 mmol) were suspended in tetrahydrofuran (20 mL) 4-Methylmorpholine (1 5 mL, 13 32 mmol) was added The resulting mixture was stirred for 1 5 hours at room temperature $NH_4OH$ (10 mL, 148 00 mmol) was added and the reaction was stirred for 0 5 hours at room temperature $H_2O$ (50 mL) and tetrahydrofuran (50 mL) were added and the organic layer was separated The aqueous phase was extracted with ethyl acetate (75 mL) and the combined organics were washed with saturated $Na_2CO_3$ (50 mL), 1*N* HCl (50 mL), and brine (50 mL) The organic phase was dried over $Na_2SO_4$ and evaporated The resulting solid was washed with diethyl ether to give a white solid (1 86 g, 93%) $^1H$ NMR (400 MHz, DMF-$d_6$) δ 8 20 (br s, 1H), 8 10-8 07 (m, 1H), 7 79 (s, 1H), 7 79 (*app* q, *J* = 7 83 Hz, 1H), 7 66 (*app* t, *J* = 7 79 Hz, 1H), 7 57-7 54 (m, 1H), 7 46 (br s, 1H), 7 36-7 19 (m, 2H), 6 74 (s, 1H), 5 43 (s, 2H), 2 04 (s, 3H) ES-HRMS *m/z* 449 0307 (M+H $C_{20}H_{15}BrF_2N_2O_3$ requires 449 0307)

Example 291



3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoic acid

Step 1 Preparation of methyl 3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoate

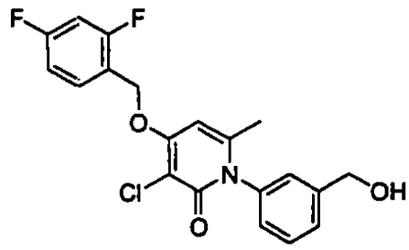


The product from step 2, Example 271 (4 54 g, 11 78 mmol) and *N*-chlorosuccinimide (1 65 g, 12 37 mmol) were suspended in dichloromethane (12 mL) Dichloroacetic acid (0 10 ml, 1 22 mmol) was added and the reaction mixture was stirred overnight at 40 °C The reaction was cooled to room temperature and a precipitate formed The precipitate was collected by filtration and washed with dichloromethane (3 x 10 mL) to afford a white solid (1 75 g, 35%) The filtrate was concentrated and subjected to chromatography (silica gel, ethyl acetate with 10% methanol/hexanes) to afforded an off white solid (1 29 g, 26%) The two solids were then combined $^1$H NMR (400 MHz, $CDCl_3$) δ 8 12 (dt, *J* = 1 38, 7 83 Hz, 1H), 7 85 (t, *J* = 1 74 Hz, 1H), 7 60-7 52 (m, 2H), 7 37 (dq, *J* =

0 92, 7 92 Hz, 2H), 6 95 (*app* dt, *J* = 2 55, 8 32 Hz, 1H), 6 89-6 83 (m, 1H), 6 1 (s, 1H), 5 24 (s, 2H), 3 90 (s, 3H), 1 96 (s, 3H) ES-HRMS *m/z* 420 0783 (M+H $C_{21}H_{16}ClF_2NO_4$ requires 420 0809)

Step 2 Methyl 3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoate ( from step 1) (2 90 g, 6 91 mmol) was dissolved in methanol (5 mL) and tetrahydrofuran (12 mL) 4*N* NaOH (4 3 mL, 17 27 mmol) was added The resulting mixture was stirred for 1 5 hours at room temperature The reaction was acidified (pH-2) with 4*N* HCl The precipitate was collected by filtration to afford an off white solid (2 36 g, 84%) $^1$H NMR (400 MHz, DMSO-$d_6$ ) δ 8 01 (dt, *J* = 1 41, 7 55 Hz, 1H), 7 76 (*app* t, *J* = 1 68 Hz, 1H), 7 69-7 53 (m, 3H), 7 36-7 14 (m, 2H), 6 69 (s, 1H), 5 32 (s, 2H), 1 93 (s, 3H) ES-HRMS *m/z* 406 0662 (M+H $C_{20}H_{14}ClF_2NO_4$ requires 406 0652)

Example 292

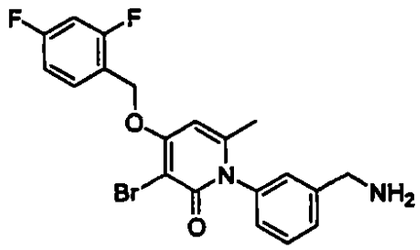



3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[3-(hydroxymethyl)phenyl]-6-methylpyridin-2(1H)-one

The starting material (0 550 g, 1 540 mmol) and *N*-chlorosuccinimide (0 211 g, 1 602 mmol) were suspended in dichloromethane (15 mL). Dichloroacetic acid (0 01 mL, 0 154

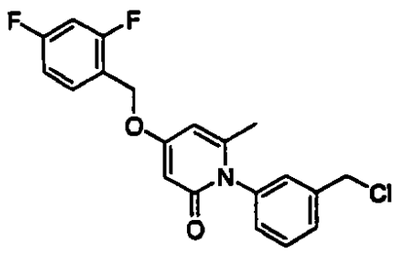
mmol) was added and the reaction mixture heated to 40 °C for 9 hours The reaction was cooled to room temperature and a precipitate formed The precipitate was collected by filtration and washed with dichloromethane (3 x 10 mL) to afford a white solid (0 286 g, 47%) $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7 38 (*app* q, *J* = 7 35 Hz, 1H), 7 30-7 24 (m, 2H), 7 00 (br s, 1H), 6 85 (*app* dt, *J* = 2 37, 6 24 Hz, 1H), 6 82-6 67 (m, 2H), 6 01 (s, 1H), 5 07 (s, 2H), 4 48 (d, *J* = 5 24 Hz, 2H), 1 81 (*app* d, *J* = 0 40 Hz, 3H) ES-HRMS *m/z* 392 0885 (M+H $C_{20}H_{16}ClF_2NO_3$ requires 392 0860)

Example 293



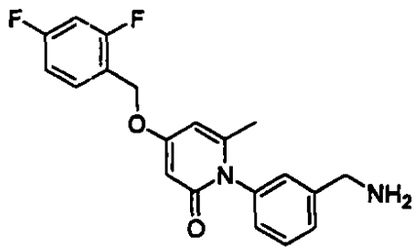
1-[3-(aminomethyl)phenyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one

Step 1 Preparation of 1-[3-(chloromethyl)phenyl]-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one



2,4,6-Trichloro-[1,3,5]-triazine (3 09 g, 16 78 mmol) was dissolved in *N,N*-dimethylformamide (45 mL) The reaction mixture was stirred at room temperature for 1 hour and then dichloromethane (90 mL) was added The alcohol (5 72 g, 15 99 mmol) was then added The reaction mixture was stirred at room temperature for 1 hour The reaction mixture was diluted with dichloromethane (200 mL) and the organic phase was washed with $H_2O$ (200 mL), saturated $Na_2CO_3$ (200 mL), 1*N* HCl (200 mL), and brine (200 mL) The organic phase was dried over $MgSO_4$ and evaporated to give an orange solid (5 95 g, 99%)

Step 2 Preparation of 1-[3-(aminomethyl)phenyl]-4-[(2,4-difluorobenzyl)oxy]-6- methylpyridin-2(1H)-one

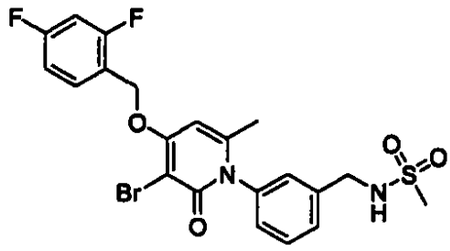


1-[3-(chloromethyl)phenyl]-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one from step 1 (1 00 g, 2 66 mmol) was suspended in methanol (5 mL) The suspension was then brought to -78 °C and $NH_3$ was bubbled through the reaction mixture for 10 minutes The reaction was then slowly allowed to warm to room temperature and stirred at room temperature for 4 days The reaction was concentrated and the residue taken up in $CH_2Cl_2$ and filtered to remove excess salt The filtrate was concentrated to afford a tan solid (0 94 g, 99%)

Step 3 Preparation of title compound 1-[3-(aminomethyl)phenyl]-4-[(2,4-difluorobenzyl)oxy]-6-

methylpyridin-2(1H)-one from step 3 (3 89 g, 10 93 mmol) suspended in acetonitrile (42 mL) was cooled in an ice-bath *N*-bromosuccinimide (2 04 g, 11 47 mmol) was added and the ice-bath was removed The reaction mixture was stirred for 1 5 hours at room temperature The reaction was diluted with acetonitrile (100 mL) and the precipitate that formed was collected by filtration and washed with acetonitrile (3 x 30 mL) to afford an off-white solid (2 74 g, 58%) $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7 67-7 59 (m, 3H), 7 34-7 31 (m, 2H), 7 04 (*app* t, *J* = 8 72 Hz, 2H), 7 05-6 88 (m, 2H), 6 13 (s, 1H), 5 30 (s, 2H), 3 95 (s, 1H), 2 01 (s, 3H) ES-HRMS *m/z* 435 0538 (M+H $C_{20}H_{17}BrF_2N_2O_2$ requires 435 0514)

Example 294

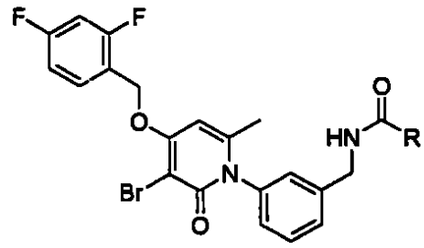


N-{3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzyl}methanesulfonamide

To a reaction vessel (borosilicate culture tube) was added EXAMPLE 293 (0 200 g, 0 459 mmol) and *N*,*N*-dimethylformamide (4 mL) A stock solution of 4-methylmorpholine in *N*,*N*-dimethylformamide (1 8 mL, 1 0 M) was added to the reaction vessel and the parallel reaction apparatus was then orbitally shaken (Labline Benchtop Orbital Shaker) at approximately 200 RPM at room temperature for 10 minutes A stock solution of

methanesulfonyl chloride in *N,N*-dimethylformamide (4 50 mL, 0 15 M) was then added to the reaction vessel and the reaction apparatus was orbitally shaken at room temperature for 2 hours At this time the reaction was diluted with dichloromethane (4 mL) and treated with approximately 2 1 g of polyamine resin (2 63 mmol/g) and approximately 0 8 g of methylisocyanate functionalized polystyrene (1 7 mmol/g) and the orbital shaking was continued at 200 RPM at room temperature overnight The reaction vessel was then opened and the solution phase products were separated from the insoluble quenched byproducts by filtration and collection into a vial After partial evaporation the insoluble byproducts were rinsed with dichloromethane (2 x 5 mL) The filtrate was evaporated by blowing $N_2$ over the vial while heating (60 °C) in a reaction block (KEM-Lab Parallel Reactor) to give a yellow solid (0 190 g, 81%) $^1$H NMR (400 MHz, $CD_3OD$) δ 7 63 (*app* q, *J* = 7 00 Hz, 1H), 7 56-7 50 (m, 2H), 7 25 (m, 1H), 7 16 (dt, *J* = 1 94, 7 25 Hz 1H), 7 04 (*app* t, *J* = 8 59 Hz, 2H), 6 58 (s, 1H), 5 34 (s, 2H), 4 30 (s, 2H), 2 87 (s, 3H), 2 03 (s, 3H) ES-HRMS *m/z* 513 0313 (M+H $C_{21}H_{19}BrF_2N_2O_4S$ requires 513 0290)

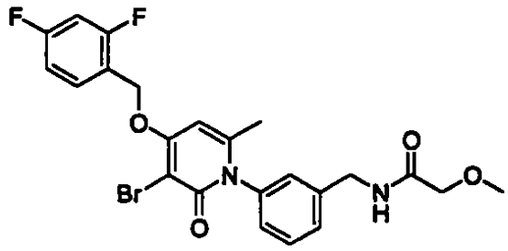
Preparation of Example 295-296



By following the method of Example 294 and replacing methanesulfonyl chloride with the appropriate acid chloride, the compounds of Examples 295-296 are prepared

| Compound No | R | % Yield | MF | M+H Requires | ES-HRMS *m/z* |
|---|---|---|---|---|---|
| Ex 295 | $CH_3$ | 78 0 | $C_{22}H_{19}BrF_2N_2O_3$ | 477 0620 | 477 0640 |
| Ex 296 | $OCH_3$ | 84 0 | $C_{22}H_{19}BrF_2N_2O_4$ | 493 0569 | 493 0591 |

Example 297

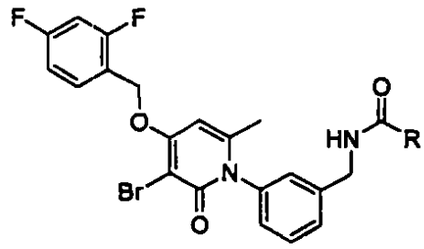


N-{3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzyl}-2-methoxyacetamide

To a reaction vessel (borosilicate culture tube) was added approximately 2 87 g of polymer bound carbodiimide resin (0 96 mmol/g) followed by a stock solution of methoxyacetic acid (8 0 mL, 0 10 M) in *N,N*-dimethylacetamide A stock solution of 1-hydroxybenzotriazole in *N,N*-dimethylacetamide (3 0 mL, 0 10 M) and *N*-methylmorpholine (6 0 mL, 0 10 M) in 1,2-dichloroethane were added to the reaction vessel The parallel reaction apparatus was then orbitally shaken (Labline Benchtop Orbital Shaker) at approximately 200 RPM at room temperature for 4 hours A stock solution of EXAMPLE 293 in

*N,N*-dimethylacetamide (5 0 mL, 0 10 M) was then added to the reaction vessel and the reaction apparatus was orbitally shaken at room temperature overnight At this time the reaction was diluted with 1,2-dichloroethane (10 mL) and treated with approximately 1 70 g of polyamine resin (2 63 mmol/g) and approximately 0 84 g of methylisocyanate functionalized polystyrene (1 50 mmol/g) and the orbital shaking was continued at 200 RPM at room temperature for 4 hours The reaction vessel was then opened and the solution phase products were separated from the insoluble quenched byproducts by filtration and collection into a vial After partial evaporation the insoluble byproducts were rinsed with *N,N*-dimethylacetamide (2 x 5 mL) The filtrate was evaporated by blowing $N_2$ over the vial while heating (60 °C) in a reaction block (KEM-Lab Parallel Reactor) and subjected to chromatography (silica gel, ethyl acetate with 10% methanol/hexanes) afforded an off white solid (0 081 g, 28%) $^1$H NMR (400 MHz, DMF-$d_6$) δ 7 59 (q, *J* = 7 65 Hz, 1H), 7 46 (*app* t, *J* = 7 55 Hz, 1H), 7 40-7 37 (m, 1H), 7 11-7 07 (m, 2H), 7 00 (t, *J* = 8 56 Hz, 2H), 6 54 (s, 1H), 5 30 (s, 2H), 4 43 (s, 2H), 3 88 (s, 2H), 3 35 (*app* d, *J* = 0 80 Hz, 2H), 1 97 (s, 3H) ES-HRMS *m/z* 507 0699 (M+H $C_{23}H_{21}BrF_2N_2O_4$ requires 507 0726)

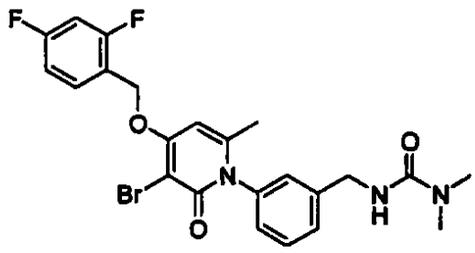
Preparation of Examples 298-300



By following the method of and replacing methoxyacetic acid with the appropriate acid, the compounds of Examples 298-300 are prepared The deprotection of the protected intermediates was accomplished with 4*N* HCl in dioxane or 1 M $K_2CO_3$ in methanol to afford the compounds as hydrochloride salts

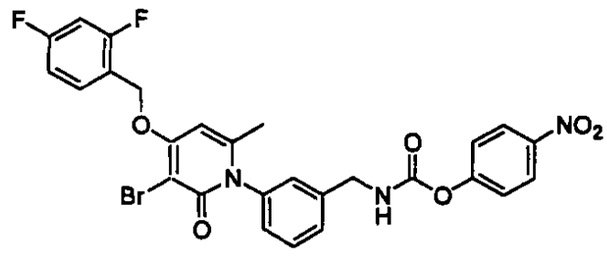
| Compound No | R | % Yield | MF | M+H Requires | ES-HRMS *m/z* |
|---|---|---|---|---|---|
| Ex 298 | $CH_2OCOCH_3$ | 35 5 | $C_{24}H_{21}BrF_2N_2O_5$ | 535 0675 | 535 0686 |
| Ex 299 | $CH_2NH_2$ | 32 6 | $C_{22}H_{20}BrF_2N_3O_3$ | 492 0729 | 492 0744 |
| Ex 300 | $CH_2OH$ | 33 4 | $C_{22}H_{19}BrF_2N_2O_4$ | 493 0569 | 493 0578 |

Example 301



N'-{3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzyl}-N,N-dimethylurea

Step 1 Preparation of 4-nitrophenyl 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzylcarbamate

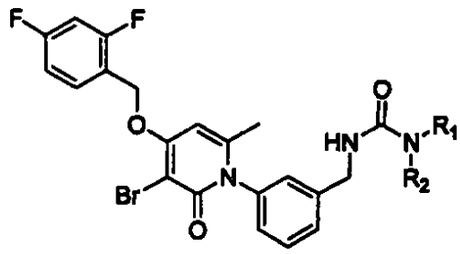


1-[3-(aminomethyl)phenyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (1 08 g, 2 48 mmol) was suspended in dichloromethane (7 5 mL) Pyridine was added (0 222 mL, 2 74 mmol) After stirring for 10 minutes at room temperature, a stock solution of 4-nitrophenyl chloroformate (5 0 mL, 0 50 M) in dichloromethane was added dropwise After stirring for 4 5 hours at room temperature, a stock solution of 4-nitrophenyl chloroformate (2 5 mL, 0 50 M) in dichloromethane was again added dropwise and st rring continued at room temperature overnight The reaction mixture was concentrated and subjected to chromatography (silica gel, ethyl acetate with 10% methanol/hexanes) afforded a yellow solid (0 85 g, 57%)

Step 2 Preparation of title compound To a reaction vessel (borosilicate culture tube) was added 4-nitrophenyl 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzylcarbamate (from step 1) (0 150 g, 0 250 mmol) and dichloromethane (2 5 mL) The parallel reaction apparatus was then orbitally shaken (Labline Benchtop Orbital Shaker) at approximately 200 RPM at room temperature for 15 minutes A stock solution of *N,N*-dimethylamine in tetrahydorfuran (0 15 mL, 2 0 M) was then added to the reaction vessel and the reaction apparatus was orbitally shaken at room temperature overnight The reaction mixture was concentrated and subjected to chromatography (silica gel, ethyl acetate with 10% methanol/hexanes) which afforded an off white solid (0 065

g, 51%) $^1$H NMR (400 MHz, DMF-$d_6$) δ 7 58 (*app* q, *J* = 7 79 Hz, 1H), 7 42 (*app* t, *J* = 7 65 Hz, 1H), 7 37 (*app* d, *J* = 7 79 Hz, 1H), 7 08 (s, 1H), 7 03 (*app* dt, *J* = 1 58, 5 37 Hz, 1H), 6 96 (*app* dt, *J* = 2 55, 8 39 Hz, 1H), 6 88-6 83 (m, 1H), 6 06 (s, 1H), 5 24 (s, 2H), 4 95 (*app* t, *J* = 5 57 Hz, 1H), 4 42 (*app* dddd, *J* = 5 10, 5 71, 10 20, 15 17 Hz, 2H), 2 90 (s, 6H), 1 96 (s, 3H) ES-HRMS *m/z* 506 0848 (M+H $C_{23}H_{22}BrF_2N_3O_3$ requires 506 0885)

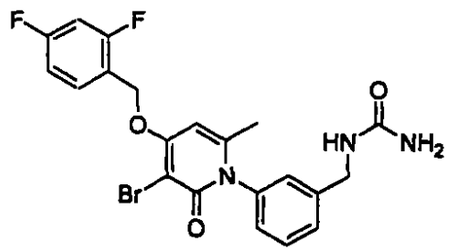
Preparation of Examples 302-303



By following the method of Example 301 and substituting *N,N*-dimethylamine with the appropriate amine, the compounds of Examples 302-303 are prepared

| Compound No | $R_1$ | $R_2$ | % Yield | MF | M+H Requires | ES-HRMS *m/z* |
|---|---|---|---|---|---|---|
| Ex 302 | H | $CH_3$ | 52 3 | $C_{22}H_{20}BrF_2N_3O_3$ | 492 0729 | 492 0737 |
| Ex 303 | $CH_2CH_2O$- | $CH_2CH_2O$- | 50 7 | $C_{25}H_{24}BrF_2N_3O_4$ | 548 0991 | 548 0962 |

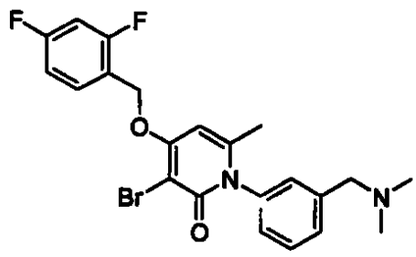
Example 304



N-{3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzyl}urea

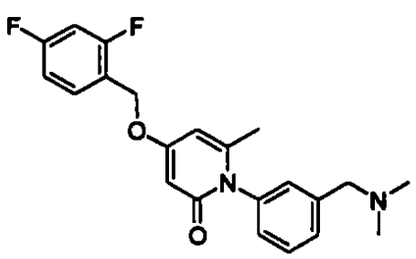
To a reaction vessel (borosilicate culture tube) was added EXAMPLE 293 (0 200 g, 0 459 mmol) and tetrahydrofuran (4 0 mL) A stock solution of 4-methylmorpholine in tetrahydrofuran (1 8 mL, 1 0 M) was added to the reaction vessel and the parallel reaction apparatus was then orbitally shaken (Labline Benchtop Orbital Shaker) at approximately 200 RPM at room temperature for 10 minutes A stock solution of trimethylsilyl isocyanate in tetrahydrofuran (4 0 mL, 0 2 M) was then added to the reaction vessel and the reaction apparatus was orbitally shaken at room temperature for two hours At this time the reaction was diluted with tetrahydrofuran (4 0 mL) and the resulting precipitate collected by filtration The solid was then washed with tetrahydrofuran (3 x 5 mL) to afford a white solid (0 214 g, 97%) $^1$H NMR (400 MHz, $CD_3OD$) δ 7 72 (*app* q, *J* = 7 83 Hz, 1H), 7 55 (*app* t, *J* = 8 06 Hz, 1H), 7 46 (d, *J* = 7 52 Hz, 1H), 7 25-7 14 (m, 4H), 6 65 (s, 1H), 5 65 (*app* t, *J* = 0 80 Hz, 1H), 5 40 (s, 2H), 4 38 (s, 2H), 2 05 (s, 3H) ES-HRMS *m/z* 478 0594 (M+H $C_{21}H_{18}BrF_2N_3O_3$ requires 478 0572)

Example 305



3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-{3-[(dimethylamino)methyl]phenyl}-6-methylpyridin-2(1H)-one

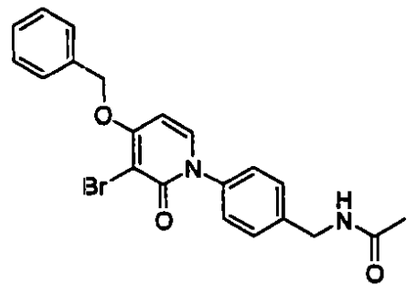
Step 1 Preparation of 4-[(2,4-difluorobenzyl)oxy]-1-{3-[(dimethylamino)methyl]phenyl}-6-methylpyridin-2(1H)-one



1-[3-(chloromethyl)phenyl]-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (from step 1 of the synthesis of EXAMPLE 293) (0 500 g, 1 330 mmol) was suspended in a stock solution of *N,N*-dimethylamine in methanol (2 0 mL, 2 0 M) and stirred overnight at room temperature Reaction was concentrated and the residue partitioned between $H_2O$ (25 mL) and ethyl acetate (25 mL) The aqueous layer was further extracted with ethyl acetate (2 x 30 mL), and the combined organics were washed with brine (30 mL), dried over $MgSO_4$, and concentrated to afford an off-white solid (0.508 g, 99%)

Step 2 Preparation of the title compound 4-[(2,4-difluorobenzyl)oxy]-1-{3-[(dimethylamino)methyl]phenyl}-6-methylpyridin-2(1H)-one from step 1 (0 200 g, 0 521 mmol) was suspended in acetonitrile (2 5 mL) and cooled in an ice-bath *N*-bromosuccinimide (0 097 g, 0 547 mmol) was added and the ice-bath was removed The reaction mixture was stirred for 1 5 hours at room temperature The reaction was diluted with acetonitrile (100 mL) The precipitate that formed was collected by filtration and washed with acetonitrile (3 x 15 mL) to afford a yellow solid (0 160 g, 66%) Chromatography (C-18, acetonitrile/$H_2O$ with 0 1% trifluoroacetic acid, followed by chromatography silica gel, ethyl acetate with 10% methanol/hexanes) afforded an off-white solid (0 024 g, 10%) $^1$H NMR (400 MHz, $CD_3OD$) δ 7 68 (*app* q, *J* = 7 85 Hz, 1H), 7 58 (*app* t, *J* = 7 65 Hz, 1H), 7 50 (*app* d, *J* = 7 85 Hz, 1H), 7 25-7 05 (m, 4H), 6 63 (s, 1H), 5 39 (s, 2H), 3 61 (*app* q, *J* = 12 08 Hz, 2H), 2 32 (s, 6H), 2 08 (s, 3H) ES-HRMS *m/z* 463 0782 (M+H $C_{22}H_{21}BrF_2N_2O_2$ requires 463 0827)

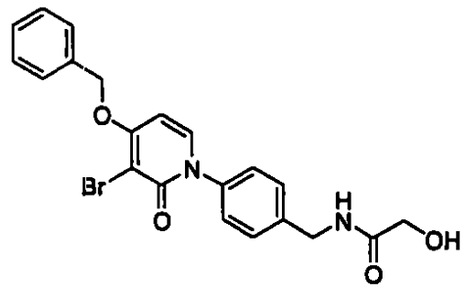
Example 306




N-{4-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]benzyl}acetamide

1-[4-(aminomethyl)phenyl]-4-(benzyloxy)-3-bromopyridin-2(1H)-one hydrochloride (0 150 g, 0 389 mmol) was dissolved in *N,N*-dimethylformamide (3 5 mL) A stock solution of 4-methylmorpholine in *N,N*-dimethylformamide (1 5 mL, 1 0 M) was added and the reaction stirred at room temperature for 10 minutes A stock solution of acetyl chloride in *N,N*-dimethylformamide (3 0 mL, 0 2 M) was then added to the reaction vessel and the reaction apparatus was orbitally shaken at 200 RPM for 2 hours at room temperature At this time the reaction was diluted with dichloromethane (4 mL) and treated with approximately 1 8 g of polyamine resin (2 63 mmol/g) and approximately 0 8 g of methylisocyanate functionalized polystyrene (1 7 mmol/g) and the orbital shaking was continued at 200 RPM at room temperature overnight The reaction vessel was then opened and the solution phase products were separated from the insoluble quenched byproducts by filtration and collection into a vial After partial evaporation the insoluble byproducts were further rinsed with dichloromethane (3 x 5 mL) and combined with the partially concentrated filtrate The resulting filtrate was concentrated by blowing $N_2$ over the vial while heating (60 °C) in a reaction block (KEM-Lab Parallel Reactor) to give an off-white solid (0 083 g, 50%) $^1$H NMR (400 MHz, $CD_3OD$) δ 7 59 (d, *J* = 7 79 Hz, 1H), 7 48-7 29 (m, 9H), 6 55 (d, *J* = 7 79 Hz, 1H), 5 35 (s, 2H), 4 39 (s, 2H), 1 98 (s, 3H) ES-HRMS *m/z* 427 0625 (M+H $C_{21}H_{19}BrN_2O_3$ requires 427 0652)

Example 307

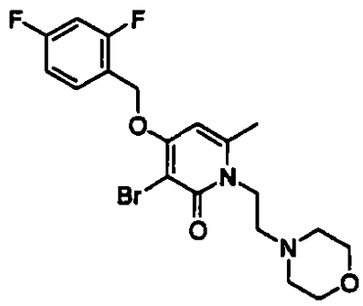


N-{4-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]benzyl}-2-hydroxyacetamide

To a reaction vessel (borosilicate culture tube) was added approximately 1 95 g of polymer bound carbodiimide resin (0 96 mmol/g) followed by a stock solution of glycolic acid (5 8 mL, 0 10 M) in *N,N*-dimethylacetamide A stock solution of 1-hydroxybenzotriazole in *N,N*-dimethylacetamide (0 4 mL, 0 10 M) and *N*-methylmorpholine in 1,2-dichloroethane (3 9 mL, 0 10 M) were added tc the reaction vessel The parallel reaction apparatus was then orbitally shaken (Labline Benchtop Orbital Shaker) at approximately 200 RPM at room temperature for 2 hours A stock solution of 1-[4-(aminomethyl)phenyl]-4-(benzyloxy)-3-bromopyridin-2(1H)-one hydrochloride in *N,N*-dimethylacetamide (0 05 M, 7 8 mL) was then added to the reaction vessel and the reaction apparatus was orbitally shaken at room temperature overnight At this time the reaction was diluted with 1,2-dichloroethane (8 mL) and treated with approximately 1 17 g of polyamine resin (2 63 mmol/g) and approximately 0 58 g of methylisocyanate functionalized polystyrene (1 50 mmol/g) and the orbital shaking was continued at 200 RPM at room temperature for 4 hours The reaction vessel was then opened and the solution phase products were separated from the insoluble quenched byproducts by filtration and collection into a vial. After

partial evaporation the insoluble byproducts were rinsed with *N,N*-dimethylacetamide (2 x 5 mL) and combined with the partially concentrated filtrate The filtrate was concentrated by blowing $N_2$ over the vial while heating (60 °C) in a reaction block (KEM-Lab Parallel Reactor) and subjected to chromatography (silica gel, ethyl acetate with 10% methanol/hexanes) which afforded an off white solid (0 081 g, 21%) $^1$H NMR (400 MHz, $CD_3OD$) δ 7 55-7 30 (m, 10H), 6 51 (d, *J* = 7 85 Hz, 1H), 5 37 (s, 2H), 4 52 (s, 2H), 4 08 (s, 2H) ES-HRMS *m/z* 443 0605 (M+H $C_{21}H_{19}BrN_2O_4$ requires 443 0601)

Example 308

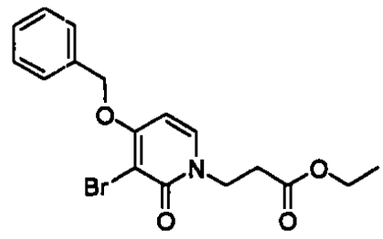


3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(2-morpholin-4-ylethyl)pyridin-2(1H)-one

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (0 100 g, 0 303 mmol), cesium carbonate (0 296 g, 0 909 mmol), and 4-(2-chloroethyl)morpholine (0 059 g, 0 394 mmol) were suspended in acetonitrile (4 mL) The reaction was stirred at 60 °C overnight $H_2O$ (25 mL) was added and the resulting precipitate was collected by filtration The solid was subjected to chromatography (silica gel, ethyl acetate with 10% methanol) afforded an off-white solid (0 040 g, 30%) $^1$H

NMR (400 MHz, $CDCl_3$) δ 7 55 (*app* q, *J* = 7 92 Hz, 1H), 6 93 (*app* t, *J* = 8 39 Hz, 1H), 6 84 (*app* t, *J* = 9 40 Hz, 1H), 5 95 (s, 1H), 5 18 (s, 2H), 4 16 (*app* t, *J* = 6 78 Hz, 2H), 3 68 (s, 4H), 2 65 (*app* t, *J* = 6 38 Hz, 2H), 2 54 (s, 4H), 2 43 (s, 3H) ES-HRMS *m/z* 443 0743 (M+H $C_{19}H_{21}BrF_2N_2O_3$ requires 443 0776)

Example 309

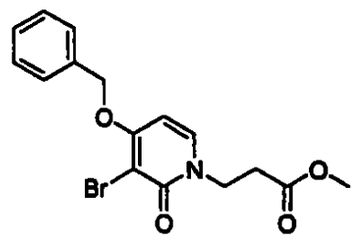


ethyl 3-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]propanoate

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (0 50 g, 1 78 mmol) and cesium fluoride (0 0027 g, 0 178 mmol) were suspended in tetrahydrofuran (10 mL) followed by dropwise addition of tetraethylortho silicate (0 37 g, 1 78 mmol) at room temperature After stirring for 10 minutes at room temperature, ethyl acrylate (0 23 g, 2 32 mmol) was added dropwise and the reaction stirred at room temperature overnight The reaction mixture was filtered through a pad of Celite® The filtrate was concentrated and the resulting residue subjected to chromatography (silica gel, ethyl acetate with 10% methanol/hexanes) to afford a white solid (0 62 g, 92%) $^1H$ NMR (400 MHz, $CDCl_3$) δ 7 42 (d, *J* = 7 79 Hz, 1H), 7 41-7 29 (m, 5H), 6 03 (d, *J* = 7 65 Hz, 1H), 5 20 (s, 2H), 4 17 (t, *J* = 5 98 Hz, 2H), 4 07 (q, *J* = 7 16 Hz, 2H), 2 83 (t,

$J$ = 5 98 Hz, 2H), 1 19 (t, $J$ = 7 18 Hz, 3H) ES-HRMS $m/z$ 380 0523 (M+H $C_{17}H_{18}BrNO_4$ requires 380 0492)

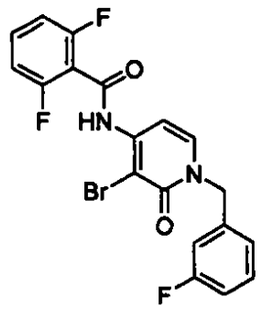
Example 310



methyl 3-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]propanoate

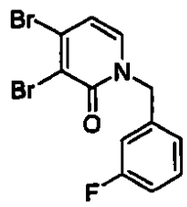
3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (5 00 g, 17 85 mmol) and cesium fluoride (0 27 g, 1 78 mmol) were suspended in tetrahydrofuran (50 mL) followed by dropwise addition of tetramethylortho silicate (2 70 g, 17 85 mmol) at room temperature After stirring for 10 minutes at room temperature, methyl acrylate (2 00 g, 23 20 mmol) was added dropwise and the reaction stirred at room temperature for 48 hours The reaction mixture was filtered through a pad of Celite® The filtrate was concentrated and the resulting residue subjected to chromatography (silica gel, ethyl acetate with 10% methanol/hexanes) to afford a white solid (6 10 g, 93%) $^1$H NMR (400 MHz, $CDCl_3$) δ 7 42 (d, $J$ = 7 65 Hz, 1H), 7 41-7 29 (m, 5H), 6 04 (d, $J$ = 7 65 Hz, 1H), 5 20 (s, 2H), 4 17 (t, $J$ = 5 91 Hz, 2H), 3 63 (s, 3H), 2 85 (t, $J$ = 5 91 Hz, 2H) ES-HRMS $m/z$ 366 0350 (M+H $C_{16}H_{16}BrNO_4$ requires 366 0335)

Example 311



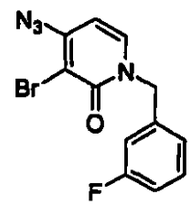
N-[3-bromo-1-(3-fluorobenzyl)-2-oxo-1,2-dihydropyridin-4-yl]-2,6-difluorobenzamide

Step 1 Preparation of 3,4-dibromo-1-(3-fluorobenzyl)pyridin-2(1H)-one



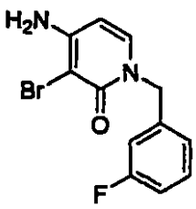
3-bromo-1-(3-fluorobenzyl)-2-oxo-1,2-dihydropyridin-4-yl trifluoromethanesulfonate (2 00 g, 4 65 mmol), KBr (5 53 g, 46 49 mmol), and 18-Crown-6 (0 10 g, 0 38 mmol) were dissolved in *N,N*-dimethylacetamide (26 mL) The reaction mixture was then heated at reflux for 16 hours The reaction was concentrated and the resulting residue was partition between water (50 mL) and ethyl acetate (3 X 50 mL) The combined organics were washed with $H_2O$ (2 X 30 mL), brine (50 mL), dried over $MgSO_4$, concentrated, and subjected to chromatography (silica gel, ethyl acetate with 10% methanol/hexane) to afford a brown solid (0 850 g, 51%)

Step 2 Preparation of 4-azido-3-bromo-1-(3-fluorobenzyl)pyridin-2(1H)-one



Sodium azide (1 08 g, 16 62 mmol) was suspended in *N,N*-dimethylformamide (10 mL) and a stock solution of 3,4-dibromo-1-(3-fluorobenzyl)pyridin-2(1H)-one (from step 1) in *N,N*-dimethylformamide (33 0 mL, 0 33 M) was added and the resulting mixture was heated to 60 °C for 4 hours Ice water (30 mL) was added and the aqueous layer was extracted with ethyl acetate (4 X 50 mL) The combined organics were washed with $H_2O$ (3 X 50 mL), brine (2 X 25 mL), dried over $MgSO_4$, concentrated, and subjected to chromatography (silica gel, ethyl acetate with 10% methanol/hexane) to afford an off-white solid (3 50 g, 98%)

Step 3 Preparation of 4-amino-3-bromo-1-(3-fluorobenzyl)pyridin-2(1H)-one hydrochloride

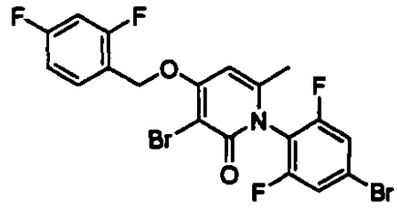


4-azido-3-bromo-1-(3-fluorobenzyl)pyridin-2(1H)-one (from step 2) (4 00 g, 12 38 mmol) was suspended in ethyl acetate (300 mL) and Fe (2 07 g, 37 14 mmol) was added A stock solution

of $NH_4Cl$ in $H_2O$ (300 mL, 0 2 M) was added and the reaction mixture was stirred at room temperature for 36 hours The reaction was filtered through a pad of Celite® and concentrated Tne resulting solid was dissolved in ethyl acetate (150 mL) and washed with water (3 X 50 mL), brine (50 mL), dried over $MgSO_4$, and concentrated $^1H$ NMR (400 MHz, $CD_3OD$) δ 7 38-7 29 (m, 2H), 7 05 (d, *J* = 7 79 Hz, 1H), 6 99 (d, *J* = 8 99 Hz, 2H), 6 03 d, *J* = 7 39 Hz 1H), 5 09 (s, 2H) ES-HRMS *m/z* 297 0023 (M+H $C_{20}H_{17}BrF_2N_2O_2$ requires 297 0033)

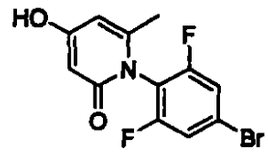
Step 4 Preparation of the title compound 4-amino-3-bromo-1-(3-fluorobenzyl)pyridin-2(1H)-one (from step 3) (0 30 g, 1 01 mmol) and 4-dimethylaminopyridine (0 002 g, 0 01 mmol) were suspended in acetonitrile (5 mL) followed by dropwise addition of triethylamine (0 2 mL, 1 41 mmol) This reaction mixture was stirred for 10 minutes at room temperature before being cooled to 0 °C 2,6-difluorobenzoyl chloride (0 37 g, 2 12 mmol) was added dropwise and the reaction was heated at reflux overnight The reaction was cooled to room temperature and 1*N* NaOH (10 mL) was added The reaction was then stirred for 45 minutes at room temperature The reaction mixture was extracted with ethyl acetate (3 x 25 mL) and the organic layer washed with 1*N* NaOH (2 X 25 mL), $H_2O$ (until pH neutral), brine (50 mL), dried over $MgSO_4$, concentrated, and subjected to chromatography (on C-18, acetonitrile/ $H_2O$ with 0 1% trifluoracetic acid) to afford a white solid (0 19 g, 43%) $^1H$ NMR (400 MHz, $CDCl_3$) δ 8 42 (br s, 1H), 7 67 (d, *J* = 7 65 Hz, 1H), 7 49 (*app* tt, *J* = 6 31, 8 60 Hz, 1H), 7 33-28 (m, 2H), 7 10-6 97 (m, 5H), 5 17 (s, 2H) ES-HRMS *m/z* 437 0083 (M+H $C_{19}H_{12}BrF_3N_2O_2$ requires 437 0107)

Ex 312



3-bromo-1-(4-bromo-2,6-difluorophenyl)-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one

Step 1 Preparation of 1-(4-bromo-2,6-difluorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one



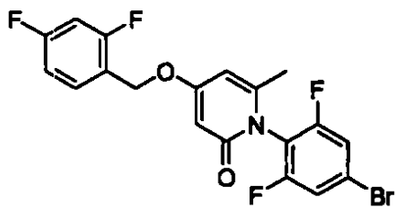
4-Hydroxy-6-methyl-2-pyrone (30 0 g, 238 mmol) and 4-bromo-2,6-difluoroaniline (49 5 g, 238 mmol) were suspended in 50 ml of 1,2-dichlorobenzene in a 250 ml, 3-necked, round bottom flask equipped with a J-Kem temperature controller probe, a Dean-Stark trap, and a heating mantle The reaction was heated to 165°C for 15 minutes, during which, water and some 1,2-dichlorobenzene was collected in the Dean-Stark trap The reaction was allowed to cool to about 80°C The flask was placed in an ice bath and about 25 ml of toluene was added and stirred After about 10 minutes, a precipitate formed The precipitate was filtered and washed 3 times with toluene, 3 times with hot water to remove excess pyrone, and dried in vacuo to give a tan solid (22 1 g, 29%) $^1$H NMR (400 MHz, DMSO-$d_6$) δ 11 00 (br s, 1H), 7 71 (d, $J$ = 6 98 Hz, 2H), 5 97 (t, $J$ = 0 88 Hz, 1H), 5 55 (d, $J$ = 2 28 Hz, 1H), 1 91 (s, 3H) LC/MS, $t_r$ = 1.96 minutes (5 to 95% acetonitrile/water over 5

240

238

minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS *m/z* 316 (M+H) ES-HRMS *m/z* 315 9779 (M+H calcd for $C_{12}H_8BrF_2NO_2$ requires 315 9779)

Step 2 Preparation of 1-(4-bromo-2,6-difluorophenyl)-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one

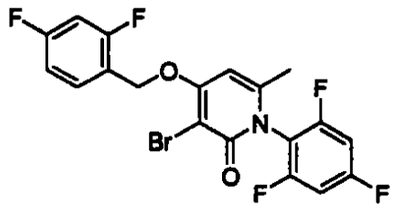



1-(4-bromo-2,6-difluorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one ( from Step 1) (5 0 g, 15 8 mmol) was stirred briskly at room temperature with 2,4-difluorobenzyl bromide (2 23 ml, 17 4 mmol) and $K_2CO_3$ (3 27 g, 23 7 mmol) in 50 ml of dimethylformamide After stirring overnight, the reaction was poured quickly into 900 ml of cold water The resulting precipitate was filtered and washed with water and hexane The product was purified using a Biotage silica chromatography system using 20% ethyl acetate/hexanes to give a beige solid (4 32 g, 62%) $^1H$ NMR (400 MHz, $CDCl_3$) δ 7 41 (*app* q, *J* = 6 31 Hz, 1H), 7 25 (dd, *J* = 8 33, 1 74 Hz, 2H), 6 91 (dt, *J* = 9 2, 0 8 Hz, 1H), 6 86 (dt, *J* = 9 2, 0 8 Hz, 1H), 5 95 (d, *J* = 2 56 Hz, 1H), 5 92 (dd, *J* = 2 56, 0 94 Hz, 1H), 5 01 (s, 2H), 1 98 (s, 3H) LC/MS, $t_r$ = 3 04 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS *m/z* 442 (M+H) ES-HRMS *m/z* 442 0057 (M+H calcd for $C_{19}H_{12}BrF_4NO_2$ requires 442 0060)

Step 3 Preparation of the title compound 1-(4-bromo-2,6-difluorophenyl)-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-

2(1H)-one ( from Step 2) (500 mg, 1 13 mmol) was stirred at room temperature with *N*-bromosuccinimide (221 mg, 1 24 mmol) in 5 ml of $CH_2Cl_2$ for 1 5 hours The reaction was evaporated on a rotary evaporator and the resulting solid was washed 4 times with acetonitrile and dried *in vacuo* to yield a white solid (478 mg, 92%) $^1$H NMR (300 MHz, $CDCl_3$) δ 7 62 (*app* q, *J* = 6 64 Hz, 1H), 7 31 (d, *J* = 6 85 Hz, 2H), 7 01 (*app* t, *J* = 8 36 Hz, 1H), 6 96 (dt, *J* = 9 46, 2 21 Hz, 1H), 6 19 (s, 1H), 5 30 (s, 2H), 2 10 (s, 3H), LC/MS, $t_r$ = 3 17 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS *m/z* 520 (M+H) ES-HRMS *m/z* 521 9134 (M+H calcd for $C_{19}H_{11}Br_2F_4NO_2$ requires 521 9146)

Ex 313



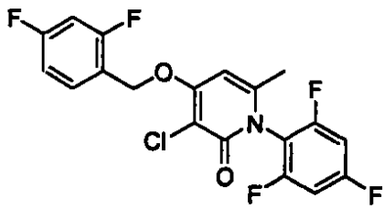
3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(2,4,6-trifluorophenyl)pyridin-2(1H)-one

The title compound was produced essentially as in Example 313, using 2,4,6-trifluoroaniline instead of 4-bromo-2,6-difluoroaniline $^1$H NMR (300 MHz, $CDCl_3$) δ 7 62 (*app* q, *J* = 7 79 Hz, 1H), 7 01 (*app* dt, *J* = 8 26, 2 01 Hz, 1H), 6 95 - 6 85 (m, 3H), 6 19 (s, 1H), 5 30 (s, 2H), 2 11 (s, 3H), LC/MS, $t_r$ = 2 81 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 460 (M+H) ES-HRMS *m/z* 459 9954 (M+H calcd for $C_{19}H_{11}BrF_5NO_2$ requires 459 9966)

241

239

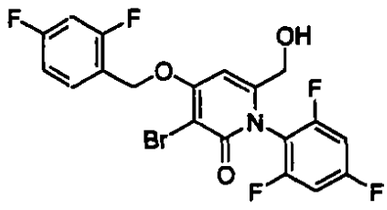
Ex 314



3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(2,4,6-trifluorophenyl)pyridin-2(1H)-one

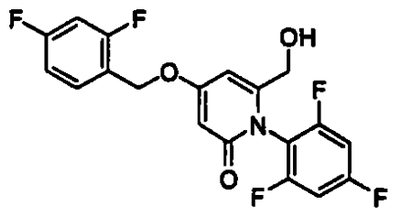
4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(2,4,6-trifluorophenyl)pyridin 2(1H)-one (350 mg, 0 92 mmol) was refluxed with *N*-chlorosuccinimide (147 mg, 1 1 mmol) and dichloroacetic acid (0 038 ml, 0 46 mmol) in 5 ml of $CH_2Cl_2$ overnight The reaction was evaporated on a rotary evaporator and the resulting solid was washed 4 times with acetonitrile and dried *in vacuo* to yield a white solid (217 mg, 57%) $^1H$ NMR (300 MHz, $CDCl_3$) δ 7 60 (*app* q, *J* = 7 75 Hz, 1H), 7 00 (*app* dt, *J* = 8 23, 2 05 Hz, 1H), 6 93 - 6 86 (m, 3H), 6 22 (s, 1H), 5 30 (s, 2H), 2 12 (s, 3H), LC/MS, $t_r$ = 2 78 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 416 (M+H) ES-HRMS *m/z* 416 0472 (M+H calcd for $C_{19}H_{11}ClF_5NO_2$ requires 416 0471)

Ex 315



3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-(hydroxymethyl)-1-(2,4,6-
trifluorophenyl)pyridin-2(1H)-one

Step 1 Preparation of 4-[(2,4-difluorobenzyl)oxy]-6-(hydroxymethyl)-1-(2,4,6-trifluorophenyl)pyridin-2(1H)-one



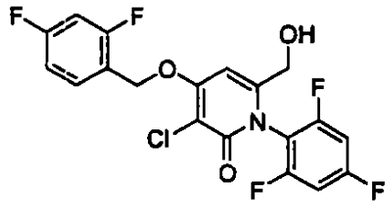
4-[(2,4-Difluorobenzyl)oxy]-6-methyl-1-(2,4,6-trifluorophenyl)pyridin-2(1H)-one (9 0 g, 23 6 mmol) was heated to 135°C overnight with $SeO_2$ (13 1 g, 118 mmol) in 75 ml of 1,4-dioxane in a 350 ml sealed glass pressure vessel The reaction mixture was cooled and placed on a plug of silica gel and washed with 5% methanol in $CH_2Cl_2$ The filtrate was evaporated and the resulting solid was washed with diethyl ether and dissolved in hot ethyl acetate The insoluble Se salts were filtered off and the organic layer was evaporated 7 01g (17 6 mmol) of a 3 1 ratio of aldehyde to desired alcohol was isolated The mixture was stirred with $NaBH_4$ (802 mg, 21 2 mmol) in 30 ml of methanol at room temperature for 1 hour The reaction was evaporated and $CH_2Cl_2$ and acetonitrile were used to dissolve the bulk of the solid The remaining insoluble solid was filtered off The organic layer was washed 3 times with $NH_4Cl$, dried over $MgSO_4$ and evaporated The resulting solid was washed 3 times with diethyl ether and dried *in vacuo* to yield a light orange solid (4 35 g, 46%) $^1H$ NMR (300 MHz, DMSO-$d_6$) δ 7 68 (*app* q, $J$ = 7 92 Hz, 1H), 7 47 (*app* t, $J$ = 8 57 Hz, 2H), 7 35 (dt, $J$ = 9 87, 2 42 Hz, 1H), 7 18 (dt, $J$ = 8 31, 1 71 Hz, 1H), 6 21 (d, $J$ = 2 42 Hz, 1H), 6 07 (d, $J$ = 2 62 Hz, 1H), 5 67 (br s, 1H), 5.18 (s, 2H), 3 98

242

(s, 2H), LC/MS, $t_r$ = 2 31 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 398 (M+H) 240

Step 2 Preparation of the title compound 4-[(2,4-Difluorobenzyl)oxy]-6-(hydroxymethyl)-1-(2,4,6-trifluorophenyl)pyridin-2(1H)-one ( from step 1) (2 1 g, 5 28 mmol) was stirred at room temperature with *N*-bromosuccinimide (1 13 g, 6 34 mmol) in 5 ml $CH_2Cl_2$ for 2 hours The reaction was evaporated on a rotary evaporator and the resulting solid was washed 4 times with acetonitrile and dried *in vacuo* to yield a white solid (1 35 g, 54%) $^1$H NMR (300 MHz, $CD_3OD$) δ 7 69 (*app* q, *J* = 6 65 Hz, 1H), 7 20 (*app* t, *J* = 8 36 Hz, 2H), 7 09 (*app* t, *J* = 8 46 Hz, 2H), 6 88 (s, 1H), 5 46 (s, 2H), 4 21 (s, 2H), LC/MS, $t_r$ = 2 48 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 476 (M+H) ES-HRMS *m/z* 475 9907 (M+H calcd for $C_{19}H_{11}BrF_5NO_3$ requires 475 9915)

Ex 316

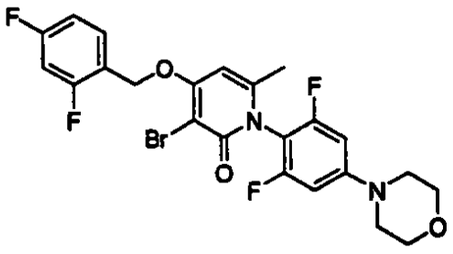



3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-(hydroxymethyl)-1-(2,4,6-trifluorophenyl)pyridin-2(1H)-one

4-[(2,4-Difluorobenzyl)oxy]-6-(hydroxymethyl)-1-(2,4,6-trifluorophenyl)pyridin-2(1H)-one (2 1 g, 5 28 mmol) was

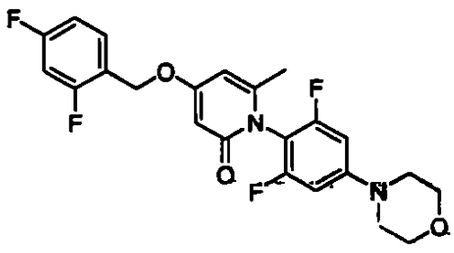
refluxed with *N*-chlorosuccinimide (846 mg, 6 34 mmol) and dichloroacetic acid (0 87 ml, 10 56 mmol) in 5 ml $CH_2Cl_2$ overnight The reaction was evaporated on a rotary evaporator and the resulting oil was triturated with diethyl ether to obtain a solid The solid was washed 4 times with acetonitrile Chromatography was done using a Biotage silica gel system with 60% ethyl acetate/hexanes The recovery was poor from the column to give a white solid (109 mg, 5%) $^1$H NMR (300 MHz, $CD_3OD$) δ 7 67 (*app* q, *J* = 7 85 Hz, 1H), 7 24 - 7 06 (m, 4H), 6 90 (s, 1H), 5 45 (s, 2H), 4 22 (s, 2H), LC/MS, $t_r$ = 2 71 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 432 (M+H) ES-HRMS *m/z* 432 0413 (M+H calcd for $C_{19}H_{11}ClF_5NO_3$ requires 432 0420)

Ex 317



3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluoro-4-morpholin-4-ylphenyl)-6-methylpyridin-2(1H)-one

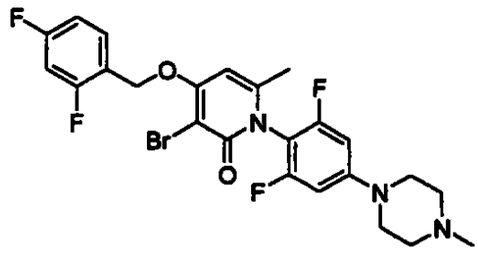
Step 1 Preparation of 4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluoro-4-morpholin-4-ylphenyl)-6-methylpyridin-2(1H)-one



4-[(2,4-Difluorobenzyl)oxy]-6-methyl-1-(2,4,6-trifluorophenyl)pyridir-2(1H)-one (870 mg, 2 28 mmol) was heated to 100°C with $K_2CO_3$ (630 mg, 4 56 mmol) in 5 ml of morpholine for 36 hours The reaction was added to 200 ml of cold water and the resulting solid was washed with water and 50 50 diethyl ether/hexanes and dried *in vacuo* to give a beige solid (738 mg, 72%) $^1$H NMR (400 MHz, $CDCl_3$) δ 7 41 (*app* q, *J* = 7 70 Hz, 1H), 6 93 - 6 85 (m, 2H), 6 49 (d, *J* = 10 47 Hz, 2H), 5 96 (d, *J* = 2 41 Hz, 1H), 5 89 (d, *J* = 1 75 Hz, 1H), 5 00 (s, 2H), 3 83 (t, *J* = 4 83 Hz, 4H), 3 19 (t, *J* = 4 84 Hz, 4H), 1 99 (s, 3H), LC/MS, $t_r$ = 3 09 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 449 (M+H) ES-HR/MS *m/z* 449 1485 (M+H calcd for $C_{23}H_{20}F_4N_2O_3$ requires 449 1483)

Step 2 Preparation of the title compound 4-[(2,4-Difluorobenzyl)oxy]-1-(2,6-difluoro-4-morpholin-4-ylphenyl)-6-methylpyridin-2(1H)-one ( from step 1) (500 mg, 1 12 mmol) was stirred at room temperature with *N*-bromosuccinimide (236 mg, 1 33 mmol) in 5 ml of $CH_2Cl_2$ for 2 hours The reaction was evaporated on a rotary evaporator and the resulting oil was triturated with diethyl ether to obtain a solid The solid was washed 4 times with acetonitrile and dried *in vacuo* to yield a white solid (171 mg, 29%) $^1$H NMR (400 MHz, $CDCl_3$) δ 7 58 (*app* q, *J* = 7 74 Hz, 1H), 6 96 (*app* t, *J* = 8 39 Hz, 1H), 6 86 (dt, *J* = 9 46, 2 28 Hz, 1H), 6 50 (d, *J* = 10 74 Hz, 2H), 6 09 (s, 1H), 5 24 (s, 2H), 3 84 (t, *J* = 4 84 Hz, 4H), 3 20 (t, *J* = 4 83 Hz, 4H), 2 07 (s, 3H), LC/MS, $t_r$ = 3 18 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 527 (M+H) ES-HRMS *m/z* 527 0570 (M+H calcd for $C_{23}H_{19}BrF_4N_2O_3$ requires 527 0588)

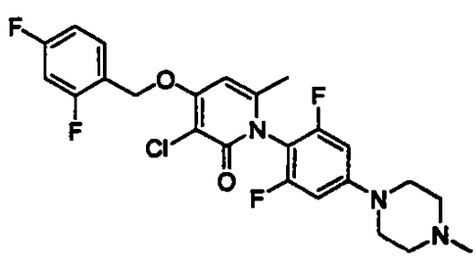
Ex 318



3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[2,6-difluoro-4-(4-methylpiperazin-1-yl)phenyl]-6-methylpyridin-2(1H)-one

The title compound was prepared essentially as in Example 317, using 1-methylpiperazine instead of morpholine $^1$H NMR (400 MHz, $CDCl_3$) δ 7 57 (*app* q, *J* = 7 79 Hz, 1H), 6 96 (dt, *J* = 8 19, 1 88 Hz, 1H), 6 86 (*app* dt, *J* = 9 44, 2 48 Hz, 1H), 6 52 (d, *J* = 10 61 Hz, 2H), 6 14 (s, 1H), 5 24 (s, 2H), 3 72 (br s, 4H), 3 51 (d, *J* = 11 27 Hz, 2H), 3 07 (br s, 2H), 2 85 (d, *J* = 4 29 Hz, 3H), 2 06 (s, 3H), LC/MS, $t_r$ = 2 50 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 540 (M+H) ES-HRMS *m/z* 540 0930 (M+H calcd for $C_{24}H_{22}BrF_4N_3O_2$ requires 540 0904)

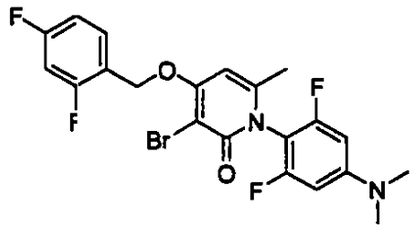
Ex 320



3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[2,6-difluoro-4-(4-methylpiperazin-1-yl)phenyl]-6-methylpyridin-2(1H)-one

4-[(2,4-Difluorobenzyl)oxy]-1-[2,6-difluoro-4-(4-methylpiperazin-1-yl)phenyl]-6-methylpyridin-2(1H)-one (1 3 g, 2 82 mmol) was stirred at reflux with *N*-chlorosuccinimide (451 mg, 3 38 mmol) and dichloroacetic acid (0 17 ml, 1 41 mmol) in 6 ml $CH_2Cl_2$ overnight LC-MS showed 33% completion More *N*-chlorosuccinimide (271 mg, 2 23 mmol) was added and refluxed overnight The reaction was evaporated on a rotary evaporator and the resulting oil was triturated with ethyl acetate to obtain a solid The solid was washed 4 times with etnyl acetate and with diethyl ether and dried in vacuo to obtain a white solid (606 mg, 43%) $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7 66 (br q, $J$ = 7 74 Hz, 1H) 7 33 (br t, $J$ = 9 00 Hz, 1H), 7 16 (br t, $J$ = 7 65 Hz, 1H) 6 96 (d, $J$ = 11 81 Hz, 2H), 6 79 (s, 1H), 5 33 (s, 2H), 3 61 (br m, 4H), 3 25 (br m, 4H), 3 21 (br s, 3H), 2 04 (s, 3H), LC/MS, $t_r$ = 2 45 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 496 (M+H) ES-HRMS *m/z* 496 1400 (M+H calcd for $C_{24}H_{22}ClF_4N_3O_2$ requires 496 1409)

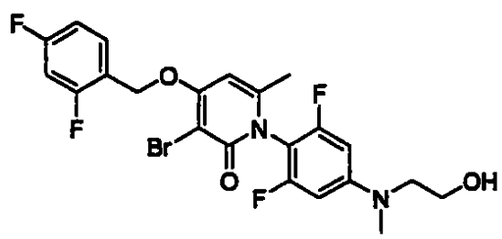
Example 321



3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[4-(dimethylamino)-2,6-difluorophenyl]-6-methylpyridin-2(1H)-one

The title compound was prepared essentially as described in Example 317, using dimethylamine instead of morpholine $^1$H NMR (400 MHz, $CDCl_3$) δ 7 59 (q, *J* = 7 74 Hz, 1H), 6 95 (dt, *J* = 8 32, 1 61 Hz, 1H), 6 85 (*app* dt, *J* = 9 54, 2 41 Hz, 1H), 6 27 (d, *J* = 11 01 Hz, 2H), 6 08 (s, 1H), 5 23 (s, 2H), 2 98 (s, 3H), 2 07 (s, 3H), LC/MS, $t_r$ = 3 35 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 485 (M+H) ES-HRMS *m/z* 485 0447 (M+H calcd for $C_{21}H_{17}BrF_4N_2O_2$ requires 485 0482)

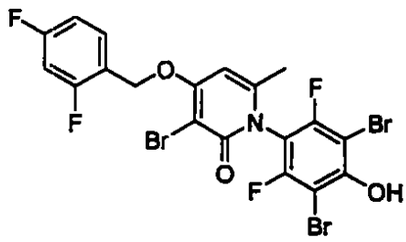
Example 322



3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-{2,6-difluoro-4-[(2-hydroxyethyl)(methyl)amino]phenyl}-6-methylpyridin-2(1H)-one

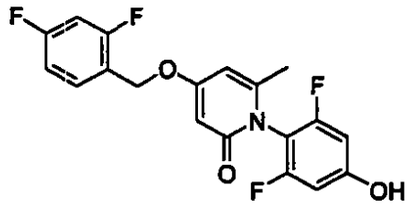
The title compound was prepared essentially as in Example 317, using 2-(methylamino)ethanol instead of morpholine $^1$H NMR (400 MHz, $CDCl_3$) δ 7 58 (q, *J* = 7 74 Hz, 1H), 6 95 (dt, *J* = 8 24, 1 66 Hz, 1H), 6 85 (*app* dt, *J* = 9 49, 2 37 Hz, 1H), 6 35 (d, *J* = 11 01 Hz, 2H), 6 10 (s, 1H), 5 23 (s, 2H), 3 77 (t, *J* = 5 77 Hz, 2H), 3 45 (t, *J* = 5 78 Hz, 2H), 2 99 (s, 3H), 2 08 (s, 3H), LC/MS, $t_r$ = 2 96 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 515 (M+H) ES-HRMS *m/z* 515 0576 (M+H calcd for $C_{22}H_{19}BrF_4N_2O_3$ requires 515 0588)

Example 323



3-bromo-1-(3,5-dibromo-2,6-difluoro-4-hydroxyphenyl)-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one

Step 1 Preparation of 4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluoro-4-hydroxyphenyl)-6-methylpyridin-2(1H)-one

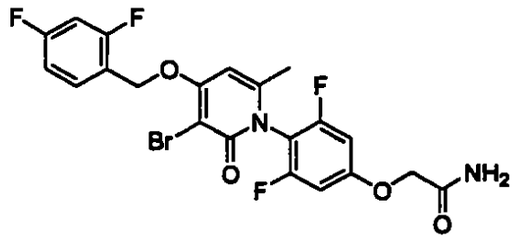


4-[(2,4-Difluorobenzyl)oxy]-6-methyl-1-(2,4,6-trifluorophenyl)pyridin-2(1H)-one (step 2 above) (10 0 g, 26 2 mmol) was heated to 45°C with $KOSiMe_3$ (10 08 g, 78 6 mmol) in 50 ml of tetrahydrofuran for 4 days The reaction was diluted with 30 ml of ethyl acetate and washed with 1N HCl and water, dried over $MgSO_4$, and evaporated to give an orange solid The solid was stirred in hot 60% ethyl acetate/hexanes and filtered to give a white solid, which was dried *in vacuo* to obtain a white solid (3 79 g, 38%) The filtrate was found to contain a mixture of desired product and the ortho substituted regioisomer $^1H$ NMR (400 MHz, $CDCl_3$) δ 7 42 (*app* q, *J* = 7 70 Hz, 1H), 6 95 - 6 83 (m, 2H), 6 34 (d, *J* = 9 40 Hz, 2H), 6 05 (*app* s, 2H), 5 06 (s, 2H), 2 01 (s, 3H), LC/MS, $t_r$ = 2 80 minutes (5 to 95% acetonitrile/water over 5 ~~minutes at 1~~

ml/min, at 254 nm, at 50°C), ES-MS *m/z* 380 (M+H) ES-HRMS *m/z* 380 0926 (M+H calcd for $C_{19}H_{13}F_4NO_3$ requires 380 0904)

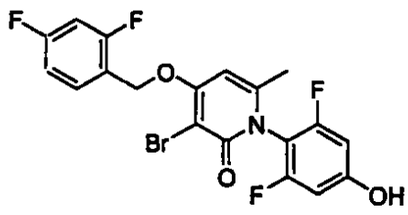
Step 2 Preparation of the title compound 4-[(2,4-Difluorobenzyl)oxy]-1-(2,6-difluoro-4-hydroxyphenyl)-6-methylpyridin-2(1H)-one ( from step 1) (3 73 g, 8 14 mmol) was stirred as a suspension at room temperature with *N*-bromosuccinimide (1 52 g, 8 55 mmol) in 30 ml $CH_2Cl_2$ overnight LC-MS showed a 60% starting material The solid was filtered off, dissolved in 30 ml of $CH_2Cl_2$/*N,N*-dimethylformamide and stirred with more *N*-bromosuccinimide (0 76 g, 4 28 mmol) overnight LC-MS showed the tri-brominated product as the major product The reaction was poured into water and extracted with n-butanol The combined organic layers were evaporated on a rotary evaporator and the resulting solid was washed with diethyl ether and dried *in vacuo* to yield a white solid (873 mg, 17%) $^1$H NMR (400 MHz, $CDCl_3$) δ 7 67 (*app* q, *J* = 7 80 Hz, 1H), 7 32 (dt, *J* = 4 86, 2 11 Hz, 1H), 7 16 (dt, *J* = 8 48, 1 84 Hz, 1H), 6 79 (s, 1H), 5 35 (s, 2H), 2 08 (s, 3H), LC/MS, $t_r$ = 3 26 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 616 (M+H) ES-HRMS *m/z* 615 8234 (M+H calcd for $C_{19}H_{10}Br_3F_4NO_3$ requires 615 8200)

Example 324



2-{4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-3,5-difluorophenoxy}acetamide

Step 1 Preparation of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluoro-4-hydroxyphenyl)-6-methylpyridin-2(1H)-one

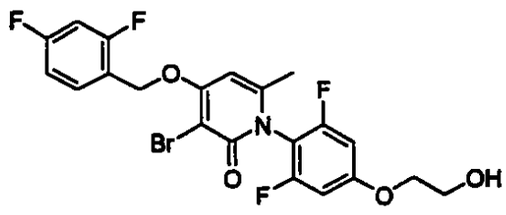


3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(2,4,6-trifluorophenyl)pyridin-2(1H)-one ( above) (7 5 g, 16 3 mmol) was heated to 45°C with $KOSiMe_3$ (10 08 g, 78 6 mmol) in 50 ml of tetrahydrofuran for 48 hours The reaction was diluted with 30 ml of ethyl acetate and washed with 1N HCl and water, dried over $MgSO_4$, and evaporated to give a black oil The oil was dissolved in ethyl acetate A precipitate formed upon standing, which was filtered, washed with ethyl acetate and dried in vacuo to obtain a white solid (2 80 g, 37%) The filtrate showed the presence of desired product and the ortho substituted regioisomer $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 7 66 (q, $J$ = 7 92 Hz, 1H), 7 32 (dt, $J$ = 8 77, 2 19 Hz, 1H), 7 15 (m, 1H), 6 73 (s, 1H), 6 67 (d, $J$ = 9 66 Hz, 2H), 5 33 (s, 2H), 2 03 (s, 3H), LC/MS, $t_r$ = 2 92 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS $m/z$ 458 (M+H) ES-HRMS $m/z$ 457 9995 (M+H calcd for $C_{19}H_{12}BrF_4NO_3$ requires 458 0009)

Step 2 Preparation of the title compound 3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluoro-4-hydroxyphenyl)-6-methylpyridin-2(1H)-one ( from step 1) (500 mg, 1 09 mmol) was

stirred briskly with 2-bromoacetamide (196 mg, 1 43 mmol) and $K_2CO_3$ (282 mg, 2 05 mmol) in 5 ml of *N,N*-dimethylformamide at room temperature for 24 hours The reaction was poured quickly into cold water and the resulting solid was filtered, washed with water, acetonitrile, and diethyl ether, and dried *in vacuo* to give a white solid (289 mg, 51%) $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7 66 (q, *J* = 7 92 Hz, 1H), 7 61 (br s, 1H), 7 45 (br s, 1H), 7 33 (dt, *J* = 10 07, 2 15 Hz, 1H), 7 16 (dt, *J* = 8 53, 1 88 Hz, 1H), 6 99 (d, *J* = 9 54 Hz, 2H), 6 76 (s, 1H), 5 34 (s, 2H), 2 03 (s, 3H), LC/MS, $t_r$ = 2 70 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 515 (M+H) ES-HRMS *m/z* 515 0245 (M+H calcd for $C_{21}H_{15}BrF_4N_2O_4$ requires 515 0224)

Example 325

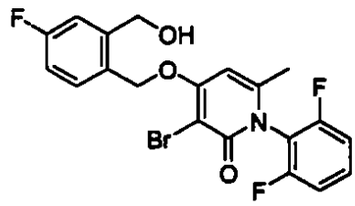



3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[2,6-difluoro-4-(2-hydroxyethoxy)phenyl]-6-methylpyridin-2(1H)-one

The title compound was prepared by a procedure similar to the one described for Example 324 $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7 66 (q, *J* = 7 92 Hz, 1H), 7 33 (dt, *J* = 10 04, 2 19 Hz, 1H), 7 17 (dt, *J* = 8 68, 1 84 Hz, 1H), 6 99 (d, *J* = 9 67 Hz, 2H), 6 75 (s, 1H), 5 34 (s, 2H), 4 92 (t, *J* = 4 86 Hz, 1H), 4 07 (t, *J* = 4 77 Hz, 2H), 3 70 (t, *J* = 4 83 Hz, 2H), 2 03 (s, 3H), LC/MS, $t_r$ = 2 81 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 502 (M+H)

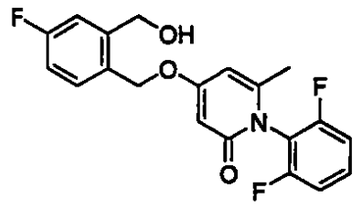
ES-HRMS *m/z* 502 0291 (M+H calcd for $C_{21}H_{16}BrF_4NO_4$ requires 502 0272)

Example 326



3-bromo-1-(2,6-difluorophenyl)-4-{[4-fluoro-2-(hydroxymethyl)benzyl]oxy}-6-methylpyridin-2(1H)-one

Step 1 Preparation of 1-(2,6-difluorophenyl)-4-{[4-fluoro-2-(hydroxymethyl)benzyl]oxy}-6-methylpyridin-2(1H)-one

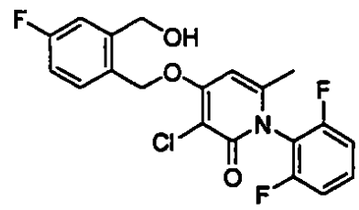


1-(2,6-Difluorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one (step 1) (3 0 g, 12 65 mmol) was dissolved in *N,N*-dimethylformamide and cooled to 0°C Triphenylphosphine (3 98 g, 15 18 mmol) and diethyl azodicarboxylate (2 39 ml, 15 18 mmol) were added and stirred for 10 minutes 1,2-Bis(hydroxymethyl)-4-fluorobenzene (2 57 g, 16 44 mmol) was added and stirred at 0°C for 1 hour, then allowed to warm to room temperature and stirred overnight LC-MS showed only 1 product, not a mixture of regioisomers, as expected The reaction was added to water and extracted 3 times with ethyl acetate The combined organic layers were dried over $MgSO_4$ and evaporated A Biotage silica column was done using 60% ethyl acetate/hexanes as an eluent Desired product, with a substantial impurity was obtained Another Biotage silica

column was ran using 30% ethyl acetate/hexanes to obtain pure product The resulting oil was triturated with diethyl ether to obtain a white solid (720 mg, 15%) $^1$H NMR (300 MHz, $CDCl_3$) δ 7 51 - 7 39 (m, 2H), 7 26 (dd, *J* = 9 62, 2 51 Hz, 1H), 7 13 - 7 01 (m, 3H), 6 03 (d, *J* = 2 42 Hz, 1H), 5 96 (d, *J* = 2 41 Hz, 1H), 5 06 (s, 2H), 4 73 (*s*, 2H), 2 81 (br s, 1H), 2 02 (s, 3H), LC/MS, $t_r$ = 2 37 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 376 (M+H) ES-HR/MS *m/z* 376 1181 (M+H calcd for $C_{20}H_{16}F_3NO_3$ requires 376 1155) Identity of the positional isomer was determined from hmbc, 2-D NMR experiments using H to C 2- and 3- bond coupling

Step 2 Preparation of the title compound 1-(2,6-Difluorophenyl)-4-{[4-fluoro-2-(hydroxymethyl)benzyl]oxy}-6-methylpyridin-2(1H)-one ( from step 1) (350 mg, 0 93 mmol) was stirred at room temperature with *N*-bromosuccinimide (199 mg, 1 12 mmol) in 1 5 ml $CH_2Cl_2$ for 1 5 hours The reaction was evaporated on a rotary evaporator and the resulting solid was washed 4 times with acetonitrile and dried *in vacuo* to yield a white solid (197 mg, 47%) $^1$H NMR (300 MHz, $CDCl_3$) δ 7 53 - 7 43 (m, 2H), 7 25 (dd, *J* = 9 46, 2 62 Hz, 1H), 7 11 - 7 03 (m, 3H), 6 25 (s, 1H), 5 31 (s, 2H), 4 81 (s, 2H), 2 28 (br s, 1H), 2 10 (s, 3H), LC/MS, $t_r$ = 2 38 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 454 (M+H) ES-HRMS *m/z* 454 0247 (M+H calcd for $C_{20}H_{15}BrF_3NO_3$ requires 454 0260)

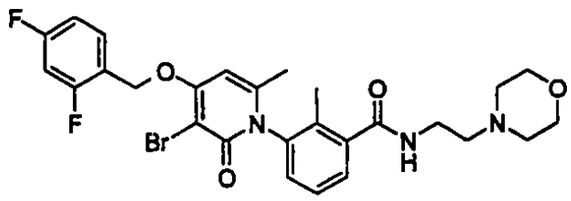
Example 327



3-chloro-1-(2,6-difluorophenyl)-4-{[4-fluoro-2-(hydroxymethyl)benzyl]oxy}-6-methylpyridin-2(1H)-one

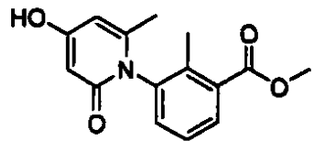
1-(2,6-Difluorophenyl) 4-{[4-fluoro-2-(hydroxymethyl)benzyl]oxy}-6-methylpyridin-2(1H)-one (step 1 above) (275 mg, 0 73 mmol) was stirred at reflux with *N*-chlorosuccinimide (117 mg, 0 88 mmol) and dichloroacetic acid (0 03 ml, 0 36 mmol) in 1 5 ml $CH_2Cl_2$ overnight The reaction was evaporated on a rotary evaporator and the resulting solid was washed 4 times with ethyl acetate and with diethyl ether and dried *in vacuo* to obtain a white solid (65 5 mg, 22%) $^1H$ NMR (300 MHz, $CDCl_3$) δ 7 52 - 7 43 (m, 2H), 7 26 (dd, *J* = 9 38, 2 52 Hz, 1H), 7 12 - 7 04 (m, 3H), 6 27 (s, 1H), 5 32 (s, 2H), 4 82 (s, 2H), 2 29 (br s, 1H), 2 11 (s, 3H), LC/MS, $t_r$ = 2 32 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 410 (M+H) ES-HRMS *m/z* 410 0755 (M+H calcd for $C_{20}H_{15}ClF_3NO_3$ requires 410 0765)

Example 328



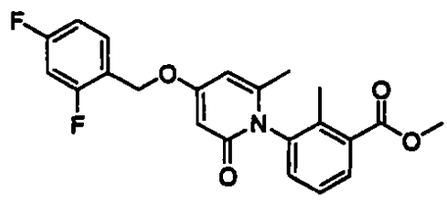
3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-2-methyl-N-(2-morpholin-4-ylethyl)benzamide

Step 1 Preparation of methyl 3-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)-2-methylbenzoate



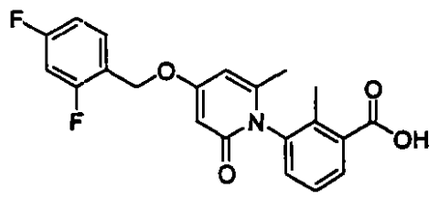
4-Hydroxy-6-methyl-2-pyrone (72 6 g, 576 mmol) and methyl-3-amino-2-methylbenzoate (100 g, 605 mmol) were suspended in 75 ml of 1,2-dichlorobenzene in a 500 ml, 3-necked round bottom flask equipped with a J-Kem temperature controller probe, a Dean-Stark trap, and a heating mantle The reaction was heated to 165°C for 15 minutes, during which, water and some 1,2-dichlorobenzene was collected in the Dean-Stark trap The reaction was allowed to cool to about 80°C The flask was placed in an ice bath and about 300 ml of toluene was added and stirred After about 30 minutes, a precipitate formed The precipitate was filtered and washed 3 times with toluene, 3 times with hot water to remove excess pyrone, and dried *in vacuo* to give a tan solid (44 6 g, 28% yield) $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10 66 (br s, 1H), 7 80 (dd, *J* = 7 72, 1 28 Hz, 1H), 7 33 (dd, *J* = 7 78, 1 34 Hz, 1H), 5 91 (dd, *J* = 2 41, 0 69 Hz, 1H), 5 55 (d, *J* = 2 42 Hz, 1H), 3 82 (s, 3H), 2 06 (s, 3H), 1 73 (s, 3H), LC/MS, $t_r$ = 1 85 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 274 (M+H) ES-HRMS *m/z* 274 1078 (M+H calcd for $C_{15}H_{15}NO_4$ requires 274 1074)

Step 2 Preparation of methyl 3-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-2-methylbenzoate



Methyl-3-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)-2-methylbenzoate ( from Step 1) (42 0 g, 154 mmol) was stirred briskly at room temperature with 2,4-difluorobenzyl bromide (19 7 ml, 154 mmol) and $K_2CO_3$ (31 8 g, 231 mmol) in 250 ml of *N,N*-dimethylformamide After stirring overnight, the reaction was poured into 1 L of cold water The solution was extracted 3 times with ethyl acetate and the organic layers were dried over $MgSO_4$, and evaporated The product was carried on to the next step as a crude oil (60 4 g, 85%) $^1H$ NMR (400 MHz, $CDCl_3$) δ 7 96 (dd, *J* = 7 85, 1 28 Hz, 1H), 7 45 - 7 34 (m, 2H), 7 27 - 7 23 (m, 1H), 6 94 - 6 84 (m, 2H), 5 98 (d, *J* = 2 68 Hz, 1H), 5 92 (dd, *J* = 2 69, 0 81 Hz, 1H), 5 01 (s, 2H), 3 88 (s, 3H), 2 28 (s, 3H), 1 81 (s, 3H), LC/MS, $t_r$ = 2 96 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 400 (M+H) ES-HRMS *m/z* 400 1341 (M+H calcd for $C_{22}H_{19}F_2NO_4$ requires 400 1355)

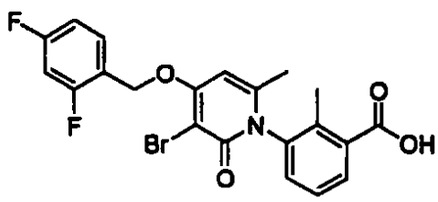
Step 3 Preparation of 3-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-2-methylbenzoic acid




Methyl 3-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-2-methylbenzoate ( from Step 2) (60 0 mg, 150 mmol) was stirred with 2 5 N NaOH (120 ml, 300 mmol) in 375 ml of tetrahydrofuran and 75 ml of water at room temperature overnight The reaction was acidified with 1 N HCl, 350 ml of water was added and the solution was extracted 3 times with ethyl acetate The combined organic layers were dried over

$MgSO_4$, filtered and evaporated The resulting solid was filtered, washed with ethyl acetate and dried *in vacuo* to yield a white solid 33 8 g, 58%) $^1H$ NMR (400 MHz, $CDCl_3$) δ 7 98 (dd, *J* = 7 92, 1 20 Hz, 1H), 7 43 (*app* q, *J* = 7 70 Hz, 1H), 7 38 (t, *J* = 7 72 Hz, 1H), 7 35 (dd, *J* = 7 81, 1 21 Hz, 1H), 6 92 - 6 84 (m, 2H), 6 17 (d, *J* = 2 56 Hz, 1H), 6 00 (dd, *J* = 2 55, 0 81 Hz, 1H), 5 05 (s, 2H), 2 30 (s, 3H), 1 84 (s, 3H), LC/MS, $t_r$ = 2 61 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 386 (M+H) ES-HR/MS *m/z* 386 1228 (M+H calcd for $C_{21}H_{17}F_2NO_4$ requires 386 1198)

Step 4 Preparation of 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-2-methylbenzoic acid



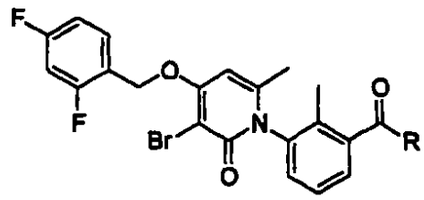
3-[4-[(2,4-Difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-2-methylbenzoic acid ( from Step 3) (23 0 g, 59 7 mmol) was stirred at room temperature with *N*-bromosuccinimide (12 74 g, 71 6 mmol) in 120 ml of $CH_2Cl_2$ for 2 hours The reaction was evaporated on a rotary evaporator and the resulting solid was stirred in acetonitrile for 1 hour, washed 7 times with acetonitrile and dried *in vacuo* to yield a white solid (19 14 g, 69%) $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 7 87 (dd, *J* = 7 52, 1 61 Hz, 1H), 7 67 (*app* q, *J* = 7 92 Hz, 1H), 7 45 - 7 37 (m, 2H), 7 33 (dt, *J* = 9 87, 2 54 Hz, 1H), 7 17 (dt, *J* = 8 50, 1 67 Hz, 1H), 6 71 (s, 1H), 5 32 (s, 2H), 2 08 (s, 3H), 1 86 (s, 3H),

LC/MS, $t_r$ = 2 69 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 464 (M+H) ES-HRMS *m/z* 464 0284 (M+H calcd for $C_{21}H_{16}BrF_2NO_4$ requires 464 0304)

Step 5 Preparation of the title compound 3-[3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-2-methylbenzoic acid ( from Step 4 above) (500 mg, 1 08 mmol) was dissolved in 5 ml of $CH_2Cl_2$ 4-(2-Aminoethyl)morpholine (170 µl, 1 29 mmol) was added, followed, in order, by EDCI (247 mg, 1 29 mmol), 1-hydroxybenzotriazole (174 mg, 1 29 mmol) and triethylamine (301 µl, 2 16 mmol) The reaction was stirred at room temperature overnight The reaction was quenched with $NH_4Cl$ and extracted 3 times with ethyl acetate The combined organic layer was dried over $MgSO_4$ and evaporated The resulting oil was triturated with diethyl ether/hexane to obtain a solid, which was dried *in vacuo* to give a white solid (472 mg, 76%) $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 7 64 (*app* q, *J* = 7 79 Hz, 1H), 7 47 (dd, *J* = 7 65, 1 01 Hz, 1H), 7 39 (t, *J* = 7 75 Hz, 1H), 7 17 (dd, *J* = 7 65, 0 81 Hz, 1H), 7 01 (dt, *J* = 8 26, 1 61 Hz, 1H), 6 9 (dt, *J* = 9 42, 2 32 Hz, 1H), 6 49 (t, *J* = 5 04 Hz, 1H), 6 18 (s, 1H), 5 30 (s, 2H), 3 73 (t, *J* = 4 53 Hz, 4H), 3 68 - 3 47 (m, 2H), 2 59 (t, *J* = 5 94 Hz, 2H), 2 51 (t, *J* = 4 33 Hz, 4H), 2 15 (s, 3H), 1 98 (s, 3H), LC/MS, $t_r$ = 2 27 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 576 (M+H) ES-HRMS *m/z* 576 1313 (M+H calcd for $C_{27}H_{28}BrF_2N_3O_4$ requires 576 1304)

Examples 329-337

The following compounds are prepared essentially according to the procedure set forth for Example 328



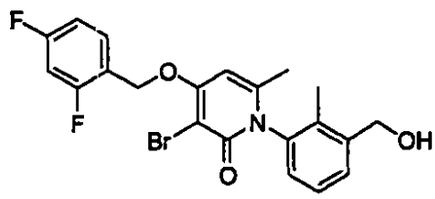
| Example No | R | MF | M+H Requires | ESHRMS m/z |
|---|---|---|---|---|
| Ex 329 | $-NHCH_2CH_2OCH_3$ | $C_{24}H_{22}BrF_2N_2O_4$ | 521 0882 | 521 0906 |
| Ex 330 | $-N(CH_3)_2$ | $C_{23}H_{20}BrF_2N_2O_3$ | 491 0776 | 491 0752 |
| Ex 331 | $-NHCH_2CH_2OH$ | $C_{23}H_{20}BrF_2N_2O_4$ | 507 0726 | 507 0689 |
| Ex 332 | $-NHCH_3$ | $C_{22}H_{18}BrF_2N_2O_3$ | 477 0620 | 477 0585 |
| Ex 333 | $-N(CH_3)CH_2CH_2OH$ | $C_{24}H_{22}BrF_2N_2O_4$ | 521 0882 | 521 0890 |
| Ex 334 | 4-methylpiperazin-1-yl | $C_{26}H_{25}BrF_2N_3O_3$ | 546 1198 | 546 1187 |
| Ex 335 | morpholin-4-yl | $C_{25}H_{22}BrF_2N_2O_4$ | 533 0882 | 533 0856 |
| Ex 336 | $-N(CH_3)CH_2CH_2OCH_3$ | $C_{25}H_{24}BrF_2N_2O_4$ | 535 1039 | 535 1055 |
| Ex 337 | $-NH_2$ | $C_{21}H_{16}BrF_2N_2O_3$ | 463 0463 | 463 0492 |

NMR characterization of compounds of Examples 329-337

| Example No | NMR Data |
|---|---|
| Ex 329 | $^1$H NMR (400 MHz $CDCl_3$) δ 7 59 (app q, $J$ = 7 79 Hz, 1H), 7 47 (dd, $J$ = 7 65, 1 08 Hz 1H), 7 34 (t, $J$ = 7 72 Hz, 1H), 7 12 (dd, $J$ = 7 78, 0 94 Hz 1H), 6 96 (app dt $J$ = 7 92, 2 27 Hz, 1H), 6 87 (dt, $J$ = 9 46 2 55 Hz, 1H), 6 29 (m, 1H) 6 12 (s, 1H), 5 25 (s, 2H), 3 73 - 3 65 (m, 1H), 3 56 - 3 48 (m, 3H) 3 35 (d, $J$ = 3 09 Hz, 3H), 2 09 (s, 3H) 1 93 (s 3H) |
| Ex 330 | $^1$H NMR (400 MHz $CDCl_3$) δ 7 59 (app q, $J$ = 7 79 Hz, 1H), 7 34 (t, $J$ = 7 66 Hz, 1H), 7 28 (dd, $J$ = 7 66, 1 21 Hz, 1H), 7 07 (dd, $J$ = 7 65, 1 08 Hz, 1H), 6 96 (app dt, $J$ = 8 52 2 02 Hz 1H), 6 87 (dt, $J$ = 9 46, 2 55 Hz, 1H), 6 29 (m, 1H), 6 12 (s, 1H), 5 25 (s, 2H), 3 11 (s, 3H), 2 82 (s, 3H), 1 96 (s, 3H), 1 95 (s, 3H) |
| Ex 331 | $^1$H NMR (400 MHz, $CDCl_3$) δ 7 59 (app q $J$ = 7 74 Hz, 1H), 7 46 (d, $J$ = 6 71 Hz 1H), 7 32 (t, $J$ = 7 72 Hz, 1H), 7 07 (d, $J$ = 6 85 Hz, 1H), 6 98 (m 2H) 6 87 (dt, $J$ = 9 47, 2 41 Hz, 1H) |

| | |
|---|---|
| | 6 15 (s 1H) 5 26 (s 2H) 3 71 (t *J* = 4 97 Hz 2H), 3 60 - 3 45 (m 2H) 2 06 (s 3H) 1 95 (s 3H) |
| Ex 332 | $^1$H NMR (400 MHz $CDCl_3$) δ 7 59 (*app* q, *J* = 7 79 Hz 1H) 7 42 (dd, *J* = 7 66 0 94 Hz 1H), 7 31 (t, *J* = 7 72 Hz 1H) 7 09 (dd, *J* = 7 79 0 94 Hz 1H) 6 96 (*app* dt *J* = 8 26 1 61 Hz 1H) 6 87 (dt, *J* = 9 44 2 49 Hz, 1H), 6 12 (s, 1H) 5 25 (s 2H) 2 96 (d *J* = 4 83 Hz 3H) 2 07 (s 3H) 1 93 (s, 3H) |
| Ex 333 | $^1$H NMR (300 MHz DMSO-$d_6$) δ 7 73 (q, *J* = 7 92 Hz, 1H) 7 44 - 7 20 (m, 5H), 6 75 (s 1H) 5 37 (s 2H) 4 83 (br s, 1H), 3 65 (br s 2H) 3 45 - 3 33 (m 2H) 2 81 (s 3H) 1 93 (d, *J* = 3 42 Hz 3H) 1 85 (d, *J* = 8 06 Hz, 3H) |
| Ex 334 | $^1$H NMR (300 MHz DMSO-$d_6$) δ 7 67 (*app* q *J* = 7 92 Hz 1H), 7 40 (t *J* = 7 78 Hz, 1H) 7 34 (dt *J* = 9 87 2 55 Hz 1H) 7 27 (d, *J* = 7 52 Hz 1H), 7 24 (d *J* = 7 79 Hz 1H) 7 17 (dt *J* = 8 41, 1 97 Hz, 1H) 6 71 (s, 1H), 5 32 (s 2H), 3 63 (m 2H) 3 29 (br s, 1H), 3 09 (br s 2H) 2 34 (t, *J* = 4 57 Hz 2H), 2 20 (br s, 2H), 2 16 (s 3H) 1 88 (d, *J* = 8 86 Hz, 3H) 1 80 (d *J* = 4 83 Hz 3H) |
| Ex 335 | $^1$H NMR (300 MHz $CDCl_3$) δ 7 64 (*app* q, *J* = 7 79 Hz, 1H), 7 42 (t, *J* = 7 65 Hz, 1H) 7 33 (d, *J* = 7 66 Hz 1H) 7 14 (d *J* = 7 65 Hz, 1H) 7 00 (dt *J* = 8 76 2 21 Hz, 1H) 6 91 (dt, *J* = 9 47 2 42 Hz, 1H), 6 17 (s 1H) 5 29 (s 2H) 3 98 - 3 92 (m, 1H), 3 80 - 3 77 (m, 3H), 3 59 (br s, 2H) 3 29 (t *J* = 4 43 Hz, 2H), 2 04 (s, 3H) 2 00 (s 3H) |
| Ex 336 | $^1$H NMR (300 MHz $CDCl_3$) δ 7 65 (*app* q, *J* = 7 79 Hz 1H) 7 43 - 7 32 (m, 2H) 7 12 (dd *J* = 7 66, 1 21 Hz 1H), 7 00 (dt, *J* = 9 06 1 51 Hz 1H) 6 92 (dt *J* = 9 42 2 52 Hz, 1H), 6 16 (s 1H), 5 30 (s 2H) 3 69 (t *J* = 5 04 Hz, 2H) 3 39 (s 3H) 3 26 (s, 1H) 3 19 (s 1H) 2 91 (s, 3H) 2 04 (s 3H), 2 00 (s 3H) |
| Ex 337 | $^1$H NMR (300 MHz DMSO-$d_6$) δ 7 91 (br s, 1H), 7 73 (*app* q *J* = 7 85 Hz, 1H) 7 53 - 7 20 (m 5H) 6 74 (s 1H) 5 37 (s 2H) 1 99 (s, 3H) 1 92 (s 3H) |

Example 338

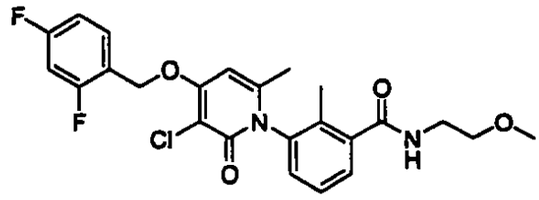



3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[3-(hydroxymethyl)-2-methylphenyl]-6-methylpyridin-2(1H)-one

3-[3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-2-methylbenzoic acid (Step 4 above) (2 0 g, 4 31

mmol) was cooled to 0°C in 10 ml of tetrahydrofuran 19 5 ml of 1M $BH_3$ THF in tetrahydrofuran was added and stirred overnight, allowing the temperature to rise to room temperature The reaction was cooled back down to 0°C and ice chips were added to quench the reaction The slurry was extracted 3 times with an ethyl acetate/tetrahydrofuran mixture The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated to give a white solid (1 73 g, 89%) $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7 67 (*app* q, *J* = 7 92 Hz, 1H), 7 46 (d, *J* = 7 52 Hz, 1H), 7 32 (dt, *J* = 10 74, 2 42 Hz, 1H), 7 30 (t, *J* = 7 72 Hz, 1H), 7 17 (dt, *J* = 8 46, 1 88 Hz, 1H), 7 03 (d, *J* = 7 38 Hz, 1H), 6 68 (s, 1H), 5 32 (s, 2H), 4 51 (s, 2H), 3 29 (d, *J* = 9 40 Hz, 1H), 1 85 (s, 3H), 1 81 (s, 3H), LC/MS, $t_r$ = 2 64 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 450 (M+H) ES-HRMS *m/z* 450 0480 (M+H calcd for $C_{21}H_{18}BrF_2NO_3$ requires 450 0511)

Example 339

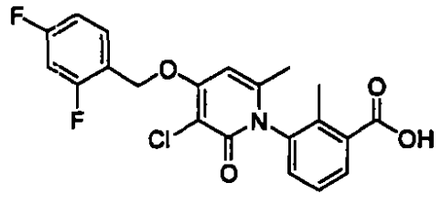


3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-N-(2-methoxyethyl)-2-methylbenzamide

Step 1 Preparation of 3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-2-methylbenzoic acid

252

230

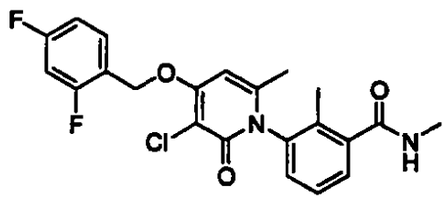


3-[4-[(2,4-Difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-2-methylbenzoic acid (Step 3 above) (10 0 g, 25 9 mmol) was refluxed with *N*-chlorosuccinimide (4 15 g, 31 1 mmol) and dichloroacetic acid (1 06 ml, 12 9 mmol) in 50 ml of $CH_2Cl_2$ overnight The reaction was evaporated on a rotary evaporator and the resulting solid was stirred in acetonitrile for 30 minutes, washed 4 times with acetonitrile and dried *in vacuo* to yield a white solid (8 3 g, 78%) $^1$H NMR (300 MHz, DMSO-$d_6$) δ 7 93 (dd, *J* = 7 15, 1 92 Hz, 1H), 7 72 (*app* q, *J* = 7 92 Hz, 1H), 7 52 - 7 35 (m, 2H), 7 22 (dt, *J* = 8 47, 2 01 Hz, 1H), 6 80 (s, 1H), 5 38 (s, 2H), 2 14 (s, 3H), 1 93 (s, 3H), LC/MS, $t_r$ = 2 64 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 420 (M+H) ES-HRMS *m/z* 420 0806 (M+H calcd for $C_{21}H_{16}ClF_2NO_4$ requires 420 0809)

Step 5 Preparation of the title compound 3-[3-Chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-2-methylbenzoic acid ( from Step 1 above) (500 mg, 1 19 mmol) was dissolved in 5 ml of $CH_2Cl_2$ 2-Methoxyethylamine (129 µl, 1 49 mmol) was added, followed, in order, by EDCI (286 mg, 1 49 mmol), 1-hydroxybenzotriazole (202 mg, 1 49 mmol) and triethylamine (332 µl, 2 38 mmol) The reaction was stirred at room temperature overnight The reaction was quenched with $NH_4Cl$ and extracted 3 times with ethyl acetate The combined organic layer was dried over $MgSO_4$ and evaporated The resulting solid was dried *in vacuo* to give a white solid (401 mg, 71%) $^1$H NMR (400 MHz, $CDCl_3$) δ 7 56 (*app* q, *J* = 7 74 Hz,

1H), 7 47 (d, *J* = 6 98 Hz, 1H), 7 34 (t, *J* = 7 72 Hz, 1H), 7 11 (d, *J* = 7 25 Hz, 1H), 6 95 (dt, *J* = 8 23, 1 66 Hz, 1H), 6 87 (dt, *J* = 9 51, 2 46 Hz, 1H), 6 35 (br s, 1H), 6 15 (s, 1H), 5 25 (s, 2H), 3 72 - 3 63 (m, 1H), 3 58 - 3 49 (m, 3H), 3.35 (s, 3H), 2 09 (s, 3H), 1 93 (s, 3H), LC/MS, $t_r$ = 2 56 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 477 (M+H) ES-HRMS *m/z* 477 1363 (M+H calcd for $C_{24}H_{23}ClF_2N_2O_4$ requires 477 1387)

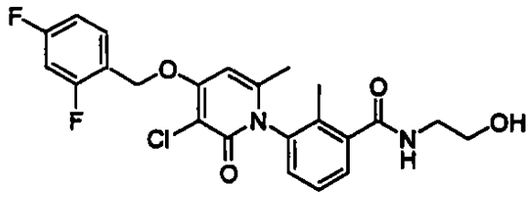
Example 340



3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-N,2-dimethylbenzamide

The title compound was prepared by a procedure similar to the one described for Example 337, where methylamine was used as the amine and the product was obtained in 73% yield $^1$H NMR (300 MHz, DMSO-$d_6$) δ 8 37 (*app* d, *J* = 4 64 Hz, 1H), 7 72 (*app* q, *J* = 7 92 Hz, 1H), 7 44 - 7 35 (m, 4H), 7 22 (dt, *J* = 8 54, 1 61 Hz, 1H), 6 78 (s, 1H), 5 37 (s, 2H), 2 79 (d, *J* = 4 43 Hz, 3H), 1 95 (s, 3H), 1 94 (s, 3H), LC/MS, $t_r$ = 2 46 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 433 (M+H) ES-HRMS *m/z* 433 1163 (M+H calcd for $C_{22}H_{19}ClF_2N_2O_3$ requires 433 1125)

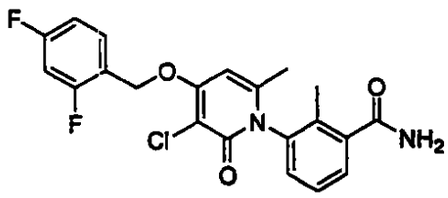
Example 341



3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-N-(2-hydroxyethyl)-2-methylbenzamide

The title compound was prepared by a procedure similar to the one described for , where ethanolamine was used as the amine and the product was obtained in 65% yield $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8 39 (t, *J* = 5 51 Hz, 1H), 7 67 (*app* q, *J* = 7 88 Hz, 1H), 7 43 - 7 33 (m, 3H), 7 23 (d, *J* = 7 25 Hz, 1H), 7 17 (dt, *J* = 8 39, 1 66 Hz, 1H), 6 74 (s, 1H), 5 32 (s, 2H), 3 48 (br s, 2H), 3 31 - 3 26 (m, 2H), 1 90 (s, 3H), 1 89 (s, 3H), LC/MS, $t_r$ = 2 34 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 463 (M+H) ES-HRMS *m/z* 463 1220 (M+H calcd for $C_{23}H_{21}ClF_2N_2O_4$ requires 463 1231)

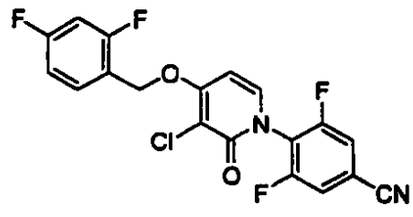
Example 342



3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-2-methylbenzamide

3-[3-Chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-2-methylbenzoic acid (Step 1 above) (500 mg, 1 19 mmol) was stirred with 2-chloro-4,6-dimethoxy-1,3,5-triazine (251 mg, 1 43 mmol) and *N*-methylmorpholine (392 µl, 3 57 mmol) in 5 ml of tetrahydrofuran at room temperature for 2 hours 2 5 ml of $NH_4OH$ was added and stirred at room temperature for 2 5 hours The reaction was diluted with tetrahydrofuran and ethyl acetate and extracted The combined organic layers were washed with $NaHCO_3$, 1 N HCl, and brine, dried over $MgSO_4$, filtered and evaporated The resulting solid was dried *in vacuo* to obtain a white solid (313 mg, 63%) $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 7 87 (br s, 1H), 7 66 (q, *J* = 7 83 Hz, 1H), 7 48 - 7 30 (m, 3H), 7 23 (d, *J* = 7 52 Hz, 1H), 7 17 (t, *J* = 7 65 Hz, 1H), 6 73 (s, 1H), 5 32 (s, 2H), 1 94 (s, 3H), 1 88 (s, 3H), LC/MS, $t_r$ = 2 44 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 419 (M+H) ES-HRMS *m/z* 419 0963 (M+H calcd for $C_{21}H_{17}ClF_2N_2O_3$ requires 419 0969)

Example 343

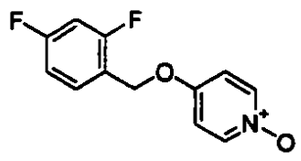


4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzonitrile

254

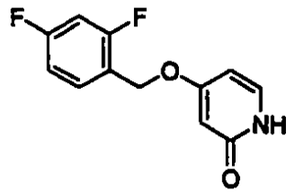
252

Step 1 Preparation of 4-[(2,4-difluorobenzyl)oxy]pyridine 1-oxide



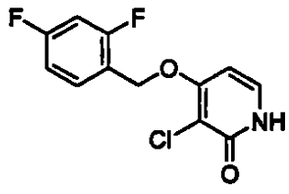
2, 4-difluorobenzyl alcohol (100 g, 0 694 mol) and 4-nitropyridine N-oxide (98 g, 0 700 mol)are combined with 250 g $Cs_2CO_3$ (1 1 eq) in 2 5 L anhydrous dimethylformamide and heated to 80°C with stirring The reaction was followed by $^{19}$F-NMR (crude reaction mixture with external $D_2O$ reference) and complete after 40 h The mixture was filtered hot, product crystallized out on cooling 90 21 g (55%) of white plates were collected by filtration and washed with diethyl ether The mother liquor was diluted with 2 5 L diethyl ether and stored in the freezer overnight, yielding a second crop 68 76 g (41%, combined yield 96%) $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 8 06 (m, 2 H), 7 61 (quartet, $J$ = 8 45 Hz, 1H), 7 30 (t, $J$ = 10 37 Hz,1H), 7 12, (t, $J$ = 8 45 Hz, 1H), 7 09 (d, $J$ = 5 06 Hz, 2H), 5 14 (s, 2H) $^{19}$F-NMR (400 MHz, DMSO-$d_6$) δ -109 43 (quintet, $J$ = 7 78 Hz, 1F), -113 82 (quartet, $J$ = 9 55 Hz, 1F) LC/MS $t_r$ = 3 90 minutes (0-95% acetonitrile/water, 0 05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C) ES-MS $m/z$ 238 (M+H)

Step 2 Preparation of 4 [(2,4-difluorobenzyl)oxy]-pyridin-2(1H)-one (7)



4-[(2,4-difluorobenzyl)oxy]pyridine 1-oxide ( from Step 1) (30 0 g , 0 127 mol), anhydrous potassium acetate (25 g, 0 25 mol), acetic anydride (25 g, 0 25 mol), and 10 ml acetic acid were combined in a 250-ml round-bottomed flask with overhead stirring and heated to 130°C for 4 hours The mixture was concentrated under vacuum, the solids dissolved in 95 ml acetonitrile 5 ml water, filtered through charcoal and poured into 600 ml ice with stirring The mixture was allowed to stand overnight at room temperature, then 9 62 g (30%) product collected by filtration as a medium brown solid (adequate for the next step without purification) $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 11 10 (s, 1H), 7 59 (quartet, $J$ = 9 91 Hz, 1H), 7 29 (t, $J$ = 10 36 Hz, 1H), 7 21 (d, $J$ = 8 20 Hz, 1H), 7 11 (t, $J$ = 8 48 Hz, 1H), 5 83 (m, 2H), 5 02 (s, 2H) $^{19}$F-NMR (400 MHz, DMSO-$d_6$) δ -109 57(quintet, $J$ = 7 66 Hz, 1F) -113 88 (quartet, $J$ = 8 93 Hz, 1F) LC/MS $t_r$ = 4 29 minutes (0-95% acetonitrile/water, 0 05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 254 nm, at 50°C) ES-MS $m/z$ 238 (M+H)

Step 3 Preparation of 3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1H)-one

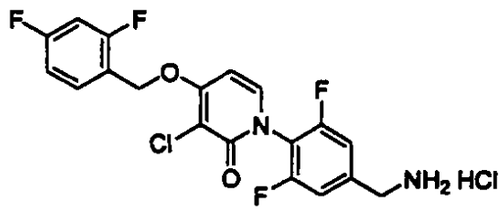


4-[(2,4-difluorobenzyl)oxy]-pyridin-2(1H)-one ( from Step 2) (8 60 g, 36 3 mmol) was stirred in 150 ml dimethylformamide and treated with N-chlorosuccinimide (5 4 g, 39 9 mmol) After 15 hours, the precipitate was collected by filtration (5 11 g, 52%) yielding a lustrous white solid The mother liquor was diluted to 500 ml with diethyl ether, providing 2 47 g (25%) in a second crop $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 11 87 (s, 1H), 7 60 (quartet, $J$ = 6 34 Hz, 1H), 7 43 (d, $J$ = 7 58 Hz, 1H), 7 31 (dt, $J$ = 10 08, 2 21 Hz, 1H), 7 14 (dt, $J$ = 8 65, 1 79 Hz, 1H), 6 44 (d, $J$ = 7 49 Hz, 1H), 5 28 (s, 1H) $^{19}$F-NMR (400 MHz, DMSO-$d_6$) δ -109 58 (quintet, $J$ = 7 75 Hz, 1F), -113 68 (quartet, $J$ = 8 68 Hz, 1F) LC/MS $t_r$ = 4 47 minutes (0-95% acetonitrile/water, 0 05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 254 nm, at 50°C) ES-MS $m/z$ 272, 274 3 1 (M+H)

Step 4 Preparation of the title compound 3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1H)-one ( from step 3) (3 25 g, 11 9 mmol) was combined with $Cs_2CO_3$ (3 93 g, 12 1 mmol) in 50 ml dimethylformamide and heated to 70°C, stirring under nitrogen 3,4,5-trifluorobenzonitrile (1 83 g, 11 9 mmol) was added After 4 hours, the mixture was filtered, concentrated *in vacuo*, washed thrice with hot cyclohexane, dissolved in tetrahydrofuran, treated with $MgSO_4$ and charcoal, and filtered The solution was evaporated leaving a fine white solid (3 99 g, 82%) $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 8 12 (d, $J$ = 7 59 Hz, 2H), 7 92 (d, $J$ = 8 31 Hz, 1H), 7 65 (quartet, $J$ = 6 77, 1H), 7 34 (dt, $J$ = 9 81, 2 71 Hz, 1H), 7 16 (dt, $J$ = 8 59, 2 50 Hz, 1H), 6 87 (d, $J$ = 8 01 Hz, 1H), 5 39 (s, 2H) $^{19}$F-NMR (400 MHz, DMSO-$d_6$) δ -109 17 (quintet, $J$ = 8 97 Hz, 1F), -113 51(quartet, $J$ = 9 53 Hz, 1F) -116 32 (d, $J$ = 7 69 Hz, 2F) LC/MS $t_r$ = 5 51 minutes (0-

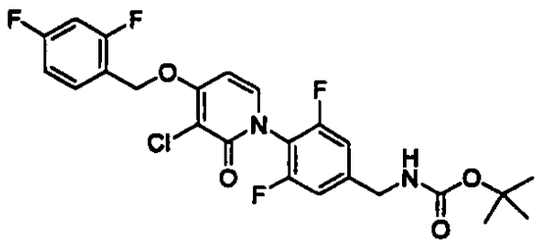
95% acetonitrile/water, 0 05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C) ES-MS *m/z* 409 (M+H) ES-HRMS *m/z* 409 0351 (M+H calcd for $C_{19}H_{10}ClF_4N_2O_2$ requires 409 0361)

Example 344



1-[4-(aminomethyl)-2,6-difluorophenyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1H)-one hydrochloride

Step 1 Preparation of tert-butyl 4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzylcarbamate



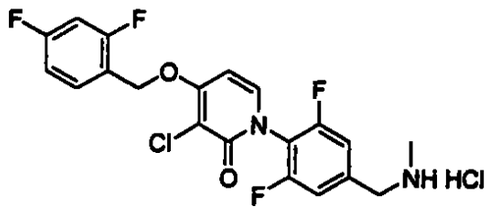
4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzonitrile (2 84 g, 6 95 mmol), di-t-butyl-dicarbonate (3 18 g, 14 6 mmol), and nickel(II) chloride (0 90 g, 6 95 mmol) were combined with 40 ml methanol and 40 ml tetrahydrofuran and cooled to 0°C stirring in an ice bath Sodium borohydride (1 33 g, 35 2 mmol) was added in small

portions over 10 minutes to control foaming, and the reaction was stirred 1 hour Additional sodium borohydride (0 50 g, 13 2 mmol) was required to force the reaction to completion by LC A color change from yellow to black persisted on completion The mixture was filtered through a bed of charcoal layered on anhydrous $MgSO_4$ and evaporated to dryness Excess di-t-butyl-dicarbonate and byproduct t-butanol were removed by repeated heating with water to 80°C *in vacuo*, giving the product as a fine white powder (3 11 g, 87%) $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 7 89 (d, *J* = 8 04 Hz, 1H), 7 65 (quartet, *J* = 6 73 Hz, 1H), 7 55 (t, *J* = 6 73 Hz,1H), 7 34, (dt, *J* = 10 05, 2 51 Hz, 1H), 7 16 (m, 3H), 6 77 (d, *J* = 8 18 Hz, 1H), 5 34 (s, 2H), 4 18 (d, *J* = 5 68 Hz, 2H), 1 34 (s, 9H) $^{19}$F-NMR (400 MHz, DMSO-$d_6$) δ -109 26 (quintet, *J* = 6 91 Hz, 1F), -113 53 (quartet, *J* = 7 73 Hz, 1F), -120 32(d, *J* = 8 91 Hz, 2F) LC/MS $t_r$ = 5 90 minutes (0-95% acetonitrile/water, 0 05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C) ES-MS *m/z* 513 (M+H) ES-HRMS *m/z* 513 1164 (M+H calcd for $C_{24}H_{22}ClF_4N_2O_4$ requires 513 1199)

Step 2 Preparation of the title compound tert-butyl 4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzylcarbamate ( from step 3) (1 39 g, 2 71 mmol) was dissolved in 20 ml tetrahydrofuran and treated with 4 ml concentrated hydrochloric acid The solution was evaporated and dried *in vacuo* to a fine white solid (1 20 g, 99%) $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 8 54 (m, 2H), 7 86 (d, *J* = 7 57 Hz, 1H), 7 65 (quartet, *J* = 7 62, 1H), 7 50 (d, *J* = 9 25 Hz, 2H), 7 34 (dt, *J* = 10 50, 2 45 Hz, 1H), 7 16 (dt, *J* = 8 38, 2 55 Hz, 1H), 6 78 (d, *J* = 7 86 Hz, 1H), 5 37 (s, 2H), 4 10 (br s, 2H), 4 97-3 14 (v br s, 3H) $^{19}$F-NMR

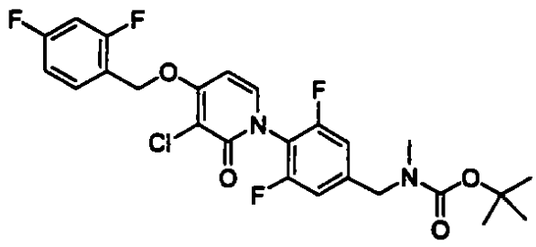
(400 MHz, DMSO-$d_6$) δ -109 21 (quintet, $J$ = 7 77 Hz, 1F), -113 51(quartet, $J$ = 8 95 Hz, 1F), -119 56 (d, $J$ = 9 44 Hz, 2F) LC/MS $t_r$ = 4 33 minutes (0-95% acetonitrile/water, 0 05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C) ES-MS $m/z$ 413 (M+H) ES-HRMS $m/z$ 413 0712 (M+H calcd for $C_{19}H_{14}ClF_4N_2O_2$ requires 413 0674)

Example 345



3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{2,6-difluoro-4-[(methylamino)methyl]phenyl}pyridin-2(1H)-one hydrochloride

Step 1 Preparation of tert-butyl 4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzyl(methyl)carbamate

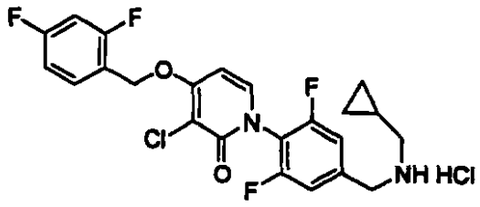


tert-butyl 4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzylcarbamate ( from Step 1) (252 mg, 0 491 mmol) and iodomethane (75 mg, 0 528 mmol) are combined in 8 ml anhydrous dimethylformamide Sodium hydride 60% in mineral oil (30 mg, 0 75 mmol) was added and

the mixture stirred under nitrogen at room temperaure for 1 hour Saturated aqueous $NH_4Cl$ was added (4 ml) followed by 20 ml water and the product was extracted into ethyl acetate, washed with brine, dried over $MgSO_4$, filtered, and evaporated to give the product as a white powder (208 mg, 80%) $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 7 87 (d, $J$ = 7 85 Hz, 1H), 7 64 (quartet, $J$ = 6 66 Hz, 1H), 7 32, (dt, $J$ = 9 39, 3 29 Hz, 1H), 7 13 (m, 3H), 6 77 (d, $J$ = 7 94 Hz, 1), 5 38 (s, 2H), 4 43 (s, 2H), 2 90 (s, 3H), 1 40 (br m, 9H) $^{19}$F-NMR (400 MHz, DMSO-$d_6$) δ -109 25 (quintet, $J$ = 8 93 Hz, 1F), -113 53 (quartet, $J$ = 9 73 Hz, 1F), -119 89(d, $J$ = 9 35 Hz, 2F) LC/MS $t_r$ = 6 16 minutes (0-95% acetonitrile/water, 0 05% trifluoroacetic acid, over 6 minutes, then 95% acetonitrile for 2 minutes, at 1 ml/min with detection at 215 nm, at 50°C) ES-MS $m/z$ 527 (M+H) ES-HRMS $m/z$ 527 1338 (M+H calcd for $C_{25}H_{24}ClF_4N_2O_4$ requires 527 1355)

Step 2 Preparation of the title compound tert-butyl 4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzyl(methyl)carbamate ( from step 1) (188 mg, 0 357 mmol) was subjected to the conditions of Step 2, yielding a fine white solid (165 mg, 100%) $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 9 30 (br s, 2H), 7 89 (d, $J$ = 7 99 Hz, 1H), 7 65 (quartet, $J$ = 7 64, 1H), 7 55 (d, $J$ = 8 66 Hz, 2H), 7 34 (dt, $J$ = 9 93, 2 57 Hz, 1H), 7 17 (dt, $J$ = 8 49, 2 48 Hz, 1H), 6 81 (d, $J$ = 8 01 Hz, 1H), 5 39 (s, 2H), 4 21 (s, 2H), 2 56 (s, 3H) $^{19}$F-NMR (400 MHz, DMSO-$d_6$) δ -109 20 (quintet, $J$ = 7 56 Hz 1F), -113 52(quartet, $J$ = 9 67 Hz, 1F), -119 21 (d, $J$ = 8 79 Hz, 2F) LC/MS $t_r$ = 4 30 minutes (0-95% acetonitrile/water, 0 05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C) ES-MS $m/z$ 427 (M+H) ES-HRMS $m/z$ 427 0816 (M+H calcd for $C_{20}H_{16}ClF_4N_2O_2$ requires 427 0831)

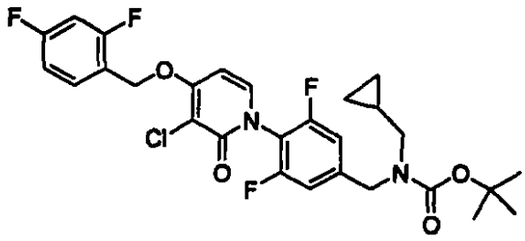
Example 346



3-chloro-1-(4-{[(cyclopropylmethyl)amino]methyl}-2,6-difluorophenyl)-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1H)-one hydrochloride

The title compound was prepared by direct analogy with , replacing iodomethane with bromocyclopropylmethane and extending the reaction time to 6 hours in Step 1

Step 1



1 tert-butyl 4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzyl(cyclopropylmethyl)carbamate

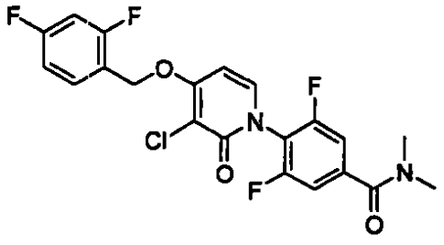
$^1$H-NMR (400 MHz, DMSO-$d_6$) δ 7 89 (d, $J$ = 7 91 Hz, 1H), 7 65 (quartet, $J$ = 6 81 Hz, 1H), 7 33, (dt, $J$ = 9 90, 2 26 Hz, 1H), 7 17 (m, 3H), 6 77 (d, $J$ = 7 90 Hz, 1), 5 38 (s, 2H), 4 51 (s, 2H), 3 10 (br s, 2H), 1 36 (m, 9H), 0 97 (br s, 1H), 0 38 (m, 2H), 0 18 (m, 2H) $^{19}$F-NMR (400 MHz, DMSO-$d_6$) δ -109 25

(quintet, $J$ = 7 77 Hz, 1F), -113 54 (quartet, $J$ = 9 02 Hz, 1F), -120 24(m, 2F) LC/MS $t_r$ = 5 99 minutes (0-95% acetonitrile/water, 0 05% trifluoroacetic acid, over 6 minutes, then 95% acetonitrile for 2 minutes, at 1 ml/min with detection at 215 nm, at 50°C) ES-MS $m/z$ 567 (M+H) ES-HRMS $m/z$ 567 1653 (M+H calcd for $C_{28}H_{28}ClF_4N_2O_4$ requires 567 1668)

Step 2 Title compound

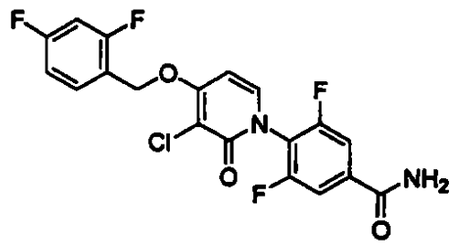
$^1$H-NMR (400 MHz, DMSO-$d_6$) δ 9 51 (br s, 2H), 7 87 (d, $J$ = 7 96 Hz, 1H), 7 63 (m, 3H), 7 33 (dt, $J$ = 9 93, 2 65 Hz, 1H), 7 16 (dt, $J$ = 8 36, 2 32 Hz, 1H), 6 81 (d, $J$ = 7 92 Hz, 1H), 5 38 (s, 2H), 4 22 (br s, 2H), 2 82 (br s, 2H), 1 10 (m, 1H), 0 57 (m, 2H), 0 36 (m, 2H) $^{19}$F-NMR (400 MHz, DMSO-$d_6$) δ -109 25 (quintet, $J$ = 7 69 Hz, 1F), -113 54(quartet, $J$ = 9 35 Hz, 1F), -120 24 (m, 2F) LC/MS $t_r$ = 4 55 minutes (0-95% acetonitrile/water, 0 05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C) ES-MS $m/z$ 467 (M+H) ES-HRMS $m/z$ 467 1119 (M+H calcd for $C_{23}H_{20}ClF_4N_2O_2$ requires 467 1144)

Example 347



4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluoro-*N*,*N*-dimethylbenzamide

Step 1 Preparation of 4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzamide



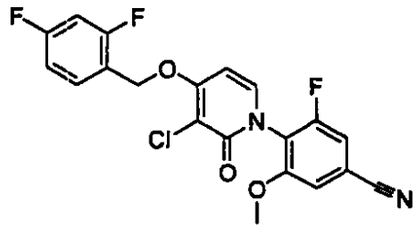
4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzonitrile (540 mg, 1 32 mmol) and potassium trimethylsilonate 90% (375 mg, 2 63 mmol) are combined in 8 ml anhydrous toluene and heated to reflux with stirring After 10 minutes, the mixture allowed to cool then partitioned between saturated aqueous ammonium chloride and ethyl acetate The aqueous layer is extracted twice with ethyl acetate, the combined organics are washed with brine, dried over $MgSO_4$, and evaporated *in vacuo* The crude product is taken up in tetrahydrofuran and filtered through charcoal layered over silica gel, and the solution evaporated *in vacuo* to give the product as a white powder (468 mg, 83%) $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 8 22 (br s, 2H), 7 92 (d, $J$ = 7 84 Hz, 1H), 7 78 (d, $J$ = 8 45, 2H), 7 65 (quartet, $J$ = 8 40 Hz, 1H), 7 34, (dt, $J$ = 10 09, 2 58 Hz, 1H), 7 17 (dt, $J$ = 8 72, 2 30 Hz, 1H), 6 83 (d, $J$ = 7 91 Hz, 1H), 5 39 (s, 2H) $^{19}$F-NMR (400 MHz, DMSO-$d_6$) δ -109 21 (quintet, $J$ = 7 43 Hz, 1F), -113 52 (quartet, $J$ = 9 62 Hz, 1F), -118 74 (d, $J$ = 8 88 Hz, 2F) LC/MS $t_r$ = 4 67 minutes (0-95% acetonitrile/water, 0 05% trifluoroacetic acid, over 6 minutes, then 95% acetonitrile for 2 minutes, at 1 ml/min with detection at 215 nm, at 50°C)

ES-MS *m/z* 427 (M+H) ES-HRMS *m/z* 427 0454 (M+H calcd for $C_{19}H_{12}ClF_4N_2O_3$ requires 427 0467)

Step 2 Preparation of the title compound

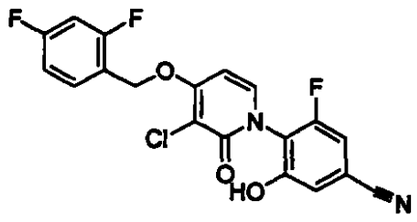
4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzamide ( from step 1) (243 mg, 0 357 mmol) was subjected to the conditions of Step 1, with the exception that two equivalents of sodium hydride 60% in mineral oil and iodomethane were used instead of one (46 mg, 0 69 mmol and 103 mg, 0 724 mmol respectively) $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 7 92 (d, *J* = 7 76 Hz, 1H), 7 66 (quartet, *J* = 7 33, 1H), 7 44 (d, *J* = 7 59 Hz, 2H), 7 34 (dt, *J* = 9 88, 2 63 Hz, 1H), 7 17 (dt, *J* = 8 35, 2 06 Hz, 1H), 6 83 (d, *J* = 7 55 Hz, 1H), 5 39 (s, 2H), 2 98 (s, 3H), 2 91 (s, 3H) $^{19}$F-NMR (400 MHz, DMSO-$d_6$) δ -109 22 (quintet, *J* = 8 10 Hz, 1F), -113 53(quartet, *J* = 9 18 Hz, 1F), -118 88 (d, *J* = 7 77 Hz, 2F) LC/MS $t_r$ = 5 13 minutes (0-95% acetonitrile/water, 0 05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C) ES-MS *m/z* 455 (M+H) ES-HRMS *m/z* 455 0791 (M+H calcd for $C_{21}H_{16}ClF_4N_2O_3$ requires 455 0780)

Example 348




4-[3-chloro-4-[(2,4-d_fluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3-fluoro-5-methoxybenzonitrile

Step 1 Preparation of 4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3-fluoro-5-hydroxybenzonitrile



4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzonitrile (522 mg, 1 28 mmol) and potassium trimethylsilonate 90% (655 mg, 4 60 mmol) are combined in 8 ml anhydrous tetrahydrofuran and stirred under nitrogen at room temperature for 2 hours The precipitated potassium salt of was collected by filtration, washed with a minimum of tetrahydofuran, and dried *in vacuo* A portion of this salt (275 mg, 0 618 mmol) was dissolved in 5 ml water, the pH was adjusted below 6 with concentrated hydrochloric acid, the product collected by filtration, washed with water, sucked dry under a blanket of dry nitrogen, and dried further *in vacuo* overnight (251 mg, 100%, 98% overall) $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 11 46 (br s, 1H), 7 74 (d, $J$ = 7 81 Hz, 1H), 7 67 (quartet, $J$ = 6 76 Hz, 1H), 7 52 (d, $J$ = 8 76, 1H), 7 364, (dt, $J$ = 10 18, 2 37 Hz, 1H), 7 24 (br s, 1H), 7 17 (br t, $J$ = 8 75, 1H), 6 74 (d, $J$ = 8 04 Hz, 1H), 5 39 (s, 2H) $^{19}$F-NMR (400 MHz, DMSO-$d_6$) δ -109 26 (quintet, $J$ = 8 50 Hz, 1F), -113 52 (quartet, $J$ = 9 29 Hz, 1F), -118 06 (d, $J$ = 9 38 Hz, 1F) LC/MS $t_r$ = 5 13 minutes (0-95% acetonitrile/water, 0 05% trifluoroacetic acid, over 6 minutes, then 95% acetonitrile for 2 minutes, at 1 ml/min with detection at 215 nm, at 50°C)

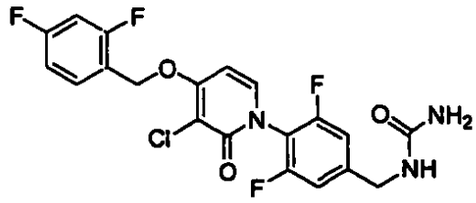
260
258

ES-MS *m/z* 407 (M+H) ES-HRMS *m/z* 407 0381 (M+H calcd for $C_{19}H_{11}ClF_3N_2O_3$ requires 407 0405)

Step 2 Preparation of the title compound

The potassium salt of 4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3-fluoro-5-hydroxybenzonitrile ( from Step 1) (273 mg, 0 614 mmol) was stirred in 5 ml anhydrous dimethylformamide under nitrogen Iodomethane (93 mg, 0 66 mmol) was added, and stirring continued for 2 hr The mixture was diluted to 50 ml with ice-cold water, and the white precipitate collected by filtration The precipitate was washed thrice with water, sucked dry under a blanket of nitrogen, and dried further *in vacuo* overnight (242 mg, 87%) $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 7 73 (m, 2H), 7 65 (m, 2H), 7 34 (dt, *J* = 9 90, 2 39 Hz, 1H), 7 17 (dt, *J* = 8 75, 2 47 Hz, 1H), 6 75 (d, *J* = 7 97 Hz, 1H), 5 37 (s, 2H), 3 84 (s, 3H) $^{19}$F-NMR (400 MHz, DMSO-$d_6$) δ -109 24 (quintet, *J* = 7 85 Hz, 1F), -113 54(quartet, *J* = 9 83 Hz, 1F), -118 33 (d, *J* = 7 77 Hz, 1F) LC/MS $t_r$ = 5 40 minutes (0-95% acetonitrile/water, 0 05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C) ES-MS *m/z* 421 (M+H) ES-HRMS *m/z* 421 0522 (M+H calcd for $C_{20}H_{13}ClF_3N_2O_3$ requires 421 0561)

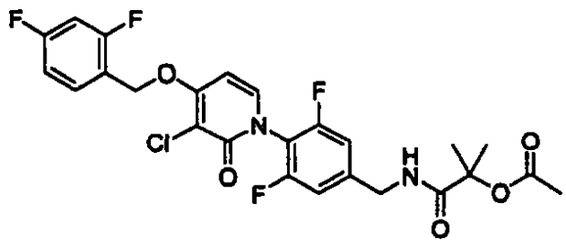
Example 349



*N*-{4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzyl}urea

Step 1 Preparation of the title compound 1-[4-(aminomethyl)-2,6-difluorophenyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1H)-one hydrochloride (162 mg, 0 361 mmol) is dissolved in 4 ml 50% aqueous acetic acid and treated with potassium cyanate (59 mg, 0 72 mmol) The mixture was stirred 2 hr, then the mixture was diluted to 50 ml with cold water, and the crude product, contaminated with the acetamide, was purified by silica gel chromatography, eluting first with 20% ethanol in hexane then 40% ethanol in hexane The 50% fractions were pooled by TLC and evaporated, giving the product as a fine white powder (65 mg, 40%) $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 7 87 (d, $J$ = 8 07 Hz, 1H), 7 64 (quartet, $J$ = 6 53 Hz, 1H), 7 33, (dt, $J$ = 9 47, 1 99 Hz, 1H), 7 15 (m, 3H), 6 76 (d, $J$ = 7 97 Hz, 1H), 6 59 (m, 1H), 5 65 (br s, 2H), 5 38 (s, 2H), 4 22 (m, 2H) $^{19}$F-NMR (400 MHz, DMSO-$d_6$) δ -109 22 (quintet, $J$ = 7 86 Hz, 1F), -113 51 (quartet, $J$ = 9 40 1F), -120 65 (d, $J$ = 8 75 Hz, 2) LC/MS $t_r$ = 4 85 minutes (0-95% acetonitrile/water, 0 05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C) ES-MS $m/z$ 456 (M+H)

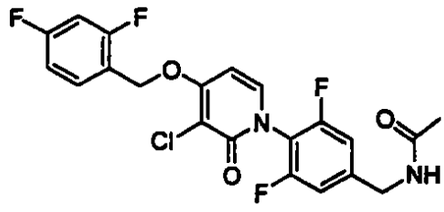
Example 350



2-({4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzyl}amino)-1,1-dimethyl-2-oxoethyl acetate

Step 1 Preparation of the title compound 1-[4-(aminomethyl)-2,6 difluorophenyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1H)-one hydrochloride (225 mg, 0 501 mmol) is dissolved in a solution of 10 ml tetrahydrofuran and triethylamine (111 mg, 1 10 mmol) 2-acetoxy-2-methyl-propionyl chloride (85 mg, 0 516 mmol) is added, and the mixture stirred for 30 minutes before partitioning between saturated aqueous ammonium chloride and ethyl acetate The layers are seperated, and the aqueous phase extracted twice with ethyl acetate The combined organics are washed with water and brine, then dried over $MgSO_4$, filtered, and evaporated in vacuo, giving the product as a fine white powder (254 mg, 94%) $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 8 47 (t, $J$ = 6 16 Hz, 1H), 7 88 (d, $J$ = 7 71 Hz, 1H), 7 65 (quartet, $J$ = 7 24 Hz, 1H), 7 34, (dt, $J$ = 10 04, 2 49 Hz, 1H), 7 16 (m, 3H), 6 77 (d, $J$ = 7 78 Hz, 1H), 5 38 (s, 2H), 4 32 (d, $J$ = 5 93 2H), 2 02 (s, 3H), 1 48(s, 6H) $^{19}$F-NMR (400 MHz, DMSO-$d_6$) δ -109 26 (quintet, $J$ = 9 00 Hz, 1F), -113 52 (quartet, $J$ = 9 52 Hz, 1F), -120 62 (d, $J$ = 9 09 Hz, 2F) LC/MS $t_r$ = 5 43 minutes (0-95% acetonitrile/water, 0 05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C) ES-MS $m/z$ 541 (M+H) ES-HRMS $m/z$ 541 1128 (M+H calcd for $C_{25}H_{22}ClF_4N_2O_5$ requires 541 1148)

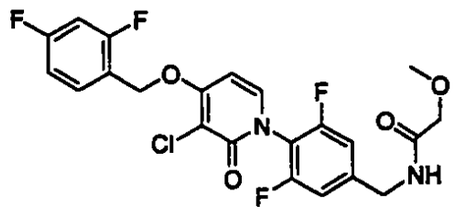
Example 351



*N*-{4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]-3,5-difluorobenzyl}acetamide

The compound was prepared in the following the produre for Example 350, substituting acetyl chloride (24 mg, 0 30 mmol) for 2-acetoxy-2-methyl-propionyl chloride (128 mg, 96%) $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 8 48 ( br s, 1H), 7 87 (d, $J$ = 7 28 Hz, 1H), 7 64 (quartet, $J$ = 8 01 Hz, 1H), 7 33, (dt, $J$ = 9 87, 2 25 Hz, 1H), 7 17 (m, 3H), 6 76 (d, $J$ = 8 25 Hz, 1H), 5 38 (s, 2H), 4 30 (m, 2H), 1 88(s, 3H) $^{19}$F-NMR (400 MHz, DMSO-$d_6$) δ -109 22 (quintet, $J$ = 8 04 Hz, 1F), -113 52 (quartet, $J$ = 9 91 Hz, 1F), -120 43 (d, $J$ = 8 77 Hz, 2F) LC/MS $t_r$ = 5 04 minutes (0-95% acetonitrile/water, 0 05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C) ES-MS $m/z$ 555 (M+H) ES-HRMS $m/z$ 455 0824 (M+H calcd for $C_{21}H_{16}ClF_4N_2O_3$ requires 455 0780)

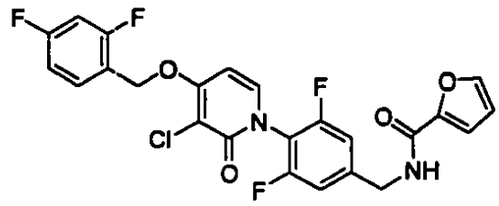
Example 352



*N*-{4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzyl}-2-methoxyacetamide

The compound was prepared in the following the produre for EXAMPLE 350, substituting 2-methoxy-acetyl chloride (45 mg, 0 415 mmol) for 2-acetoxy-2-metnyl-propionyl chloride (124 mg, 78%) $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 8 56 (t, $J$ = 6 77 Hz, 1H), 7 90 (d, $J$ = 7 85 Hz, 1H), 7 67 (quartet, $J$ = 7 67 Hz, 1H), 7 36, (dt, $J$ = 10 03, 2 36 Hz, 1H), 7 20 (m, 3H), 6 79 (d, $J$ = 8 07 Hz, 1H), 5 40 (s, 2H), 4 37 (d, $J$ = 6 28 Hz, 2H), 3 91(s, 2H), 3 35 (s, 3 H) $^{19}$F-NMR (400 MHz, DMSO-$d_6$) δ -109 23 (quintet, $J$ = 8 29 Hz, 1F), -113 50 (quartet, $J$ = 9 36 Hz, 1F), -120 43 (d, $J$ = 9 07 Hz, 2F) LC/MS $t_r$ = 5 13 minutes (0-95% acetonitrile/water, 0 05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C) ES-MS $m/z$ 485 (M+H) ES-HRMS $m/z$ 485 0856 (M+H calcd for $C_{22}H_{18}ClF_4N_2O_4$ requires 485 0886)

Example 353

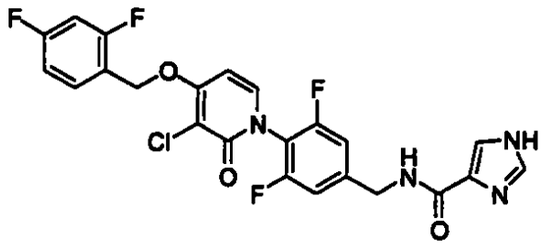



*N*-{4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzyl}-2-furamide

The compound was prepared in the following the produre for EXAMPLE 350, substituting furoyl chloride (62 mg, 0 48 mmol) for 2-acetoxy-2-methyl-propionyl chloride Yield 142 mg, 85% $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 9 07 (t, $J$ = 6 14 Hz, 1H), 7 90 (d, $J$ = 7 88 Hz, 1H), 7 87 (dd, $J$ = 1 69, 0 80 Hz, 1H), 7 67 (td, $J$ = 8.46, 6.80 Hz, 1H), 7 35, (dt, $J$ = 10 00, 2.81 Hz, 1H), 7 26 (d, $J$ = 8.78 Hz, 2H), 7 18 (ddt, $J$ = 8.58, 2 30, 1 07 Hz,

1H), 7 16 (dd, $J$ = 3 52, 0 77 Hz, 1H), 6 79 (d, $J$ = 8 07 Hz, 1H), 6 64 (dd, $J$ = 3 16, 1 73 Hz, 1H), 5 40 (s, 2H), 4 49 (d, $J$ = 6 13 Hz, 2H) $^{19}$F-NMR (400 MHz, DMSO-$d_6$) δ -109 23 (quintet, $J$ = 7 65 Hz, 1F), -113 50 (quartet, $J$ = 9 84 Hz, 1F), -120 29 (d, $J$ = 9 41 Hz, 2F) LC/MS $t_r$ = 5 32 minutes (0-95% acetonitrile/water, 0 05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C) ES-MS $m/z$ 507 (M+H) ES-HRMS $m/z$ 507 0716 (M+H calcd for $C_{24}H_{16}ClF_4N_2O_4$ requires 507 0729)

Example 354

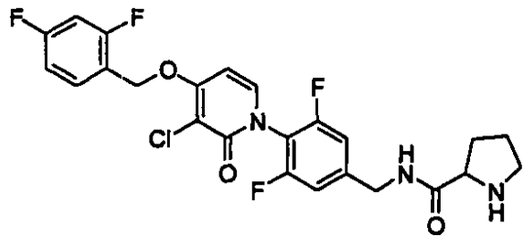


*N*-{4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzyl}-1H-imidazole-4-carboxamide

Step 1 Preparation of the title compound 1-[4-(aminomethyl)-2,6-difluorophenyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1H)-one hydrochloride (150 mg, 0 334 mmol) is dissolved in a solution of 4 ml tetrahydrofuran and triethylamine (35 mg, 0 35 mmol) 4-imidazolecarboxylic acid (62 mg, 0 56 mmol), 1-hydroxybenzotriazole hydrate (90 mg, 0 67 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (128 mg, 0 668 mmol), and triethylamine (100 mg, 0 989 mmol) were combined in 5 ml tetrahydrofuran and stirred under nitrogen The solution containing 1-[4-(aminomethyl)-2,6-difluorophenyl]-3-chloro-4-

[(2,4-difluorobenzyl)oxy]pyridin-2(1H)-one hydrochloride was added in one portion, rinsing with 2 ml tetrahydrofuran Stirring was continued at room temperature overnight, then the reaction was poured into 90 ml of icewater, and the product collected by filtration and dried *in vacuo* (254 mg, 94%) $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 12 55 (br s, 1H), 8 73 (t, $J$ = 6 57 Hz, 1H), 7 90 (d, $J$ = 7 87 Hz, 1H), 7 75 (s, 1H), 7 67 (m, 2H), 7 35, (dt, $J$ = 10 04, 2 54 Hz, 1H), 7 21 (m, 3H), 6 78 (d, $J$ = 8 04 Hz, 1H), 5 39 (s, 2H), 4 47 (m, 2H) $^{19}$F-NMR (400 MHz, DMSO-$d_6$) δ -109 26 (quintet, $J$ = 7 87 Hz, 1F), -113 52 (quartet, $J$ = 9 30 Hz, 1F), -120 59 (d, $J$ = 9 21 Hz, 2F) LC/MS $t_r$ = 4 48 minutes (0-95% acetonitrile/water, 0 05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C) ES-MS $m/z$ 507 (M+H) ES-HRMS $m/z$ 507 0818 (M+H calcd for $C_{23}H_{16}ClF_4N_4O_3$ requires 507 0842)

Example 355

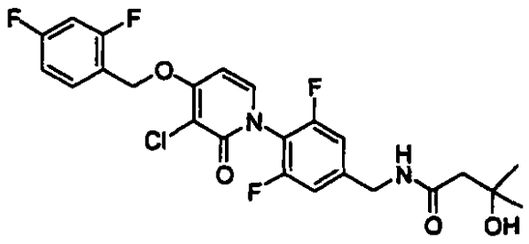


*N*-{4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzyl}-5-oxoprolinamide

Step 1 Preparation of the title compound
The compound was prepared following the procedure for Example 354, substituting 2-pyrrolidone-5-carboxylic acid for 4-imidazolecarboxylic acid $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 8 67 (t,

$J$ = 6 08 Hz, 1H), 7 88 (m, 1H), 7 65 (qr, $J$ = 7 57, 1H), 7 34, (dt, $J$ = 9 32, 2 63 Hz, 1H), 7 22 (d, $J$ = 9 36, 2H), 7 17 (dt, $J$ = 8 51, 2 55 Hz, 1H), 6 77 (d, $J$ = 7 66 Hz, 1H), 5 73 (s, 1H), 5 38 (s, 2H), 4 35 (d, $J$ = 5 74, 2H), 4 05 (m, 1H), 2 15 (m, 2H), 1 90 (m, 2H) $^{19}$F-NMR (400 MHz, DMSO-$d_6$) δ -109 25 (quintet, $J$ = 7 72 Hz, 1F), -113 52 (quartet, $J$ = 8 94 Hz, 1F), -120 39 (d, $J$ = 9 11 Hz, 2F) LC/MS $t_r$ = 4 81 minutes (0-95% acetonitrile/water, 0 05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C) ES-MS $m/z$ 524 (M+H) ES-HRMS $m/z$ 524 0998 (M+H calcd for $C_{24}H_{19}ClF_4N_3O_4$ requires 524 0995)

Example 356

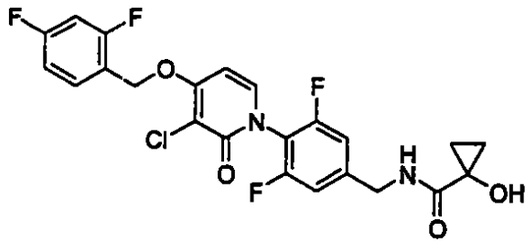


*N*-{4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzyl}-3-hydroxy-3-methylbutanamide

Step 1 Preparation of the title compound
The compound was prepared following the procedure for , substituting 2-hydroxy-2-methyl butyric acid for 4-imidazolecarboxylic acid $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 8 43 (t, $J$ = 6 04 Hz, 1H), 7 88 (d, $J$ = 8 01, 1H), 7 65 (qr, $J$ = 6 84, 1H), 7 34, (dt, $J$ = 10 13, 2 55 Hz, 1H), 7 22 (d, $J$ = 8 74, 2H), 7 16 (dt, $J$ = 8 57, 2 45 Hz, 1H), 6 77 (d, $J$ = 7 89 Hz, 1H), 5 38 (s, 2H), 4 75 (s, 0 5H (OH)), 4 35 (d, $J$ = 6 48,

2H), 2 28 (s, 2H), 1 47 (s, 0 5H(OH)), 1 16 (s, 6H) $^{19}$F-NMR (400 MHz, DMSO-$d_6$) δ -109 26 (quintet, $J$ = 7 79 Hz, 1F), -113 53 (quartet, $J$ = 9 23 Hz, 1F), -120 49 (d, $J$ = 9 39 Hz, 2F) LC/MS $t_r$ = 5 08 minutes (0-95% acetonitrile/water, 0 05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C) ES-MS $m/z$ 513 (M+H) ES-HRMS $m/z$ 513 1177 (M+H calcc for $C_{24}H_{22}ClF_4N_2O_4$ requires 513 1199)

Example 357

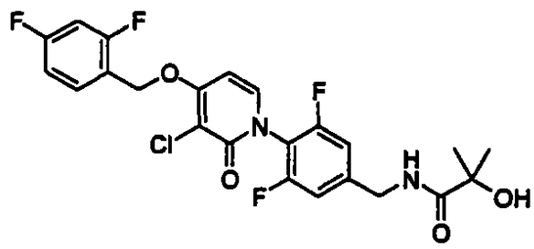


*N*-{4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzyl}-1-hydroxycyclopropanecarboxamide

Step 1 Preparation of the title compound
The compound was prepared following the procedure for , substituting 1-hydroxy-1-cyclopropanecarboxylic acid for 4-imidazolecarboxylic acid $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 8 70 (t, $J$ = 6 26 Hz, 1H), 7 89 (d, $J$ = 6 31, 1H), 7 65 (qr, $J$ = 6 83, 1H), 7 34 (t, $J$ = 10 58 Hz, 1H), 7 19 (m, 3H), 6 77 (d, $J$ = 7 70 Hz, 1H), 5 38 (s, 2H), 4 35 (d, $J$ = 5 66, 2H), 1 14 (s, 1H), 1 02 (m, 2H), 0 84 'm, 2H) $^{19}$F-NMR (400 MHz, DMSO-$d_6$) δ -109 25 (quintet, $J$ = 8 05 Hz, 1F), -113 53 (quartet, $J$ = 8 27 Hz, 1F), -120 59 (d, $J$ = 8 99 Hz, 2F) LC/MS $t_r$ = 5 01 minutes (0-95% acetonitrile/water, 0 05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C)

ES-MS *m/z* 497 (M+H) ES-HRMS *m/z* 497 0873 (M+H calcd for $C_{23}H_{18}ClF_4N_2O_4$ requires 497 0886)

Example 358



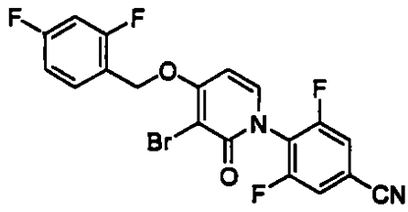
*N*-{4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzyl}-2-hydroxy-2-methylpropanamide

Step 1 Preparation of the title compound
The compound was prepared following the procedure for , substituting 2-hydroxyisobutyric acid for 4-imidazolecarboxylic acid $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 8 48 (t, *J* = 6 41 Hz, 1H), 7 89 (d, *J* = 7 78, 1H), 7 65 (qr, *J* = 9 10, 1H), 7 33 (dt, *J* = 10 12, 2 41 Hz, 1H), 7 17 (m, 3H), 6 77 (d, *J* = 7 69 Hz, 1H), 5 38 (s, 2H), 4 31 (d, *J* = 6 50, 2H), 1 41 (s, 1H), 1 33 (s, 6H) $^{19}$F-NMR (400 MHz, DMSO-$d_6$) δ -109 25 (quintet, *J* = 7 49 Hz, 1F), -113 53 (quartet, *J* = 9 64 Hz, 1F), -120 59 (d, *J* = 8 68 Hz, 2F) LC/MS $t_r$ = 5 05 minutes (0-95% acetonitrile/water, 0 05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C) ES-MS *m/z* 499 (M+H) ES-HRMS *m/z* 499 1020 (M+H calcd for $C_{23}H_{20}ClF_4N_2O_4$ requires 499 1042)

Example 359

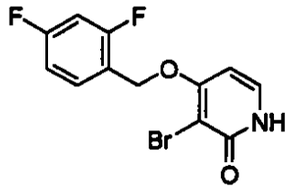
265

263



4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzonitrile

Step 1 Preparation of 3-bromo-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1H)-one



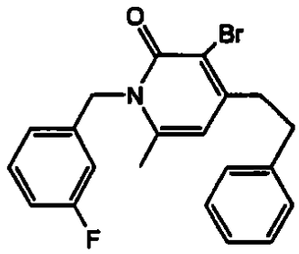
The compound was prepared in the following the produre for 3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1H)-one (, Step 3), substituting *N*-bromosuccinimide for *N*-chlorosuccinimide $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 11 85 (br s, 1H), 7 61 (m, 1H), 7 46 (d, $J$ = 7 36 Hz, 1H), 7 30, (m, 1H), 7 14 (m, 1H), 6 40 (d, $J$ = 7 71 Hz, 1H), 5 26 (s, 2H) $^{19}$F-NMR (400 MHz, DMSO-$d_6$) δ -109 69 (quintet, $J$ = 7 93 Hz, 1F), -113 63 (quartet, $J$ = 9 55 Hz, 1F) LC/MS $t_r$ = 4 48 minutes (0-95% acetonitrile/water, 0 05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C) ES-MS $m/z$ 316 (M+H)

Step 2 Preparation of the title compound

The compound was prepared following the procedure for 4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzonitrile (, Step 4), substituting 3-bromo-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1H)-one ( from step 1) (1 92 g,

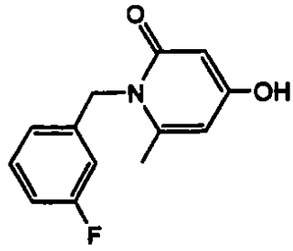
6 06 mmol) for 3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1H)-one (, from Step 3) $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 8 13 ( d, $J$ = 7 24 Hz, 2H), 7 95 (d, $J$ = 7 76 Hz, 1H), 7 66 (quartet, $J$ = 8 71 Hz, 1H), 7 34, (dt, $J$ = 9 94, 2 53 Hz, 1H), 7 17 (dt, $J$ = 8 64, 2 33 Hz, 1H), 6 82 (d, $J$ = 7 77 Hz, 1H), 5 39 (s, 2H) $^{19}$F-NMR (400 MHz, DMSO-$d_6$) δ -109 28 (quintet, $J$ = 7 98 Hz, 1F), -113 45 (quartet, $J$ = 9 29 Hz, 1F), -116 30 (d, $J$ = 7 44 Hz, 2F) LC/MS $t_r$ = 5 48 minutes (0-95% acetonitrile/water, 0 05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C) ES-MS $m/z$ 453 (M+H) ES-HRMS $m/z$ 452 9836 (M+H calcd for $C_{19}H_{10}BrF_4N_2O_2$ requires 452 9856)

Example 360



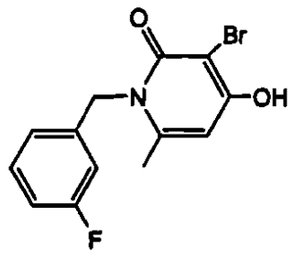

3-Bromo-1-(3-fluorobenzyl)-6-methyl-4-(2-phenylethyl)pyridin-2(1H)-one

Step 1 Preparation of 1-(3-fluorobenzyl)-4-hydroxy-6-methylpyridin-2(1H)-one



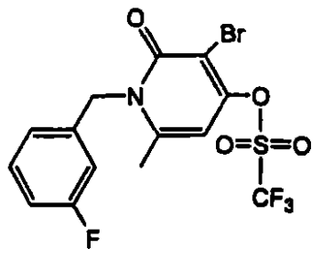
A mixture of 4-hydroxy-6-methyl-2-pyrone (2 5 g, 0 02 mol) and 3-fluorobenzylamire (2 5 g, 0 02 mol) in n-butanol (15 0 mL) was heated to reflux for 16 h under argon atmosphere Butanol wad distilled in vacuo, the residue was triturated with EtOAc, cooled and filterd the precipitate It was washed with cold EtOAc, and dried to give 0 86 g of the title compound as a pale yellow powder 1H- NMR (CD3OD/400 MHz) δ 7 31 (m, 1H), 7 0 - 6 85 (m, 2H), 6 83 (d, 1H, J = 9 6 Hz), 5 96 (d, 1H, J = 2 0 Hz), 5 80 (d, 1H, J = 2 0 Hz), 5 30 (s, 2H), and 2,24 (s, 3H), ESMS m/z = 234 ( MH+)

Step 2 Preparation of 3-bromo-1-(3-fluorobenzyl)-4-hydroxy-6-methylpyridin-2(1H)-cne



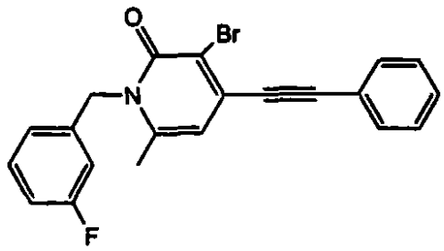

A mixture of 1-(3-fluorobenzyl)-4-hydroxy-6-methylpyridin-2(1H)-one ( 0 8 g, 0 0034 mol), NBS (0 64 g, 0 0036 mol) in dichloromethane (15 0 mL) was stirred at room temperature, under argon atmosphere After 1 5 h, the reaction mixture was diluted with dichloromethane (15 0 mL), cooled and filterd the solids The residue was washed with dichloromethane and dried in vacuo to give 0 93 g of the title compound as a white powder 1H- NMR (CD3OD/400 MHz) δ 7 33 (m, 1H), 7 2 - 6 8 (m, 3H), 6 07 (s, 1H), 5 34 (s, 2H), 2 26 (s, 3H), ESHRMS m/z 312 0016 (M+H C13H12NO2BrF requires 312 0035)

Step 3 Preparation of 3-bromo-1-(3-fluorobenzyl)-6-methyl-2-oxo-1,2-dihydropyridin-4 yl trifluoromethanesulfonate



To a suspension of 3-bromo-1-(3-fluorobenzyl)-4-hydroxy-6-methylpyridin-2(1H)-one (0 86 g, 0 0028 mol) in dichloromethane (15 0 mL) cooled to -30 °C, triethyl amine (0 5 mL, 0 004 mol) and trflic anhydride (0 7 mL, 0 0042 mol) were added and stirred for 1 h The resulting orange solution was poured into ice cold water (25 mL) and extracted with dichloromethane ( 2 x 25 mL) The combined organic extracts were washed with water, dried (Na2SO4) and concentrated under reduced pressure The resulting residue was purified by silica gel flash chromatography using 1 1 EtOAc/hexane v/v to afford 1 0 g (85%) the title compound as a light brown solid $^1$H- NMR (CDCl3/400 MHz) δ 7 32 (m,1H), 7 0 - 6 85 (m, 3H), 6 18 (s, 1H), 5 32 (s, 2H), and 2 34 (s, 3H), ESHRMS m/z 443 9492 (M+H C14H11NO4BrF4S requires 443 9528)

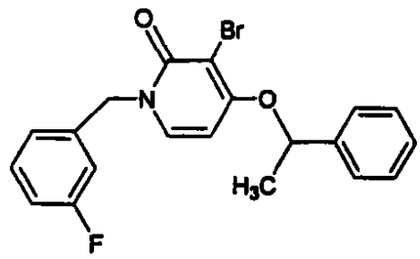
Step 4 Preparation of 3-bromo-1-(3-fluorobenzyl)-6-methyl-4-(phenylethynyl)pyridin-2(1H)-one



A solution of 3-bromo-1-(3-fluorobenzyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl trifluoromethanesulfonate (1 0 g, 0 0022 mol) and phenylacetylene (0 3 mL, 0 0029 mol) in DMF (5 0 mL) was degassed using house vacuum, and purged with argon (3 cycles)
Then added diisopropylethylamine, (0 5 mL) followed by the addition of PdCl2(PPh3)2 (0 36 g) The reaction mixture was heated at 65 °C for 1 5 h under argon atmosphere The solvents were distilled in vacuc, and the residue was purified by silica gel flash chromatography using EtOAc/hexane (2 3 v/v) to afford 0 65 g (70%) of the title compound as a brown colored amorphous solid $^1$H- NMR (CD3OD/400 MHz) δ 7 59 (m, 2H), 7 45 - 7 3 (m, 4H), 7 05 - 6 85 (m, 3H), 6 44 (s, 1H), 5 41 (s, 2H), and 2 31 (s, 3H), $^{19}$F-NMR (CD3OD/400 MHz) δ - 116 33 (m ), ESHRMS m/z 396 0373 (M+H C21H16NOBrF 396 0399)

Step 5 Preparation of 3-bromo-1-(3-fluorobenzyl)-6-methyl-4-(2-phenylethyl)pyridin-2(1H)-one
To a solution of 3-bromo-1-(3-fluorobenzyl)-6-methyl-4-(phenylethynyl)pyridin-2(1H)-one (0 55 g, 0 0014 mol) in EtOAc (10 0 mL) and EtOH (10 0 mL) was added PtO2 (0 05g) and stirred in an atmosphere of hydrogen gas at 15 psi for 30 min The catalyst was removed by filtration, the filtrate was concentrated and the residue was purified by silica gel flash chromatography using 25% EtOAc in hexane as the eluent
The appropriate fractions were combined (visualized under UV) and concentrated to dryness $^1$H- NMR (CD3OD/400 MHz) δ 7 35 (m, 1H), 7 31 - 7 16 (m, 5H), 6 99(m, 1H), 6 91 (m, 1H), 6 81 (m, 1H), 6 20 (s, 1H), 5 41 (s, 2H), 2 94 (m, 4H), and 2 24 (s, 3H), $^{19}$F-NMR (CD3OD/400 MHz) δ -115 01 (m ), ESHRMS m/z 400 0695 (M+H C21H20NOBrF 400 0712)

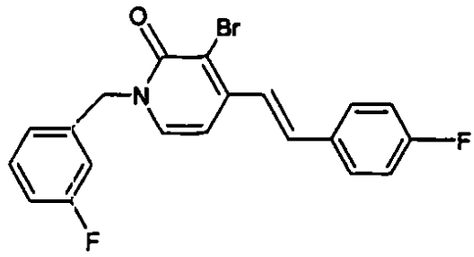
Example 361



3-bromo-1-(3-fluorobenzyl)-4-(1-phenylethoxy)pyridin-2(1H)-one

A mixture of 3-bromo-1-(3-fluorobenzyl)-4-hydroxypyridin-2(1H)-one (0 2 g, 0 72mmol), potassium carbonate (0 1 g, 0 72 mmol) and (1-bromoethyl)benzene (0 19 g, 1 mmol) in DMF (3 0 mL) was stirred at room temperature for 16 h DMF was distilled in vacuo, and the residue was purified by flash chromatography (EtOAc in hexane (1 3 v/v) to give pale yellow syrup This material was further purified by reverse-phase HPLC using 10 - 90% acetonitrile/water gradient (30 min), at flow rate of 100 mL/min The appropriate fractions were combined, concentrated to a small volume (20 mL), added EtOAc (25 mL) and washed successively with satd sod bicarbonate, water, and dried ($Na_2SO_4$) EtOAc was removed under reduced pressure and residue was dried in vacuo to afford the title compound (0 15 g, 52%) as an amorphous substance $^1H$ NMR ($CD_3OD$/ 400 MHz) δ 7 56 (d, 1H, J = 7 6 Hz), 7 4 - 7 2 (m, 5H), 7 0 (m, 3H), 6 28 (d, 1H, J = 7 6 Hz), 5 65 (m, 1H), 5 19 (d x d, 2H, J = 14 8 Hz), and 1 64 (d, 3H, J = 6 4 Hz), ES-HRMS m/z 402 0492(M+H $C_{20}H_{18}NO_2Br$, requires 402 0499)

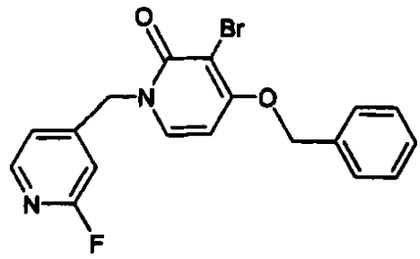
Example 362



3-bromo-1-(3-fluorobenzyl)-4-[(E)-2-(4-fluorophenyl)ethenyl]pyridin-2(1H)-one

A mixture of 3-bromo-1 (3-fluorobenzyl)-2-oxo-1,2-dihydropyridin-4-yl trifluoromethanesulfonate (1 0 g, 0 0023 mol), and 4-fluorostyrene (0 33 mL,, 0 0028 mol) in degassed DMF (10 0 ml) containing diisopropyl ethyl amine (0 37 g, 0 0029 mol) was treated with $PdCl_2(PPh_3)_2$ (0 32 g, 0 46 mmol) and heated at 65 °C under argon atmosphere for 16 h DMF was distilled in vacuo, and the residue was purified by flash chromatography (EtOAc/ hexane 1 4 v/v) to afford a yellow substance which was further purified by by reverse-phase HPLC using 10 - 90% acetonitrile/water gradient (30 min), at flow rate of 100 mL/min The appropriate fractions were combined, concentrated to a small volume (20 mL), added EtOAc (25 mL) and washed successively with satd sod bicarbonate, water, and dried ($Na_2SO_4$) EtOAc was removed under reduced pressure and residue was dried ir vacuo to afford the title compound (0 06 g, 6%) as yellow powder $^1H$ NMR ($CD_3OD$/ 400 MHz) δ 7 68 (m, 3H), 7 39 (m, 3H), 7 2 - 7 0 (m, 5H), 6 82 (d, 1H, J = 7 2 Hz), and 5 22 (s, 2H), $^{19}F$ NMR($CD_3OD$/ 400 MHz) δ -113 9(m) and -115 (m), ES-HRMS m/z 402 0305 ($M+HC_{20}H_{15}NOF_2Br$, requires 402 0300)

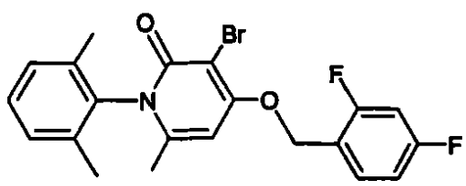
Example 363



4-(Benzyloxy)-3-bromo-1-[(6-fluoropyridin-3-yl)methyl]pyridin-2(1H)-one

A mixture of 4-(benzyloxy)-3-bromopyridin-2(1H)-one (0 2 g, 0 00076 mol), 5-bromomethyl-2-fluoropyridine (0 25 g, 0 0013 mol) and pot Carbonate (0 15 g, 0 0011 mol) in DMF (3 0 ml) was stirred at room temperature for 16 h under argon atmosphere DMF was distilled in vacuo and the residue was partitioned between water (15 ml) and EtOAc (25 mL) The organic phase was washed with water, dried ($Na_2SO_4$) and concentrated under reduced pressure $^1H$ NMR ($CD_3OD$/ 400 MHz) δ 8 22 (m, 1H, 2 4 Hz), 7 92(m, 1H), 7 82 (d, 1H, J = 7 6 Hz), 7 44 - 7 31 (m 5H), 7 03( m, 1H) 6 49 (d, 1H, J = 7 6 Hz),5 29 (s, 2H), and 5 20 (s, 2H), $^{19}F$ NMR($CD_3OD$/ 400 MHz) δ -72 30 (d, J = 6 0 Hz) and -115 (m), ES-HRMS m/z 389 0295 (M+H $C_{18}H_{15}N_2O_2FBr$, requires 389 0309)

Example 364

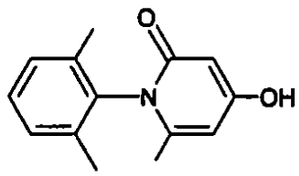


3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-dimethylphenyl)-6-methylpyridin-2(1H)-one

269
267

STEP1

Preparation of

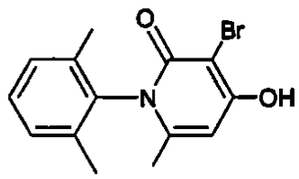


1-(2,6-dimethylphenyl)-4-hydroxy-6-methylpyridin-2(1H)-one

A mixture of 4-hydroxy-6-methyl-2-pyrone (2 5 g, 0 02 mol), 2,6 dimethylaniline (2 4 g, 0 02 mol), and p-toluenesulfonic acid (0 2 g) as heated at 140 °C for 3 h under nitrogen atmosphere The reaction mixture was cooled, triturated with acetonitrile , cooled and filtered the solids $^1$H NMR ($CD_3OD$/ 400 MHz) δ 7 22 (m, 3H ), 6 12 (d, 1H, J = 1 6 Hz), 5 83 (d, 1H, J = 1 8 Hz), 2 00 (s, 6H), and 1 82 (s, 3H), ESMS m/z 229 (M+H)

Step 2

Preparation of



3-Bromo-1-(2,6-dimethylphenyl)-4-hydroxy-6-methylpyridin-2(1H)-one

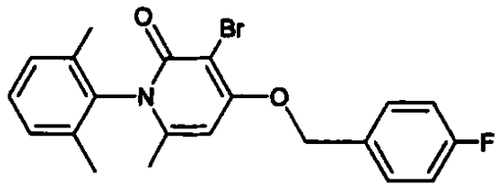
A mixture of 1-(2,6-dimethylphenyl)-4-hydroxy-6-methylpyridin-2(1H)-one (0 4 g, 0 00175 mol), and NBS (0 35 g, 0 0019 mol) in dichloromethane (10 0 ml) was stirred at room temperature under nitrogen atmosphere After 1 h, the

solids were filtered, washed with dicholoromethane to give 0 42 g (78%) of the title compd as a pale yellow powder $^1$H NMR ($CD_3OD$/ 400 MHz) δ 7 22 (m, 3H ), 6 21 (s, 1H), 1 99 (s, 6H), and 1 82 (s, 3H), ESMS m/z 308/310 (M+H)

Step 3

A mixture of 3-Bromo-1-(2,6-dimethylphenyl)-4-hydroxy-6-methylpyridin-2(1H)-one (0 15 g, 0 00049 mol), 2,4 difluorobenzyl bromide (0 12 g, 0 00058 mol) and potassium carbonate (0 075 g, 0 00054 mol) in DMF 3 00 mL) was stirred at room temperature uder argon atmosphere for 2h It was then heated at 60 °C for 30 min and concentrated in vacuo The residue was purified by flash chromatography $^1$H NMR ($CD_3OD$/ 400 MHz) δ 7 62 (m, 1H), 7 28 ( m,3H), 7 04 (m, 2H), 6 68 (s, 1H), 5 35 (m, 1H), 1 98 (s, 6H), and 1 92 (s, 3H), ES-HRMS m/z 434 0574 (M+H $C_{21}H_{19}NO_2F_2Br$, requires 434 0562)

Example 365

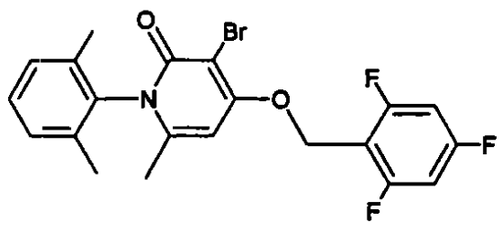



3-Bromo-1-(2,6-dimethylphenyl)-4-[(4-fluorobenzyl)oxy]-6-methylpyridin-2(1H)-one

The title compound was prepared by a procedure similar to the one described for Example 364 $^1$H NMR ($CD_3OD$/ 400 MHz) δ 7 58 (m, 2H), 7 23 (m, 3H), 7 15 (m, 2H), 6 62 (s, 1H), 5 32

(s, 2H), 1 98 (m, 6H), and 1 91 (s, 3H), ES-HRMS m/z 416 0670 (M+H $C_{21}H_{20}NO_2FBr$, requires 416 0656)

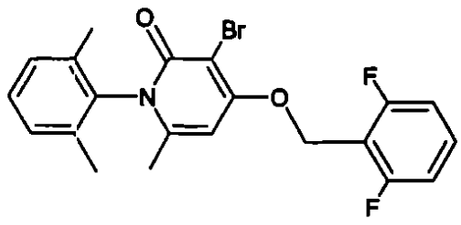
Example 366



3-Bromo-1-(2,6-dimethylphenyl)-6-methyl-4-[(2,4,6-trifluorobenzyl)oxy]pyridin-2(1H)-one

The title compound was prepared by a procedure similar to the one described for EXAMPLE 364 $^1$H NMR ($CD_3OD$/ 400 MHz) δ 7 19 (m, 3H), 6 95 (m, 2H), 6 69 (s, 1H), 5 29 (s, 2H), 1 95 (s, 6H), and1 90 (s, 3H), ES-HRMS m/z 452 0471 (M+H $C_{21}H_{18}NO_2F_3Br$, requires 452 0468)

Example 367

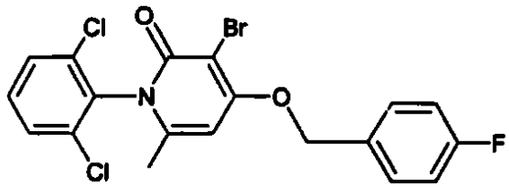


3-Bromo-4-[(2,6-difluorobenzyl)oxy]-1-(2,6-dimethylphenyl)-6-methylpyridin-2(1H)-one

The title compound was prepared by a procedure similar to the one described for EXAMPLE 364 $^1$H NMR ($CD_3OD$/ 400 MHz) δ

7 46 (m, 1H), 7 24 (m, 3H), 7 08 (m, 2H), 6 74 (s, 1H), 5 38 (s, 2H), 1 99 (s, 6H), and 1 94 (s, 3H), ES-HRMS m/z 434 0589 (M+H $C_{21}H_{19}NO_2F_2Br$, requires 434 0562)

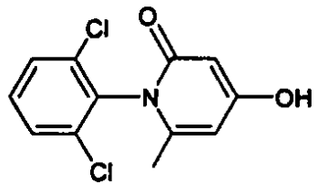
Example 368



3-Bromo-1-(2,6-dichlorophenyl)-4-[(4-fluorobenzyl)oxy]-6-methylpyridin-2(1H)-one

Step 1

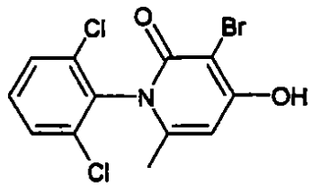
Preparation of 1-(2,6-dichlorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one



This compound was prepared by a procedure similar to the one described in step 1 for EXAMPLE 364 Yield 28%, $^1$H NMR (CD3OD) δ 7 6 (m, 2H), 7 48 (m, 1H), 6 10 (dd, 1H), 5 78 (d, 1H, J = 2 4 Hz), 1 91 (s, 3H), ( ES-MS m/z = 270 ($MH^+$ ),

Step 2

Preparation of 3-bromo-1-(2,6-dichlorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one

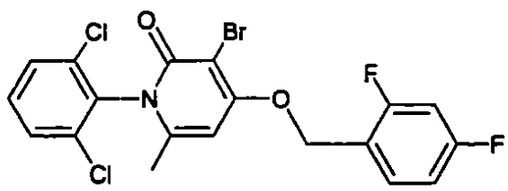


This compound was prepared by a procedure similar to the one described in step 2 for EXAMPLE 364 Yield 78%, $^1$H NMR (400 MHz) $CD_3OD$ δ 7 61 (m, 2H), 7 49 (m, 1H), 6 2 (s, 1H), and 1 91 (s, 3H), ES-MS, m/z = 348 ($MH^+$)

Step 3

This compound was prepared by a procedure similar to the one described in step 3 for EXAMPLE 364 Yield 44%, $^1$H NMR ($CD_3OD$) δ 7 62 (d, 2H, J = 8 0 Hz), 7 51 (m, 3H), 7 15 (m, 2H), 6 64 (s, 1H), 5 33 (s, 2H), and 2 0 (s, 3H), $^{19}$F NMR ($CD_3OD$) δ -166 21 (m), ES-HRMS m/z 455 954_(M+H $C_{19}H_{14}NO_2Cl_2BrF$, requires 455 9564)

Example 369



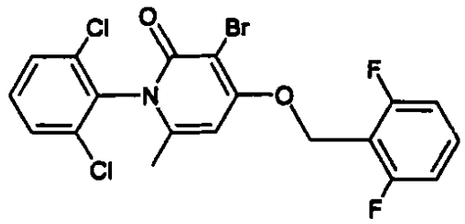
3-Bromo-1-(2,6-dichlorophenyl)-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one

This compound was prepared by a procedure similar to the one described for EXAMPLE 368

Yield 64%, $^1$H NMR ($CD_3OD$/400 MHz δ 7 62 (m, 3H), 7 48 (m, 1H), 7 05 (m, 2H), 6 70 (s, 1H), 5 36 (s, 2H), and 2 02 (s, 3H), $^{19}$F NMR ($CD_3OD$) δ -111 43 (m) and

-115 89 (m), ES-HRMS m/z 473 9450 (M+H $C_{19}H_{13}NO_2Cl_2BrF_2$, requires 473 9469)

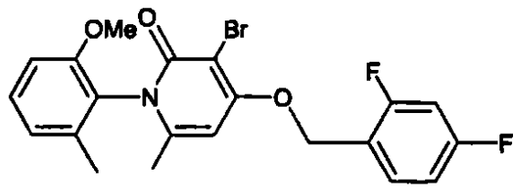
Example 370



3-Bromo-1-(2,6-dichlorophenyl)-4-[(2,6-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one

This compound was prepared by a procedure similar to the one described for EXAMPLE 368 Yield 78%, $^1H$ NMR ($CD_3OD$/400 MHz) δ 7 62 (d, 2H, J = 8 0 Hz), 7 52 (m, 2H), 7 1 (m, 2H), 6 77 (s, 1H), and 2 04 (s, 3H), $^{19}F$ NMR ($CD_3OD$) δ -117 04 (m), ES-HRMS m/z 473 9468 (M+H $C_{19}H_{13}NO_2Cl_2BrF_2$, requires 473 9469)

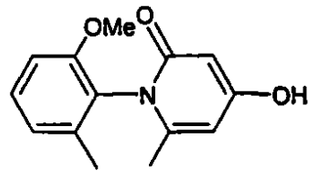
Example 371



3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2-methoxy-6-methylphenyl)-6-methylpyridin-2(1H)-one

Step 1

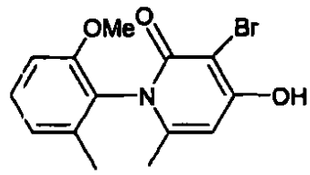
Preparation of 4-hydroxy-1-(2-methoxy-6-methylphenyl)-6-methylpyridin-2(1H)-one



This compound was prepared by a procedure similar to the one described in step 1 for EXAMPLE 368 Yield 21%, $^1$H NMR ($CD_3OD$/400 MHz) δ 7 31 (m, 1H), 6 94 (m, 2H), 6 05 (d, 1H, J = 2 4 Hz), 5 78 (d, 1H, J = 2 4 Hz), 3 76 (s, 3H), 2 00 (s, 3H) and 1 83 (s, 3H), ES-HRMS m/z 246 1092 (M+H $C_{14}H_{16}NO_3$, requires 246 1123)

Step 2

Preparation of 3-bromo-4-hydroxy-1-(2-methoxy-6-methylphenyl)-6-methylpyridin-2(1H)-one



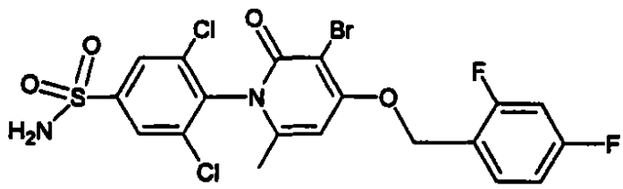
This compound was prepared by a procedure similar to the one described in step 2 for EXAMPLE 368 Yield 58%, $^1$H NMR ($CD_3OD$/400 MHz) δ 7 34 (m, 1H), 6 96 m (2H), 6 15 (s, 1H), 3 76 (s, 3H), 1 99 (s, 3H), and 1 83 (s, 3H), ESMS m/z 324 (M+H)

Step 3

This compound was prepared by a procedure similar to the one described for EXAMPLE 368 Yield 60%, $^1$H NMR ($CD_3OD$/400MHz) δ 7 63 (m, 1H), 7 36 (m, 1H), 7 01 (m, 4H), 6 61 (s, 1H), 5 33 (s, 2H), 3 76 (s, 3H), 1 99(s, 3H), and 1 95 (s, 3H), $^{19}$F NMR

($CD_3OD$/400 MHz) δ -111 64 (m), and -116 03 (m), ES-HRMS m/z 450 0532 (M+H $C_{21}H_{19}NO_3Cl_3BrF_2$, requires 450 0511)

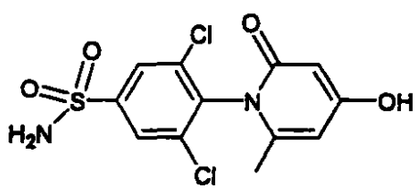
Example 372



4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-3,5-dichlorobenzenesulfonamide

Step 1

Preparation of 3,5-dichloro-4-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)benzenesulfonamide



A mixture of 4-hydroxy-6-methylpyrone ((1 2 g, 0 0095 mol), and 2,6-dichlorosulphanilamide (2 4 g, 0 0099 mol) was heated at 170 °C under argon for 20 min The resulting dark colored melt was cooled and the crude material was first purified by flash chromatography (EtOAc) to give partially purified material which contained the desired product This was further purified by reverse-phase HPLC using 10 - 90% $CH_3CN$/Water (30 min gradient) at a flow rate of 100 mL/min The appropriate fractions (m/z = 349 )were combined and freeze

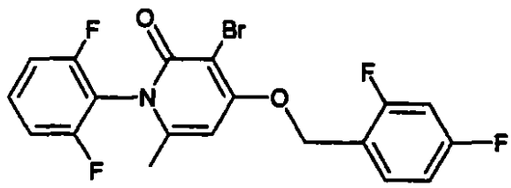
dried to afford 0 19 g of 3,5-dichloro-4-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)benzenesulfonamide as pale yellow solid $^1$H NMR ($CD_3OD$/400 MHz) δ8 06(s, 2H), 6 13 (d, 1H, J = 1 6 Hz), 5 78 (d, 1H, J = 1 6 Hz), and 1 94 (s, 3H)), ES-HRMS m/z 348 9819 (M+H $C_{12}H_{11}N_2O_4SCl_2$ requires 348 9811)

Step 2

A mixture of 3,5-dichloro-4-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)benzenesulfonamide (0 18 g, 0 0005 mol), N-bromosuccinimide (0 1 g, 0 00056 mol)in acetici acid (2 0 mL) was stirred at room temperature under argon atmosphere for 1 h Acetic acid was removed in vacuo, the residue was dissolved in DMF (2 0 mL), and added 2,4 difluorobenzyl bromide (0 128 g, 0 0005 mol), potassium carbonate (0 1 g, 0 0007 mol) The resulting mixture was stirred at room temperature for 1 h The solvents were distilled in vacuo, and the residue was purified by flash chromatography (EtOAc/hexane 1 3 v/v) to give 0 14 g of partially purified product This was further purified by reverse-phase HPLC using 10 - 90% $CH_3CN$/Water (30 min gradient) at a flow rate of 100 mL/min The appropriate fractiors (m/z = 553 ) were combined and freeze dried to afford 0 045 g of pale yellow powder This was partitioned between EtOAc (25 ml) and 5% sod bicarbonate The organic phase was washed with water, dried ($Na_2SO_4$) and concentrated under reduced pressure This material was dried invacuo to afford the title compound (0 033 g) as a white amorphous substance

$^1$H NMR ($CDCl_3$/400 MHz) δ7 99(s, 2H), 7 59 (m, 1H), 6 98 (m, 1H), 6 85 (m, 1H), 6 23 (s, 1H), 5 69 (s, 2H), 5 28 (s, 2H), 1 97 (s, 3H), and 1,76 (br, 2H), ES-HRMS m/z 552 7214 (M+H $C_{19}H_{14}BrCl_2N_2O_4S$ requires 552 9197)

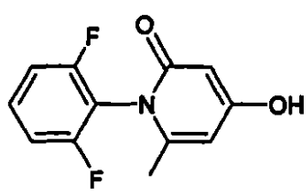
Example 373



3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one

Step 1

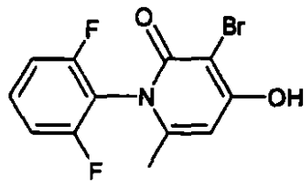
Preparation of 1-(2,6-difluorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one



A mixture of 4-hydroxy-6-methyl-2-pyrone (10 0 g, 0 079 mol) and 2,6 difluoroaniline (9 5 g, 0 073 mol) was heated at 170 °C under argon atmosphere for 20 min The water formed was removed using a Dean-stark apparatus The melt was cooled, the dark solid was tritutrated with EtOAc , and filtered This material was washed thoroughly with EtOAc to afford the desired product 1-(2,6-difluorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one 6 5 g (35%) as a light brown solid $^1$H NMR ($CD_3OD$/400 MHz) δ 7 56 (m, 1H), 7 19 (m, 2H), 6 09 (m, 1H ), 5 77 (d, 1H, J = 2 4 Hz), and 1 99 (s, 3H), ES-HRMS m/z 238 0679 (M+H $C_{12}H_{10}NO_2F_2$ requires 238 0674)

Step 2

Preparation of 3-bromo-1-(2,6-difluorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one



The title compound was prepared by a procedure described in step2 for EXAMPLE 364

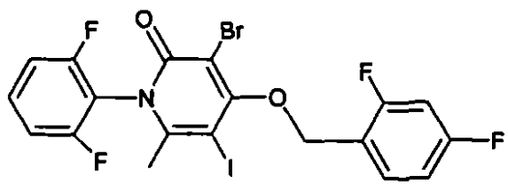
Yield 79%, $^1$H NMR ($CD_3OD$/400 MHz) δ 7 58 (m, 1H), 7 21 (m, 2H), 6 19 (d, 1H, J = 0 8 Hz), 1 99 (s, 3H), ES-HRMS m/z 315 9811 (M+H $C_{12}H_9NO_2F_2Br$ requires 315 9779)

Step 3

This compound was prepared by a procedure described in step 3 for EXAMPLE 364

Yield 63%, $^1$H NMR ($CD_3OD$) δ 7 58 (m, 2H), 7 23 (m, 2H), 7,06 (m, 2H), 6 68 (s, 1H), 5 36 (s, 2H), and 2 10 (s, 3H), $^{19}$F NMR ($CD_3OD$) δ −111 50(m), -115 96(m), and -121 93 (m), ES-HRMS m/z 442 0061 (M+H $C_{19}H_{13}NO_2F_4Br$ requires 442 0060)

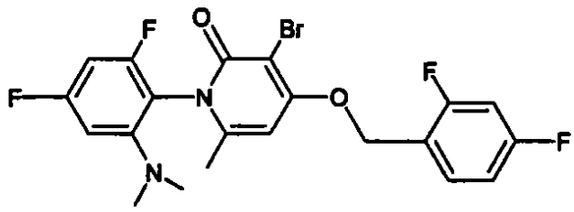
Example 374



3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-5-iodo-6-methylpyridin-2(1H)-one

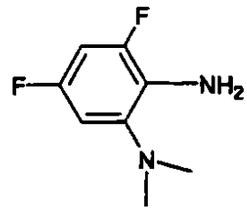
A solution of 3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one (0 3 g, 0 00068 mol) and N-iodosuccinimide (0 22 g, 0 00098 mol) in dichloroethane , containing dichloroacetic acid (0 1 mL) was heated to reflux for 6 h under argon atmosphere After the removal of the solvents under reduced pressure, the residue was partitioned between, dichloromethane (20 mL) and 5% sod sulphite (10 mL) The organic phase was washed with water, dried ($Na_2SO_4$), and concentrated under reduced pressure The residue was purified by flash chromatography (25% EtOAc in hexane) to afford the title compound (0 125 g, 32 %) as a pale yellow powder $^1H$ NMR ($CDCl_3$/400 MHz) δ 7 68 (m, 1H), 7 46 (m, 1H), 7 11 (m, 2H), 6 95 (m, 1H), 6 85 (m, 1H), 5 23 (s, 2H), and 2 38 (s, 3H), $^{19}F$ NMR ($CDCl_3$) δ -109 15 (m), -112 95 (m), -118 50 (m), ES-HRMS m/z 567 9014 (M+H $C_{19}H_{12}NO_2F_4BrI$ requires 567 9027)

Example 375



3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-[2-(dimethylamino)-4,6-difluorophenyl]-6-methylpyridin-2(1H)-one

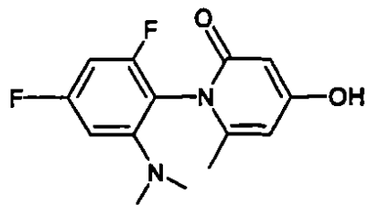
Step 1



3,5-difluoro-N~1~,N~1~-dimethylbenzene-1,2-diamine

To a solution of 2,4,6-trifluoronitrobenzene (2 58 g, 0 0145 mol) in THF (20 0 ml) was added a solution of N,N-dimethylamine in THF (8 5 mL of 2M soln) and stirred for 45 min at 0 °C It was then stirred at room temperature for 30 min and concentrated to dryness The resulting material was dissolved in EtOH (25 mL), added Pd/C (10%, 0 6 g) and hydrogenated at 50 psi ior 4 h The catalyst was removed by filtration, and the filtrate was concentrated to dryness under reducued pressure Te residue was partitioned between sod bicarbonate (10%, 25 mL) and EtOAc (30 mL) The organic phase was washed with water, dried ($Na_2SO_4$), and concentrated to dryness to afford the title compound (1 3 g, 50%) as a dark colored solid $^1H$ NMR ($CDCl_3$/400 MHz) δ 6 52 (m, 2H), 3 64 ( br, 2H), and 2 65 (s, 6H), ES-HRMS m/z 172 0772 (M+ $C_8H_{10}N_2F_2$ requires 172 0810)

Step 2

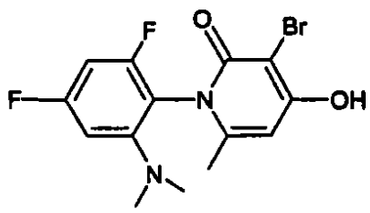


1-[2-(dimethylamino)-4,6-difluorophenyl]-4-hydroxy-6-methylpyridin-2(1H)-one

An intimate mixture of 4-hydroxy-6-methyl-2-pyrone (1 3 g, 0 0103 mol), and 3,5- difluoro-N,N-dimethylbenzene-1,2-diamine (1 4 g, 0 008 mol) was heated at 160 °C under argon for 15 min The dark colored reaction mixture was cooled, triturated with EtOAc (15 ml), and filtered The solids were washed with warm EtOAc, followed by hexane and dried to give the title compound as a light blue solid (0 4 g, 14 %) Analalytically pure sample was prepared by reverse-phase HPLC purification using 10 -90% $CH_3CN$/Water (30 min gradient) at a flow rate of 100 mL/min The appropriate fractions were combined and freeze-dried to give the title compound $^1H$ NMR ($CD_3OD$/400 MHz) δ 6 61 (m, 2H), 6 08 (d, 1H, J = 2 0 Hz), 6 78 (d, 1H, J = 2 0 Hz), 2 69 (s, 6H), and 1 94 (s, 3H), ES-HRMS m/z 281 1084 (M+H $C_{14}H_{15}N_2O_2F_2$ requires 281 1096)

Step 2

Preparation of




3-bromo-1-[2-(dimethylamino)-4,6-difluorophenyl]-4-hydroxy-6-methylpyridin-2(1H)-one

The title compound was prepared by a procedure described in step2 for EXAMPLE 364 Yield 71%, $^1H$ NMR ($CD_3OD$/400 MHz) δ 6 62 (m, 2H), 6 17 (s, 1H), 2 67 (s, 6H), and 1 94 (s, 3H), ES-HRMS m/z 359 0188 (M+H $C_{14}H_{14}N_2O_2F_2Br$ requires 359 0201)

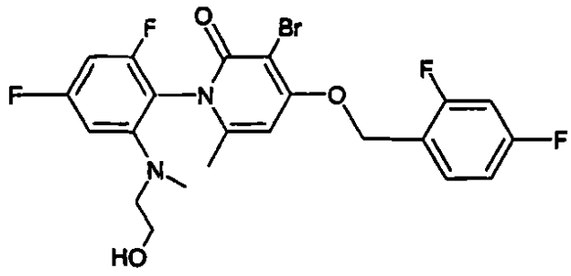
Step 3

This compound was prepared by a procedure described in step 3 for EXAMPLE 364

Yield 34%, $^1$H NMR ($CDCl_3$/400 MHz) δ 7 62 (m, 1H), 6 98 (m, 1H), 6 85 (m, 1H), 6 46 (m, 2H), 6 11 (s, 1H), 5 24 (s, 2H), 2 66 (s, 6H), and 1 98 (s, 3H), $^{19}$F NMR ($CDCl_3$/400 MHz) δ -108 06 (m), -109 60 (m), - 115 02 (m), and -116 01 (m), ES-HRMS m/z 485 0451 (M+H $C_{21}H_{18}N_2O_2F_4Br$ requires 485 0482)

The title compound was prepared by stirring a suspension of thet product of step 3, above, (0 14 g) with 4N HCl in dioxane (0 7 mL) at room temperature for 30 min The mixture was concentrated to dryness $^1$H NMR ($CD_3OD$/400 MHz) δ 7 62 (m, 1H), 7 02 (m, 2H), 6 65 (m, 3H), 5 34 (s, 2H), 2 66 (s, 6H), and 2 05 (s, 3H), ESMS m/z = 485

Example 376

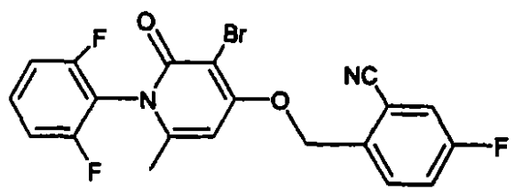



3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-{2,4-difluoro-6-[(2-hydroxyethyl)(methyl)amino]phenyl}-6-methylpyridin-2(1H)-one

The title compound was prepared by a similar procedure described for EXAMPLE 375, replacing N,N-dimethyl group by N-Methyl-aminoethanol $^1$H NMR ($CDCl_3$/400 MHz) δ 7 59 (m, 1H), 6 98 (m, 1H), 6 85 (m, 1H), 6 61 (m, 1H), 6 52 (m, 1H), 6 17 (m, 1H), 5 25 (s, 2H), 3 63 (m, 1H), 3 53 (m, 1H), 3 26 (m, 1H),

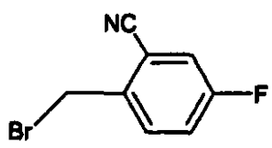
3 0 (m, 1H), 2 66 (s, 6H), and 2 09 (s, 3H), ES-HRMS m/z 515 0512 (M+H $C_{22}H_{20}N_2O_3F_4Br$ requires 515 0588)

Example 377



2-({[3-Bromo-1-(2,6-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl]oxy}methyl)-5-fluorobenzonitrile

Step 1



2-(Bromomethyl)-5-fluorobenzonitrile

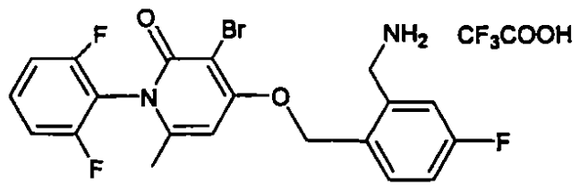
A mixture of 5-fluoro-2-methylbenzonitrile ( 2 0 g, 0 015 mol), NBS (3 2 g, 0 018 mol) and benzoylperoxide (0 25 g) in carbontetrachloride (25 0 ml) was heated to reflux for 6 h, under argon atmosphere The reaction mixture was cooled and filtered The filtrate was concentrated under reduced pressure, and the residue was purified by flash chromatography (5% EtOAc in hexane ) to afford 2-(Bromomethyl)-5-fluorobenzonitrile (1 9 g, 60%) as a colorless liquid $^1$H NMR ($CDCl_3$/400 MHz) δ 7 59(m) 7 58 (m, 1H), 7 38 (m, 1H), and 7 25 (m, 1H)

Step 2

A mixture of 3-bromo-1-(2,6-difluorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one.

1 0 g, 0 0032 mol), potassium carbonate (0 65 g, 0 0047 mol) and 2-(Bromomethyl) 5-fluorobenzonitrile (0 95 g, 0 0045 mol) in dimethylacetamide (15 0 ml) was stirred at room temperature under argon atmosphere After 1h, dimethylacetamide was distilled in vacuo and the residue was partitioned between dichloromethane (50 ml) and 55 citric acid (15 mL) The organic phase was washed with water, dried ($Na_2SO_4$), and concentrated to dryness The resulting material was triturated with EtOAc, filtered, washed with EtOAc and dried to afford the title compound (0 86 g, 60%) as a white powder $^1H$ NMR (DMSO-$d_6$/400 MHz) δ 7 95 (m, 1H), 7 81 (m, 1H), 7 68 (m, 2H), 7 37 (m, 2H), 6 79 (s, 1H), 5 45 (s, 2H), and 2 03 (s, 3H), $^{19}F$- NMR (DMSO-$d_6$) δ -111 31 (m), -120 34 (m), ES-HRMS m/z 449 0094 (M+H $C_{20}H_{13}N_2O_2F_3Br$ requires 449 0107)

Example 378

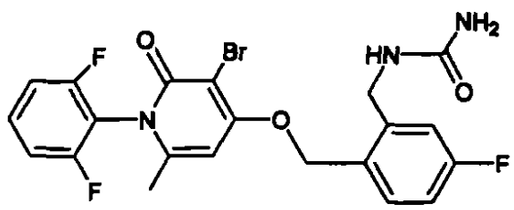



4-{[2-(Aminomethyl)-4-fluorobenzyl]oxy}-3-bromo-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one trifluoroacetate

To a cold suspension of 2-({[3-Bromo-1-(2,6-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl]oxy}methyl)-5-fluorobenzonitrile (0 3 g, 0 00066 mol) in THF (3 0 mL), was added $BH_3$ THF (1 0 mL) After stirring at room temperature for 15 min, the reaction mixture was heated to reflux for 30 min under argon atmosphere The resulting clear solution cooled,

added MeOH (2 0 mL), concentrated under reduced pressure, and the residue was purified by reverse-phase HPLC purification using 10 -90% $CH_3CN$/Water (30 min gradient) at a flow rate of 100 mL/min The appropriate fractions (m/z= 453 M+H) were combined and freeze-dried to give the title compound (0 16 g, 43%) as its trifluoroacetate salt $^1H$ NMR (DMSO-$d_6$/400 MHz) δ 8 19 (br, 3H), 7 65 (m, 2H), 7 37 (m, 4H), 6 78 (s, 1H), 5 42 (s, 2H), 4 21 (br, 2H), and 2 04 (s, 3H), $^{19}F$ NMR (DMSO-$d_6$/400 MHz) δ -112 96 (m), and -120 41 (m), ES-HRMS m/z 453 0387 (M+H $C_{20}H_{17}N_2O_3F_3Br$ requires 453 0420)

Example 379

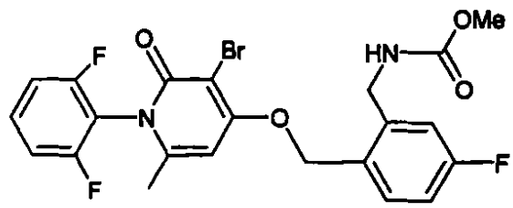


N-[2-({[3-bromo-1-(2,6-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl]oxy}methyl)-5-fluorobenzyl]urea

To a suspension of 4-{[2-(aminomethyl)-4-fluorobenzyl]oxy}-3-bromo-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one trifluoroacetate (0 13g, 0 00023 mol) in THF (3 0 mL), was added triethyl amine (0 07 mL, 0 0005 mol) followed by the addition of trimethylsilylisocyanate (0 066 mL) The reaction mixture was stirred at room temperature for 1 h, and the desired product was isolated by reverse-phase HPLC purification using 10 -90% $CH_3CN$/Water (30 min gradient) at a flow rate of
100 mL/min The appropriate fractions (m/z= 496 M+H) were combined and freeze-dried, and the residue was partitioned between 5% sod bicarbonate (20 mL) and dichloromethane (20

mL) The organic phase was wasned with water, dried ($Na_2SO_4$) and concentrated to dryness under reduced pressure, to afford the title compound as a white amorphous powder (0 065 g) $^1H$ NMR (DMSO-$d_6$/400 MHz) δ 7 62 (m, 1H), 7 52 (m, 1H), 7 35 (m, 2H), 7 09 (m, 2H), 6 77 (s, 1H), 6 51 (t, 1H), 5 61 (s, 2H), 5 38 (s 2H), 4 28 (d, 2H, J = 6 0 Hz), and 2 02 (s, 3H), $^{19}F$ NMR (DMSO-$d_6$/400 MHz) δ 114 044 (m), and -120 31 (m), ES-HRMS m/z 496 0460 (M+H $C_{21}H_{18}N_1O_3F_3Br$ requires 496 0478)

Example 380

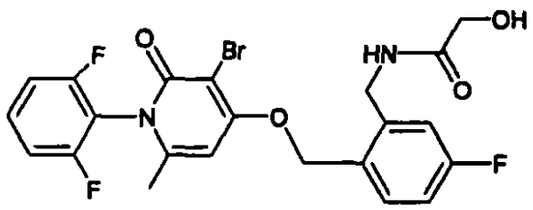



Methyl 2-({[3-bromo-1-(2,6-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl]oxy}methyl)-5-fluorobenzylcarbamate

To solution of 4-{[2-(aminomethyl)-4-fluorobenzyl]oxy}-3-bromo-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one trifluoroacetate (0 12g, 0 00021 mol) in dimethylacetamide (2 0 mL) at 0 °C, was added triethylamine (0 06 mL, 0 00043 mol) followed by the addition of methylchloroformate (0 05 mL) The reaction mixture was stirred at room temperature for 30 min under argon atmosphere Dimethylacetamide was distilled in vacuo and the residue was partitioned between dichloromethane (10 mL) and 5% citric acid (10 mL) The organic phase was washed with water, dried ($Na_2SO_4$) and concentrated to dryness The resulting residue was purified by flash chromatography (60%EtOAc in hexane) to afford the title compound (0 09 g, 75%) as a white amorphous powder $^1H$ NMR (DMSO-$d_6$/400 MHz) δ 7 68 (m, 1H), 7 62 (m, 1H), 7 59 (m, 1H),

7 38 (m, 2H), 7 115 (m, 2H), 6 78 (s, 1H), 5 38 (s, 2H), 4 31 (d, 2H, J = 6 0 Hz), 3 53 (s, 3H), and 2 03(s, 3H), $^{19}F$ NMR (DMSO-$d_6$/400 MHz) δ -113 77 (m), and -120 33 (m), ES-HRMS m/z 511 0508 (M+H $C_{22}H_{19}N_2O_4F_3Br$ requires 511 0475)

Example 381

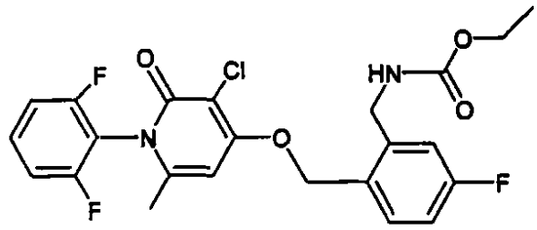



N-[2-({[3-bromo-1-(2,6-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl]oxy}methyl)-5-fluorobenzyl]-2-hydroxyacetamide

To a suspension of 4-{[2-(aminomethyl)-4-fluorobenzyl]oxy}-3-bromo-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one trifluoroacetate (0 12g, 0 00021 mol) in THF (2 0 mL) at 5 °C, was added triethyl amine (0 036 g, 0 00035 mol) followed by the addition of acetoxyacetyl chloride (0 05 mL) The mixture was stirred at room temperature for 30 min, diluted with cold water (10 mL), and extracted the products with dichloromethane ( 2 x 10 mL) The combined organic extracts were washed with water, dried ($Na_2SO_4$) and concentrated to dryness The residue was dissolved in ethanol (0 5 mL), added 1N NaoH (0 5 mL)and stirred at room temperature for 1 h The resulting solution was diluted with water (15 mL), and extracted with dichloromethane (2 x 10 mL) The combined dichloromethane extracts were washed with water, dried ($Na_2SO_4$) and concentrated to dryness The residue was purified by flash chromatography (1% MeOH in EtOAc) to afford the title compound

(0 032 g, 30 %) as a white amorphous powder $^1$H NMR ($CDCl_3$/400 Hz) δ7 45 (m, 2H), 7 18 (m, 1H), 7 05 (m, 3H), 6 23 (s, 1H), 5 24 (s, 2H), 4 56 (d, 2H, J = 6 4 Hz), 4 08 (d, 2H, J = 5 2 Hz), 2 79 (t, 1H), and 2 08 (s, 3H,) $^{19}$F NMR ($CDCl_3$/400 MHz) δ - 111 88 (m), and -118 62 (m), ES-HRMS m/z 511 0482 (M+H $C_{22}H_{19}N_2O_4F_3Br$ requires 511 0475)

Example 382

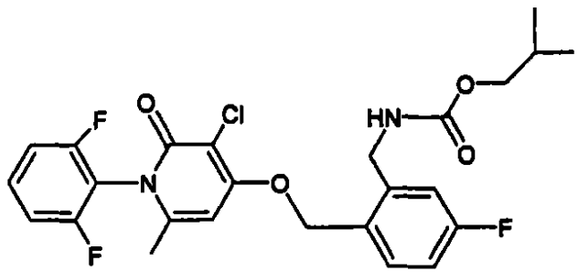



Ethyl 2-({[3-chloro-1-(2,6-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl]oxy}methyl)-5-fluorobenzylcarbamate

To solution of 4-{[2-(aminomethyl)-4-fluorobenzyl]oxy}-3-chloro-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one trifluoroacetate (0 3g, 0 00057 mol) in dimethylacetamide (3 0 mL) was added N-methymorpholine (0 064 g, 0 00064 mol), followed by addition of ethylchloroformate (0 06 mL) and stirred at - 10 °C, for 30 min The solvents were distilled in vacuo and the residue was purified by reverse-phase HPLC purification using 10 -90% $CH_3CN$/Water (30 min gradient) at a flow rate of 100 mL/min The appropriate fractions (m/z= 481 M+H) were combined and freeze-dried, and the residue was partitioned between 5% sod bicarbonate (20 mL) and dichloromethane (20 mL) The organic phase was washed with water, dried ($Na_2SO_4$) and concentrated to dryness under reduced pressure, to afford the title compound as a white amorphous powder (0 15 g, 55%) $^1$H NMR ($CD_3OD$/400MHz) δ7 61 (m, 1H), 7 52

(m, 1H), 7 26 (-t, 2H, J = 8 4 Hz), 7 12 (dd, 1H), 7 05 (3d, 1H, J = 2 4 Hz), 6 74 (s, 1H), 5 40 (s, 2H), 4 42 (s, 2H), 4 05 (q, 2H, J = 7 2 Hz), 2 12 (s, 3H), and 1 21 (t, 3H, J = 7 2 Hz ), ES-HRMS m/z 481 1118 (M+H $C_{23}H_{21}N_2O_4F_3Cl$ requires 481 1136)

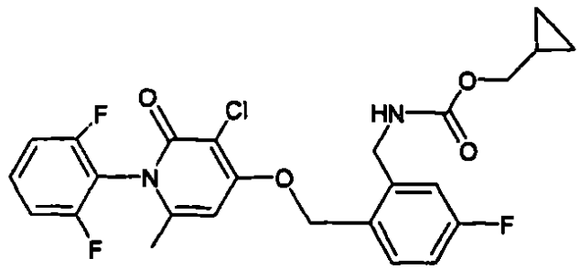
Example 383




Isobutyl 2-({[3-chloro-1-(2,6-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl]oxy}methyl)-5-fluorobenzylcarbamate

The title compound was prepared by a procedure similar to the one described for EXAMPLE 382 Yield 57 %, $^1H$ NMR ($CD_3OD$/400 MHz) δ 7 61 (m, 1H), 7 51 (m, 1H), 7 24 (-t, 2H, J = 8 0 Hz), 7 18 (m, 1H), 7 06 (m, 1H), 6 74 (s, 1H), 5 40 (s, 2H), 4 21 (s, 2H), 3 79 (d 2H, J = 6 8 Hz), 2 12 (s, 3H), 1 85 (m, 1H), and 0 91 (d, 6H, J = 6 4 Hz), ES-HRMS m/z 509 1422 (M+H $C_{25}H_{25}N_2O_4F_3Cl$ requires 509 1449)

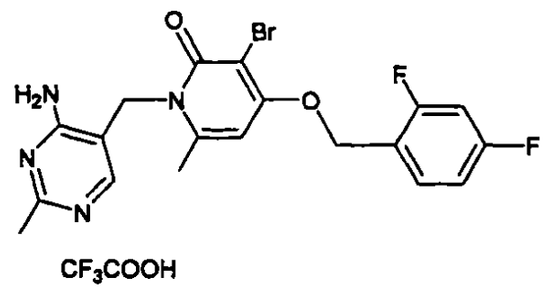
Example 384



Cyclopropylmethyl 2-({[3-chloro-1-(2,6-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl]oxy}methyl)-5-fluorobenzylcarbamate

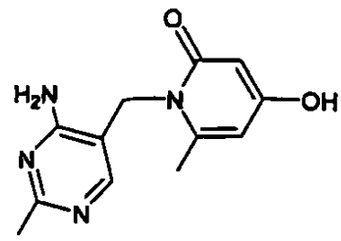
The title compound was prepared by a procedure similar to the one described for EXAMPLE 382 Yield 46%, $^1$H NMR ($CD_3OD$/400 Hz) δ 7 61 (m, 1H), 7 55 (m, 1H), 7 24 (~ t, 2H, J = 7 6 Hz), 7 18 (m, 1H), 7 05 (m, 1H), 6 73 (s, 1H), 5 40 (s, 2H), 4 42 (s, 2H), 3 83 (d, 2H, J = 7 2 Hz), 2 12 (s, 3H), 1 1 (br, 1H), 0 58 (-d, 2H), and 0 22 (~ d, 2H), ES-HRMS m/z 507 1316 (M+H $C_{25}H_{23}N_2O_4F_3Cl$ requires 507 1293)

Example 385



1-[(4-amino-2-methylpyrimidin-5-yl)methyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one trifluoroacetate

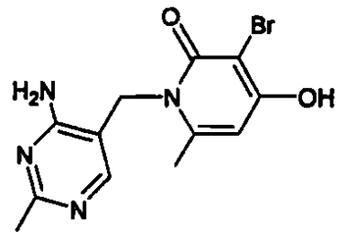
Step 1



1-[(4-amino-2-methylpyrimidin-5-yl)methyl]-4-hydroxy-6-methylpyridin-2(1H)-one

A mixture of 4-hydroxy-6-methyl-2-pyrone (0 9 g, 0 007 mol) and 4-amino-5-aminomethyl-2-methylpyrimidine (1 0 g, 0 007 mol) in water (10 0 ml) was heated at 100 °C for 1 h under argon atmosphere The reaction mixture was cooled, and filtered the yellow precipitate It was washed successively with cold water, ethanol, and dried in vacuo to afford the title compound (1 01 g, 51%) as a pale yellow powder $^1$H NMR (DMSO-$d_6$/400 MHz) δ 7 62 (s, 1H), 7 04 (s, 1H), 5 83 (d, 1H, J = 2 0 Hz), 5 58 (d, 1H, J = 2 0 Hz), 4 92 (s, 2H), 2 24 (s, 3H), and 2 22 (s, 3H), ES-HRMS m/z 325 0304 (M+H $C_{12}H_{14}N_4O_2Br$ requires 325 0295)

Step 2



1-[(4-amino-2-methylpyrimidin-5-yl)methyl]-3-bromo-4-hydroxy-6-methylpyridin-2(1H)-one

A mixture of 1-[(4-amino-2-methylpyrimidin-5-yl)methyl]-4-hydroxy-6-methylpyridin-2(1H)-one (0 5 g, 0 002 mol), and NBS (0 4 g, 0 002 mol) in glacial acetic acid (5.0 ml) was stirred

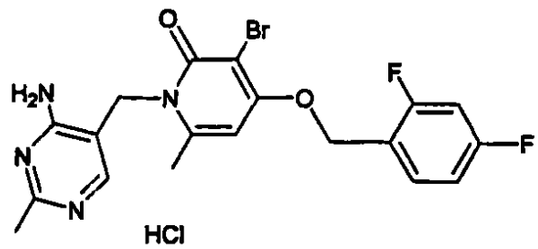
at room temperature for 1 h under argon atmosphere Acetic acid was removed in vacuo, residue was triturated with EtOAc containing 10 % EtOH, and filtered The pale yellow precipitate was washed with EtOAc containing 10% EtOH and dried in vacuo to afford the title compound (0 47 g, 725) as a pale yellow powder

$^1$H NMR ($CD_3OD$/400 MHz) δ 7 62 (s, 1H), 6 09 (s, 1H), 5 15 (s, 2H), 2 42 (s, 3H), and 2 33 (s, 3H), ES-HRMS m/z 247 1160 (M+H $C_{12}H_{15}N_4O_2$ requires 247 1190)

Step 3

To suspension of 1-[(4-amino-2-methylpyrimidin-5-yl)methyl]-3-bromo-4-hydroxy-6-methylpyridin-2(1H)-one (1 0 g, 0 0031 mol) and potassium carbonate (0 0 g, 0 004 mol) in dimethylacetamide (10 0 mL) was added 2,4 difluorobenzyl bromide (0 62 mL, 0 0048 mol) and stirred at room temperature for 2 hours Dimethylacetamide was distilled in vacuo and the residue was purified by reverse-phase HPLC using 10 - 90% $CH_3CN$/Water (30 min gradient) at a flow rate of 100 mL/min The appropriate fractions (m/z = 566 )were combined and freeze dried to afford 0 65 g (37 %) of the title compound as its trifluoroacetate salt $^1$H NMR ($CD_3OD$/400 MHz) δ 7 65 (s, 1H), 7 58 (m, 1H), 7 05 (m, 2H), 6 61 (s, 1H), 5 31 (s, 2H), 5 18 (s, 2H), 2 51 (s 3H), and 2 46 (s, 3H), $^1$H NMR ($CD_3OD$/400 MHz) δ -111 39 (m ), and -115 98 (m), ES-HRMS m/z 451 0590 (M+H $C_{19}H_{18}N_4O_2BrF_2$ requires 451 0576)

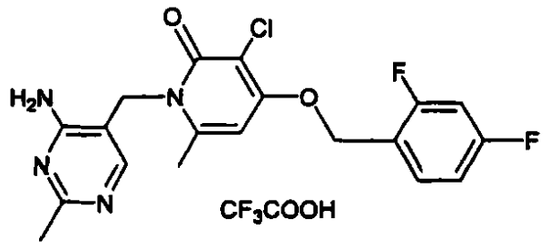
Example 386




1-[(4-amino-2-methylpyrimidin-5-yl)methyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one hydrochloride

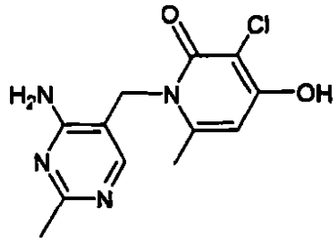
Ion exchange (25g) BioRad AG 2X8 resin (200-400 mesh chloride form) was washed with 1M HCl (150 mL), and equilibrated for 2 5 h This resin was loaded onto a column, and added a solution of Example 385 (3 3 g, 5 8 mmol) in water/$CH_3CN$ (1 1) The column was eluted slowly over 1 h, fractions were collected, and freeze dried to afford the desired HCl salt (2 2 g, 72%) as a white solid $^1$H-NMR ($CD_3OD$, 400Hz) δ 7 60 (m, 2H), 7 21 (m, 2H), 6 62 (s, 1H), 5 31 (s, 2H), 5 18 (s, 2H), 2 52 (s, 3H), 2 47 (s,3H), ES-HRMS m/z 451 0544/453 0577 (M+H $C_{19}H_{17}N_4O_2F_2Br$ requires 451 0581/453 0563)

Example 387




1-[(4-amino-2-methylpyrimidin-5-yl)methyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one trifluoroacetate

Step 1 Preparation of 1-[(4-amino-2-methylpyrimidin-5-yl)methyl]-3-chloro-4-hydroxy-6-methylpyridin-2(1H)-one

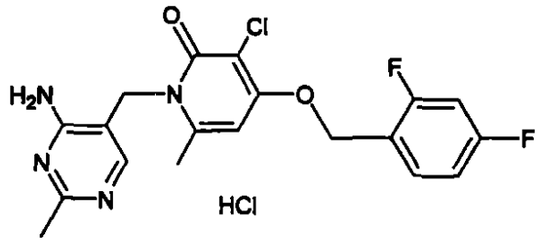


$^1$H NMR ($CD_3OD$, 400Hz) δ 7 62 (m, 1H), 6 11 (s, 1H), 5 13 (s, 2H), 2 66 (s, 3H), 2 42 (s,3H), ES-HRMS m/z 281 0793 (M+H $C_{12}H_{13}N_4O_2Cl$ requires 281 0800)

Step 2 Preparation of 1-[(4-amino-2-methylpyrimidin-5-yl)methyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one trifluoroacetate

The title compound was prepared by a procedure similar to the one described for Example 385 step 2 $^1$H NMR ($CD_3OD$, 400Hz) δ 7 59 (m, 2H), 7 03 (m, 2H), 6 63 (s, 1H), 5 31 (s, 2H), 5 17 (s, 2H), 2 48 (s, 3H), 2 46 (s, 3H), ES-HRMS m/z 407 1097 (M+H $C_{19}H_{17}N_4O_2ClF_2$ requires 407 1081)

Example 388

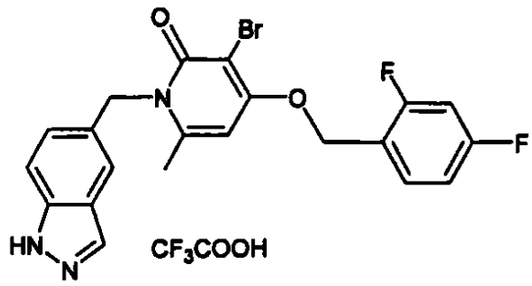


1-[(4-amino-2-methylpyrimidin-5-yl)methyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one hydrochloride

Ion exchange (12 5g) BioRad AG 2X8 resin (200-400 mesh chloride ~~form~~) was washed with 1M HCl (150 mL), and

equilibrated for 2 5 h This resin was loaded onto a column, and added a solution of EXAMPLE 387 (1 2 g, 2 4 mmol) in water/$CH_3CN$ (1 1) The column was eluted slowly over 1 h, fractions were collected,and freeze dried to afford the desired HCl salt (1 03 g, 97%) as a white solid $^1H$ NMR ($CD_3OD$, 400Hz) δ 7 60 (m, 2H), 7 04 (m, 2H), 6 64 (s, 1H), 5 31 (s, 2H), 5 17 (s, 2H), 2 50 (s, 3H), 2 47 (s, 3H), ES-HRMS m/z 407 1079 (M+H $C_{19}H_{17}N_4O_2ClF_2$ requires 407 1081)

Example 389

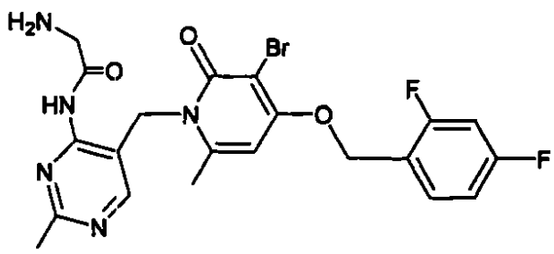



3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-(1H-indazol-5-ylmethyl)-6-methylpyridin-2(1H)-one trifluoroacetate

To a mixture of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (0 55 g, 0 0017 mol) and 5-(bromomethyl)-1-tetrahydro-2H-pyran-2-yl-1H-indazole (0 5 g, 0 0017 mol) in THF (10 0 mL) was added NaH (0 045 g, 0 0019 mol) and heated at
60 °C for 16 h under argon atmosphere THF was distilled under reduced pressure, and the residue was suspended in EtOAc, added acetic acid (0 5 mL) and the product was purified by flash chromatography (80% EtOAc in hexane) The appropriate fractions were combined and concentrated to give an amorphous substance (0 31 g) This was stirred with trifluoroacetic (0 5 mL) for 30 min, the solution was diluted with acetonitrile (5 mL) and the product was isolated by reverse-

phase HPLC using 10 - 90% $CH_3CN$/Water (30 min gradient) at a flow rate of 100 mL/min The appropriate fractions (m/z = 460 ) were combined and freeze dried to afford 0 14 g (52%) of the title compound as its trifluoroacetate salt $^1H$ NMR ($CD_3OD$/400 MHz) δ 7 97 (s, 1H), 7 62 (m, 1H), 7 51 (m, 1H), 7 45 (s, 1H), 7 25 (m, 1H), 7 03 (t, 2H), 6 49 (s, 1H), 5 53 (s, 2H), 5 29 (s, 2H), and 2 40 (s, 3H), $^{19}F$ NMR ($CD_3OD$/400 MHz) δ -111 69 (m), -116 09 (m), ES-HRMS m/z 460 0432 (M+H $C_{21}H_{17}N_3O_2BrF_2$ requires 460 0467)

Example 390

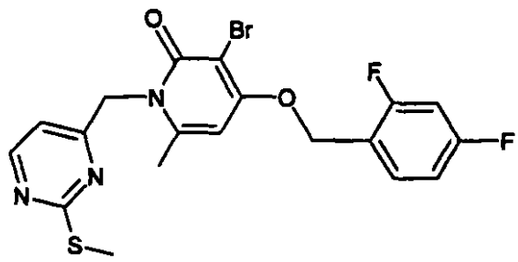



N-1~-(5-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-2-methylpyrimidin-4-yl)glycinamide trifluoroacetate

To a solution of BOC-Gly-OH (0 19 g, 0 0011 mol) in DMF (2 0 mL), was added N-methylmorpholine (0 14 mL, 0 0011 mol), followed by the addition of isobutylchloroformate (0 15 mL, 0 0011 mol) and stirred at -10 °C for 15 min Then added a solution of 1-[(4-amino-2-methylpyrimidin-5-yl)methyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one trifluoroacetate (0/125 g, 0 00022 mol) in DMF ( 2,0 mL) containing diisopropylethylamine (0 1 g, 0 006 mL) and the resulting mixture was stirred for 16 h, at room temperature The solvents were distilled in vacuo and the residue was

purified by by reverse-phase HPLC using 10 - 90% $CH_3CN$/Water (30 min gradient) at a flow rate of 100 mL/min The appropriate fractions (m/z = 608/610) were combined and freeze dried to afford 0 025 g of white powder This was stirred with trifluoroacetic acid (0 5 mL) for 1 h and product was isolated by reverse-phase HPLC using 10 - 90% $CH_3CN$/Water (30 min gradient) at a flow rate of 100 mL/min The appropriate fractions (m/z = 508/510) were combined and freeze dried to afford the title compound (0 02 g) as a white powder $^1H$ NMR ($CD_3OD$/400 MHz) δ 8 18 (s, 1H), 7 61 (m, 1H), 7 02 (m, 2H), 6 59 (s, 1H), 5 30 (s, 4H), 4 23 (s, 2H), 2 60 (s, 3H), and 2 47 (s, 3H), ES-HRMS m/z 508 0797 (M+H $C_{21}H_{21}N_5O_3BrF_2$ requires 508 0790)

Example 391




3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-{[2-(methylthio)pyrimidin-4-yl]methyl}pyridin-2(1H)-one

Step 1




4-(Bromomethyl)-2-(methylthio)pyrimidine

284

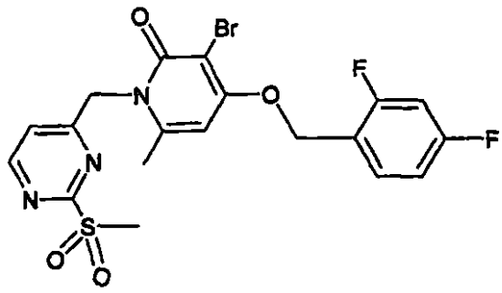
282

To a solution of 4-methyl-2-methylthiopyrimidine (12 6 g, 0 09 mol) in acetic acid (50 0 mL) was added bromine (5 5 mL, 0 11 mol) and heated at 80 °C under argon atmosphere for 2 h Acetic acid was distilled in vacuo, the residue was triturated with dichloromethane (100 0 mL) and poured into satd sod bicarbonate solution (200 0 mL) Additional dichloromethane (100 0 ml) was added and stirred for 15 min The organic phase was washed with water ( 3 x 100 mL), dried ($Na_2SO_4$), and concentrated under reduced pressure The dark colored residue was purified by flash chromatography (EtOAc/hexane 1 4 v/v) to afford 4-(bromomethyl)-2-(methylthio)pyrimidine (10 9 g, 55%) as a dark colored liquid $^1H$ NMR ($CDCl_3$/400 MHz) δ 8 50 (d, 1H, J = 4 8 Hz), 7 09 (d, 1H, J = 4 8 Hz), 4 34 (s, 2H), and 2 56 (s, 3H), ESMS m/z 219 (M+H)

Step 2

To a mixture of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one 5 0 g, 0 015 mol) and 4-(Bromomethyl)-2-(methylthio)pyrimidine (4 0 g, 0 018 mol) in THF (50 0 mL) was added NaH (0 4 g, 0 0017) and stirred at 55 °C under argon for 16 h The reaction mixture was concentrated under reduced pressure and the residue was partitioned between 5% citric acid (25 mL) and EtOAc (50 mL) A precipitate was formed, it was filtered, washed with water, EtOAc, and dried in vacuo to afford the title compound (4 2 g, 59 %) as a light brown powder, $^1H$ NMR ($CD_3OD$/400 MHz) δ 8 45 (d, 1H, J = 5 2 Hz), 7 5 (m, 1H), 7 06 (d over m, 2H, J = 5 2 Hz), 6 54 (s, 1H), 5 39 (s, 2H), 5 32 (s, 2H), 2 43 (s, 3H), 2 33 (s 3H), ES-HRMS m/z 468 0173 (M+H $C_{19}H_{17}N_3O_2BrSF_2$ requires 468 0187)

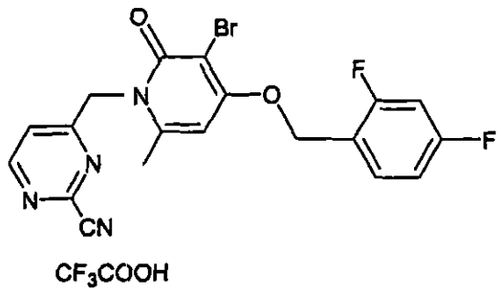
Example 392



3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-{[2-(methylsulfonyl)pyrimidin-4-yl]methyl}pyridin-2(1H)-one

A suspension of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-{[2-(methylthio)pyrimidin-4-yl]methyl}pyridin-2(1H)-one 0 28 g, 0 0006 mol), and magnesium monoperoxyphthalate hexahydrate 90 6 g, 0 0012 mol) in acetonitrile (8 0 ml) and water (2 0 ml) was stirred at room temperature for 16 h The resulting clear solution was concentrated under reduced pressure, and the residue was partitioned between dichloromethane (30 mL) and water (20 mL) The organic phase was washed with water, dried ($Na_2SO_4$) and concentrated to afford the title compound (0 27 g, 90%) as a pale yellow substance $^1H$ NMR ($CD_3OD$/400 MHz) δ8 91 (d, 1H, J = 5 2 Hz), 7 63 (d over m, 2H, J = 5 2 Hz), 7 03 (m, 2H), 6 58 (s, 1H), 5 54 (s, 2H), 5 33 (s, 2H), 3 28 (s, 3H), and 2 49 (s, 3H), $^{19}F$ NMR ($CD_3OD$/400 MHz) δ −111 58 (m ), -115 98 (m), ES-HRMS m/z 500 0113 (M+H $C_{19}H_{17}N_3O_4BrSF_2$ requires 500 0086)

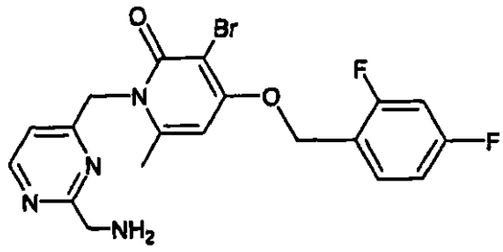
Example 393




4-{[3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrimidine-2-carbonitrile trifluoroacetate

A mixture of 3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-{[2-(methylsulfonyl)pyrimidin-4-yl]methyl}pyridin-2(1H)-one (1 0 g, 0 002 mol ) and NaCN (0 15 g, 0 0031 mol) in DMF (5 0 mL) was stirred at room temperature for 2 h under argon atmosphere DMF was distilled in vacuo, the residue was triturated with acetonitrile (10 mL) and water (10 mL), and filtered the red colored precipitate It was washed with acetonitrile and dried to afford the title compound (0 26 g) The washings and the fitrate were combined and purified by reverse-phase HPLC using 10 - 90% acetonitrile/water gradient (30 min) at a flow rate of 100 mL/min to give an additional 0 5 g of the title compound $^1$H NMR ($CD_3OD$/400 MHz) δ 8 83 (d, 1H, J = 5 2 Hz), 7 62 (d over m, 2H, J = 5 2 Hz), 7 00 (m, 2H), 6 58 (s, 1H), 5 46 (s, 2H), 5 33 (s, 2H), and 2 47 (s, 3H), $^{19}$F NMR ($CD_3OD$/400 MHz) δ −111 64 (m), -116 03 (m), ES-HRMS m/z 447 0278 (M+H $C_{19}H_{14}N_4O_2BrF_2$ requires 447 0263)

Example 394



$CF_3COOH$

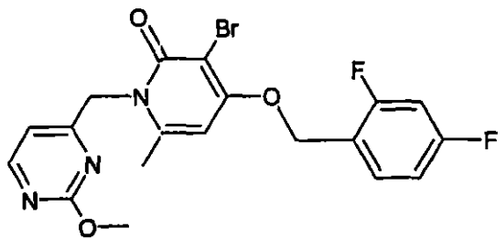
4-{[2-(Aminomethyl)-4-fluorobenzyl]oxy}-3-bromo-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one trifluoroacetate

To a solution of 4-{[3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrimidine-2-carbonitrile trifluoroacetate (0 3 g 0 00066mol) in a solvent mixture of EtOAc (15 0 mL) and acetic acid (5 0 mL), was added Pd/C (10 % , 0 18 g) and stirred in an atmosphere of hydrogen at 15 psi for 2 h The catalyst was removed by filtration The filtrate was concentrated to dryness and the residue was residue was purified by reverse-phase HPLC using 10 - 90% acetonitrile/water gradient (30 min) at a flow rate of 100 mL/min The appropriate fractions (m/z = 451) were combined and freeze dried to afford (0 32 g, 645) of the title compound as its trifluoroacetate salt $^1H$ NMR (DMSO-$d_6$/400 mHz) δ 8 78 (d, 1H, J = 5 2 Hz), 8 28 (br, 2H), 7 62 (m, 1H), 7 38 (m, 1H), 7 25 (d, 1H, J = 5 2 Hz), 7 18 (m 1H), 6 62 (s, 1H), 5 32 (s, 2H), 5 29 (s, 2H), 4 24 (s, 2H), and 2 46 (s, 3H), $^{19}F$ NMR (DMSO-$d_6$/400 MHz) δ -109 59 (m), -113 67 (m), ES-HRMS m/z 451 0530 (M+H $C_{19}H_{18}N_4O_2BrF_2$ requires 451 0576)

Example 395

286

284

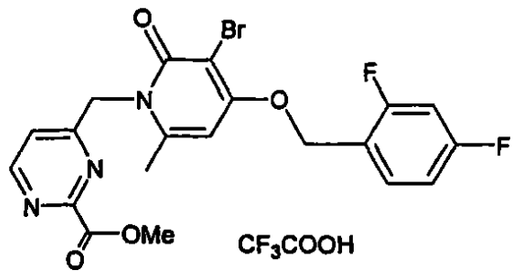


$CF_3COOH$

3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-[(2-methoxypyrimidin-4-yl)methyl]-6-methylpyridin-2(1H)-one trifluoroacetate

A solution of 4-{[3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrimidine-2-carbonitrile trifluoroacetate (0 13 g, 0 00023 mol) in MeOH (2 0 mL) was treated with 1N NaOH (0 5 mL) After stirring at room temperature for 3h, it was heated at 60 °C for an additional 3 h and left overnight roon temperature The resulting solution was diluted with acetonitrile, and purified by reverse-phase HPLC using 10 - 90% acetonitrile/water gradient (30 min) at a flow rate of 100 mL/min The appropriate fractions (m/z = 452 ) were combined and freeze dried to afford the title compound ( 0 015 g) as a white powder $^1H$ NMR ($CD_3OD$) δ 8 84 (d, 1H, J = 5 2 Hz)
7 62 (d, 1H, J = 5 2 Hz), 7 05 (m, 2H), 6 57 (s, 1H), 5 49 (s, 2H), 5 32 (s, 2H), 3 96 (s, 3H), and 2 49 (s, 3H), ES-HRMS m/z 452 0440 (M+H $C_{19}H_{17}N_3O_3BrF_2$ requires 452 0416)

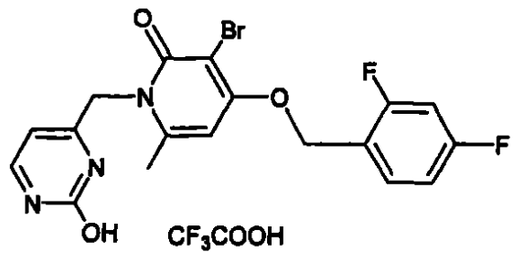
Example 396



Methyl 4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrimidine-2-carboxylate trifluoroacetate

The title compound was obtained as a second product in the formation of 3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-[(2-methoxypyrimidin-4-yl)methyl]-6-methylpyridin-2(1H)-one trifluoroacetate $^1$H NMR ($CD_3OD$/400 MHz) δ 8 46 (d, 1H, J = 5 2 Hz), 7 62 (m, 1H), 7 00 (m 2H), 6 93 (d, 1H, J = 5 2 Hz), 6 55 (s, 1H), 5 39 (s, 2H), 5 32 (s, 2H), 3 85 (s, 3H), and 2 44 (s, 3H), ES-HRMS m/z 480 0340 (M+H $C_{20}H_{17}N_3O_4BrF_2$ requires 480 0365)

Example 397



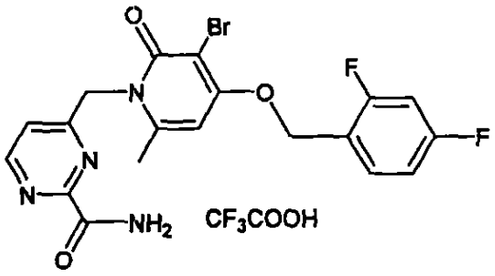
3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-[(2-hydroxypyrimidin-4-yl)methyl]-6-methylpyridin-2(1H)-one trifluoroacetate

A mixture of 4-{[3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrimidine-2-carbonitrile trifluoroacetate (0 2 g, 0 00035 mol) potassium fluoride on

aluminum oxide (0 25 g) in t-butanol (5 0 mL) was refluxed for 4 h under argon atmosphere The reaction mixture was cooled, filtered the precipitate and washed with ethanol The combined filtrate and washings were concentrated to dryness and the residue was purified by reverse-phase HPLC using 10 - 90% acetonitrile/water gradient (30 min) at a flow rate of 100 mL/min The appropriate fractions (m/z = 452) were combined and freeze dried to afford the title compound ( 0 05 g) as a white powder

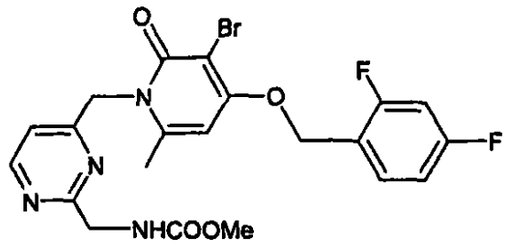
$^1$H NMR (DMSO-$d_6$/400 Mz) δ 7 85 (d, 1H J = 6 4 Hz), 7 64 (m, 1H), 7 30 (m 1H), 7 15 (m 1H), 6 55 (s, 1H), 6 22 (d, 1H, J = 6 4 Hz), 5 28 (s, 2H), 5 12 (d, 2H), and 2 29 (s, 3H), $^{19}$F- NMR (DMSO-$d_6$/400 MHz) δ - 109 69 (m), and -113 67 (m), ES-HRMS m/z 438 0228 (M+H $C_{18}H_{15}N_3O_3BrF_2$ requires 438 0259)

Example 398




4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrimidine-2-carboxamide trifluoroacetate

The title compound was obtained by a procedure described for Example 397 $^1$H NMR (DMSO-$d_6$/400 MHz) δ 8 82 (d, 1H J = 5 2 Hz), 8 01 (br, 1H), 7 79 (br 1H), 7 64 (m, 1H), 7 34 (m , 2H), 7 16 (m 1H), 6 62 (s, 1H), 5 36 (s, 2H), 5 30 (s, 2H), and 2 38 (s, 3H), $^{19}$F NMR (DMSO-$d_6$/400 MHz) δ - 109 64 (m), and -113 66 (m), ES-HRMS m/z 465 0385 (M+H $C_{19}H_{16}N_4O_3BrF_2$ requires 465 0368)



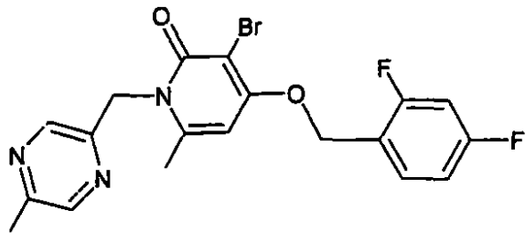

Example 399

Methyl (4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrimidin-2-yl)methylcarbamate

To a solution of 4-{[2-(Aminomethyl)-4-fluorobenzyl]oxy}-3-bromo-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one trifluoroacetate (0 13 g, 0 00023 mol) in dimethylacetamide (1 0 mL), was added triethylamine (0 04 mL, 0 0003 mol), followed by the addition of methylchloroformate (0 05 mL) and stirred at 0 °C for 30 min under argon atmosphere The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (2 x 20 mL), The combined organic extracts were washed with water, dried ($Na_2SO_4$) and concentrated to dryness The resulting residue was purified by flash chromatography (5% MeOH in EtOAc) to afford the title compound (0 055 g, 37%) as pale yellow powder $^1H$ NMR (DMSO-$d_6$/400 MHz) δ 8 65 (d, 1H J = 5 6 Hz), 7 63 (1H), 7 5 (m, 1H), 7 28 (m 1H), 7 13 (m, 2H), 6 59 (s, 1H), 5 28 (s, 4H), 5 26 (d, 2H, J = 6 0 Hz), and 2 46 (s, 3H), $^{19}F$ NMR (DMSO-$d_6$/400 MHz) δ - 109 64 (m), and -113 71 (m), ES-HRMS m/z 509 0621 (M+H $C_{21}H_{20}N_4O_4BrF_2$ requires 509 0630)

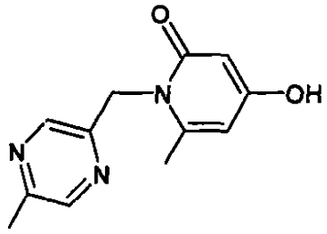
Example 400

288
286



3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[(5-methylpyrazin-2-yl)methyl]pyridin-2(1H)-one

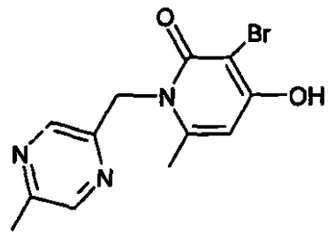
Step 1



4-hydroxy-6-methyl-1-[(5-methylpyrazin-2-yl)methyl]pyridin-2(1H)-one

A mixture of 4-hydroxy-6-methyl-2-pyrone (5 0 g, 0 04 mol) and 5-aminomethyl-2-methylpyrazine (5 0 g, 0 041 mol) in water (25 0 ml) was heated at 100 °C for 1 h under argon atmosphere The reaction mixture was ccoled, and filtered the yellow precipitate It was washed with ethanol, and dried in vacuo to afford the title compound (5 8 g, 63%) as a pale yellow powder $^1$H NMR (DMSO-$d_6$/400 MHz) δ 10 43 (br, 1H), 8 38(d, 2H, J = 5 2 Hz), 5 77 (d, 1H, J = 2 0 Hz), 5 58 (d, 1H, J = 2 0 Hz), 4 92 (s, 2H), 2 24 (s, 3H), and 2 22 (s, 3H), ESMS m/z 232 (M+H)

Step 2



3-Bromo-4-hydroxy-6-methyl-1-[(5-methylpyrazın-2-yl)methyl]pyrıdın-2(1H)-one

The title compound was prepared by a procedure described in step 2 for Example 385

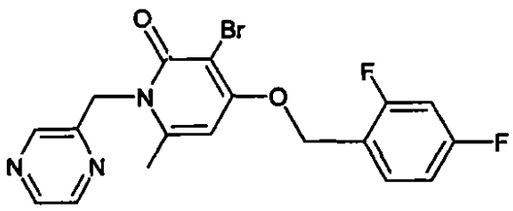
Yield 64%, $^1$H NMR ($CD_3OD$/400 MHz) δ8 47 (s, 1H), 8 42 (s, 1H), 6 07 (s, 1H), 5 38 (s, 2H), 2 51 (s, 3H), and 2 44 (s, 3H), ESMS m/z 310 and 312 (M+H)

Step 3

To a mixture of 3-Bromo-4-hydroxy-6-methyl-1-[(5-methylpyrazın-2-yl)methyl]pyrıdın-2(1H)-one (0 45 g, 0 0015 mol), and potassium carbonate (0 25 g, 0 0018 mol) in dimethylacetamide (5 0 mL) was added 2,4 difluorobenzyl bromide (0 25 mL 0 0019 mol)and stirred at room temperature under argon for 1 h Dimethylacetamide was distilled in vacuo and the residue was partitioned between $CH_2Cl_2$ (20 mL) and water (20 mL) The organic phase was washed with water, dried ($Na_2SO_4$) and concentrated under reduced pressure The resulting material was purified by flash chromatography (EtOAc/hexane 4 1 v/v) as the eluent The appropriate fractions (m/z = 451/453) were combined and concentrated under reduced pressure to give a white (0 25 g, 38% )solid $^1$H NMR ($CD_3OD$/400 MHz) δ8 49 (s, 1H), 8 40 (s, 1H), 7 60 (m, 1H), 6 99 (m, 2H), 6 51 (s, 1H), 5 42 (s, 2H), 5 29 (s, 2H), 2 54 (s, 3H), and 2 50 (s, 3H), $^{19}$F NMR ($CD_3OD$/400 MHz) δ-117 70(m), and -

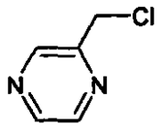
116 09 (m), ES-HRMS m/z 436 0439 (M+H $C_{19}H_{17}N_3O_2BrF_2$ requires 436 0467)

Example 401



3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(pyrazin-2-ylmethyl)pyridin-2(1H)-one

Step 1



2- Chloromethylpyrazine

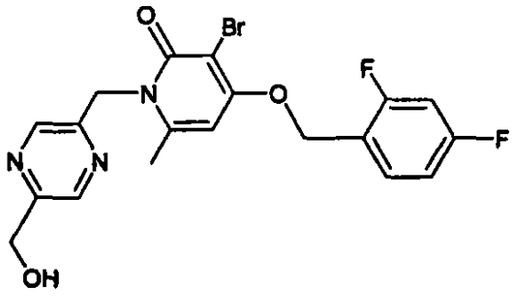
A mixture of 2-methylpyrazine (3 5 g, 0 037 mol), NCS (6 3 g, 0 047 mol) and benzoyl peroxide (0 05 g) was heated to reflux for 16 h under argon atmosphere It was filtered and the filtrate was concentrated to dryness The resulting residue was purified by flash chromatography using 30 % EtOAc in hexane to afford 2-chloromethylpyrazine as a dark colored liquid (1 7 g, 36 5) $^1$H NMR ($CD_3OD$/400 MHz) δ 8 75 (d, 1H, J = 1 2 Hz), 8 58 (m, 1H), 8 56 (m, 1H), and 4 75 (s, 2H), ESMS m/z = 129 (M+H)

Step 2

3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (1 8 g, 0 0055 mol) and 2- chloropyrazine (0 8 g, 0 00625) were suspended in THF (25 mL), then added NaH (0 15 g, 0 0062 mol), KI (0 1 g) and the mixture was heated at 65 °C under argon atmosphere for 16 h The reaction mixture was cooled, added acetic acid (0 5 mL) and concentrated to dryness under reduced pressure The residue was stirred with a mixture of water (50 mL) and EtoAc (25 mL) and filtered the precipitate It was washed with water, and acetonitrile an dried in vacuo to afford 1 7 g of light brown powder $^1$H NMR ($CD_3OD$/400 MHz) δ 8 65 (d, 1H), 8 49 (m, 1H), 8 47 9m, 1H), 7 61 (~ q, 1H), 7 02 (m, 2H), 6 52 (s, 1H), 5 47 (s, 2H), 5 23 (s, 2H), and 2 53 (s, 3H),

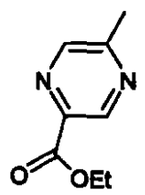
$^{19}$F NMR ($CD_3OD$/400 MHz) δ -111 72(m), and -116 07 (m), ES-HRMS m/z 422 0283 (M+H $C_{18}H_{15}N_3O_2BrF_2$ requires 422 0310)

Example 402




3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-{[5-(hydroxymethyl)pyrazin-2-yl]methyl}-6-methylpyridin-2(1H)-one

Step 1

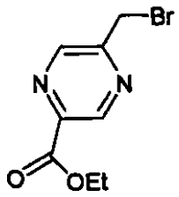



Ethyl 5-methylpyrazine-2-carboxylate

287
290

A solution of 5-methylpyrazine-2-carboxylic acid (15 0 g, 0 109 mol) in ethanol (70 0 mL) containing (1 5 g, 0 0079 mol) was heated to reflux for 4 h under argon atmosphere The dark colored solution was cooled, added sod bicarbonate (1 0 g) and concentrated under reduced pressure The residue was partitioned between water (50 mL) and EtOAc (100 mL) The organic layer was washed with water (2 x 25 mL), dried ($Na_2SO_4$), and concentrated under reduced pressure to afford ethyl 5-methylpyrazine-2-carboxylate (12 05 g, 67%) as an orange colored liquid $^1H$ NMR ($CD_3OD$/400 MHz) δ 9 1 (d 1H, J = 1 2 Hz), 8 62 (d, 1H, J = 1 2 Hz), 4 45 (q, 2H, J = 7 2 Hz), 2 63 (s, 3H), and 1,41 (t, 3H, J = 7 2 Hz), ESMS m/z 167 (M+H)

Step 2

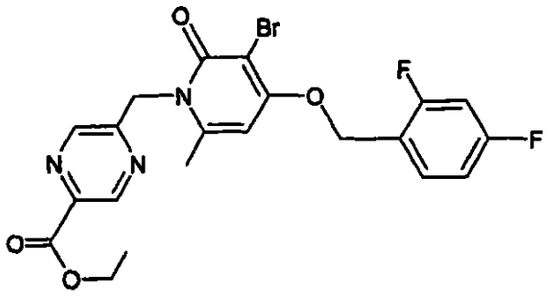



Ethyl 5-(bromomethyl)pyrazine-2-carboxylate

A solution of ethyl 5-methylpyrazine-2-carboxylate (12 0 g, 0 072 mol) in glacial acetic acid (60 mL) containing bromine (4 0 mL) was heated at 80 °C under anhydrous conditions for 45 min After the removal of acetic acid in vacuo, the residue was partitioned between saturated, bicarbonate (100 mL) and EtOAc (3 x 30 mL) The combined EtOAc extracts were washed with water (2 x 25 mL), dried ($Na_2SO_4$), and concentrated under reduced pressure The resulting liquid was purified by flash chromatography (20 %EtOAc in hexane) to afford ethyl-(5bromomethylpyrazine-2-carboxylate (7 7 g, 44%) as an orange

colored liquid $^1$H NMR ($CD_3OD$/400 MHz) δ 9 18 (d 1H, J = 1 2 Hz), 8 85 (d, 1H, J = 1 2 Hz), 4 71 (d, 2H), 4 47 (q, 2H, J = 7 2 Hz), and 1 42 (t, 3H, J = 7 2 Hz), ES-HRMS m/z 244 9942 (M+H $C_8H_{10}N_2O_2Br$ requires 244 9920)

Step 3



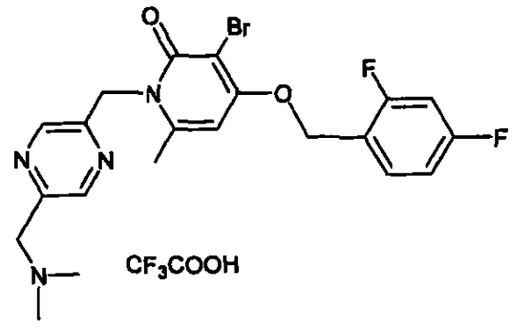
Ethyl 5-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrazine-2-carboxylate

To a mixture of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (6 0 g, 0 018 mol) and ethyl 5-(bromomethyl)pyrazine-2-carboxylate (4 9 g, 0 02 mol) in THF (50 0 mL) was added NaH (0 5 g) and heated at 55 °C under argon atmosphere for 3 h The reaction mixture was cooled , added acetic acid (1 2 ml)and concentrated under reduced pressure The residue was triturated with water and filtered the solid It was washed with water, followed by ethanol and dried in vacuo to afford the title compound (3 0 g, 78% )as alight brown powder $^1$H NMR ($CD_3OD$/400 MHz) δ 9 10 (d 1H, J = 1 2 Hz), 8 77 (d, 1H, J = 1 2 Hz), 7 61 (m, 1H), 7 01 (m 2H), 6 54 (s, 1H), 5 54 (s, 2H), 5 30 (s, 2H), 4 43 (q, 2H, J = 6 8 Hz), 2 52 (s, 3H), and 1,39 (t, 3H, J = 6 8 Hz), $^{19}$F NMR ($CD_3OD$/400 MHz) δ −111 64 (m), and -116 04 (m), ES-HRMS m/z 494 0482 (M+H $C_{21}H_{19}N_3O_4BrF_2$ requires 494 0522)

Step 4

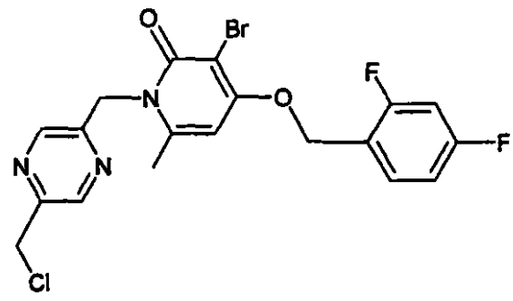
To a suspension of ethyl 5-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrazine-2-carboxylate (2.0 g, 0.004 mol) in t-butanol (15.0 mL and THF (5.0 mL) was added $NaBH_4$ (0.18 g, 0.0047 mol) and the mixture was stirred at room temperature for 16 h under argon atmosphere. It was cooled, added MeOH (5.0 mL) and acetic acid (1.0 mL) and concentrated to dryness. The residue was triturated with water and filtered. It was washed with water, dried in vacuo and purified by flash chromatography (1% MeOH in EtOAc to afford the title compound (0.75 g, 41%) as a pale yellow powder. $^1H$ NMR ($CD_3OD$/400 MHz) δ 8.58 (d, 1H, J = 1.6 Hz), 8.56 (d, 1H, J = 1.6 Hz), 7.6 (m, 1H), 7.01(m, 2H), 6.52 (s, 1H), 5.46 (s, 2H), 5.29 (s, 2H), 4.71 (s, 2H), and 2.54 (s, 3H). $^{19}F$ NMR ($CD_3OD$/400 MHz) δ -111.70(m), and -116.06 (m). ES-HRMS m/z 452.0394 (M+H $C_{19}H_{17}N_3O_3BrF_2$ requires 452.0416)

Example 403




3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-({5-[(dimethylamino)methyl]pyrazin-2-yl}methyl)-6-methylpyridin-2(1H)-one trifluoroacetate

Step 1



3-Bromo-1-{[5-(chloromethyl)pyrazın-2-yl]methyl}-4-[(2,4-difluorobenzyl)oxy]-6-methylpyrıdın-2(1H)-one

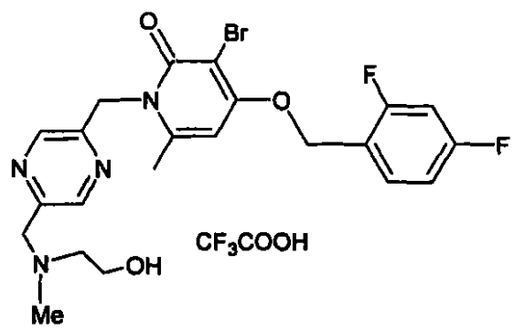
Cyanurylchloride (0 42g, 0 0023 mol) was added to DMF (0 52 mL) and stirred at room temperature for 15 mın Then added dichloromethane (15 mL) followed by the addition of 3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-{[5-(hydroxymethyl)pyrazın-2-yl]methyl}-6-methylpyrıdın-2(1H)-one 1 0 g, 0 0022 mol) and reaction mixture was stirred at room temperature under argon atmosphere After 1 h, an additional 1 0 mL of DMF was added and the reaction was allowed to proceed for another hour, when a clear solution was obtained The solution was diluted with dichloromethane (20 mL) and washed with water, dried ($Na_2SO_4$), and concentrated to dryness under reduced pressure The residue was triturated with EtOAc, filtered, washed with EtOAc and dried to afford 0 79 g ( 77%) of the title compound as a pale yellow powder $^1H$ NMR ($CD_3OD$/400MHz) δ 8 66 (s, 2H), 7 73 (m, 1H), 7 05 (m, 2H), 6 56 (s, 1H), 5 52 (s, 2H), 5 33 (s, 2H), 4 74 (s, 2H), and 2 57 (s, 3H), ES-HRMS m/z 470 0051 (M+H $C_{19}H_{16}N_3O_2BrClF_2$ requires 470 0077)

Step 2

A suspension of 3-Bromo-1-{[5-(chloromethyl)pyrazin-2-yl]methyl}-4-[(2,4-difluorobenzyl)oxy]-6-methylpyrıdın-2(1H)-

one (0 25 g, 0 00053 mol) in THF (1 0 mL) was treated with N, N,-dimethyl amine (1 0 mL of 2M soln in THF) and stirred at room temperature for 16 h The reaction mixture was concentrated and the title compound was isolated by reverse-phase HPLC using 10 - 90% acetonitrile/water gradient (30 min) at a flow rate of 100 mL/min The appropriate fractions (m/z = 479) were combined and freeze dried to afford the title compound (0 27 g, 87%) as a white powder $^1$H NMR ($CD_3OD$/400MHz) δ 8 78 (d 1H, J Hz), 8 56 (d, 1H, J = 1 2 Hz), 7 61 (m 1H), 7 01 (m, 2H), 6 55 (s, 1H), 5 49 (s, 2H), 5 30 (s, 2H), 4 52 (s, 2H), 2 94 (s, 6H) and 2 57 (s, 3H), $^{19}$F NMR ($CD_3OD$) = δ −111 56 (m) and −116 02 (m), ES-HRMS m/z 479 0885 (M+H $C_{21}H_{22}N_4O_2BrF_2$ requires 479 0389)

Example 404



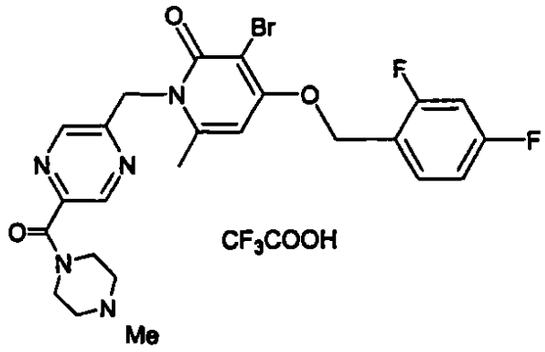

3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-[(5-{[(2-hydroxyethyl)(methyl)amino]-methyl}pyrazin-2-yl)methyl]-6-methylpyridin-2(1H)-one trifluoroacetate

The title compound was prepared in a similar manner as described for Example 403, substituting N-methylaminoethanol for N, N-dimethylamine Yield = 78%,

$^1$H NMR ($CD_3OD$/400MHz) δ 8 78 (d 1H, J Hz), 8 59 (d 1H, J = 1 2 Hz), 7 6 (m, 1H), 7 01 (m, 2H), 6 55 (s, 1H), 5 49 (s,

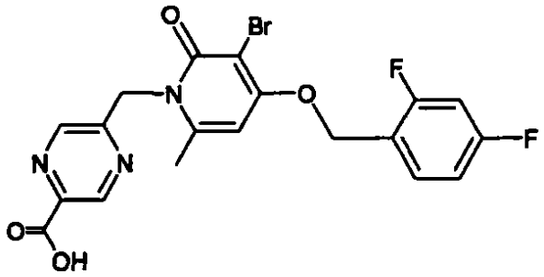
2H), 5 30 (s, 2H), 3 89 (~t, 2H), 2 97 (s, 3H), and 2 57 (s, 3H), $^{19}F$ NMR ($CD_3OD$/400 MHz) = δ −111 56 (m) and −116 04 (m), ES-HRMS m/z 509 0964 (M+H $C_{22}H_{24}N_4O_3BrF_2$ requires 509 0994)

Example 405




3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-({5-[(4-methylpiperazin-1-yl)carbonyl]pyrazin-2-yl}methyl)pyridin-2(1H)-one trifluoroacetate

Step 1




5-{[3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrazine-2-carboxylic acid

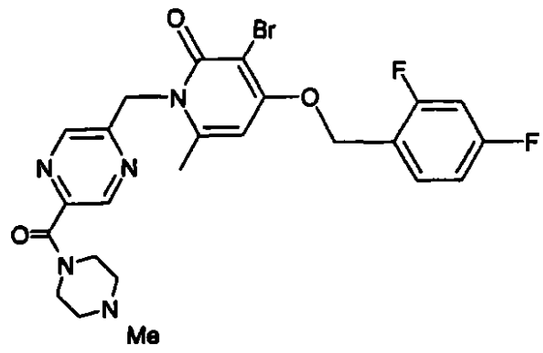
A suspension of ethyl 5-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrazine-2-carboxylate (0 18 g, 0 002 mol) and 1N NaOH (0 6 mL in 1 1 v/v EtOH/Water) was stirred at room temperature for 1 5 h The reaction mixture was acidified with 5% citric acid and filtered the

precipitate It was washed with water, followed by ethanol and dried in vacuo to afford the title compound (0 14 g, 77%) as a light brown powder $^1$H NMR ($CD_3OD$/400 MHz) = δ 9 03 (s 1H), 8 60 (s, 1H), 7 61 (m 1H), 7 00 (m, 2H), 6 52 (s, 1H), 5 51 (s, 2H), 5 30 (s 2H), and 2 52 (s, 3H), $^{19}$F NMR ($CD_3OD$/400 MHz) = δ −111 75 (m) and -116 06 (m), ES-HRMS m/z 466 0209 (M+H $C_{19}H_{15}N_4O_3BrF_2$ requires 466 0209)

Step 2

To a solution of 5-{[3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrazine-2-carboxylic acid (0 28 g, 0 0006 mol) in DMF (3 0 mL), at -15 °C, was added isobutylchloroformate (0 08 g, 0 0006 mol), followed by the addition of N-methylmorpholine (0 06 g, 0 00063 mol) and stirred under argon for 15 min N-methylpiperazine (0 072 g, 0 00072 mol) in DMF (2 0 mL) was then added to the reaction and the mixture was stirred at room temperature for 3 h After the removal of the solvents in vacuo, the residue was purified by reverse-phase HPLC using 10 - 90% acetonitrile/water gradient (30 min) at a flow rate of 100 mL/min The appropriate fractions (m/z = 548) were combined and freeze dried to afford the title compound ( 0 32 g, 80%) as a white powder $^1$H NMR ($CD_3OD$/400 MHz) δ 8 89 (d 1H, J = 1 6 Hz), 8 73 (d, 1H, J = 1 6 Hz), 7 61 (m, 1H), 7 01 (m,2H), 6 56 (s, 1H), 5 50 (s, 2H), 5 30 (s, 2H), 2 9 (s, 3H), and 2 57 (s, 3H), $^{19}$F NMR ($CD_3OD$/400 MHz) = δ - 109 36 (m) and - 114 91(m), ES-HRMS m/z 548 1090 (M+H $C_{24}H_{25}N_5O_3BrF_2$ requires 548 1103)

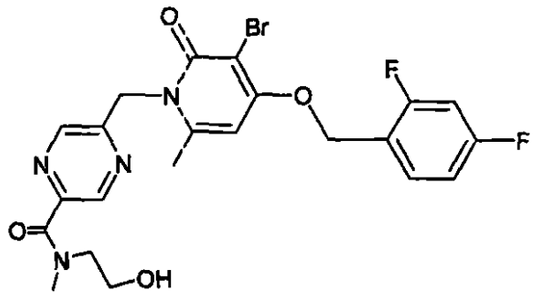
Example 406




3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-({5-[(4-methylpiperazin-1-yl)carbonyl]pyrazin-2-yl}methyl)pyridin-2(1H)-one

A solution of 3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-({5-[(4-methylpiperazin-1-yl)carbonyl]pyrazin-2-yl}methyl)pyridin-2(1H)-one trifluoroacetate (0 17 g, 0 00026 mol) in 0 1N NaOH (25 mL) was stirred at room temperature for 15 min and extracted the product in ethyl acetate (2 x 20 mL) The combined organic extracts were washed with water (2 x 20 mL), dried ($Na_2SO_4$) and concentrated to dryness The residue was dried in vacuo to afford the title product (0 09 g, 64%) as a white powder $^1H$ NMR ($CD_3OD$/400 MHz) δ 8 69 (d 1H, J = 1 2 Hz), 8 67 (d, 1H, J = 1 2 Hz), 7 60 (m, 1H), 7 00 (m, 2H), 6 54 (s, 1H), 5 50 (s, 2H), 5 30 (s, 2H), 3 78 (t, 2H, J = 4 8 Hz), 3 58 (t, 2H, J = 4 8 Hz), 2 526 (s, 3H), 2 53 (t, 2H, J = 4 8 Hz), 2 44 (t, 2H, J = 4 8 Hz), and 2 31 (s, 3H), $^{19}F$ NMR ($CD_3OD$/400 MHz) = δ -111 65 (m) and -116 06 (m), ES-HRMS m/z 548 1123 (M+H $C_{24}H_{25}N_5O_3BrF_2$ requires 548 1103)

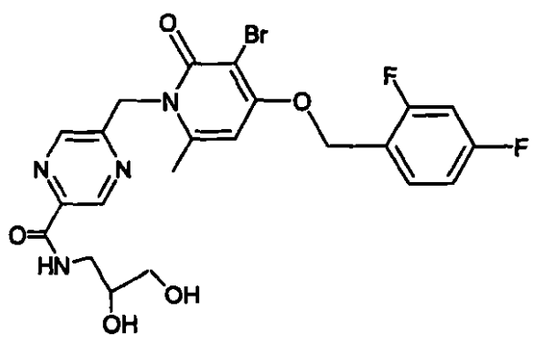
Example 407



5-{[3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl} N-(2-hydroxyethyl)-N-methylpyrazine-2-carboxamide

The title compound was prepared in a similar manner as described for Example 405 , substituting N-methylpiperazine by N-methylethanolamine Yield = 60%, $^1$H NMR ($CD_3OD$/400 MHz) δ 8 69 (d 1H, J = 1 2 Hz), 8 64 (d 1H, J = 1 2 Hz), 7 61 (m, 1H), 7 00 (m, 2H), 6 54 (s, 1H), 5 49 (s 2H), 5 30 (s, 2H), 3 81 (~ t, 1H), 3 66 (m, 2H) 3 56 (t, 1H, J = 5 2 Hz), 3 12 (d, 3H J = 7 6 Hz), 2 56 (s, 3H), $^{19}$F NMR ($CD_3OD$/400 MHz) δ −109 64 (m) and −113 66 (m), ES-HRMS m/z 523 0743 (M+H $C_{22}H_{22}N_4O_4BrF_2$ requires 523 0797)

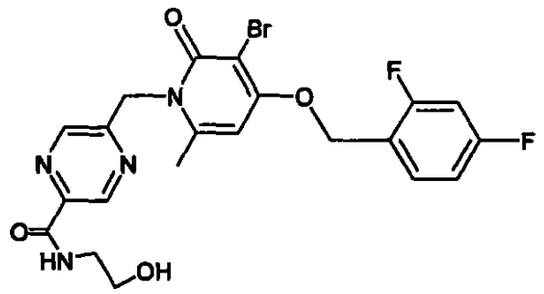
Example 408



5-{[3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-N-(2,3-dihydroxypropyl)pyrazine-2-carboxamide

The title compound was prepared in a similar manner as described for EXAMPLE 405, substituting N-methylpiperazine by 3-amino-1,2-propanediol Yield = 56%, $^1$H NMR ($CD_3OD$/400 MHz) δ 9 09 (d 1H, J = 1 2 Hz), 8 70 (d 1H, J = 1 2 Hz), 7 60 (m,1H), 7 00 (m, 2H), 6 54 (s, 1H), 5 53 (s 2H), 5 30 (s, 2H), 3 80 (m, 1H), 3 61 (dd, 1H), 5 53 (d, 2H), J = 5 2 Hz), 3 42 (dd, 1H), and 2 55 (s, 3H), $^{19}$F NMR ($CD_3OD$/400 MHz) δ -109 65 (m), and -113 67(m), ES-HRMS m/z 539 0703 (M+H $C_{22}H_{22}N_4O_4BrF_2$ requires 539 0736)

Example 409

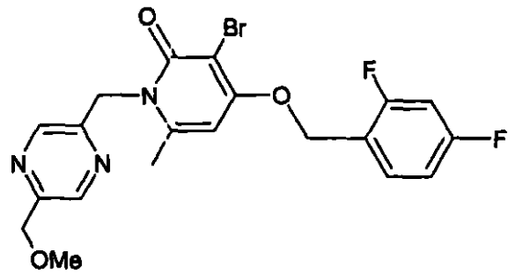



5-{[3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-N-(2-hydroxyethyl)pyrazine-2-carboxamide

The title compound was prepared in a similar manner as described for EXAMPLE 405, substituting N-methylpiperazine by 2-aminoethanol Yield = 46%, $^1$H NMR ($CD_3OD$/400 Hz) δ 9 08 (d 1H, J = 1 2 Hz), 8 70 (d, 1H, J = 1 2 Hz), 7 601 (m, 1H), 7 01 (m, 2H), 6 54 (s, 1H), 5 53 (s, 2H), 5 30 (s, 2H), 3 69 (t, 2H, J = 6 0 Hz), 3 53 (t, 2H, J = 6 0 Hz), 2 55 (s, 3H), ), $^{19}$F

NMR ($CD_3OD$/400 Hz) δ −111 67 (m) and −116 07(m), ES-HRMS m/z 509 0616 (M+H $C_{21}H_{20}N_4O_4BrF_2$ requires 509 0630)

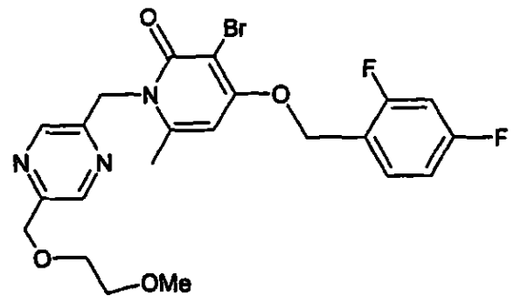
Example 410




3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-{[5-(methoxymethyl)pyrazin-2-yl]methyl}-6-methylpyridin-2(1H)-one

To a solution of 3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-{[5-(hydroxymethyl)pyrazin-2-yl]methyl}-6-methylpyridin-2(1H)-one (0 35 g, 0 00078 mol) in DMF at 0 °C, was added NaH (0 022 g, 0 00092 mol) and stirred for 10 min Iodomethane (0 05 mL) was added to the reaction and the mixture was stirred at 10 °C for 3 h DMF was distilled in vacuo and the residue was partitioned between 5% citric acid and EtOAc (15 0 mL) The organic phase was washed with water, dried ($Na_2SO_4$) and concentrated to dryness The residue was purified by flash chromatography (EtOAc), and the appropriate fractions were combined and concentrated to a pale yellow powder $^1H$ NMR ($CD_3OD$/400 MHz) δ 8 59 (s), 8 55 (s, 1H), 7 60 (m, 1H), 6 99 (m, 2H), 6 52 (s, 1H), 5 47 (s, 2H), 5 30 (s, 2H), 4 57 (s, 2H), 3 44 (s, 2H), and 2 54 (s, 3H), $^{19}F$ NMR ($CD_3OD$/400 Hz) δ −111 69 (m) and −116 09(m), ES-HRMS m/z 466 0577 (M+H $C_{21}H_{19}N_3O_3BrF_2$ requires 466 0572)

Example 411

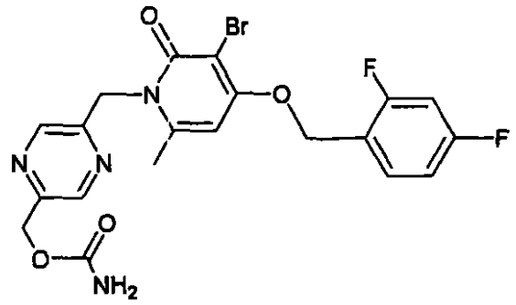



3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-({5-[(2-methoxyethoxy)methyl]pyrazin-2-yl}methyl)-6-methylpyridin-2(1H)-one

To a solution of 3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-{[5-(hydroxymethyl)pyrazin-2-yl]methyl}-6-methylpyridin-2(1H)-one (0 25 g, 0 00055 mol) in dimethyl acetamide at 0 °C, was added NaH (0 016 g, 0 00067 mol) and stirred for 15 min 2-Methoxyethyl bromide (0 09 g, 0 00-65 mol) was then added , and the mixture was stirred at room temperature for 6 h Dimethylacetamide was distilled in vacuo and the product was purified by reverse-phase HPLC using 10 - 90% acetonitrile/water gradient (30 min) at a flow rate of 100 mL/min The appropriate fractions (m/z = 510) were combined and freeze dried to afford the title compound (0 32 g, 80%) as a white powder

$^1$H NMR ($CD_3OD$/400 Hz) δ 8 59 (s 1H), 8 58 (s, 1H), 7 60 (m , 1H), 7 02 (m, 2H), 6 52 (s, 1H), 5 45 (s, 2H), 5 29 (s, 2H), 4 67 (s, 2H), 3 71 (~t, 2H, ), 3 57 (~t, 2H), 3 34 (s, 3H), and 2 54 (s, 3H), ES-HRMS m/z 510 0852 (M+H $C_{20}H_{18}N_4O_4BrF_2$ requires 510 0835)

Example 412

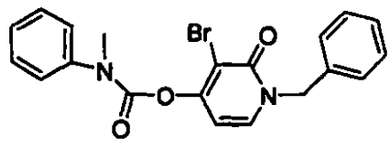


(5-{[3-Bromo-4-[(2,4-diflucrobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrazin-2-yl)methyl carbamate

To a suspension of 3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-{[5-(hydroxymethyl)pyrazin-2-yl]methyl}-6-methylpyridin-2(1H)-one (0 21 g, 0 00055 mol) in THF (5 0 mL) and DMF (2 0 mL), was added 4-nitrophenylchloroformate (0 1 g, 0 0005 mol) and cooled to 0 °C Triethylamine (0 052g, 0 0005 mol) was then added, stirred at room temperature for 1 h, and at 65 °C for an additional 1h It was cooled in an ice bath and added 2M ammonia in propanol (1 0 mL) and stirred at room temperature for 2 h After the removal of the solvents under reduced pressure, the residue was partitioned between 5% sod bicarbonate, and EtOAc (25 mL) The organic phase was washed with 5% sod bicarbonate, (3 x 25 mL), water (3 x 25 mL), dried ($Na_2SO_4$) and concentrated under reduced pressure The resulting substance was purified by isolated by reverse-phase HPLC using 10 -90% $CH_3CN$/Water (30 min gradient) at a flow rate of 100 mL/min The appropriate fractions (m/z= 495 M+H) were combined and freeze-dried, and the residue was partitioned between 5% sod bicarbonate (20 mL) and EtOAc (25 mL) The organic phase was washed with water, dried ($Na_2SO_4$) and concentrated to dryness uncer reduced pressure, to afford the title compound as a white powder (0 065 g)

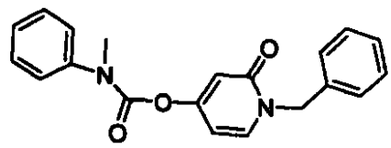
$^1$H NMR ($CD_3OD$/400 MHz) δ 8 61 (br s, 1H), 8 54 (br s, 1H), 7 60 )m 1H), 7 02 (m, 2H), 6 52 (s, 1H), 5 47 (s, 2H), 5 29 (s, 2H), 5 15 (s, 2H), and 2 54 (s, 3H) $^{19}$F NMR ($CD_3OD$) δ -111 70 (m), and -116 09 (m), ES-HRMS m/z 495 0449 (M+H $C_{20}H_{18}N_4O_4BrF_2$ requires 495 0474)

Example 413



1-benzyl-3-bromo-2-oxo-1,2-dihydropyridin-4-yl methyl(phenyl)carbamate

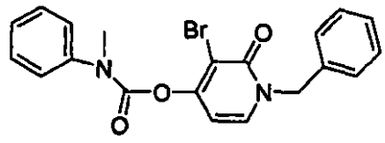
Step 1 Preparation of 1-benzyl-2-oxo-1,2-dihydropyridin-4-yl methyl(phenyl)carbamate



To a chilled solution of 1-benzyl-4-hydroxypyridin-2(1H)-one (0 375 g, 1 86 mmol) in anhydrous acetonitrile (10 mL) was added triethylamine (0 206 g, 2 04 mmol) followed by N-methyl-N-phenylcarbamoyl chloride (0 379 g, 2 24 mmol) The reaction mixture was stirred under nitrogen atmosphere at 0° C for 30 minutes then at room temperature for 1hour The reaction was monitored by TLC (5% methanol in dichloromethane) The solvent was removed under reduced pressure and the residue was washed with 10% citric acid and extracted with ethyl acetate The organic extracts were combined, washed with water and dried over anhydrous $Na_2SO_4$ The solvent was removed under

reduced pressure to afford a yellow syrup The residue was purified by flash chromatography (silica gel) using 5% MeOH in $CH_2Cl_2$ to give the desired product (0 382g, 61%) as a white semisolid $^1$H-NMR ($d_6$-DMSO, 400 MHz) δ7 8 (d, 1H, J= 7 2 Hz), 7 39 (m, 10H), 6 19 (s, 2H), 5 03 (s, 2H), 3 29 (s, 3H), ES-HRMS m/z 335 1396 (M+H calculated for $C_{20}H_{19}N_2O_3$ requires 335 1418)

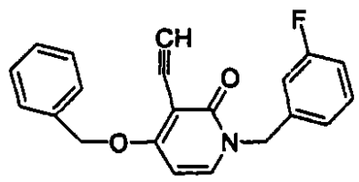
Step 2 Preparation of 1-benzyl-3-bromo-2-oxo-1,2-dihydropyridin-4-yl methyl(phenyl)carbamate




To a solution of 1-benzyl-2-oxo-1,2-dihydropyridin-4-yl methyl(phenyl)carbamate (0 38 g, 1 13 mmol) in anhydrous $CH_2Cl_2$ (7 mL) was added N-Bromosuccinimide (NBS, 0 24 g, 1 34 mmol) The reaction was stirred overnight at room temperature under nitrogen atmosphere The reaction mixture was purified by flash chromatography (silica gel) using ethyl acetate/hexane (1 1 v/v) The appropriate fractions were collected according to ES MS (M+H 413) and concentrated The dried product showed about 14% of di-bromonated product by analytical HPLC The compounds were separated by reverse phase HPLC using a 10-90% acetonitrile in water (30 minute gradient) at a 100 mL/min flow rate to afford (after lyophilization) the salt of the desired compound The salt was diluted in ethyl acetate and washed with $NaHCO_3$ The organic extracts were dried over anhydrous $Na_2SO_4$ and concentrated to afford the desired compound (0 271 g, 58%) as a beige solid $^1$H-NMR ($d_6$-DMSO, 400 MHz) δ7 94 (d, 1H, J= 7 2 Hz), 7 29 (m, 10H), 6 48 (s, 1H),

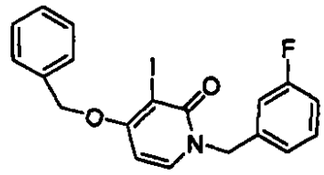
5 12 (s, 2H), 3 33 (s, 3H), ES-HRMS m/z 413 0495 (M+H calculated for $C_{20}H_{18}O_3Br$ requires 413 0496)

Example 414



4-(benzyloxy)-3-ethynyl-1-(3-fluorobenzyl)pyridin-2(1H)-one

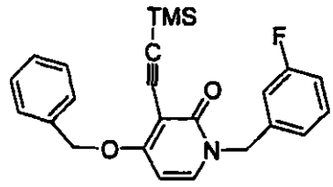
Step 1 Preparation of 4-(benzyloxy)-1-(3-fluorobenzyl)-3-iodopyridin-2(1H)-one



A mixture of 4-(benzyloxy)-1-(3-fluorobenzyl)pyridin-2(1H)-one (4 83 g, 15 6 mmol) in anhydrous acetonitrile (55 mL) and N-iodosuccinimide (NIS, 3 86 g, 17 1 mmol) was heated at 65° C under nitrogen for 4 hours The reaction mixture was concentrated under reduced pressure and the residue was purified by flash chromatography (silica gel) using ethyl acetate/hexane (1 1 v v) The appropriate fractions were collected according to ES MS (M+H 436) and washed with $Na_2SO_3$ to remove the color impurities The fractions were concentrated under reduced pressure and dried in vacuo to afford the desired product (6 15 g, 90%) as a light yellow solid $^1$H-NMR ($CD_3OD$, 400 MHz) δ7 73 (d, 1H, J= 7 6 Hz), 7 47 (d, 2H, J= 7 2 Hz), 7 39 (m, 4H), 7 08 (m, 3H), 6 39 (d, 1H,

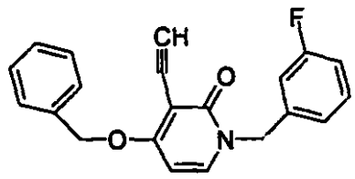
J= 8 0 Hz), 5 29 (s, 2H), 5 19 (s, 2H), ES-HRMS m/z 436 0210 (M+H calculated for $C_{19}H_{16}NO_2FI$ requires 436 0196)

Step 2 Preparation of 4-(benzyloxy)-1-(3-fluorobenzyl)-3-[(trimethylsilyl)ethynyl]pyridin-2(1H)-one



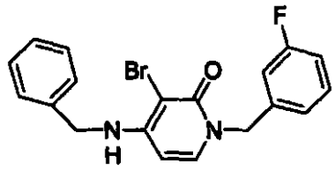

Degassed a solution of 4-(benzyloxy)-1-(3-fluorobenzyl)-3-iodopyridin-2(1H)-one (2 01 g, 4 62 mmol) in anhydrous acetonitrile (25 mL) under argon atmosphere Triethylamine (1 11 g, 11 mmol) was added and quickly degassed The reaction mixture was chilled in an ice bath for 15 minutes before adding bistriphenylphosphine-palladium chloride (0 34 g, 0 48 mmol) and cuprous iodide (0 2 g) The reaction was stirred at room temperature for 30 minutes before heating at 60° C under an atmosphere of argon for 2 hours The reaction mixture was filtered through a bed of celite and the filtrate was concentrated under reduced pressure The dark brown residue was diluted with $CH_2Cl_2$ (100 mL) and washed with water The organic extracts were combined, dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure The dark brown residue was purified by flash chromatography using 30% ethyl acetate in hexane The appropriate fractions were combined and concentrated under reduced pressure to afford the desired product (1 34 g, 72%) as a light yellow solid $^1$H-NMR ($CD_3OD$, 400 MHz) δ 7 74 (d, 1H, J= 7 6 Hz), 7 47 (d, 2H, J= 7 6 Hz), 7 35 (m, 4H) 09 (m, 3H), 6 46 (d, 1H, J= 7 6 Hz), 5 26 (s, 2H), 5 13 (s, 2H), 0 13 (s, 9H), ES-HRMS m/z 406 1638 (M+H calculated for $C_{24}H_{25}NO_2FSi$ requires 406 1610)

Step 3 Preparation of 4-(benzyloxy)-3-ethynyl-1-(3-fluorobenzyl)pyridin-2(1H)-one



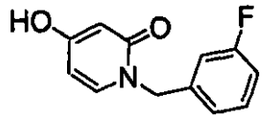

To a solution of 4-(benzyloxy)-1-(3-fluorobenzyl)-3-[(trimethylsilyl)ethynyl]pyridin-2(1H)-one (1 31 g, 3 2 mmol) in anhydrous acetonitrile (25 mL) at 0° C was added tetrabutylammonium fluoride (0 611g, 1 93 mmol) The reaction was stirred at 0° C for 15 minutes then for 1 hour at room temperature The reaction was concentrated under reduced pressure and the residue was diluted with ethyl acetate and washed with water The organic extracts were combined, dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure The residue was purified by flash chromatography (silica gel) using ethyl acetate in hexane (1 1 v/v) The appropriate fractions were combined and concentrated under reduced pressure to afford the desired product (0 779 g, 72%) as a gold solid $^1$H-NMR ($CD_3OD$, 400 MHz) δ7 73 (d, 1H, J= 7 6 Hz), 7 43 (d, 2H, J= 7 2 Hz), 7 35 (m, 4H), 7 09 (m, 3H), 6 45 (d, 1H, J= 7 6 Hz), 5 27 (s, 2H), 5 13 (s,2H), 3 78 (s, 1H), ES-HRMS m/z 334 1243 (M+H calculated for $C_{21}H_{17}NO_2F$ requires 334 1234)

Example 415



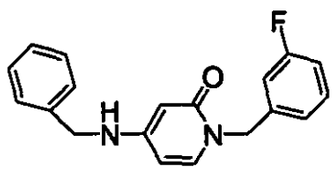
4-(benzylamino)-3-bromo-1-(3-fluorobenzyl)pyridin-2(1H)-one

Step 1 Preparation of 1-(3-fluorobenzyl)-4-hydroxypyridin-2(1H)-one



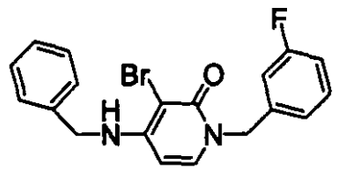
In a Fischer-Porter bottle, added a solution of 4-(benzyloxy)-1-(3-fluorobenzyl)pyridin-2(1H)-one (4 5 g, 14 56 mmol) in absolute ethanol (20 mL) Flushed the solution with nitrogen then added palladium catalyst (1 05 g, 10% Pd/C) Sealed bottle and evacuated system The system was purged with hydrogen gas (2 X 15 psi) to check for leaks The reaction was charged with hydrogen (35 psi) and stirred at room temperature for 45 minutes The system was evacuated and flushed with nitrogen The reaction was filtered and the catalyst was carefully washed with fresh ethanol The filtrate was concentrated under reduced pressure $^1$H-NMR ($CD_3OD$, 400 MHz) δ7 54 (d, 1H, J= 7 6 Hz), 7 32 (m, 1H), 7 06 (d, 1H, J= 7 6 Hz), 6 99 (m, 2H), 6 05 (dd, 1H, J= 2 4 Hz, 2 8 Hz), 5 83 (d, 1H, J= 2 4 Hz), 5 09 (s, 2H), ES-HRMS m/z 220 0774 (M+H calculated for $C_{12}H_{11}NO_2F$ requires 220 0787)

Step 2 Preparation of 4-(benzylamino)-1-(3-fluorobenzyl)pyridin-2(1H)-one



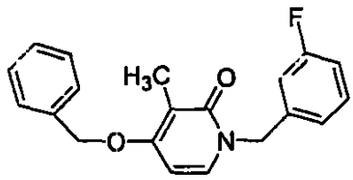
A mixture of 1-(3-fluorobenzyl)-4-hydroxypyridin-2(1H)-one (1 005 g, 4 5 mmol) in benzylamine (15 mL) was heated at reflux (185° C) under nitrogen atmosphere for 24 hours The reaction was monitored by ES-MS (MH+ 309) The solvent was removed by vacuum distillation to give a yellow residue $^1$H-NMR ($CD_3OD$, 400 MHz) δ7 31 (m, 7H), 7 03 (m, 3H), 5 98 (d, 1H, J= 7 2 Hz), 5 45 (s, 1H), 5 00 (s, 2H), 4 30 (s, 2H), ES-HRMS m/z 309 1403 (M+H calculated for $C_{19}H_{18}N_2OF$ requires 309 1375)

Step 3 Preparation of 4-(benzylamino)-3-bromo-1-(3-fluorobenzyl)pyridin-2(1H)-one



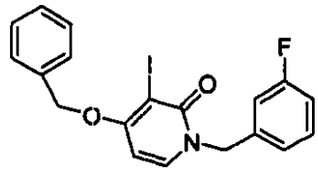

To a solution of 4-(benzylamino)-1-(3-fluorobenzyl)pyridin-2(1H)-one (0 50 g, 1 62 mmol) in anhydrous $CH_2Cl_2$ (10 mL) was added N-bromosuccinimide (NBS, 0 30 g, 1 7 mmol) The reaction was stirred at room temperature under a nitrogen atmosphere for 3 hours The reaction mixture was purified by flash chromatography (silica gel) using ethyl acetate in hexane (1 1 v/v) The appropriate fractions were combined and concentrated $^1$H-NMR ($CD_3OD$, 400 MHz) δ7 41 (d, 1H, J= 7 6 Hz), 7 31 (m, 6H), 7 04 (m, 3H), 5 99 (d, 1H, J= 7 6 Hz), 5 08 (s, 2H), 4 53 (s, 2H), ES-HRMS m/z 387 0508 (M+H calculated for $C_{19}H_{17}N_2OBrF$ requires 387 0504)

Example 416



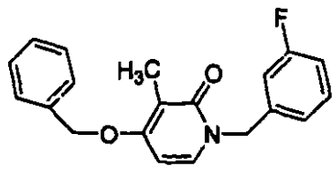
4-(benzyloxy)-1-(3-fluorobenzyl)-3-methylpyridin-2(1H)-one

Step 1 Preparation of 4-(benzyloxy)-1-(3-fluorobenzyl)-3-iodopyridin-2(1H)-one



A mixture of 4-(benzyloxy)-1-(3-fluorobenzyl)pyridin-2(1H)-one (4 83 g, 15 6 mmol) and N-iodosuccinimide (NIS, 3 86 g, 17 1 mmol) in anhydrous acetonitrile (55 mL) was heated at 65° C for 4 hours under nitrogen atmosphere The reaction mixture was concentrated under reduced pressure and the residue was purified by flash chromatography (ethyl acetate/hexane 1 1 v/v) The appropriate fractions were collected according to ES MS (M+H 436) and washed with $Na_2SO_3$ to remove the color impurities The fractions were concentrated under reduced pressure and dried in vacuo to afford the desired product (6 15 g, 90%) as a light yellow solid $^1$H-NMR ($CD_3OD$, 400 MHz) δ7 73 (d, 1H, J= 7 6 Hz), 7 36 (m, 6H), 7 08 (m, 3H), 6 39 (d, 1H, J= 8 0 Hz), 5 28 (s, 2H), 5 19 (s, 2H), ES-HRMS m/z 436 0196 (M+H calculated for $C_{19}H_{16}NO_2FI$ requires 436 0210)

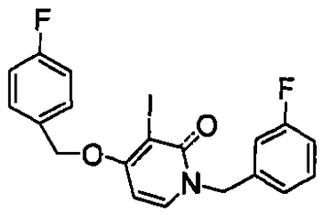
Step 2 Preparation of 4-(benzyloxy)-1-(3-fluorobenzyl)-3-methylpyridin-2(1H)-one



To a degassed solution of 4-(benzyloxy)-1-(3-fluorobenzyl)-3-iodopyridin-2(1H)-one (1 03 g, 2 36 mmol) in anhydrous DMF (15 mL) under argon atmosphere was added triethylamine (1 11 g, 11 mmol) The reaction mixture was chilled in an ice bath for 15 minutes before adding tetramethyl tin (2 10 g, 11 75 mmol) followed by bistriphenylphosphine-palladium chloride (0 166 g, 0 24 mmol) The reaction was stirred at room temperature for 30 minutes before heating at 95° C under an atmosphere of argon for 3 hours The reaction mixture was filtered through a bed of celite and the filtrate was concentrated under reduced pressure The dark brown residue was diluted with ethyl acetate (100 mL) and washed with water The organic extracts were combined, dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure The dark brown residue was purified by flash chromatography (30% ethyl acetate in hexane) The appropriate fractions were combined and concentrated under reduced pressure to afford the desired product (0 1758 g, 22%) as a light yellow solid The product was further purified by reverse phase HPLC using a 10-90% acetonitrile/water (30 minute gradient) at a 100 mL/min flow rate, to afford a cleaner product as a light yellow solid (0 0975g, 8%) $^1$H-NMR ($CD_3OD$, 400 MHz) δ7 58 (d, 1H, J= 7 6 Hz)), 7 35 (m, 6H), 6 98 (m, 3H), 6 46 (d, 1H, J= 7 6 Hz), 5 19 (s, 2H), 5 15 (s, 2H), 2 0 (s, 3H), ES-HRMS m/z 324 1366 (M+H calculated for $C_{20}H_{19}NO_2F$ requires 324 1394)

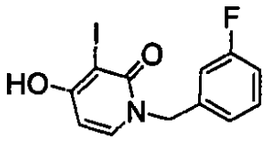
Example 417

298
301



1-(3-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]-3-iodopyridin-2(1H)-one

Step 1 Preparation of 1-(3-fluorobenzyl)-4-hydroxy-3-iodopyridin-2(1H)-one



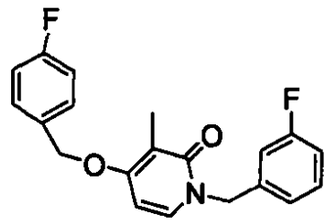
To a mixture of 1-(3-fluorobenzyl)-4-hydroxypyridin-2(1H)-one (1 1 g, 5 mmol) in acetonitrile (15 mL) was added N-iodosuccinimide (1 1 g, 5 5 mmol) along with a ca amount of dichloroacetic acid (0 1 mL) The reaction mixture stirred at room temperature for 1 hour under nitrogen The mixture was chilled in an ice bath and filtered cold with fresh $MeCl_2$ The beige solid was dried to afford the desired iodinated intermediate (1 21g, 69%) ES-LRMS m/z 346

Step 2 Preparation of 1-(3-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]-3-iodopyridin-2(1H)-one

To a mixture of 1-(3-fluorobenzyl)-4-hydroxy-3-iodopyridin-2(1H)-one (0 5g, 1 44 mmol) in DMF (5 mL) was added $K_2CO_3$ (0 199g, 1 44 mmol) followed by the addition of 4-fluorobenzyl bromide (0 189 mL, 1 51 mmol) The reaction

mixture stirred at room temperature for 30 minutes The mixture was diluted with ethyl acetate (50 mL) and washed with water The organic extracts were dried over anhydrous $Na_2SO_4$ and concentrated to dryness $^1$H-NMR ($CD_3OD$, 400 MHz) δ7 75 (d, 1H, J= 7 6 Hz), 7 49 (q, 2H), 7 34 (q, 1H), 7 11(m, 5H), 6 40 (d, 1H, J= 7 6 Hz), 5 26 (s, 2H), 5 19 (s, 2H), ES-HRMS m/z 454 0098 (M+H calculated for $C_{19}H_{15}NO_2F_2I$ requires 454 0110)

Example 418



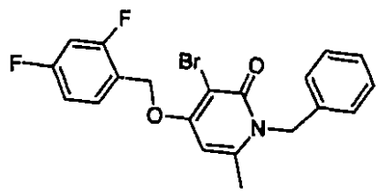

1-(3-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]-3-methylpyridin-2(1H)-one

To a degassed solution of 1-(3-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]-3-iodopyridin-2(1H)-one (0 804g, 1 7 mmol) in DMF (10 mL) and LiCl (0 25g, 5 9 mmol) was added tetramethyltin (0 49 mL, 3 54 mmol) followed by bistriphenylphosphine-palladium chloride catalyst (0 124g, 0 177 mmol) The reaction mixture was heated in an oil bath (85°-90° C) under nitrogen for 3 hours The solvent was concentrated and the residue was diluted with ethyl acetate and washed with water The organic extracts were dried over anhydrous $Na_2SO_4$ and concentrated to dryness The residue was purified by flash column chromatography (20% ethyl acetate in hexane) The appropriate fractions were concentrated $^1$H-NMR ($CD_3OD$, 400 MHz) δ 7 59 (d, 1H, J=7 6 Hz), 7 46 (m, 2H), 7 34 (m, 1H), 7 10 (m, 4H), 6 46 (d, 1H, J=7 6 Hz), 5 17 (s, 2H),

399
30

5 15 (s, 2H), 1 99 (s, 3H), ES-HRMS m/z 342 1314 (M+H calculated for $C_{20}H_{18}NO_2F_2$ requires 342 1300)

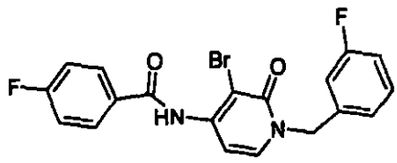
Example 419



1-benzyl-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one

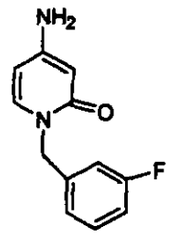
To a degassed cold solution of DMF (10 mL) and $PPh_3$ (resin, 0 93 g, 2 75 mmol) was added DEAD (0 44 mL, 2 75 mmol) The reaction mixture stirred at -10°C for 20 minutes under nitrogen A solution of 1-benzyl-3-bromo-4-hydroxy-6-methylpyridin-2(1H)-one (0 62 g, 2 1 mmol) and 2,4-difluorobenzylalcohol (0 283 mL, 2 5 mmol) in DMF (10 mL) was added to the resin suspension The reaction mixture stirred at -10° C for 30 minutes and then allowed to stir at room temperature for 1 hour The resin was filtered and rinsed with fresh MeOH and the filtrate was concentrated The residue was dissolved in ethyl acetate and purified by flash column chromatography (ethyl acetate/hexane 1 1 v/v) The appropriate fractions were concentrated $^1$H-NMR ($CD_3OD$, 400 MHz) δ 7 62 (m, 1H), 7 31 (m, 3H), 7 1 (d, 2H, J= 7 2 Hz), 7 02 (t, 2H, J= 8 6 Hz), 6 48 (s, 1H), 5 42 (s, 2H), 5 28 (s, 2H), 2 34 (s, 3H), ES-HRMS m/z 420 0399/422 0380 (M+H calculated for $C_{20}H_{17}NO_2F_2Br$ requires 420 0405/422 0387)

Example 420



N-[3-bromo-1-(3-fluorobenzyl)-2-oxo-1,2-dihydropyridin-4-yl]-4-fluorobenzamide

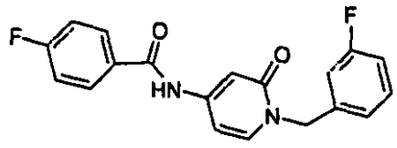
Step 1 Preparation of 4-amino-1-(3-fluorobenzyl)pyridin-2(1H)-one



In a Fischer-Porter bottle, added a solution of 4-(benzylamino)-1-(3-fluorobenzyl)pyridin-2(1H)-one (2 5g, 8 11 mmol) in glacial acetic acid (20 mL) After the solution was flushed with nitrogen, catalyst was added (10%Pd/C, 2 0g) The vessel was sealed, evacuated, and purged with hydrogen gas The system was charged with hydrogen gas (50psi) and the mixture stirred at room temperature for 4 hours The system was evacuated and flushed with nitrogen The reaction mixture was filtered through a bed of celite and washed with fresh ethanol The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography (hexane/ethyl acetate 3 4 v/v) The filtrate was concentrated $^1$H-NMR ($CD_3OD$, 400 MHz) δ 7 32 (q, 1H), 7 02 (m, 3H), 5 93 (dd, 1H, J= 2 4 Hz, 2 8 Hz), 5 58 (d, 1H, J= 2 4 Hz), ES-HRMS m/z 219 0966 (M+H calculated for $C_{12}H_{12}N_2OF$ requires 219 0928)

300 303

Step 2 Preparation of 4-fluoro-N-[1-(3-fluorobenzyl)-2-oxo-1,2-dihydropyridin-4-yl]benzamide

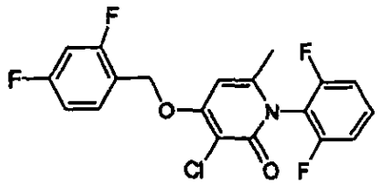


To a solution of 4-amino-1-(3-fluorobenzyl)pyridin-2(1H)-one (0 263 g, 1 2 mmol) in acetonitrile (7 mL) was added a DMAP (ca ), triethylamine (0 25 mL, 1 8 mmol) and 4-fluorobenzoyl chloride (0 213 mL, 1 8 mmol) The reaction mixture stirred at 0° C for 25 minutes and then filtered The solid was washed with 10% citric acid and water to afford the desired compound (0 326 g, 79%) after drying $^1$H-NMR ($d_6$DMSO, 400 MHz) δ 7 98 (m, 2H), 7 71 (d, 1H, J= 7 6 Hz), 7 35 (m, 3H), 7 08 (m, 3H), 6 98 (d, 1H, J= 2 4 Hz), 6 61 (dd, 1H, J= 2 4 Hz, 2 4 Hz), 5 03 (s, 2H), ESLRMS m/z 341 1

Step3 Preparation of N-[3-bromo-1-(3-fluorobenzyl)-2-oxo-1,2-dihydropyridin-4-yl]-4-fluorobenzamide

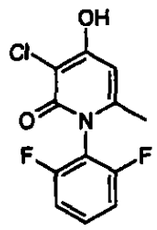
To a mixture of 4-fluoro-N-[1-(3-fluorobenzyl)-2-oxo-1,2-dihydropyridin-4-yl]benzamide (0 305g, 0 89 mmol) in acetonitrile (7 mL) was added NBS (0 159g, 0 89 mmol) The reaction mixture stirred at room temperature for 1 5 hours The filtrate was removed under reduced pressure and the residue was purified by flash column chromatography (ethyl acetate/hexane 1 1 v/v) The fractions were concentrated $^1$H-NMR ($CD_3OD$, 400 MHz) δ 8 03 (m, 2H), 7 79 (d, 1H, J= 7 6 Hz), 7 47 (d, 1H, J= 8 0 Hz), 7 28 (m, 3H), 7 12 (m, 3H), 5 23 (s, 2H), ES-HRMS m/z 419 0202/421 0191 (M+H calculated for $C_{19}H_{14}N_2O_2F_2Br$ requires 419 0201/421 0183)

Example 421



3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one

Step 1 Preparation of 3-chloro-1-(2,6-difluorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one



To a mixture of 1-(2,6-difluorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one (0 30 g, 1 26 mmol) in dichloromethane (5 mL) was added NCS (2 52 g, 1 90 mmol) The reaction mixture stirred at room temperature under nitrogen for 4 5 hours The suspension was cooled in ice bath, filtered, and the solid was rinsed with fresh dichloromethane to afford the desired product (0 271 g, 79%) as a white solid $^1$H-NMR ($CD_3OD$, 400 MHz) δ 7 58 (m, 1H), 7 22 (m, 2H), 6 20 (s 1H), 2 00 (s, 3H), ES-HRMS m/z 272 0287 (M+H calculated for $C_{12}H_9NO_2F_2Cl$ requires 272 0290)

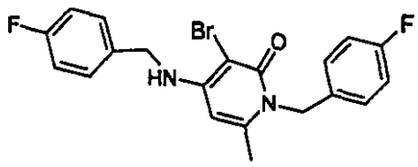
Step 2 Preparation of 3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one

To a solution of 3-chloro-1-(2,6-difluorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one (0 27 g, 1 00 mmol) in DMA

361
304

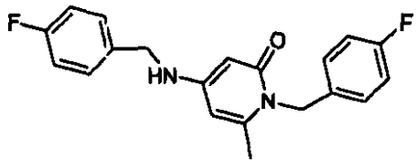
(5 mL) was added $K_2CO_3$ followed by the addition of 2,4-difluorobenzyl bromide (0 128 mL, 1 mmol) The reaction mixture stirred at room temperature for 2 hours and then was diluted in water The reaction mixture was extracted with ethyl acetate, the organic extracts were dried over $Na_2SO_4$ and the filtrate was concentrated The resulting residue was purified by flash column chromatography (ethyl acetate/hexane 3 4 v/v) to afford the desired product $^1$H-NMR ($CD_3OD$, 400 MHz) δ 7 60 (m, 2H), 7 25 (m, 2H), 7 04 (m, 2H), 6 71 (s, 1H), 5 36 (s, 2H), 2 11 (s, 3H) ES-HRMS m/z 398 0551 (M+H calculated for $C_{19}H_{13}NO_2F_4Cl$ requires 398 0571)

Example 422




3-bromo-1-(4-fluorobenzyl)-4-[(4-fluorobenzyl)amino]-6-methylpyridin-2(1H)-one

Step 1 Preparation of 1-(4-fluorobenzyl)-4-[(4-fluorobenzyl)amino]-6-methylpyridin-2(1H)-one



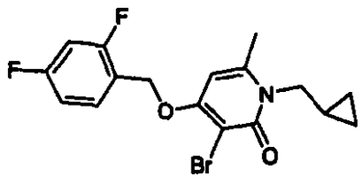

A mixture of 4-hydroxy-6-methylpyrone (5 0 g, 0 04 mol) and 4-fluorobenzylamine (10 0 g 0 08 mol) in n-butanol (25 0 mL) was heated to reflux for 24 hours under argon atmosphere The resulting solution was concentrated to dryness under reduced pressure The residue was triturated with ethyl acetate and filtered It was thoroughly washed with ethyl

acetate and dried to afford the title compound as a pale yellow powder (4 1 g 30%) $^1$H-NMR ($CD_3OD$, 400 MHz) δ 7 33 (q, 2H), 7 04 (m, 5H), 5 85 (d, 1H, J= 2 0 Hz), 5 44 (d, 2H, J= 2 4 Hz), 5 20 (s, 1H), 4 29 (s, 2H), 2 17 (s, 3H), ES-HRMS m/z 341 1488 (M+H calculated for $C_{20}H_{19}N_2OF_2$ requires 341 1460)

Step 2 Preparation of 3-bromo-1-(4-fluorobenzyl)-4-[(4-fluorobenzyl)amino]-6-methylpyridin-2(1H)-one

To a solution of 1-(4-fluorobenzyl)-4-[(4-fluorobenzyl)amino]-6-methylpyridin-2(1H)-one (0 2857 g, 0 84 mmol) in $MeCl_2$ was added NBS (0 156 g, 0 88 mmol) The reaction stirred at room temperature under nitrogen for 45 minutes The reaction mixture was diluted with $MeCl_2$ and washed with $NaHCO_3$ The organic extracts were washed with water, dried over $Na_2SO_4$, and concentrated to afford the desired product (0 3242 g, 92%) as a yellow solid $^1$H-NMR ($CD_3OD$, 400 MHz) δ 7 32 (q, 2H), 7 04 (m, 6H), 5 91 (s, 1H), 5 28 (s, 2H), 4 50 (s, 2H), 2 17 (s, 3H), ES-HRMS m/z 419 0549/421 0537 (M+H calculated for $C_{20}H_{18}N_2OBrF_2$ requires 419 0565/421 0547)

Example 423

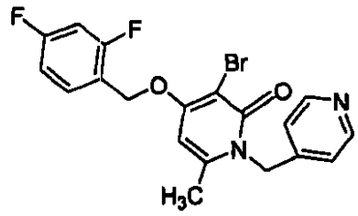



3-bromo-1-(cyclopropylmethyl)-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one

302
305

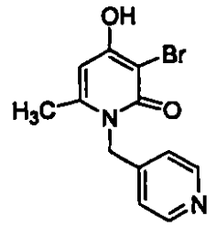
To a mixture of 3-bromo-1-(cyclopropylmethyl)-4-hydroxy-6-methylpyridin-2(1H)-one (0 276 g, 1 07 mmol) and $K_2CO_3$ (0 148 g, 1 07 mmol) in DMA (4 mL) was added 2, 4-difluorobenzyl bromide (0 14 ml, 1 07 mmol) The mixture stirred at room temperature for 1 5 hours The reaction mixture was diluted in water and extracted with ethyl acetate The organic extracts were dried over $Na_2SO_4$ and concentrated The residue was purified by flash column chromatography (ethyl acetate/hexane 1 1 v/v) The appropriate fractions were combined, and concentrated $^1$H-NMR ($CD_3OD$, 400 MHz) δ 7 60 (q, 1H), 7 04 (m, 2H), 6 42 (s, 1H), 5 26 (s, 2H), 4 06 (s, 1H), 4 04 (s, 1H), 2 50 (s, 3H), 0 53 (m, 2H), 0 43 (m, 2H), ES-HRMS m/z 384 0392 (M+H calculated for $C_{17}H_{17}N_2OBrF_2$ requires 384 0405)

Example 424




3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(pyridin-4-ylmethyl)pyridin-2(1H)-one

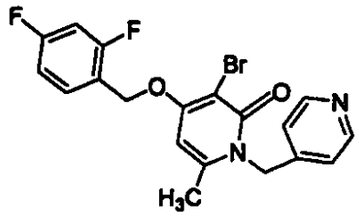
Step 1 Preparation of 3-bromo-4-hydroxy-6-methyl-1-(pyridin-4-ylmethyl)pyridin-2(1H)-one



Commercially available 4-hydroxy-6-methyl pyrone (10 g, 79 3 mmol) was condensed with commercially available 4-(aminomethyl) pyridine (8 mL, 79 3 mmol) in water (50mL) The mixture was heated in an oil bath at reflux for 1 hour under nitrogen The solvent was evaporated MS and $^1$H-NMR were consistent with the desired desbrominated structure $^1$H-NMR ($CD_3OD$, 400 MHz) δ 8 45 (dd, 2H, J= 1 6 Hz,1 6 Hz), 7 15 (d, 2H, J= 6 0 Hz), 6 00 (d, 1H, J= 2 0 Hz), 5 80 (d, 1H, J= 2 4 Hz), 5 34 (s, 2H), 2 23 (s, 3H), ES-LRMS (M+H) m/z 217

To a suspension of the above compound (0 801 g, 3 7 mmol) in $MeCl_2$ (10 mL) was added NBS (0 725 g, 4 07 mmol) The reaction mixture stirred at room temperature for 30 minutes under nitrogen The suspension was chilled in an ice bath and filtered The solid was washed with fresh $MeCl_2$ and dried to afford a beige solid (0 9663 g, 88%) after drying $^1$H-NMR ($CD_3OD$, 400 MHz) δ8 47 (d, 2H, J= 5 2 Hz), 7 16 (d, 2H, J= 6 0 Hz), 6 09 (s, 1H), 5 40 (s, 2H), 2 24 (s, 3H), ES-LRMS (M+H) m/z 295/297

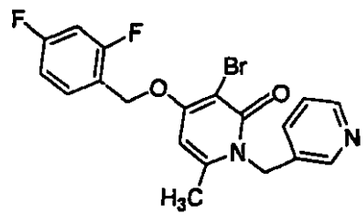
Step 2 Preparation of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(pyridin-4-ylmethyl)pyridin-2(1H)-one




To a cold solution of 2,4-difluorobenzylalcohol (0 569 mL, 5 1 mmol) in THF (5 mL) was added $PPh_3$ (resin, 2 55 g, 7 65 mmol) followed by the addition of DIAD (1 48 mL, 7 65 mmol) The reaction mixture stirred at -10°C for 15 minutes under nitrogen A solution of 3-bromo-4-hydroxy-6-methyl-1-(pyridin-4-ylmethyl)pyridin-2(1H)-one (1 0 g, 3 4 mmol), in DMF (10 mL) was added to the resin suspension The reaction

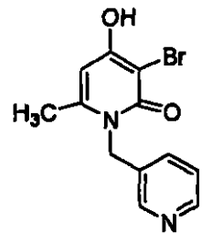
mixture stirred at 0° C for 1 5 hours and then allowed to stir at room temperature overnight The resin was filtered and rinsed with fresh MeOH and the filtrate was concentrated The residue was dissolved in ethyl acetate and purified by flash column chromatography (ethyl acetate) The appropriate fractions were concentrated $^1$H-NMR ($CD_3OD$, 400 MHz) δ 8 47 (d, 2H, J= 5 6 Hz), 7 63 (q, 1H), 7 15 (d, 1H, J= 5 6 Hz), 7 05 (m, 2H), 6 55 (s, 1H), 5 45 (s, 2H), 5 31 (s, 2H), 2 35 (s, 3H) ES-HRMS m/z 421 0366/423 0355 (M+H calculated for $C_{19}H_{16}N_2O_2F_2Br$ requires 421 0358/423 0339)

Example 428



3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one

Step 1 Preparation of 3-bromo-4-hydroxy-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one

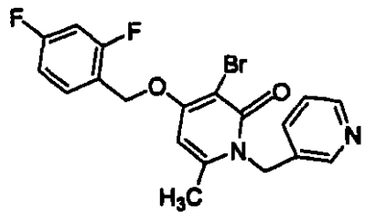


Commercially available 4-hydroxy-6-methyl pyrone (15 g, 119 0 mmol) was condensed with commercially available 3-(aminomethyl) pyridine (12 10 mL, 119 0 mmol) in water (75

mL) The mixture was heated in an oil bath at reflux for 1 hour under nitrogen The solvent was evaporated $^1$H-NMR ($CD_3OD$, 400 MHz) δ 8 43 (d, 1H, J= 4 8 Hz), 8 38 (s, 1H), 7 60 (d, 1H, J= 8 0 Hz), 7 39 (dd, 1H, J= 4 8 Hz, 4 8 Hz), 5 97 (d, 1H, J= 2 0 Hz), 5 79 (d, 1H, J= 2 4 Hz), 5 33 (s, 2H), 2 28 (s, 3H), ES-LRMS (M+H) m/z 217

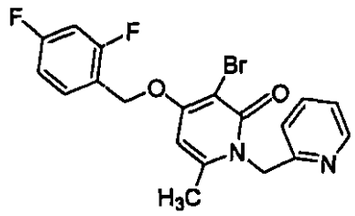
To a suspension of the above compound (5 01 g, 23 1 mmol) in $MeCl_2$ (50 mL) was added NBS (4 53 g, 25 4 mmol) The reaction mixture stirred at room temperature for 30 minutes under nitrogen The suspension was chilled in an ice bath and filtered The solid was washed with fresh $MeCl_2$ and dried to afford a beige solid (7 89 g, 114%) after drying $^1$H-NMR ($CD_3OD$, 400 MHz) δ 8 44 (d, 1H, J= 4 4 Hz), 8 39 (s, 1H), 7 62 (d, 1H, J= 7 6 Hz), 7 39 (dd, 1H, J= 5 2 Hz, 4 4 Hz), 6 07 (s, 1H), 5 39 (s, 2H), 2 29 (s, 3H), ES-LRMS (M+H) m/z 295/297

Step 2 Preparation of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one



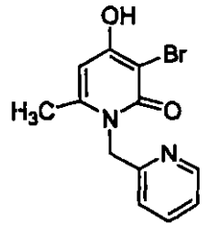

The compound was prepared essentially as described in Step 2 of example 424 using 3-bromo-4-hydroxy-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one $^1$H-NMR ($CD_3OD$, 400 MHz) δ 8 45 (d, 1H, J= 4 4 Hz), 8 41 (s, 1H), 7 63 (m, 2H), 7 41 (dd, 1H, J= 5 2 Hz, 4 8 Hz), 7 02 (m, 2H), 6 52 (s, 1H), 5 44 (s, 2H), 5 29 (s, 2H), 2 40 (s, 3H), ES-HRMS m/z 421 0355/423 0358 (M+H calculated for $C_{19}H_{16}N_2O_2F_2Br$ requires 421 0358/423 0339)

Example 435



3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(pyridin-2-ylmethyl)pyridin-2(1H)-one

Step 1 Preparation of 3-bromo-4-hydroxy-6-methyl-1-(pyridin-2-ylmethyl)pyridin-2(1H)-one

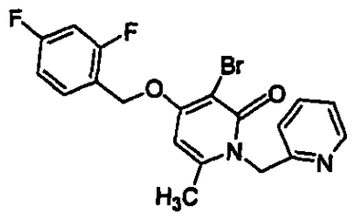


Commercially available 4-hydroxy-6-methyl pyrone (5 g, 39 6 mmol) was condensed with commercially available 2-(aminomethyl) pyridine (4 03 mL, 39 6 mmol) in water (25 mL) The mixture was heated in an oil bath at reflux for 1 5 hour under nitrogen The solvent was evaporated MS and $^1$H-NMR were consistent with the desired desbromonated structure $^1$H-NMR ($CD_3OD$, 400 MHz) δ8 47 (d, 1H, J= 4 8 Hz), 7 75 (ddd, 1H, J= 2 0 Hz, 1 6 Hz, 1 6 Hz), 7 28 (dd, 1H, J= 4 8 Hz, 4 8 Hz), 7 11(d, 1H, J= 7 6 Hz), 5 98 (d, 1H, J= 2 4 Hz), 5 77 (d, 1H, J= 2 4 Hz), 5 35 (s, 2H), 2 28 (s, 3H), ES-LRMS (M+H) m/z 217

To a suspension of the above compound (3 0 g, 13 8 mmol) in $MeCl_2$ (30 mL) was added NBS (2 71 g, 15 18 mmol) The reaction mixture stirred at room temperature for 2 5 hours under nitrogen The suspension was chilled in an ice bath and filtered The solid was washed with fresh $MeCl_2$ and dried to afford a beige solid (3 18 g, 77%) after drying $^1$H-NMR

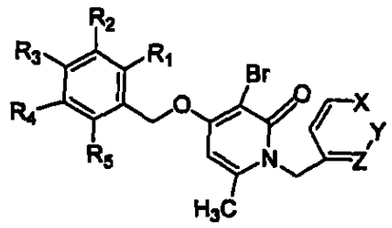
($CD_3OD$, 400 MHz) δ 8 46 (d, 1H, J= 4 8 Hz), 7 76 (ddd, 1H, J= 2 0 Hz, 1 6 Hz, 1 6 Hz), 7 29 (dd, 1H, J= 5 2 Hz, 5 2 Hz), 7 17 (d, 1H, J= 8 0 Hz), 6 07 (s, 1H), 5 40 (s, 2H), 2 30 (s, 3H), ES-LRMS (M+H) m/z 295/297

Step 2 Preparation of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(pyridin-2-ylmethyl)pyridin-2(1H)-one



The compound was prepared essentially as described in Step 2 of example 424 using 3-bromo-4-hydroxy-6-methyl-1-(pyridin-2-ylmethyl)pyridin-2(1H)-one $^1$H-NMR ($CD_3OD$, 400 MHz) δ 8 45 (d, 1H, J= 4 4 Hz), 7 76 (ddd, 1H, J= 2 0 Hz, 2 0 Hz, 1 6 Hz), 7 62 (q, 1H), 7 29 (dd, 1H, J= 5 2 Hz, 5 6 Hz), 7 21 (d, 1H, J= 8 0 Hz), 7 04 (m, 2H), 6 51 (s, 1H), 5 45 (s, 2H), 5 29 (s, 2H), 2 42 (s, 3H), ES-HRMS m/z 421 0354/423 0332 (M+H calculated for $C_{19}H_{16}N_2O_2F_2Br$ requires 421 0358/423 0339)

Examples 425-427, 429-435, 436-437



The following compounds were prepared essentially according to the procedures set forth above for Example 424, using the products of Step 1 of Examples 424, 428, or 435

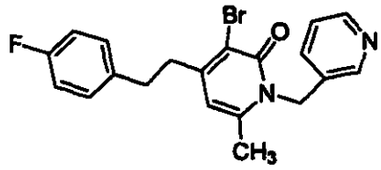
| Ex No | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | X | Y | Z | MF | M+H m/z required | ES-HRMS m/z |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 425 | H | H | F | H | H | N | CH | CH | $C_{19}H_{16}N_2O_2FBr$ | 403 0452/ 405 0434 | 403 0444 405 0414 |
| 426 | F | H | F | H | F | N | CH | CH | $C_{19}H_{14}N_2O_2F_3Br$ | 439 0264/ 441 0245 | 439 027( 441 027 |
| 427 | F | H | H | H | F | N | CH | CH | $C_{19}H_{15}N_2O_2F_2Br$ | 421 0358/ 423 0339 | 421 037 423 036 |
| 429 | H | H | F | H | H | CH | N | CH | $C_{19}H_{16}N_2O_2FBr$ | 403 0487/ 405 0438 | 403 048 405 043 |
| 430 | F | H | F | H | F | CH | N | CH | $C_{19}H_{14}N_2O_2F_3Br$ | 439 0264/ 441 0245 | 439 026 441 024 |
| 431 | F | H | H | H | H | CH | N | CH | $C_{19}H_{16}N_2O_2FBr$ | 403 0452/ 405 0434 | 403 048 405 047 |
| 432 | F | H | F | F | H | CH | N | CH | $C_{19}H_{14}N_2O_2F_3Br$ | 439 0264/ 441 0245 | 439 026 441 023 |
| 433 | F | H | Cl | H | H | CH | N | CH | $C_{19}H_{15}N_2O_2FClBr$ | 437 0062/ 439 0041 | 437 006 439 004 |
| 434 | Cl | H | F | H | H | CH | N | CH | $C_{19}H_{15}N_2O_2FClBr$ | 437 0062/ 439 0041 | 437 004 439 004 |
| 435 | F | H | H | H | F | CH | N | CH | $C_{19}H_{15}N_2O_2F_2Br$ | 421 0358/ 423 0339 | 421 037 423 033 |
| 436 | H | H | F | H | H | CH | CH | N | $C_{19}H_{16}N_2O_2FBr$ | 403 0452/ 405 0434 | 403 045 405 037 |
| 437 | F | H | F | H | F | CH | CH | N | $C_{19}H_{14}N_2O_2F_3Br$ | 439 0264/ 441 0245 | 439 026 441 024 |
| 438 | F | H | F | F | H | CH | CH | N | $C_{19}H_{14}N_2O_2F_3Br$ | 439 0264/ 441 0245 | 439 026 441 024 |

NMR characterization of compounds of Examples 425-427, 429-435, 436-437

| Ex No | NMR Data |
|---|---|
| 425 | $^1$H-NMR ($CD_3OD$ 400 MHz) δ 8 47 (d 2H J= 5 6 Hz), 7 50 (q 2H), 7 14 (m 4H) 6 49 (s 1H) 5 44 (s 2H) 5 27 (s, 2H) 2 32 (s 3H |
| 426 | $^1$H-NMR ($CD_3OD$, 400 MHz) δ 8 48 (dd, 2H, J= 1 6 Hz), 7 15 (d 2H J= 6 0 Hz) 6 98 (t, 2H, J= 1 2 Hz), 6 60 (s 1H) 5 45 (s, 2H) 5 29 (s, 2H) 2 36 (s, 3H) |

| | |
|---|---|
| 427 | $^1$H NMR ($CD_3OD$, 400 MHz) δ 8 47 (d 2H J = 1 6 Hz) 7 45 (m, 1H) 7 16 (d 2H, J = 5 6 Hz), 7 06 (t, 2H J = 8 4 Hz), 6 62 (s, 1H), 5.46 (s, 2H), 5 34 (s, 2H) and 2 37 (s, 3H) |
| 429 | $^1$H-NMR ($CD_3OD$, 400 MHz) δ 8 45 (d, 1H, J= 4 4 Hz) 8 40 (s 1H), 7 62 (d 1H, J= 8 0 Hz), 7 49 (q, 2H), 7 41 (dd, 1H, J= 4 8 Hz, 4 8 Hz), 7 14 (t 2H, J= 8 8 Hz) 6 46 (s 1H), 5 43 (s 2H), 5 26 (s, 2H), 2.38 (s, 3H) |
| 430 | $^1$H-NMR ($CD_3OD$, 400 MHz) δ 8 45 (d, 1H, J= 3 6 Hz) 8 42 (d, 1H J= 1 2 Hz) 7 60 (d, 1H, J= 8 4 Hz), 7 41 (dd, 1H J= 5 2 Hz 4 8 Hz), 6 97 (m 2H), 6 57 (s, 1H), 5 45 (s, 2H) 5 27 (s, 2H), 2 42 (s, 3H) |
| 431 | $^1$H-NMR ($CD_3OD$, 400 MHz) δ 8 45 (d, 1H, J= 4 4 Hz), 8 41 (d, 1H, J= 1 6 Hz), 7 58 (m, 2H), 7 41 (m, 2H), 7 22 (m, 2H), 6 51 (s, 1H), 5.44 (s, 2H), 5 34 (s, 2H), 2 39 (s, 3H) |
| 432 | $^1$H-NMR ($CD_3OD$, 400 MHz) δ 8 45 (d, 1H, J= 4 0 Hz) 8 41 (d, 1H, J=1 6 Hz) 7 63 (d 1H J= 7 6 Hz), 7 53 (m 1H) 7 41 (dd, 1H, J= 5 6 Hz, 5 2 Hz) 7 26 (m 1H), 6 51 (s, 1H) 5 45 (s, 2H), 5 29 (s, 2H), 2 40 (s, 3H) |
| 433 | $^1$H-NMR ($CD_3OD$, 400 MHz) δ 8 45 (d, 1H, J= 4 0 Hz) 8 41 (d, 1H, J= 1 6 Hz), 7 60 (m 2H) 7 39 (dd, 1H, J= 5 2 Hz), 7 28 (s 1H), 7 26 (s 1H), 6 50 (s, 1H) 5 44 (s, 2H), 5 31 (s 2H), 2 40 (s 3H) |
| 434 | $^1$H-NMR ($CD_3OD$, 400 MHz) δ 8 45 (d 1H, J= 4 0 Hz) 8 41 (d, 1H, J= 1 6 Hz), 7 68 (m, 2H), 7 39 (dd, 1H, J= 4 8 Hz, 4 8 Hz), 7 31 (dd, 1H, J= 2 4 Hz, 2 8 Hz), 7 16 (ddd, 1H, J= 2 8 Hz, 2 8 Hz, 2 8 Hz) 6.50 (s, 1H), 5 45 (s, 2H) 5 32 (s 2H) 2 41 (s 3H) |
| 435 | $^1$H-NMR ($CD_3OD$, 400 MHz) δ 8 45 (d, 1H, J= 4 0 Hz), 8 42 (s 1H) 7 60 (d, 1H J= 8 0 Hz), 7 47 (m, 1H) 7 40 (dd, 1H, J= 5 2 Hz, 4 8 Hz) 7 07 (m, 2H) 6 59 (s, 1H) 5 45 (s 2H) 5 32 (s, 2H), 2.41 (s, 3H) |
| 436 | $^1$H-NMR ($CD_3OD$ 400 MHz) δ 8 45 (d 1H J= 4 8 Hz), 7 76 (ddd 1H, J= 2 0 Hz, 1 6 Hz, 1 6 Hz), 7 51 (q, 2H) 7 30 (dd, 1H, J= 5 2 Hz), 7 19 (d 1H, J= 7 6 Hz), 7 14 (t, 2H J= 8 8 Hz), 6 46 (s, 1H), 5.44 (s, 2H), 5 26 (s, 2H), 2 40 (s 3H) |
| 437 | $^1$H-NMR ($CD_3OD$, 400 MHz) δ 8 46 (d, 1H, J= 4 8 Hz), 7 76 (ddd, 1H, J=2 0 Hz, 1 6 Hz, 1 6 Hz), 7 29 (dd, 1H, J= 4 8 Hz, 5 2 Hz), 7 21 (d, 1H, J= 7 6 Hz), 6 69 (dd, 2H, J= 8 0 Hz, 7 6 Hz), 6 57 (s, 1H), 5.46 (s, 2H), 5 28 (s 2H), 2 43 (s 3H) |
| 438 | $^1$H-NMR ($CD_3OD$, 400 MHz) δ 8 45 (d, 1H, J= 4 4 Hz), 7 76 (ddd, 1H, J= 2 0 Hz, 1 6 Hz, 1 6 Hz), 7 55 (m 1H), 7 26 (m, 3H), 6 50 (s 1H), 5.46 (s, 2H), 5 29 (s, 2H) 2 42 (s, 3H) |

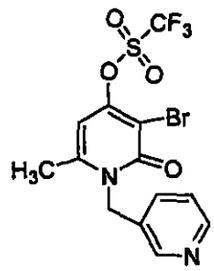
Example 439




3-bromo-4-[2-(4-fluorophenyl)ethyl]-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one

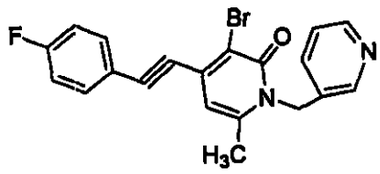
306

Step 1 Preparation of 3-bromo-6-metnyl-2-oxo-1-(pyridin-3-ylmethyl)-1,2-dihydropyridin 4-yl trifluoromethanesulfonate



To a chilled suspension (-30° C) of 3-bromo-4-hydroxy-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one (0 481g, 1 63 mmol) in dichloromethane (6 mL) was added triethylamine (0 28 mL, 2 04 mmol), followed by the addition of a solution of trifluoromethanesulfonic anhydride (0 4 mL, 2 44 mmol) in dichloromethane (3 mL) The reaction mixture stirred at -30° C under nitrogen for 1 hour The reaction mixture was diluted with dichloromethane and washed with cold $NaHCO_3$/water The organic extracts were dried over $Na_2SO_4$ and the filtrate was concentrated under reduced pressure to afford the desired compound as a yellow semisolid (0 6675 g, 95%) after drying ES-LRMS (M+H) m/z 427 1/429 1

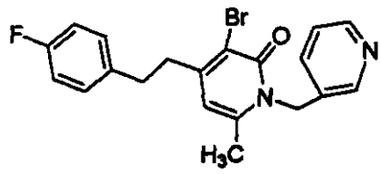
Step 2 Preparation of 3-bromo-4-[(4-fluorophenyl)ethynyl]-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one



To a degassed solution of 3-bromo-6-methyl-2-oxo-1-(pyridin-3-ylmethyl)-1,2-dihydropyridin-4-yl trifluoromethanesulfonate (0 6675 g, 1 56 mmol) in DMF (9 mL),

DIEA (0 35 mL, 2 03 mmol), 4-fluorophenylacetylene (0 235 mL, 1 95 mmol) and $PdCl_2(PPh_3)_2$ (0 11g) were added The reaction mixture stirred at room temperature under nitrogen for 1 hour and then heated in an oil bath (65°C) under nitrogen overnight The solvents were distilled in vacuo and the residue was purified by flash column chromatography (5% methanol in ethyl acetate) The extracts were concentrated to afford the desired compound (0 432 g, 69%) after drying $^1$H-NMR ($CD_3OD$, 400 MHz) δ 8 45 (s, 2H), 7 96 (s, 1H), 7 64 (m, 3H), 7 41 (dd, 1H, J= 4 8 Hz, 4 8 Hz), 7 18 (t, 2H, J= 8 8 Hz), 6 46 (s, 1H), 5 45 (s, 2H), 2 37 (s, 3H), ES-HRMS m/z 397 0361/399 0310 (M+H calculated for $C_{20}H_{15}N_2OFBr$ requires 397 0346/399 0328)

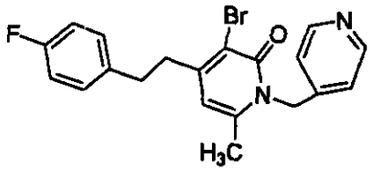
Step 3 Preparation of 3-bromo-4-[2-(4-fluorophenyl)ethyl]-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one




A suspension of 3-bromo-4-[(4-fluorophenyl)ethynyl]-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one (0 430 g, 1 01 mmol) in Ethyl acetate (5 mL) and EtOH (5 mL), containing $PtO_2$ (0 015 g) was stirred in an atmosphere of hydrogen (15 psi) in a Fischer- Porter bottle for 2 hours The reaction mixture was filtered and the filtrate was concentrated to reduce volume The material was purified by flash column chromatography (ethyl acetate) The appropriate fractions were combined and concentrated under reduced pressure to afford the desired product (0 0943 g, 22 %) as a sticky semisolid after drying $^1$H-NMR ($CD_3OD$, 400 MHz) δ 8 46 (d,

2H, J= 26 4 Hz), 7 60 (d, 1H, J= 8 0 Hz), 7 41 (dd, 1H, J= 4 8 Hz, 4 8 Hz), 7 21 (m, 2H), 6 97 (t, 2H, J= 8 8 Hz), 6 24 (s, 1H), 5 43 (s, 2H), 2 93 (m, 4H), 2 31 (s, 3H), ES-HRMS m/z 401 0645/403 0603 (M+H calculated for $C_{20}H_{19}N_2OFBr$ requires 401 0659/403 0641)

Example 440

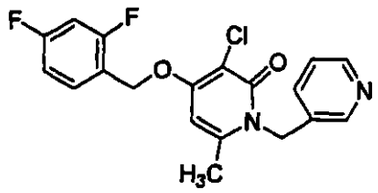



3-bromo-4-[2-(4-fluorophenyl)ethyl]-6-methyl-1-(pyridin-4-ylmethyl)pyridin-2(1H)-one

The title compound was prepared by a procedure similar to the one described for step 1 to step3 (0 374 g, 25%) MS and $^1$H-NMR for step 1 were consistent with the desired structure $^1$H-NMR ($CD_3OD$, 400 MHz) δ 8 80 (d, 2H, J= 6 8 Hz), 7 89 (d, 2H, J= 6 8 Hz), 6 61 (s, 1H), 5 66 (s, 2H), 2 45 (s, 3H), ES-HRMS m/z 427 9645/429 9625 (M+H calculated for $C_{13}H_{11}N_2O_4SF_3Br$ requires 427 9599/429 9578)

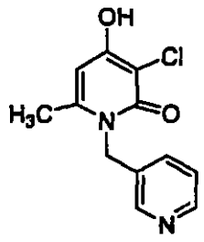
MS and $^1$H-NMR for step 3 were consistent with the desired structure $^1$H-NMR ($CD_3OD$, 400 MHz) δ 8 48 (d, 2H, J= 5 2 Hz), 7 21 (m, 2H), 7 13 (d, 2H, J= 5 2 Hz), 6 98 (t, 2H, J= 9 0 Hz), 6 26 (s, 1H), 5 43 (s, 2H), 2 95 (m, 4H), 2 25 (s, 3H), ES-HRMS m/z 401 0682/403 0536 (M+H calculated for $C_{20}H_{19}N_2OFBr$ requires 401 0659/403 0641)

Example 441



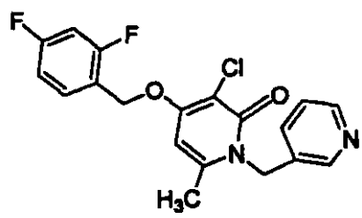
3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one

Step 1 Preparation of 3-chloro-4-hydroxy-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one



To a suspension of 4-hydroxy-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one (1 016 g, 4 7 mmol) in $MeCl_2$ (10 mL) was added NCS (1 21 g, 1 78 mmol) The reaction mixture stirred at room temperature for 24 hours under nitrogen The suspension was chilled in an ice bath and filtered The solid was washed with fresh $MeCl_2$ and dried to afford a yellow solid (1 00 g, 85%) after drying $^1$H-NMR ($CD_3OD$, 400 MHz) δ 8 54 (m, 2H), 7 85 (d, 1H, J=1 6 Hz), 7 61 (m, 1H), 6 10 (s, 1H), 5 41 (s, 2H), 2 33 (s, 3H), ES-LRMS (M+H) m/z 251/253

Step 2 Preparation of 3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one

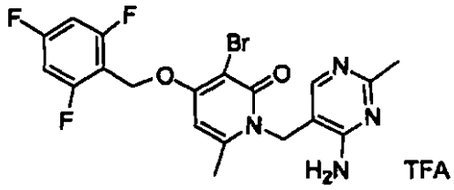


308

311

To a degassed cold solution of DMF (10 mL) and $PPh_3$ (resin, 2 2 g, 6 6 mmol) was added DEAD (1 038 mL, 6 6 mmol) The reaction mixture stirred at -10° C for 20 minutes under nitrogen A solution of 3-chloro-4-hydroxy-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one (1 00 g, 4 0 mmol) and 2 4-difluorobenzylalcohol (0 66 mL, 6 0 mmol) in DMF (10 mL) was added to the resin suspension The reaction mixture stirred at -10° C for 30 minutes and then allowed to stir at room temperature for 1 hour The resin was filtered and rinsed with fresh MeOH and the filtrate concentrated The residue was dissolved in ethyl acetate and purified by flash column chromatography (5% methanol in ethyl acetate) The appropriate fractions were concentrated $^1$H-NMR ($CD_3OD$, 400 MHz) δ 8 45 (ddd, 2H, J= 1 6Hz, 1 6 Hz, 1 6 Hz), 7 61 (m, 2H), 7 41 (dd, 1H, J= 4 4 Hz, 4 3 Hz), 7 02 (m, 2H), 6 55 (s, 1H), 5 43 (s, 2H), 5 29 (s, 2H), 2 41 (s, 3H), ES-HRMS m/z 377 0882/379 0840 (M+H calculated for $C_{19}H_{16}N_2O_2F_2Cl$ requires 377 0863/379 0840)

Example 442

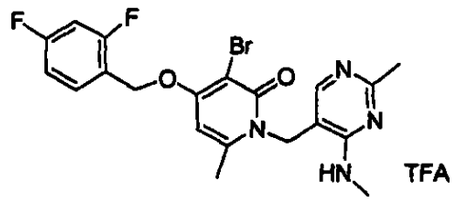



1-[(4-amino-2-methylpyrimidin-5-yl)methyl]-3-bromo-6-methyl-4-[(2,4,6-trifluorobenzyl)oxy]pyridin-2(1H)-one trifluoroacetate

The title compound was prepared by a procedure similar to the one described for Example 385, step 2 (0 142 g, 9%) $^1$H NMR ($CD_3OD$, 400 MHz) δ 7 64 (s, 1H), 7 00 (m, 2H), 6 66 (s,

1H), 5 29 (s, 2H), 5 18 (s, 2H), 2 50 (s, 3H), 2 47 (s, 3h), ES-HRMS m/z 469 0488/471 0464 (M+H calculated for $C_{19}H_{17}N_4O_2F_3Br$ requires 469 0481/471 0463)

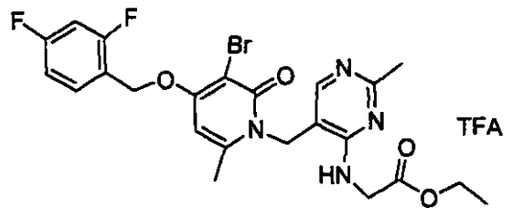
Example 443




3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-{[2-methyl-4-(methylamino)pyrimidin-5-yl]methyl}pyridin-2(1H)-one trifluoroacetate

To a solution of 1-[(4-amino-2-methylpyrimidin-5-yl)methyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one hydrochloride (0 15 g, 0 3 mmol) in DMF (3 mL) was added DBU (0 09 mL, 0 6 mmol) The solution was cooled in an ice bath and iodomethane (0 019 mL, 0 3 mmol) was added The reaction mixture stirred at room temperature under nitrogen for 2 hours The reaction was purified by reverse phase HPLC 10-90% CH3CN/water (30 minute gradient) at a flow rate of 100 mL/min The appropriate fractions (m/z= 465 M+H) were combined and freeze dried to afford the desired product (0 036 g, 25%) as a white powder $^1$H NMR ($CD_3OD$, 400 MHz) δ 7 72 (s, 1H), 7 60 (m, 1H), 7 03 (m, 2H), 6 62 (s, 1H), 5 31 (s, 2H), 5 16 (s, 2H), 3 77 (s, 3H), 2 60 (s, 3H), 2 47 (s, 3H), ES-HRMS m/z 465 0717/467 0712 (M+H calculated for $C_{20}H_{20}N_4O_2F_2Br$ requires 465 0732/467 0714)

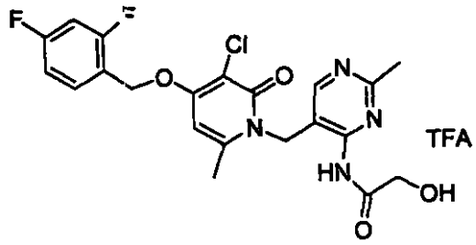
Example 444




ethyl N-(5-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-2-methylpyrimidin-4-yl)glycinate trifluoroacetate

The title compound was prepared by a procedure similar to the one described for Example 442 with the exception that the reaction mixture had to be heated at oil bath temperature 70° C for 2 days (0 1384 g, 51 %) $^1$H NMR ($CD_3OD$, 400 MHz) δ 7 78 (s, 1H), 7 61 (m, 1H), 7 03 (m, 2H), 6 61 (s, 1H), 5 30 (s, 2H), 5 18 (s, 2H), 5 03 (s, 2H), 4 27 (q, 2H), 2 55 (s, 3H), 2 46 (s, 3H), 1 28 (t, 3H, J= 7 0 Hz), ES-HRMS m/z 537 0936/539 0932 (M+H calculated for $C_{23}H_{24}N_4O_4F_2Br$ requires 537 0943/539 0926)

Example 445

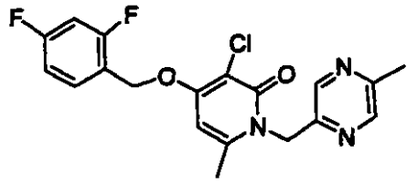



N-(5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-2-methylpyrimidin-4-yl)-2-hydroxyacetamide trifluoroacetate

To a chilled solution of 1-[(4-amino-2-methylpyrimidin-5-yl)methyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one trifluoroacetate (0 200 g, 0 38 mmol)

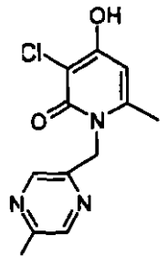
in DMF (20 mL) and a catalytic amount of DMAP was added triethylamine (0 064 mL, 0 38 mmol) The reaction stirred at -20° C and acetoxyacetyl chloride (0 082 mL, 0 76 mmol) was added The reaction stirred cold for 15 minutes and then allowed to warm up to room temperature for 3 hours The reaction was monitored by LR-ESMS m/z = 466 The reaction was incomlete after 3 hours Added acetoxyacetyl chloride (0 05 mL, 0 466 mmol), and triethylamine (0 2 mL, 1 43 mmol) to the reaction mixture and continued to stir overnight at room temperature The next morning the reaction heated at 65° C for 3 hours The solvent was removed in vacuo and 1N LiOH (2 5 mL) was added to the residue The reaction was heated at 60° C for 5 hours The reaction was diluted with acetonitrile and water (1 1) and purified by reverse phase HPLC in 10-90% $CH_3CN$/water (30 minute gradient) at a flow rate of 50 mL/min The appropriate fractions were freeze dried to afford the desired product (0 020 g, 9%) $^1H$ NMR ($CD_3OD$, 400 MHz) δ 8 04 (s, 1H), 7 6 (m, 1H), 7 02 (m, 1H), 6 59 (s, 1H), 5 30 (s, 2H), 5 24 (s, 2H), 4 26 (s, 1H), 2 60 (s, 3H), 2 43 (s, 3H), ES-HRMS m/z 465 1161 (M+H calculated for $C_{21}H_{20}N_4O_4F_2Cl$ requires 465 1136)

Example 446




3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[(5-methylpyrazin-2-yl)methyl]pyridin-2(1H)-one

Step 1 Preparation of 3-chloro-4-hydroxy-6-methyl-1-[(5-methylpyrazin-2-yl)methyl]pyridin-2(1H)-one



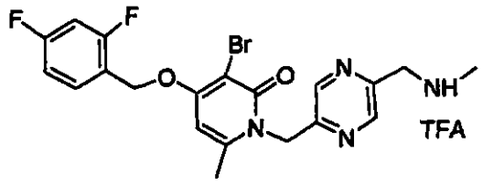
To a solution of 4-hydroxy-6-methyl-1-[(5-methylpyrazin-2-yl)methyl]pyridin-2(1H)-one (1 00g, 4 3 mmol) in glacial acetic acid (10 mL) was added NCS (0 79 g, 5 94 mmol) The reaction mixture stirred at 60° C for 6 hours The solvent was removed under reduced pressure and the resulting residue was triturated with ethyl acetate The desired product was filtered and dried (0 80 g, 69%) $^1$H NMR ($CD_3OD$, 400 MHz) δ 8 47 (s, 1H), 8 42 (s, 1H), 6 08 (s, 1H), 5 36 (s, 2H), 2 50 (s, 3H), 2 43 (s, 3H), ES-HRMS m/z 266 0691 (M+H calculated for $C_{12}H_{13}N_3O_2Cl$ requires 266 0691)

Step 2 Preparation of 3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[(5-methylpyrazin-2-yl)methyl]pyridin-2(1H)-one

To a solution of 3-chloro-4-hydroxy-6-methyl-1-[(5-methylpyrazin-2-yl)methyl]pyridin-2(1H)-one (2 48 g, 9 3 mmol) in DMA (7 mL)was added $K_2CO_3$ (1 54 g, 11 0 mmol) followed by 2,4-difluorobenzyl bromide (1 2 mL, 9 3 mmol) The reaction mixture stirred at room temperature under nitrogen for 1 5 hours The solvent was distilled in vacuo The resulting residue was diluted in dichloromethane and washed with water The organic extracts were concentrated and the resulting residue was purified by flash column chromatography (ethyl acetate) The appropriate fractions were combined, and concentrated $^1$H NMR ($CD_3OD$, 400 MHz) δ 8 49 (d, 1H, J=1 2 Hz), 8 40 (s, 1H), 7 59 (m, 1H), 7 04 (m, 2H), 6 54 (s, 1H),

5 41 (s, 2H), 5 28 (s, 2H), 2 54 (s, 3H), 2 40 (s, 3H), ES-HRMS m/z 392 1014 (M+H calculated for $C_{19}H_{17}N_3O_2ClF_2$ requires 392 0972)

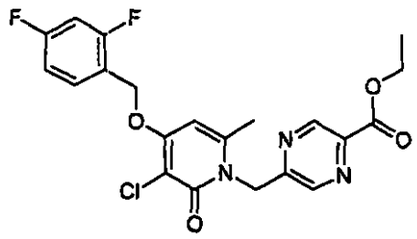
Example 447




3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-({5-[(methylamino)methyl]pyrazin-2-yl}methyl)pyridin-2(1H)-one trifluoroacetate

To a suspension of 3-bromo-1-{[5-(chloromethyl)pyrazin-2-yl]methyl}-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (0 25 g, 0 53 mmol) in THF was added methylamine (1 mL, 2 1 mmol) The reaction was sealed and stirred at room temperature overnight The reaction mixture was diluted in water acetonitrile (1 1) and purified by reverse phase HPLC 10-90% $CH_3CN$/water (30 minute gradient) at a flow rate of 70 mL/min The appropriate fractions were combined and freeze dried to afford the desired product (0 22 g, 71%) as an amorphous solid $^1H$ NMR ($CD_3OD$, 400 MHz) δ 8 73 (s, 1H), 8 55 (s, 1H), 7 6 (m, 2H), 7 02 (m, 1H), 6 54 (s, 1H), 5 47 (s, 2H), 5 29 (s, 2 H), 4 37 (s, 2 H), 2 78 (s, 3H), 2 56 (s, 3H) ES-HRMS m/z 465 0732/467 0709 (M+H calculated for $C_{20}H_{20}N_4O_2BrF_2$ requires 465 0732/467 0714)

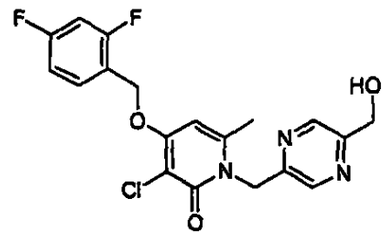
Example 448



Ethyl 5-{[3-chloro-4-[(2 4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrazine-2-carboxylate

To a mixture of 3-chloro-4-[(2 4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (0 59 g, 2 07 mmol) and ethyl 5-(bromomethyl)pyrazine-2-carboxylate (0 62 g, 2 4 mmol) in THF (15 mL) was added NaH (0 06 g, 2 4 mmol) The reaction stirred at 60° C for 3 5 hours The solvent was removed under reduced pressure and the residue was partitioned over dichloromethane and citric acid (5%) The organic extracts were washed with water and dried over $Na_2SO_4$ (anhydrous) The organic extracts were concentrated and the residue was purified by flash column chromatography (100 % ethyl acetate) The appropriate fractions were combined and concentrated under reduced pressure to remove solvent $^1H$ NMR ($CD_3OD$, 400 MHz) δ 9 11 (d, 1H, J= 1 6 Hz), 8 77 (s, 1H), 7 52 (m, 1H), 7 02 (m, 2H), 6 57 (s, 1H), 5 53 (s, 2H), 5 30 (s, 2H), 4 49 (q, 2H), 2 52 (s, 3H), 1 39 (t, 3H, J= 7 2 Hz), ES-HRMS m/z 450 1045 (M+H calculated for $C_{21}H_{19}N_3O_4ClF_2$ requires 450 01027)

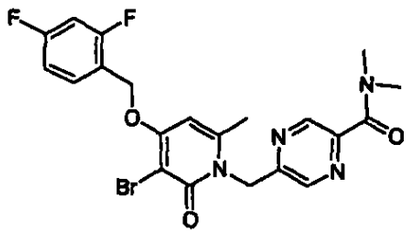
Example 449



3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[5-(hydroxymethyl)pyrazin-2-yl]methyl}-6-methylpyridin-2(1H)-one

To a suspension of ethyl 5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrazine-2-carboxylate (4 0 g, 8 9 mmol) in THF t-butanol (1 1) (10 mL) was added $NaBH_4$ (0 46 g, 12 4 mmol) The reaction stirred at room temperature under argon overnight The reaction mixture was quenched with acetic acid (2 mL) and the solvent was removed in vacuo The residue was triturated with water and filtered The solid was washed with fresh water followed by ethanol The solid was purified by flash column chromatography (100% ethyl acetate) The appropriate fractions were combined and concentrated under reduced pressure to afford the desired compound (1 58 g, 44%) as a white solid $^1H$ NMR ($CD_3OD$, 400 MHz) δ 8 59 (s, 1H), 8 56 (s, 1H), 7 52 (m, 1H), 7 01 (m, 2H), 6 55 (m, 1H), 5 45 (s, 2H), 5 29 (s, 2H), 4 71 (2H), 2 54 (s, 3H), ES-HRMS m/z 408 0940 (M+H calculated for $C_{19}H_{17}N_3O_3ClF_2$ requires 408 0921)

Example 450

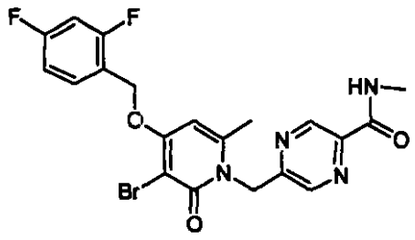


312
315

5-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-N,N-dimethylpyrazine-2-carboxamide

To a cold solution of 5-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrazine-2-carboxylic acid (0 175 g, 0 37 mmol) in DMF (5 mL, -10° C) was added IBCF (0 046 mL, 0 35 mmol) followed by NMM (0 041 mL 0 37 mmol) The reaction was activated for 20 minutes at -15° C after which dimethylamine (0 375 mL, 0 74 mmol) was added The reaction stirred at -10° C to room temperature for 45 minutes The solvent was removed in vacuo and the residue was purified by reverse phase HPLC 10-90% $CH_3CN$/water (30 minute gradient) at a flow rate of 70 mL/min The appropriate fractions were combined and freeze dried to afford the desired product (0 140g, 75%) as a white solid $^1H$ NMR ($CD_3OD$, 400 MHz) δ 8 68 (s, 1H), 8 67 (s, 1H), 7 52 (m, 1H), 7 02 (m, 2H), 6 54 (s, 1H), 5 50 (s, 2H), 5 30 (s, 2H), 3 11 (s, 3 H), 3 07 (s, 3H), 2 55 (s, 3H), ES-HRMS m/z 493 0680/495 0657 (M+H calculated for $C_{21}H_{20}N_4O_3BrF_2$ requires 493 0680/495 0657)

Example 451

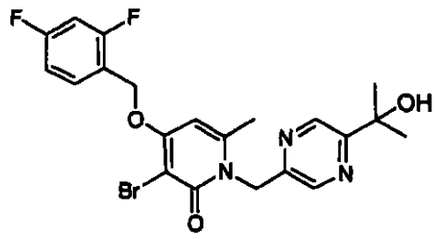



5-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-N-methylpyrazine-2-carboxamide

The title compound was prepared essentially as in Ex 450, substituting dimethylamine with methylamine $^1H$ NMR ($CD_3OD$, 400

MHz) δ 9 07 (s, 1H), 8 68 (s, 1H), 7 54 (m, 1H), 7 02 (m, 2H), 6 54 (s, 1H), 5 52 (s, 2H), 5 30 (s, 2H), 2 94 (s, 3H), 2 54 (s, 3H), ES-HRMS m/z 479 0542/481 0518 (M+H calculated for $C_{20}H_{18}N_4O_3BrF_2$ requires 479 0525, 481 0507)

Example 452

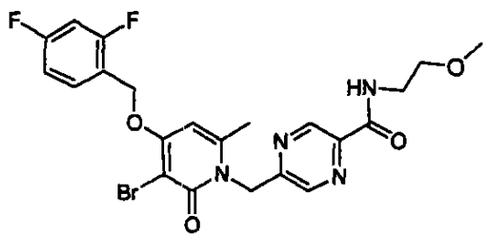


3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-{[5-(1-hydroxy-1-methylethyl)pyrazin-2-yl]methyl}-6-methylpyridin-2(1H)-one

To a cold flask of MeMgBr (1 59 mL, 1 0 mmol) was added a suspension of ethyl 5-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrazine-2-carboxylate (0 5 g, 1 0 mmol) in THF (20 mL) The reaction stirred at 0° C for 1 5 hours and then at room temperature overnight The reaction was quenched with cold citric acid (25 mL, 5%) and extracted with ethyl acetate (2 X 100 mL) The organic extracts were washed with fresh water The organic extracts were concentrated and purified by reverse phase HPLC 10-90% $CH_3CN$/water (30 minute gradient) at a flow rate of 70 mL/min The appropriate fractions were combined and freeze dried to afford the desired product (29 9 mg, 6%) $^1H$ NMR ($CD_3OD$, 400 MHz) δ 8 76 (d, 1H, J= 1 6 Hz), 8 54 (d, 1H, J= 1 2 Hz), 7 52 (m, 1H), 7 02 (m, 2H), 6 52 (s, 1H), 5 45 (s, 2H), 5 29 (s, 2H), 2 55 (s, 3H), 1 52 (s, 6H), ES-HRMS m/z 480 0745/482 0722 (M+H calculated for $C_{21}H_{21}N_3O_3BrF_2$ requires 480 0729/482 0711)

313
316

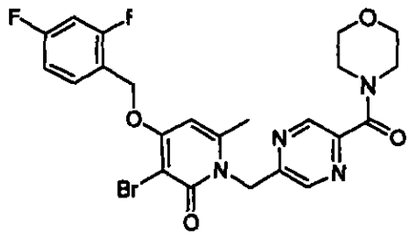
Example 453



5-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-N-(2-methoxyethyl)pyrazine-2-carboxamide

The title compound was prepared essentially as in Ex 450, substituting dimethylamine with 2-methoxyethylamine $^1$H NMR ($CD_3OD$, 400 MHz) δ 9 08 (d, 1H, J= 1 2 Hz), 8 70 (d, 1H, J= 1 2 Hz), 7 61 (m, 1H), 7 04 (m, 2H), 6 54 (s, 1H), 5 53 (s, 2H), 5 30 (s, 2H), 3 56 (m , 4H), 3 30 (s, 3H), 2 54 (s, 3H), ES-HRMS m/z 523 0822/525 0810 (M+H calculated for $C_{22}H_{22}N_4O_4BrF_2$ requires 523 0787/525 0770)

Example 454

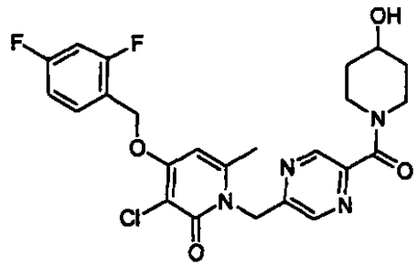


3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-{[5-(morpholin-4-ylcarbonyl)pyrazin-2-yl]methyl}pyridin-2(1H)-one

The title compound was prepared essentially as in Ex 450, substituting dimethylamine with morpholine $^1$H NMR ($CD_3OD$, 400 MHz) δ 8 77 (d, 1H, J= 1 6 Hz), 8 67 (s, 1H), 7 54 (m, 1H), 7 02 (m, 2H), 6 54 (s, 1H), 5 50 (s, 2H), 5 30 (s,

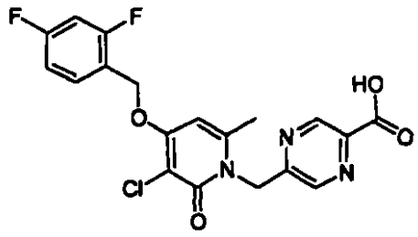
2H), 3 75 (s, 4H), 3 59 (dd, 4H, J= 5 6 Hz, 5 2 Hz), 2 55 (s, 3h), ES-HRMS m/z 535 0816/537 0817 (M+H calculated for $C_{23}H_{22}N_4O_4BrF_2$ requires 535 0787/537 0770)

Example 455



3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-({5-[(4-hydroxypiperidin-1-yl)carbonyl]pyrazin-2-yl}methyl)-6-methylpyridin-2(1H)-one

Step 1 Preparation of 5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrazine-2-carboxylic acid



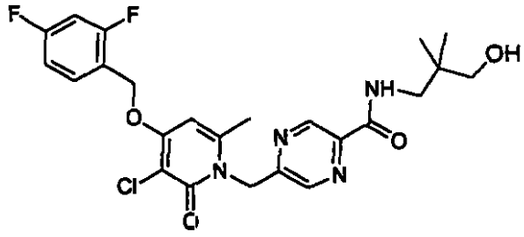
A mixture of ethyl 5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrazine-2-carboxylate (1 03g, 2 3 mmol) in 1N NaOH (3 4 ml, 3 45 mmol, EtOH/water 1 1 v/v) stirred at room temperature for 2 hours The reaction mixture was quenched with 5% citric acid and filtered The solid was washed with water and dried to afford the desired product (1 011 g, 100%) as a white solid $^1H$ NMR ($CD_3OD$, 400 MHz) δ 9 02 (s, 1H), 8 60 (s, 1H), 7 60 (m, 1H), 7 04 (m, 2H), 6 55 (s, 1H), 5 50

(s, 2H), 5 30 (s, 2H), 2 52 (s, 3H), ES-HRMS m/z 422 0732 (M+H calculated for $C_{19}H_{15}N_3O_4ClF_2$ requires 422 0714)

Step 2 Preparation of 3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-({5-[(4-hydroxypiperidin-1-yl)carbonyl]pyrazin-2-yl}methyl)-6-methylpyridin-2(1H)-one

The title compound was prepared by a procedure similar to the one described for Example 453 (0 1396 g, 47%) $^1$H NMR ($CD_3OD$, 400 MHz) δ 8 67 (s, 2H), 7 59 (m, 1H), 7 02 (m, 2H), 6 57 (s, 1H), 5 49 (s, 2H), 5 30 (s, 2H), 4 16 (m, 1H), 3 89 (septet, 1H), 3 72 (m, 1H), 3 38 (m, 2H), 2 56 (s, 3H), 1 93 (m, 1H), 1 83 (m, 1H), 1 45 (m, 2H), ES-HRMS m/z 505 1485 (M+H calculated for $C_{24}H_{24}N_4O_4ClF_2$ requires 505 1449)

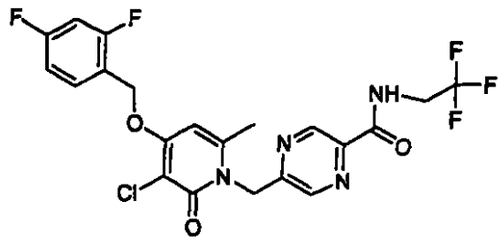
Example 456




5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-N-(3-hydroxy-2,2-dimethylpropyl)pyrazine-2-carboxamide

The title compound was prepared by a procedure similar to the one described for Example 455 (0 215 g, 71%) $^1$H NMR ($CD_3OD$, 400 MHz) δ 9 08 (d, 1H, J= 1 2 Hz), 8 71 (d, 1H, J= 1 6 Hz), 7 58 (m, 1H), 7 02 (m, 2H), 6 57 (s, 1H), 5 52 (s, 1H), 5 30 (s, 1H), 3 31 (s, 4H), 2 55 (s, 3H), 0 912 (s, 6H), ES-HRMS m/z 507 1630 (M+H calculated for $C_{24}H_{26}N_4O_4ClF_2$ requires 507 1605)

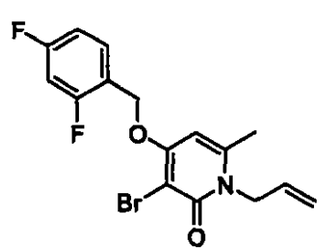
Example 457



5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-N-(2,2,2-trifluoroethyl)pyrazine-2-carboxamide

The title compound was prepared by a procedure similar to the one described for Example 455 except no purification was required, only a $NaHCO_3$/ethyl acetate extraction was needed (0 2176 g, 73%) $^1H$ NMR ($CD_3OD$, 400 MHz) δ 9 11 (d, 1H, J= 1 6Hz), 8 73 (d, 1H, J= 1 3 Hz), 7 59 (m, 1H), 7 02 (m, 2H), 6 57 (s, 1H), 5 53 (s, 2H), 5 30 (s, 2H), 4 01 (q, 2H), 2 54 (s, 3H), ES-HRMS m/z 503 0930 (M+H calculated for $C_{21}H_{17}N_4O_3ClF_5$ requires 503 0904)

Example 458



1-allyl-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one

Step 1 1-allyl-4-hydroxy-6-methylpyridin-2(1H)-one 4-hydroxy-6-methyl-2-pyrone (2g, 16 mmol) was stirred in water (25 mL) Allylamine (1 2 ml, 16mmol) was added to the

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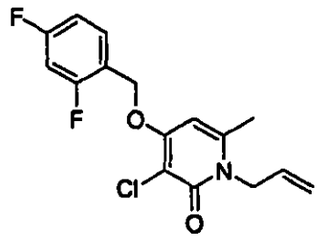
reaction The reaction was then heated to 100 °C at which point the reaction became homogeneous The reaction was stirred at 100 °C for 2h The reaction was then allowed to cool to rt after which a white precipitate formed The precipitate was isolated by suction filtration After additional washing with water, 1 8g (69%) of an off-white solid was obtained

Step 2 1-allyl-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one To a stirred solution of the above pyrone(4 0g, 24 mmol) in DMF(75ml) was added $Cs_2CO_3$ (7 8g, 24mmol) followed by addition of 2,4-diflurorbenzyl bromide(3 4 mmol, 26 4 mmol) The resulting mixture was stirred at rt for 2h Additional $Cs_2CO_3$ (1g) and bromide (1 ml) was added and the reaction was stirred for an additional 2h The $Cs_2CO_3$ was removed by suction filtration The DMF was removed under vacuum and the crude material was purified by flash chromatography Elution with ethyl acetate-hexanes (2 1 to 1 1) afforded 1 5 g (21%) of the desired compound

Step 3 1-allyl-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one To a stirred suspension of the above pyridinone (1g, 3 4 mmol) in $CH_3CN$ (10 ml) was added n-bromosuccinimide (670 mg, 3 8 mmol) The reaction mixture was stirred, at rt, for 3h The product was obtained by filtration of the reaction mixture and washing of the solid with diethyl ether $^1$H-NMR ($DMSO_{d6}$/400 MHz) δ 7 62 (app q, J = 8 8 hz, 1H), 7 31 (ddd, J = 12 0, 9 6, 2 8 hz, 1H), 7 15 (app dtd, J = 8 4, 2 4, 0 8 Hz, 1H), 6 50 (s, 1H), 5 87 (ddt, J = 12 4, 10 4, 5 6 Hz, 1H), 5 30 (s, 2H), 5 10 (dd, J = 10, 1 6 Hz, 1H), 4 87 (dd, J = 17 6 1 6 Hz, 1H), 4 64 (m, 2H), 2 34 (s, 3H), 19F-NMR ($DMSO_{d6}$/282 2 MHz) -109 68 (quin, J = 1H), -

113 66(quar, J = 1H), HRMS m/z 370 0255 (M + H calcd for $C_{16}H_{15}BrF_2NO_2$ = 370 0246)

Example 459



1-allyl-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one

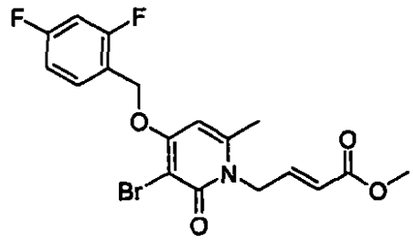
Step 1 1-allyl-3-chloro-4-hydroxy-6-methylpyridin-2(1H)-one To a stirred solution of 1-allyl-4-hydroxy-6-methylpyridin-2(1H)-one (500 mg, 3 0 mmol) in $CH_3CN$(10 ml), at rt, was added sequentially n-bromosuccinimide (440 mg, 3 3 mmol) and dichloroacetic acid (546 µl, 6 62 mmol) The resulting mixture was stirred for 2h The heterogeneous mixture was filtered and the solid was washed with additional $CH_3CN$ to give 350 mg (59%) of the desired product as a tan solid $^1$H-NMR ($DMSO_{d6}$/300 MHz) δ 11 16 (s, 1H), 5 98-5 86 (m, 2H), 5 12 (dd, J = 10 5, 1 5 Hz, 1H), 4 89 (dd, J = 17 1, 1 5 Hz, 1H), 4 63-4 61 (m, 2H), 2 29 (s, 3H) ES-HRMS m/z 200 050 (M + H calcd for $C_9H_{11}ClNO_2$ = 200 0470)

Step 2 1-allyl-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one The title compound was prepared by the procedure outline in the synthesis of Example 458, step 3 $^1$H-NMR ($DMSO_{d6}$/300 MHz) δ 7 67 (app q, J = 8 4 hz, 1H), 7 36 (app dt, J = 10 2, 2 7 hz, 1H), 7 15 (m, 1H), 6 58 (s, 1H), 5 93 (ddt, J = 15 3, 9 6, 4 8 Hz, 1H), 5 30 (s, 2H) 5 15 (dd, J = 10 2, 1 2 Hz, 1H), 4 92 (dd, J = 17 4, 1 2 Hz, 1H), 4 69-

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4 67 (m, 2H), 2 41 (s, 3H) ES-HRMS m/z 326 0760 (M + H calcd for $C_{16}H_{15}ClF_2NO_2$ = 326 0790)

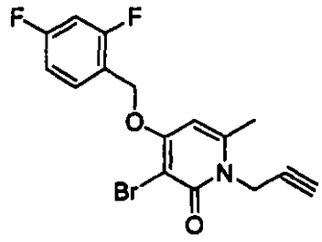
Example 460



Methyl (2E)-4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]but-2-enoate

To a stirred suspension of NaH (277 mg, 11 mmol) in anhydrous THF (30 ml), which was cooled to 0°C, was slowly added 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (3 3g, 10 mmol) The resulting slurry was stirred for 15 min, after which methyl 4-bromocrotonate (1 4 ml, 12 mmol) was added to the reaction The ice bath was removed and the reaction was heated to reflux for 16h The reaction was quenched by the addition of 1N $NH_4Cl$ The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (5x) The organics were combined, dried, and concentrated in vacuo The crude yellowish material was then triturated with $Et_2O$ to give, after filtration and drying, 1 8g (43%) of a white solid $^1$H-NMR ($DMSO_{d6}$/300 MHz) δ 7 65 (app q, J = 8 7 hz, 1H), 7 36 (app dt, J = 12 0, 3 0 hz, 1H), 7 17 (dt, J = 8 4, 1 8 Hz, 1H), 6 94 (dt, J = 15 9, 4 5 Hz, 1H), 6 57 (s, 1H), 5 52 (d, J = 15 9 Hz, 1H), 5 29 (s, 2H), 4 84 (m, 2H), 3 63 (s, 3H), 2 33 (s, 3H) ES-HRMS m/z 428 0301 (M + H calcd for $C_{18}H_{17}BrF_2NO_4$ = 428 0310)

Example 461



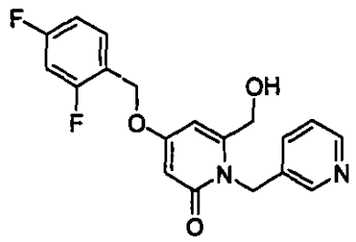
3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-prop-2-ynylpyridin-2(1H)-one

Step1 4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-prop-2-ynylpyridin-2(1H)-one The title compound was prepared by alkylation of 4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (2 5g, 10 mmol) with propargyl bromide (1 3 ml, 11 0 mmol) as described above to give 1 3g (44%) of the desired product $^1$H- NMR (DMSO$_{d6}$/300 MHz) δ 7 60 (app q, J = 8 4 hz, 1H), 7 35-7 27 (m, 1H), 7 16-7 10 (m, 1H), 5 94 (d, J = 2 1 Hz, 1H), 5 88 (d, J = 3 0 Hz, 1H), 5 03 (s, 2H), 4 76 (d, J = 2 4, Hz, 2H), 3,31 (s, 3H), 3 24 (t, J = 2 4 Hz, 1H), 2 39 (s, 3H), ES-HRMS m/z 290 0994 (M + H calcd for $C_{16}H_{14}F_2NO_2$ = 290 0993)

Step 2 Bromination of 4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-prop-2-ynylpyridin-2(1H)-one (500 mg, 1 67 mmol) with NBS (300 mg, 1 67 mmol) was carried out in the manner described above to give 350 mg (57%) of the desired compound $^1$H-NMR (DMSO$_{d6}$/300 MHz) δ 7 67 (app q, J = 9 0 hz, 1H), 7 36 (app dt, J = 10 5, 2 4 hz, 1H), 7 23-7 16 (m, 1H), 6 60 (s, 1H), 5 29 (s, 2H), 4 90 (d, J = 2 4, Hz, 1H), 3 35 (s, 3H), 3 32 (s, 1H), 2 53 (s, 3H), ES-HRMS m/z 368 0107 (M + H calcd for $C_{16}H_{13}BrF_2NO_2$ = 368 0098)

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Example 462



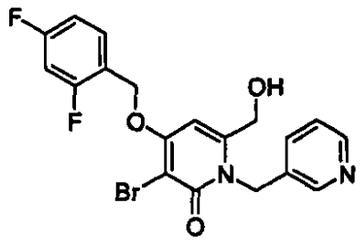
4-[(2,4-difluorobenzyl)oxy]-6-(hydroxymethyl)-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one

Step1 To a suspension of (4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one) (710 mg, 2 mmol) in dioxane (10 mL) was added selenium dioxide (1 1g 10 mmol) The resulting mixture was heated to 160 °C in a 125 mL sealed tube for 1h The reaction was filtered through a fritted funnel The filtrate was washed with (10 1) $CH_2Cl_2$-MeOH The organics were combined and concentrated in vacuo The crude material was purified by flash chromatography Elution with (50 50 → 0 100)hexanes yielded 450 mg (63%) of the aldehyde $^1$H-NMR ($DMSO_{d6}$/400 MHz) δ 9 48 (s, 1H, CHO)

Step 2 The aldehyde (350 mg, 1 mmol) was dissolved in MeOH (4 mL) and cooled to 0 °C To this mixture was added $NaBH_4$ (28 mg, 1 mmol) in one portion After 30 min, additional NaBH4 (20 mg) was added to the reaction The MeOH was then removed under vacuum The residue was diluted with 1N $NH_4Cl$ and then extracted with $CH_2Cl_2$(4X) The organics were combined, dried, and concentrated in vacuo The yellowish crude product was then taken up in (1 1) $CH_2Cl_2$-$Et_2O$ After sitting for a period of time a white precipitate resulted Filtration and washing with additional $Et_2O$ yielded, after drying, 250 mg (55%) of the desired alcohol $^1$H-NMR ($DMSO_{d6}$/400 MHz) δ 8 42 (dd, J = 4 4,

1 6 Hz, 1H) 8 37 (d, J = 1 6 Hz, 1H), 7 61 (app q, J = 8 0 Hz, 1H), 7 45 (d, J = 8 0 Hz, 1H), 7 32-7 27(M, 2H), 7 12 (dt, J = 8 4, 1 6 Hz, 1H), 6 07 (d, J = 2 8 Hz, 1H), 5 99 (d, J = 12 8 Hz, 1H), 5 63 (br s, 1H), 5 18 (s, 2H), 5 09 (s, 2H), 4 29 (s, 2H) LC/MS, $t_r$ = 1 19 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 359 1 (M+H)

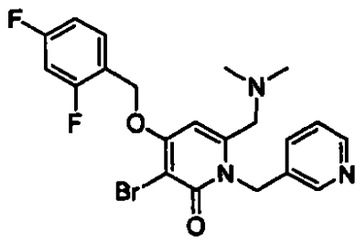
Example 463



3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-(hydroxymethyl)-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one

The title compound was prepared by bromination of as described above to give a 60% yield $^1$H-NMR ($DMSO_{d6}$/300 MHz) δ 7 93 (d, J = 7 8 Hz, 1H), 7 73-7 65 (m, 3H), 7 38 (dt, J = 10 2, 2 4 Hz, 1H), 7 21 (app t, J = 8 7 Hz, 2H), 6 74 (s, 1H), 5 38 -5 36 (m, 4H), 4 50 (s, 2H), ES-HRMS m/z 437 0311 (M + H cacld for $C_{19}H_{16}BrF_2N_2O_2$ = 437 0313)

Example 464

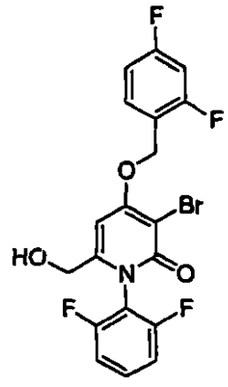


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3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-[(dimethylamino)methyl]-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one

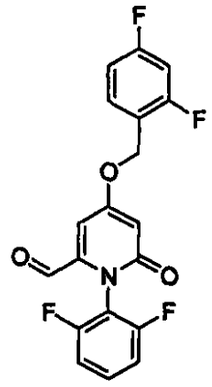
The title compound was prepared in a similar manner to the procedure outlined below for 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-[(dimethylamino)-methyl]pyridin-2(1H)-one using the aldehyde (300 mg, 0 85 mmol) described above and 2 0 N THF solution of dimethylamine (500 µL, 1 mmol) to give 110 mg (34%) of a colorless oil The oil was then dissolved in MeOH (1 mL) and stirred with fumaric acid (25 mg) for 1h The resulting precipitate was filtered, washed with diethyl ether, and dried to give the pure product as it's fumurate salt $^1$H-NMR ($DMSO_{d6}$/400 MHz) δ 8 43-8 41 (m, 1H), 8 35 (s, 1H), 7 67-7 61 (m, 1H), 7 44-7 40 (m, 1H), 7 35-7 29 (m, 2H), 7 17-7 12 (m, 1H), 6 62 (s, 1H), 6 60 (s, 1H), 5 41 (s, 2H), 5 32 (s, 2H), 3 13 (s, 2H), 2 12 (s, 6H) LC/MS, $t_r$ = 1 55 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 464 (M+H)

Example 465



3-bromo-4- [(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-(hydroxymethyl)pyridin-2(1H)-one

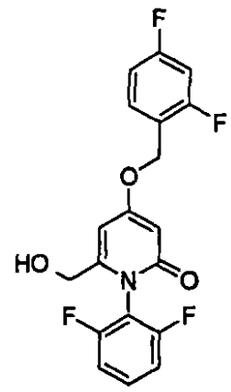
Step1 4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-oxo-1,6-dihydropyridine-2-carbaldehyde



In a 300 ml high-pressure glass reaction vessel (16 3 g, 45 mmol) was dissolved in 1,4-dioxane (90 mL) The reaction vessel was sealed and immersed in a preheated oil bath at 170 ° C The reaction was heated at 170° C (165 -170 °C) for 1 5 hours and then cooled to room temperature The reaction was worked up by filtering the reaction mixture through a plug of celite and silica gel The plug was then washed with 500 ml of methanol-$CH_2Cl_2$ mixture (1 5) The filtrate was evaporated to give 14 2 g of the desired crude aldehyde

Step 2 Preparation of 4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-(hydroxymethyl)pyridin-2(1H)-one

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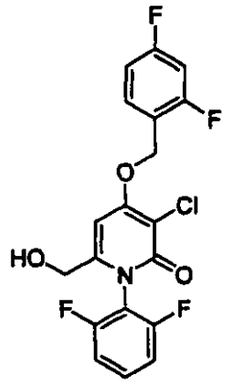


In a 500 ml three neck round bottom flask equipped with a stir bar of 4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-oxo-1,6-dihydropyridine-2-carbaldehyde (14 2 g, 37 7 mmol) was dissolved in methanol (200 mL) The reaction mixture was cooled to 0 °C and to this was added sodium borohydride (2 13g, 56 30 mmol) in a slow portion-wise fashion The reaction was stirred at 0 °C for 2 hour Excess amount of sodium borohydride was added to drive the reaction to completion After stirring for approximately 2 5 hours, the reaction was allowed to warm to room temperature and then concentrated to dryness The residue was taken up in ethyl acetate (100 mL) and washed with dilute HCl (pH of aqueous layer was approximately 4) Organic extracts were washed with brine (1X 50 ml), dried over $MgSO_4$, and concentrated in vacuo The crude product was recrystallized from ethyl acetate and hexane to yield 7 56 g (44% yield-starting from step 1) of the desired alcohol

Step 3 Preparation of the title compound
In a 100 ml round bottom flask of 4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-(hydroxymethyl)pyridin-2(1H)-one (2 49 g, 6 56 mmol), from step 2, was dissolved in acetonitrile (35 mL) The reaction mixture was cooled to 0 °C in ice bath for 10 min and then charged with N-bomosuccinamide (1 17g, 6 6 mmol) The mixture was allowed

to stir, at 0 °C, under nitrogen atmosphere for 2 hours The reaction was the worked up by removing the acetonitrile under vacuum The resulting residue was then filtered, with washing from a small amount of acetonitrile, to give a yellow solid $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7 695 - 7 588 (m, 2H), 7 368-7 314 (m, 3H), 7 175 (dt, J = 8 5, 2 5, Hz, 1H), 6 760 (s, 1H), 5 712 (t, J = 5 674 Hz, 1H), 5 384 (s, 2H), 4 004-3 990 (m, 2H), ES-HRMS m/z 458 0013 (M+H-calcd for $C_{19}H_{13}BrF_4NO_3$ requires 458 0013)

Example 466



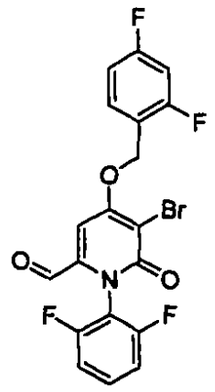

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-(hydroxymethyl)pyridin-2(1H)-one

The title compound was prepared by taking 4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-(hydroxymethyl)pyridin-2(1H)-one (1 5g, 3 9 mmol) in acetonitrile (15 mL) and adding to that N-chlorosuccinimide (580 mg, 4 3 mmol) The reaction was stirred at rt for 3h afterwhich a small amount of additional N-chlorosuccinimide (50 mg, 0 4 mmol) was added to the reaction Stirring was continued for 1h The reaction mixture was filtered through a fritted funnel to obtain the crude material $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7 69 - 7 61 (m, 2H), 7 37-7 31 (m, 3H), 7 17 (dt, J

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= 8 8, 2 0 Hz, 1H), 6 80 (s, 1H), 5 70 (t, J = 6 0 Hz, 1H), 5 38 (s, 2H), 4 01 (d, J = 6 0 Hz, 2H), ES-HRMS m/z 414 0515 (M+H calcd for $C_{19}H_{13}ClF_4NO_3$ requires 414 0520)

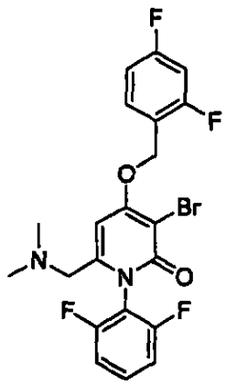
Example 467



5-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-oxo-1,6-dihydropyridine-2-carbaldehyde

Preparation of the title compound In a 50 ml one neck round bottom flask 4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-oxo-1,6-dihydropyridine-2-carbaldehyde (0 36 g, 0 95 mmol) was dissolved in acetonitrile (5 mL) The reaction mixture was cooled to 0 °C in ice bath and charged with N-bromosuccinamide (0 17 g, 0 95 mmol) The mixture was allowed to stir at 0 °C for 2 hours under nitrogen atmosphere After 2 hours, the solvent was evaporated under vacuum $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9 53 (s 1H), 7 73 - 7 67 (m, 2H), 7 62-7 54 (m, 1H), 7 35 (dt, J = 10 40, 2 56 Hz, 1H), 7 27 (t, J=8 35 Hz, 2H), 7 19 (dt, J =8 60, 2 44 Hz, 1H), 5 72 (s, 1H), 5 50 (s, 2H), ES-MS m/z 455 9836 (M+H calcd for $C_{19}H_{11}BrF_4NO_3$ requires 455 9859)

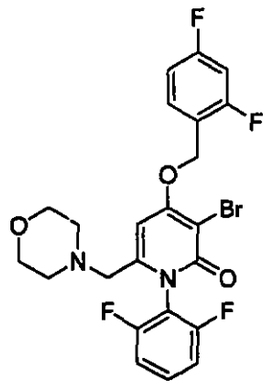
Example 468



3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-[(dimethylamino)methyl]pyridin-2(1H)-one

In a 50 ml round bottom flask 5-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-oxo-1,6-dihydropyridine-2-carbaldehyde (0 456 gm, 1 0 mmol) was stirred in dichloromethane (5 mL) To this mixture was added a 2M THF solution of dimethyl amine (1 25ml, 2 5 mmol ) The mixture was allowed to stir under nitrogen atmosphere and at room temperature for 2 hours To this mixture was then added triacetoxy sodium borohydride (0 37 g, 1 75 mmol) followed by two to three drops of acetic acid The mixture was then stirred at rt overnight The solvents were then removed by evaporation and the residue was taken up in ethyl acetate (30 ml) and washed with aqueous sodium bicarbonate and brine The organics were then combined, dried over $MgSO_4$, and concentrated in vacuo The crude product was purified by flash column chromatography using a solvent gradient of (3 1) ethyl acetate-hexane to (0 100) ethyl acetate to give 0 14 g (30 % yield) of the desired product $^1H$ NMR (300 MHz, DMSO-$d_6$) δ 7 73-7 58 (m, 2H), 7 42-7 30 (m, 3H), 7 22 (dt, J=8 73, 2 60 Hz, 1H), 6 81 (s, 1H), 5 44 (s, 2H), 3 04 (s, 2H), 1 96 (s, 6H), ES-MS m/z 485 0 (M+H) ES-HRMS m/z 485 0457 (M+H calcd for $C_{21}H_{18}BrF_4N2O_2$ requires 485 0489)

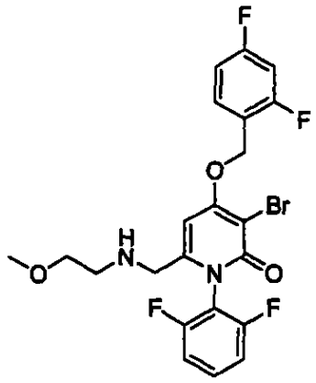
Example 469



3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-(morpholin-4-ylmethyl)pyridin-2(1H)-one

The title compound was prepared by reacting 5-bromo-4-[(2,4-difluorobenzyl)oxy]-1 (2,6-difluorophenyl)-6-oxo-1,6-dihydropyridine-2-carbaldehyde (0 456 g, 1mmol) with morpholine (0 13 ml, 1 5 mmol) and triacetoxy sodium borohydride (0 42 g, 2 0 mmol) in dichloromethane (7 mL) by using a similar procedure to the one described for Example 468 The crude product was purified by flash column chromatography Elution with (50 50 → 0 100) hexanes-ethyl acetate to give 0 15 g (29% yield) of the desired product $^1$H NMR (300 MHz, DMSO-$d_6$) δ 7 75- 7 57 (m, 2H), 7 43-7 31 (m, 3H), 7 20 (dt, J=8 64, 2 48 Hz, 2H), 6 85 (s, 1H), 5 44 (s, 2H), 3 37 (app t, J=4 37 Hz, 4H), 3 13 (s,2H), 2 08 (t, J=4 19 Hz, 4H), ES-HRMS m/z 527 0600 (M+H calcd for $C_{23}H_{20}BrF_4N_2O_3$ requires 527 0594)

Example 470



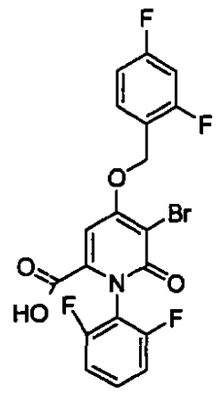
3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-{[(2-methoxyethyl)amino]methyl}pyridin-2(1H)-one

The title compound was prepared by reacting 5-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-oxo-1,6-dihydropyridine-2-carbaldehyde -(0 319 g, 0 7 mmol) with 2-methoxy ethylamine (0 086 ml, 1 0 mmol) and triacetoxy sodium borohydride (0 42 g, 2 0 mmol) in dichloromethane (4 mL) by using a procedure, similar to the one described for Example 468 The crude product was purified by flash column chromatography Elution with (50 50 → 0 100) hexanes-ethyl acetate to give 0 13 g of the desired product

$^1$H NMR (400 MHz, $CDCl_3$) δ 7 54 (q, J=6 89 Hz, 1H), 7 41 - 7 33 (m, 1H), 7 19 (s, 1H), 6 99 (t, J = 7 90 Hz, 2H), 6 90 (dt, J=7 90, 2 78, Hz, 1H), 6 80 (dt, J = 10 60, 2 34 Hz, 1H), 6 51 (s,1H), 5 24 (s,2H), 3 33 (t, J=4 69 Hz,1H), 3 30 (s, 3H), 2 57(t, J= 4 86 Hz, 2H), 1 53 (s,2H), ES-HRMS m/z 515 0548 (M+H calcd for $C_{22}H_{20}BrF_4N_2O_3$ requires 515 0594)

325
322

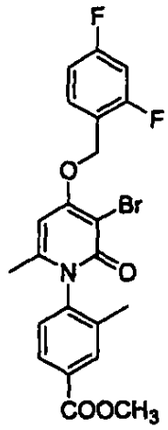
Example 471



5-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-oxo-1,6-dihydropyridine-2-carboxylic acid

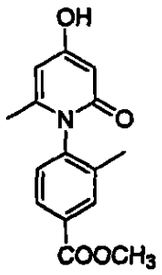
In a 100 ml round bottom flask, 3-bromo-4- [(2,4-difluorobenzyl)oxy]-1-(2,6-cifluorophenyl)-6 (hydroxymethyl)pyridin-2(1H)-one (1 70 g, 3 7 mmol) was dissolved in acetone (10 mL) and cooled to 0 °C in ice bath To the reaction was added 1M acetone solution of Jones (5 ml, excess amount) Additional Jones reagent was added over time (approximately 6 hours) until the reaction was complete The reaction was then concentrated down to dryness The residue was then taken up in ethyl acetate (10 mL) and washed with brine The dark yellow to brown colored crude product was purified by dissolving in 1N aqueous NaOH The remaining organic impurities were removed by extracting with diethyl ether The organic layers were discarded and the aqueous layer was acidified with dilute HCl (til pH app 1) to precipitate the pure acid which was then filtered and triturated with ether to obtain 1 17 g (65%) of the desired product $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7 66 (q, J= 9 41 Hz, 1H), 7 57- 7 50 (m, 1H), 7 34 (dt, J= 10 11, 2 78 Hz, 1H), 7 28-7 23 (m, 3H), 7 18 (dt, 8 90, 2 42 Hz, 1H), 5 47 (s, 2H) ES-HRMS m/z 471 9814 (M+H calcd for $C_{19}H_{11}BrF_4NO_4$ requires 471 9808)

Example 472



Methyl 4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-3-methylbenzoate

Step1 Preparation of methyl 4-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)-3-methylbenzoate

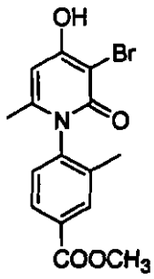


In a 50 ml one neck round bottom flask equipped with a stir bar, Dean Stark trap, and condenser 4-amino-2-methyl-methylbenzoate (1 19g, 11 63 mmol) and 4-hydroxy-6-methyl-2H-pyran-2-one (1 611g, 12 78 mmol) were mixed together and dissolved in 1,2-dichlorobenzene (5 mL) The mixture was vigorously stirred and then placed in a preheated oil bath at 165 0 °C The reaction was maintained at 165 0 °C for 1 5 hour and cooled to room temperature The reaction was worked up by diluting with toluene (10 mL) and then stirring at room temperature for 2 hours A light brown precipitate resulted The crude product was isolated by filtration and then

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363

triturated with ether $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10 64 (s, 1H), 7 93 (s,1H), 7 85 (dd, 8 46 Hz, 1H), 7 26 (d , J= 8 12 Hz, 1H), 5 91 (d, J= 2 32 Hz, 1H), 5 54 (d, J=2 32 Hz, 1H), 3 84 (s, 3H), 1 99 (s, 3H), 1 73 (s,3H) ES-HRMS m/z 272 0880 (M-H calcd for $C_{15}H_{14}NO_4$ requires 272 1001)

Step 3 Preparation of Methyl 4-(3-bromo-4-hydroxy-6-methyl-2-oxopyridin-1 (2H)-yl)-3-methylbenzoate

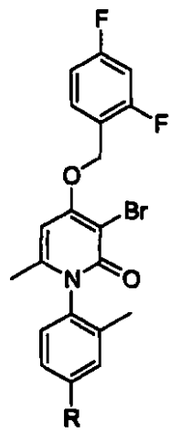



Methyl 4-(3-bromo-4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)-3-methylbenzoate was prepared by reacting - methyl 4-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)-3-methylbenzoate with N-bomosuccinamide in acetonitrile by following a procedure, similar to the one described in Example 465- step 3 $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7 95 (s, 1H), 7 87 (dd, J = 7 76, 2 02 Hz, 1H), 7 31 (d, J=8 54, 1H), 6 09 (s,1H), 3 85 (s, 3H), 1 99 (s,3H), 1 74 (s, 1H) ES-HRMS m/z 352 0195 (M+H calcd for $C_{15}H_{14}BrNO_4$ requires 352 0185)

Step 4 The title compound was prepared by taking methyl 4-(3-bromo-4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)-3-methylbenzoate (0 92 g, 2 61 mmol) and dissolving in dry DMF (5 mL) Potassium carbonate (0 432 g, 3 13 mmol) and 2,4 Difluuorobenzyl bromide (0 335 ml, 2 61 mmol) were then added The mixture was allowed to stir at room temperature for 2 hours

The reaction was then worked up by pouring it into 100 ml of ice-water which resulted in a precipitate forming which was isolated by filtering through a fritted funnel The crude product was washed with ether and dried in vacuum to give 0 85 g (76 20%) of pure product $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7 98 (d, J = 1 6 Hz, 1H), 7 88 (dd, J =8 04, 2 0 Hz, 1H), 7 69 (q, J = 8 6 Hz, 1H), 7 36-7 30 (m, 2H), 7 17 (dt, J = 8 7, 2 3 Hz, 1H), 6 71 (s,1H), 5 32 (s,2H), 3 86 (s,3H), 2 00 (s,3H), 1 86 (s, 3H) ES-HRMS m/z 478 0459 (M+H calcd for $C_{22}H_{19}BrF_2NO_4$ requires 478 0466)

Examples 473-476



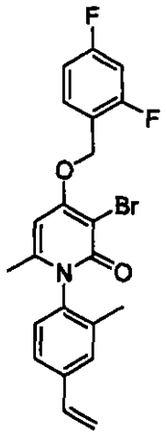

The compounds of Examples 473-476 are prepared by derivitazion of the compounds of Example 472

| Compound No | R | MF | M+H Requires | ESHRMS m/z |
|---|---|---|---|---|
| Ex 473 | -$CO_2H$ | $C_{21}H_{16}BrF_2NO_4$ | 464 0310 | 464 0324 |
| Ex 474 | -$CH_2OH$ | $C_{21}H_{18}BrF_2NO_3$ | 450 0500 | 450 0517 |
| Ex 475 | C(O)NH$(CH_2)_2OCH_3$ | $C_{24}H_{22}BrF_2N_2O_4$ | 521 0888 | 521 0865 |
| Ex 476 | C(O)$NHCH_3$ | $C_{22}H_{20}BrF_2N_2O_3$ | 477 0626 | 477 0609 |

NMR characterization of compounds of Examples 473-476

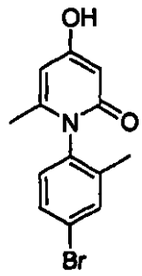
| Ex No | NMR Data |
|---|---|
| 473 | $^1$H-NMR (400 MHz DMSO-$d_6$) δ 13 11 (s 1H) 7 95 (d J = 1 70 hz 1H), 7 86 (dd, J=7 88 1 91 Hz 1H) 7 67 (dq, J = 8 47 1 89 Hz 1H), 7 36-7 30 (m, 2H), 7 17 (dt, J =8 54 2 48 Hz 1H) 6 71 (s,1H), 5 32 (s,2H) 1 99 (s, 3H) 1 87 (s 3H) |
| 474 | $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7 67 (q J =8 5 Hz 1H) 7 34 (dd J =10 04, 2 77 Hz 1H) 7 32 (s 1H), 7 24 (dd, J = 8 39,1 47 Hz 1H), 7 17 (dt, J = 8 84,2 6 Hz 1H), 7 08(d, J = 7 94 Hz 1 H) 6 66 (s,1H), 5 30 (s 2H) 5 25 (t J = 6 01 Hz 1H) 4 5 (d J =6.68 Hz, 2H), 1 91 (s 3H ) 1 86 (s 3H) |
| 475 | $^1$H NMR (400 MHz DMSO-$d_6$) δ 8 58 (app t J =5 4 Hz 1H) 7 84 (s 1H) 7 76 (dd J= 8 06 1 63 Hz 1H), 7 68 (dq J= 8 77 2 04 Hz, 1H) 7 33 (dt J=9 76 2 03 Hz 1H) 7 27 (d, J=8 34 Hz 1H) 7 17 (ddt J=8 51 2 63, 0 91 Hz, 1H) 6 70 (s 1H) 5 31 (s 2H) 4 50 (t, J=5 6 Hz , 1H), 3 47-3 36 (m 4H), 3 24 (s 3H) 1 97 (s,3H), 1 87 (s,3H) |
| 476 | $^1$H NMR (400 MHz DMSO-$d_6$' δ 8 50-8 49 (m 1H) 7 82 (s 1H) 7 74 (dd J=8 22, 1 79 Hz 1H), 7 69 (q J= 6 75 Hz 1H) 7 33 (dt J= 9 88 2 57 Hz, 1H), 7 26(d J=8 52 Hz 1H), 7 17(dt, J= 8 93 2 16 Hz 1H), 6 69 (s 1H) 5 31 (s 2H) 2 77 (d J= 4 58 Hz, 3H) 1.97 (s, 3H), 1 86 (s, 3H) |

Example 477



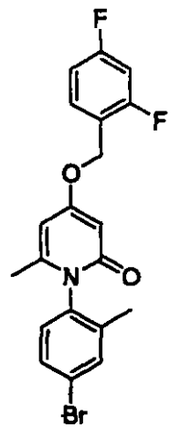

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(2-methyl-4-vinylphenyl)pyridin-2(1H)-one

Step 1- Preparation of -1-(4-bromo-2-methylphenyl)-4-hydroxy-6-methylpyridin-2(1H)-one



The title compound was prepared in a similar manner to the procedure outlined above for 4-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)-3-methylbenzoate $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10 61 (s, 1H), 7 59 (d, J= 2 84 Hz, 1H), 7 45 (dd, J= 8 39, 2 44 Hz, 1H), 7 06 (d, J= 7 44, 1H), 5 89 (d, J=2 73 Hz, 1H), 5 53(d, J=2 30, 1H), 1 91 (s, 3H), 1 75 (s, 3H) ES-HRMS m/z 294 0127 (M+H calcd for $C_{13}H_{13}BrNO_3$ requires 294 0130)

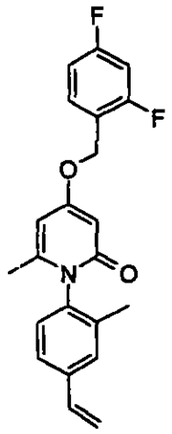
Step 2- Preparation of - 1-(4-bromo-2-methylphenyl)-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one



1-(4-bromo-2-methylphenyl)-4-hydroxy-6-methylpyridin-2(1H)-one (7 35 g, 25 0 mmol) was dissolved in DMF (15 mL) and stirred with potassium carbonate (4 14 g, 30 0 mmol) and 2,4 difluorobenzyl bromide (3 21 ml (25 0 mmol) at room temperature for 2 hours The reaction was worked up by pouring in to 300 ml ice water under continuous stirring A white precipitate was obtained which was isolated by filtering and

further purified by triturating with ether to give 3.06 g (29%) of the desired product. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.65-7.59 (m, 2H), 7.49 (dd, J=8.45, 2.22 Hz, 1H), 7.31 (dt, J=9.79, 2.22 Hz, 1H), 7.16-7.08 (m, 2H), 6.05 (d, J= 2.58 Hz, 1H), 5.93 (d, J= 2.66 Hz, 1H), 5.08 (s, 2H), 1.93 (s, 3H), 1.77 (s, 3H). ES-HRMS m/z 420.0390 (M+H calcd for $C_{20}H_{17}BrF_2NO_2$ requires 420.0411).

Step 3. Preparation of 4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(2-methyl-4-vinylphenyl)pyridin-2(1H)-one



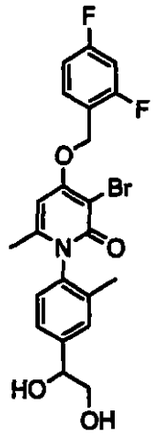
In a 50 ml round bottom flask previously evacuated and filled with nitrogen, 1-(4-bromo-2-methylphenyl)-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2 (1H)-one (0.420 g, 1.0 mmol) was dissolved in dry THF (10 mL). To this mixture was added Pd ($PPh_3$)$_4$ (0.173 g, 0.15 mmol). The reaction flask was sealed with a rubber septum, evacuated and filled with nitrogen. Under a nitrogen atmosphere, tributyl(vinyl)tin (0.35 ml, 1.2 mmol) was added to the sealed reaction mixture and stirred overnight at 50 °C.

The reaction was worked up by quenching with water and extraction of the product with ethyl acetate. The crude product was purified by column chromatography. Elution with

ethyl acetate-hexanes (50 50 → 0 100) gave 0 32 g (69%) of the desired product

Step 4 The title compound was prepared by reacting 4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(2-methyl-4-vinylphenyl)pyridin-2(1H)-one (0 64 g, 1 74 mmol) with N-bromosuccinamide (0 325 g, 1 83 mmol) in acetonitrile (9 mL) at 0°C using a similar procedure as described in step 3 of Example 465, to give 0 423 g (54 5 % after recrystallization) of the desired product $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7 67(app q, J= 7 59 Hz, 1H), 7 48(s,1H), 7 42(dd, J=8 21,1 98 Hz,1H), 7 33(dt, J=10 00, 2 27 Hz, 1H), 7 17(dt, J=8 51, 2 44 Hz, 1H), 7 13(d, J=7 88 Hz, 1H) 6 74(dd, J=11 29, 6 34 Hz, 1H), 6 67 (s,1H), 5 88(d, J= 17 85, 1H), 5 32-5 30 (m, 2H), 1 92 (s, 3H), 1 88 (s,3H) ES-HRMS m/z 446 0579 (M+H calcd for $C_{22}H_{19}BrF_2NO_2$ requires 446 0568)

Example 478

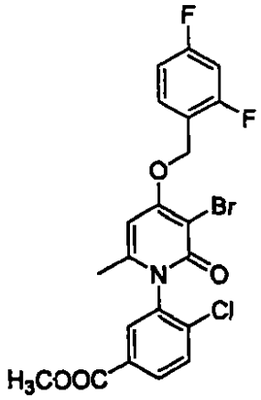



3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[4-(1,2-dihydroxyethyl)-2-methylphenyl]-6-methylpyridin-2(1H)-one

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(2-methyl-4-vinylphenyl)pyridin-2(1H)-one (0 126 g, 0 28 mmol) was

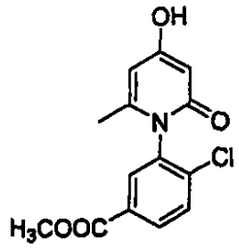
dissolved in a mixture of acetone (3 mL) and water (1 mL) To this was added 4-methylmorpholine N-oxide (0 032 g, 0 28 mmol) and catalytic amount (approximately 5 mgs) of osmium tetroxide was added, and stirred under nitrogen atmosphere After approximately 2 hours, the reaction was worked up by evaporation of the acetone The product was extracted into ethyl acetate and concentrated to give a dark colored solid which was further purified by column chromatography to give 0 049 g (37 % yield)of charcoal colored solid $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7 67 (q, J=8 24 Hz, 1H), 7 37-7 23 (m, 3H), 7 17 (dt, J= 8 62, 2 62 Hz, 1H), 7 07 (dd, J=9 36, 2 24 Hz, 1H), 6 65(s,1H), 5 30 (s, 2H), 4 74(t, J=6 16Hz, 1H), 4 57-4 50 (m, 1H), 3 45(app t, J=6 12 Hz, 2H), 3 41- 3 37 (m, 1H), 1 91(s,3H), 1 85 (s, 3H) ES-HRMS m/z 480 0625 (M+H calcd for $C_{22}H_{21}BrF_2NO_4$ requires 480 0623)

Example 479



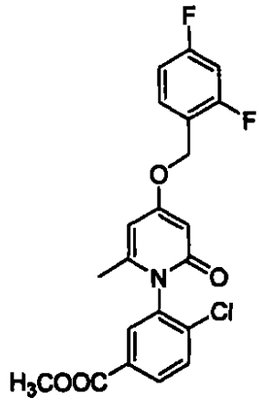

methyl 3-[3-bromo-4-[(2,4-difluorobenzyl) oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-chlorobenzoate

Step 1 Preparation of methyl 4-chloro-3-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)benzoate



A condensation reaction with methyl 3-amino-4-chlorobenzoate (14 5g, 78 2 mmol) and 4-hydroxy-6-methyl pyranone under reaction condition similar to the one described in Example 465- step 3 gave 12 32 (53 8%) of desired product

Step-3- Preparation of methyl-4-chloro-3-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoate



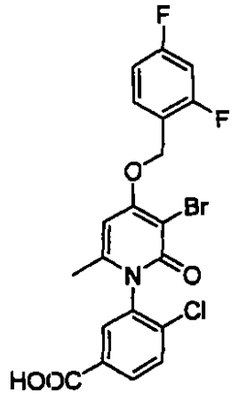
In a 250ml round bottom flask, methyl 4-chloro-3-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)benzoate (5 28 g, 18 0 mmol) from step1 was reacted with 2,4-difluoro-benzylbromide (3 72 g, 18 0 mmol) in DMF using similar procedure as in Example 472 step 3 After aqueous work up and chromatographic purification, 2 3 g (30%) pure product was obtained

Step 4 methyl 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-chlorobenzoate was prepared by reacting methyl-4-chloro-3-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoate (2 3 g, 5 47 mmol) with

327
390

N-bromosuccinamide (0 97 g, 5 47 mmol) in acetonitrile (10 mL) at 0°C, using a similar procedure as described in step 3 of Example 465, to give 1 80g (66 2 %) of the desired product $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 8 06-8 03 (m, 2H), 7 86 (d, J=9 70 Hz, 1H), 7 68 (q, J= 7 62, 1H), 7 34(dt, J=10 07, 2 46 Hz, 1H), 7 17 (dt,J= 8 72, 2 90 Hz, 1H), 6 73 (s,1H), 5 33 (s, 2H), 3 85 (s, 3H), 1 91 (s, 3H) ES-MS m/z 495 9757 (M-H calcd for $C_{21}H_{14}BrClF_2NO_4$ requires 495 9795)

Example 480

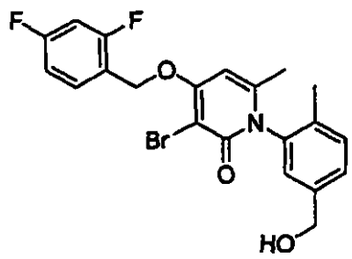



3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-chlorobenzoic acid

In a 50 ml round bottom flask, methyl-4-chloro-3-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoate (0 450 g, 0 90 mmol) was stirred in THF (5 mL) To this mixture was added NaOH (0 120 g, 3 0 mmol ) as a solution in water (1 5 mL) The reaction mixture was stirred at room temperature overnight The THF was evaporated and the residue was acidified with dilute HCl A white precipitate was obtained The product was filtered, washed with water and dried in vacuum to give 0 375 g (86 % yield ) of the desired product $^1H$ NMR (400 MHz DMSO-$d_6$) δ 7 89 (dd, J=7 78, 1 73 Hz, 1H), 7 71-7 65 (m, 2H), 7 53 (d, J=9 08Hz, 1H), 7 33 (dt,

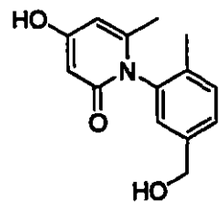
J=9 95, 2 59 Hz, 1H), 7 17 (dt, J=8 22, 2 59 Hz, 1H), 6 68 (s, 1H), 5 32(s, 2H), 1 89 (s,3H) ES-MS m/z 481 9585 (M-H calcd for $C_{20}H_{12}BrClF_2NO_4$ requires 481 9601)

Example 481



3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[5-(hydroxymethyl)-2-methylphenyl]-6-methylpyridin-2(1H)-one

Step 1 Preparation of 4-hydroxy-1-[5-(hydroxymethyl)-2-methylphenyl]-6-methyl pyridin-2(1H)-one



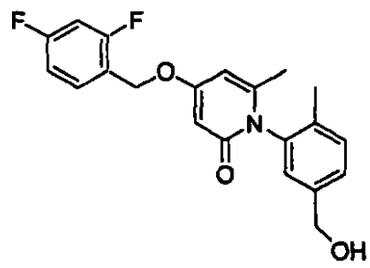
4-Hydroxy-6-methyl-2-pyrone (23 0 g, 182 2 mmol) and 3-Amino-4-methylbenzyl alcohol (25 0 g, 182 2 mmol) were taken up in 25 ml of 1,2-dichlorobenzene The solution was heated to 165°C in a 250 ml round bottom flask equipped with a J-Kem temperature controller probe, and a heating mantle In a separate 250 ml round bottom flask 4-Hydroxy-6-methyl-2-pyrone (23 0 g, 182 2 mmol) was suspended in 25 ml of 1,2-dichlorobenzene and also heated to 165°C The pyrone solution was poured into the flask containing the aniline and the reaction stirred at 165°C for 20 minutes The reaction was allowed to cool to room temperature Reaction contents were

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washed with saturated $NaHCO_3$ (aq ) Separated the organic and aqueous layers Aqueous layer was made acidic with dropwise addition of concentrated HCl The product was extracted from the acidic aqueous layer with n-BuOH N-BuOH removed in vacuo to produce a reddish brown oil (8 5 g, 19%) Contents carried forward to next reaction with no further purification $^1H$ NMR (300 MHz, $CD_3OD$) δ 7 35 (m, 2H), 7 08 (s, 1H), 6 08 (br s, 1H), 5 81 (br s, 1H), 4 60 (s, 2H), 2 01 (s, 3H), 1 87 (s, 3H) LC/MS, $t_r$ = 1 42 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 246 1131 (M+H) ES-HRMS m/z 246 1107 (M+H calcd for $C_{14}H_{16}NO_3$ requires 246 1125)

Step 2 4-[(2,4-difluorobenzyl)oxy]-1-[5-(hydroxymethyl)-2-methylphenyl]-6-methyl-pyridin-2(1H)-one

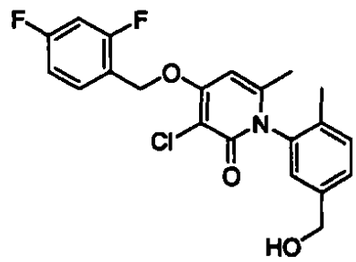



4-hydroxy-1-[5-(hydroxymethyl)-2-methylphenyl]-6-methyl pyridin-2(1H)-one ( from Step 1) (8 0 g, 32 6 mmol) was stirred briskly at room temperature with 2,4-difluorobenzyl bromide (4 2 ml, 32 6 mmol) and $K_2CO_3$ (4 5 g, 32 6 mmol) in 50 ml of dimethylformamide After stirring for 8 hours, $H_2O$ (100 ml) was added to reaction mixture The product was extracted with ethyl acetate Ethyl acetate layer was separated and dried over $Na_2SO_4$ Ethyl acetate was removed in vacuo A yellow oil was obtained The oil was passed through a plug of silica gel first eluting with 500 ml of ethyl acetate/hexane

(1 1) This eluent was set aside Next, ethyl acetate (100%) was passed through the plug until desired product was completely flushed from silica (3 liters) Solvent was removed in vacuo Light yellow oil obtained (7 5 g, 62%) $^1$H NMR (300 MHz, $CD_3OD$) δ 7 60 (app q, J = 6 44 Hz, 1H), 7 42 (d, J = 81 Hz, 2H), 7 15 (s, 1H), 7 06 (m, 2H), 6 21 (dd, J = 1 61, 1 00 Hz, 1H), 6 12 (d, J = 2 62 Hz, 1H), 5 16 (s, 2H), 4 65 (s, 2H), 2 07 (s, 3H), 1 93 (s, 3H), LC/MS, $t_r$ = 2 38 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 372 (M+H)

Step 3 Preparation of the title compound 4-[(2,4-difluorobenzyl)oxy]-1-[5-(hydroxymethyl)-2-methylphenyl]-6-methyl-pyridin-2(1H)-one ( from Step 2) (4 0 g, 10 8 mmol) was stirred at room temperature with N-bromosuccinimide (2 1 g, 11 9 mmol) in 100 ml of $CH_2Cl_2$ for 2 0 hours The reaction was evaporated on a rotary evaporator and the resulting solid was washed with acetonitrile and dried in vacuo to yield a white solid (3 9 g, 80%) $^1$H NMR (300 MHz, $CDCl_3$) δ 7 67 (app q, J = 6 24 Hz, 1H), 7 35 (d, J = 1 01 Hz, 2H), 7 10 (s, 1H), 7 04 (m, 1H), 6 91 (ddd, J = 11 08, 8 66, 2 42 Hz, 1H), 6 15 (d, J = 0 63 Hz, 2H), 5 29 (s, 2H), 4 66 (s, 2H), 2 08 (s, 3H), 1 97 (s, 3H), ES-MS m/z 450 (M+H) ES-HRMS m/z 450 0467 (M+H calcd for $C_{21}H_{19}BrF_2NO_3$ requires 450 0511)

Example 482

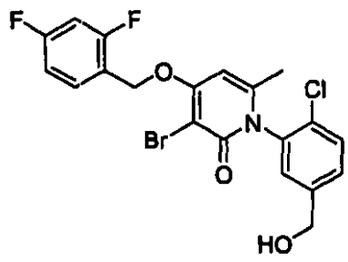


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3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[5-(hydroxymethyl)-2-methylphenyl]-6-methylpyridin-2(1H)-one

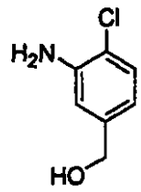
The title compound was prepared by a procedure similar to the one described for Example 481, except that the product from Step 2, Example 481 was chlorinated instead of being brominated The procedure is as follows 4-[(2,4-difluorobenzyl)oxy]-1-[5-(hydroxymethyl)-2-methylphenyl]-6-methyl-pyridin-2(1H)-one (from Step 2, Example 481 above) (7 0 g, 18 8 mmol) was refluxed with N-chlorosuccinimide (2 5 g, 18 8 mmol) in 50 ml of $CH_2Cl_2$ overnight The reaction was evaporated on a rotary evaporator and the resulting solid was stirred in MeOH The precipitate was collected on a filter pad, washed with MeOH and dried in vacuo to yield a white solid (1 6 g, 21%) $^1$H NMR (300 MHz DMF-$d_7$) δ 7 85 (app q, J = 6 44 Hz, 1H), 7 43 (d, J = 0 81, 1H), 7 42 - 7 23 (m, 3H), 6 84 (s, 1H), 5 48 (s, 2H), 4 67 (s, 2H), 2 05 (s, 3H), 2 03 (s, 3H), ES-MS m/z 406 (M+H) ES-HRMS m/z 406 1033 (M+H calcd for $C_{21}H_{16}ClF_2NO_4$ requires 406 1016)

Example 483



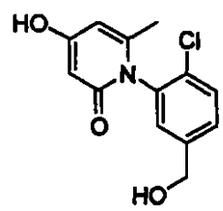

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[5-(hydroxymethyl)-2-methylphenyl]-6-methylpyridin-2(1H)-one

Step 1 Preparation of 3-amino-4-chloro-benzyl alcohol



3-Nitro-4-chloro-benzyl alcohol (23 0 g, 122 6 mmol) is taken up in isopropyl alcohol (175 ml) and water (35 ml) Iron powder (<10 micron) (68 0 g, 1 2 moles) and $NH_4Cl$ (66 0 g, 1 2 moles) are added The suspension is stirred overhead at 70°C in a three neck round bottom flask equipped with a heating mantle and a J-Kem temperature controller probe After 4 hours, isopropyl alcohol was removed in vacuo Water (100 ml) and concentrated HCl (10 ml) was added to mixture Contents are transferred to a separtory funnel and ethyl acetate is used to extract the aqueous layer of impurities The aqueous layer was then basified with 50% aqueous NaOH The product was extracted from the basic aqueous layer with ethyl acetate The ethyl acetate layer was dried over $Na_2SO_4$ and then removed in vacuo The remaining residue was taken up in 50% ethyl acetate/hexane and the precipitate was collected on a filter pad Precipitate was washed with 50% ethyl acetate/hexane to yield a flocculent brown solid (8 4 g, 44%) $^1H$ NMR (300 MHz, $CD_3OD$) δ 7 17 (d, J = 8 26 Hz, 1H), 6 86 (d, J = 2 01 Hz, 1H), 6 66 (dd, J = 2 01, 0 61 Hz, 1H), 4 51 (s, 2H), LC/MS, $t_r$ = 0 32 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C), ES-MS m/z 158 (M+H)

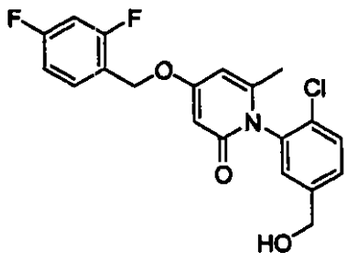
Step 2 1-[2-chloro-5-(hydroxymethyl)phenyl]-4-hydroxy-6-methylpyridin-2(1H)-one



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3-amino-4-chloro-benzyl alcohol (8 0g, 51 0 mmol) and 4-hydroxy-6-methyl-2-pyrone (6 4 g, 51 0mmol) were taken up in 1,2-dichlorobenzene (50 ml) The mixture was plunged into a 165°C oil bath where it stirred for 20 minutes The reaction was cooled to room temperature and the reaction was worked up by washing with saturated $NaHCO_3$ (aq ) and extracting impurities with ethyl acetate The product remained in the aqueous layer The basic aqueous layer was made acidic with concentrated HCl The product was extracted from the acidic aqueous layer with ethyl acetate The ethyl acetate layer was dried over $Na_2SO_4$ and the solvent removed in vacuo The product was obtained as a yellow oil in a 26% yield and was carried through to the next step with no further purification $^1H$ NMR (300 MHz, $CD_3OD$) δ 7 62 (d, J = 8 26 Hz, 2H), 7 51 (dd, J = 8 46, 2 22 Hz, 1H), 7 36 (d, J = 2 01 Hz, 1H), 6 13 (br s, 1H), 5 84 (d, J = 2 42 Hz, 1H), 4 68 (s, 2H), 1 97 (s, 3H), LC/MS, $t_r$ = 0 25 minutes and 1 41 minutes (tautomer), (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 266 (M+H)

Step 3 1-[2-chloro-5-(hydroxymethyl)phenyl]-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one

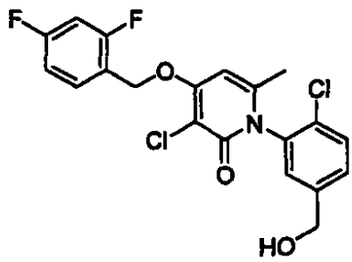



1-[2-chloro-5-(hydroxymethyl)phenyl]-4-hydroxy-6-methylpyridin-2(1H)-one ( from step 2) (3 5g, 13 2 mmol) was taken up in DMF (10 ml) and cooled to 0°C 2,4-Difluorobenzyl bromide (1 7 ml, 13 2 mmol) and $K_2CO_3$ (1 8 g, 13 2 mmol) were added and the reaction stirred for 6 hours The reaction was

worked up by adding saturated $NaHCO_3$ (aq ) and extracting with ethyl acetate The ethyl acetate extraction was washed with water, and the aqueous layer was extracted with ethyl acetate The organic layers were combined and dried over $Na_2SO_4$, filtered, and the solvent removed in vacuo The product was obtained in 83% crude yield and carried through to the next step as a brown oil LC/MS, $t_r$ = 2 48 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 392 (M+H) ES-HRMS m/z 392 0853 (M+H calcd for $C_{20}H_{17}ClF_2NO_3$ requires 392 0860)

Step 4 The title compound was prepared from 1-[2-chloro-5-(hydroxymethyl)phenyl]-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (from step 3) (1 8g, 4 6 mmol) and N-bromosuccinimide (0 82 g, 4 6 mmol) by dissolving them in $CH_2Cl_2$ (10 ml) and stirring for 2 hours at room temperature The solvent was removed in vacuo and the residue was taken up in $CH_3CN$ The precipitate was collected on a filter pad and rinsed with $CH_3CN$ to yield a white solid (370 mg, 17%) $^1H$ NMR (300 MHz, $CDCl_3$) δ 7 65 (app q, J = 6 24 Hz, 1H), 7 52 (d, J = 8 26 Hz, 1H), 7 40 (dd, J = 8 26, 2 01 Hz 1H), 7 26 (d, J = 0 81 Hz, 1H), 7 03 (m, 1H), 6 91 (ddd, J = 11 08, 8 66, 2 42 Hz, 1H), 6 17 (d, J = 0 81 1H), 5 29 (s, 2H), 4 63 (s, 2H), 2 02 (s, 3H), ES-MS m/z 471 (M+H) ES-HRMS m/z 471 9953 (M+H calcd for $C_{20}H_{16}BrClF_2NO_3$ requires 471 9944)

Example 484

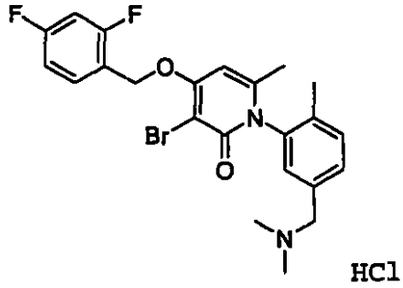


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3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[5-(hydroxymethyl)-2-methylphenyl]-6-methylpyridin-2(1H)-one

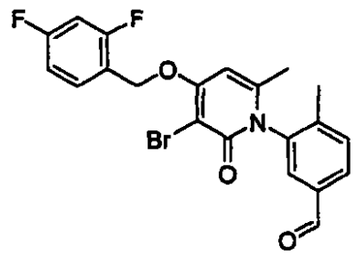
The title compound was prepared from 1-[2-chloro-5-(hydroxymethyl)phenyl]-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (2 4 g, 6 1 mmol) and NCS (815 0 mg, 6 1 mmol) in 65°C dichloroethane (20 ml) A catalytic amount of dichloroacetic acid (2 drops) was added After two hours the solvent was removed in vacuo and the residue was taken up in diethyl ether The precipitate was collected on a filter pad and then taken up in 50% ethyl acetate/hexanes to remove residual succinimide The precipitate was collected on a filter pad and then dried in vacuo to produce a white powder (180 mg, 6 9%) $^1$H NMR (300 MHz, $CDCl_3$) δ 7 61 (app q, J = 6 44 Hz, 1H), 7 52 (d, J = 8 26 Hz, 1H), 7 40 (dd, J = 8 26, 2 01 Hz 1H), 7 27 (d, J = 2 01 Hz, 1H), 7 00 (m, 1H), 6 91 (m, 1H), 6 20(s, 1H), 5 29 (s, 2H), 4 65 (s, 2H), 2 03 (s, 3H), ES-MS m/z 426 (M+H) ES-HRMS m/z 426 0453 (M+H calcd for $C_{20}H_{16}Cl2F_2NO_3$ requires 426 0470)

Example 485




3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-{5-[(dimethylamino)methyl]-2-methylphenyl}-6-methylpyridin-2(1H)-one hydrochloride

Step 1 Preparation of 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzaldehyde

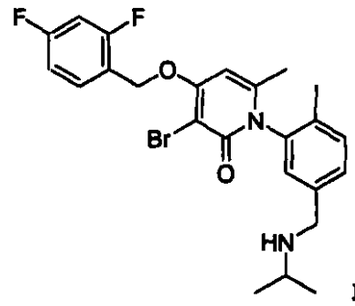


3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[5-(hydroxymethyl)-2-methylphenyl]-6-methylpyridin-2(1H)-one (1 5g, 3 33 mmol) was dissolved in 75% $CH_3CN/CH_2Cl_2$ (20ml) and cooled to 0°C Dess-Martin Periodinane(2 8 g, 6 66 mmol) was added and the reaction stirred for four hours At this time, the reaction was quenched with 5% sodium bisulfite (aq ) The product was extracted with ethyl acetate The combined organic extracts were then washed with saturated $NaHCO_3$ (aq ) The aqueous layer was extracted with ethyl acetate The combined organic extracts were dried over $Na_2SO_4$, filtered, and concentrated The resulting residue was taken up in diethyl ether and the precipitate was collected on a filter pad and washed with more diethyl ether to yield a white solid (1 35 g, 91%) $^1H$ NMR (300 MHz, $CDCl_3$) δ 10 00 (s, 1H), 7 91 (dd, J = 7 65, 1 61 Hz, 1H), 7 65 (m, 2H), 7 57 (d, J = 7 85 Hz, 1H), 7 03 (m, 1H), 6 95 (ddd, J = 12 69, 8 86, 2 62 Hz, 1H), 6 19 (s, 1H), 5 31 (s, 2H), 2 20 (s, 3H), 1 96 (s, 3H), ES-MS m/z 448 (M+H) ES-HRMS m/z 448 0347 (M+H calcd for $C_{21}H_{17}BrF_2NO_3$ requires 448 0354)

Step 2 Preparation of the title compound 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzaldehyde ( from step 1) (0 50 g, 1 11 mmol) was dissolved in $CH_2Cl_2$ ( 10 ml) N,N-dimethylamine (2 0 M in THF)

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(1 11 ml, 2 22 mmol) was added This mixture stirred for at room temperature for 12 hours Next, sodium triacetoxyborohydride (0 47 g, 2 22 mmol) was added and the reaction stirred for two more hours The reaction was washed with 1 N NaOH (aq ) and then extracted with $CH_2Cl_2$ The combined organic extracts were washed with water The aqueous layer was separated and extracted with $CH_2Cl_2$ The combined organic extracts were dried over $Na_2SO_4$, filtered and concentrated in vacuo The resulting residue was taken up in diethyl ether 1M HCl in diethyl ether (5 ml) was added and the precipitate was collected on a filter pad This precipitate was hygroscopic The hygroscopic solid was then taken up in hot ethyl acetate Hexane was added until a precipitate crashed out The precipitate was collected on a filter pad to yield a white solid (150 mg, 26%) $^1H$ NMR (400 MHz, $D_2O$) δ 7 42 (m, 3H), 7 17 (s,1H), 6 86 (m, 2H), 6 53(s, 1H), 5 20(s, 2H), 4 18(s, 1H) 2 72(s, 6H), 1 85(s, 3H), 1 82(s, 3H), ES-MS m/z 477 (M+H) ES-HRMS m/z 477 0955 (M+H calcd for $C_{23}H_{24}BrF_2N_2O2$ requires 477 0984)




HCl

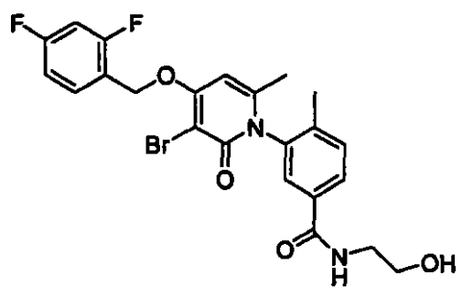
Example 486

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-{5-[(isopropylamino)methyl]-2-methylphenyl}-6-methylpyridin-2(1H)-one hydrochloride

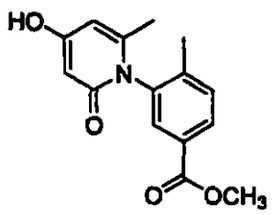
The title compound was prepared by reductive amination of 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-

1(2H)-yl]-4-methylbenzaldehyde ( from step 1) (0 50 g, 1 11 mmol) with iso-propyl amine (0 13 g, 2 22) according to the procedure described above for Example 485 (Step 2) to give the desired compound (0 49g, 84%) $^1$H NMR (400 MHz, $CD_3OD$) δ 7 64 (app quartet, J = 6 58 Hz, 1H), 7 53 (m, 2H), 7 29(br s, 1H), 7 03(m, 1H), 6 68 (s, 1H), 5 36 (s, 2H), 4 22(s, 2H), 3 46(m, 1H), 2 06 (s, 3H), 2 01 (s, 3H), 1 37 (d, J = 6 58 Hz, 6H) , ES-MS m/z 491 (M+H) ES-HRMS m/z 491 1107 (M+H calcd for $C_{24}H_{26}BrF_2N_2O2$ requires 491 1140)

Example 487



3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-N-(2-hydroxyethyl)-4-methylbenzamide

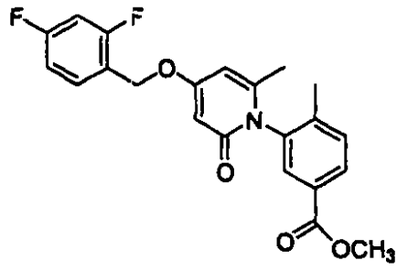


Step 1 Preparation of methyl 3-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)-4-methylbenzoate

4-Hydroxy-6-methyl-2-pyrone (22 9 g, 181 6 mmol) and methyl-3-amino-2-methylbenzoate (25 g, 151 3 mmol) were suspended in 50 ml of 1,2-dichlorobenzene in a 250 ml, 3-necked round bottom flask equipped with a J-Kem temperature controller probe, a Dean-Stark trap, and a heating mantle

The reaction was heated to 165°C for 15 minutes, during which, water and some 1,2-dichlorobenzene was collected in the Dean-Stark trap The reaction was allowed to cool to about 110°C At this point, 200 ml of toluene was added The flask was plunged into a 0°C ice bath while stirring "Oiling out" occurred Perhaps too much toluene was added so some of the solvent was removed in vacuo The oil went back into solution and a light brown precipitate remained The toluene mixture was allowed to stir for 72 hours at room temperature A precipitate was collected on a filter pad The precipitate was filtered and washed 3 times with toluene, 3 times with 50°C water to remove excess pyrone, and dried in vacuo to give a tan solid (16 5 g, 40% yield) $^1$H NMR (300 MHz, $CD_3OD$) δ 8 06 (dd, J = 8 06, 1 61 Hz, 1H), 7 80 (d, J = 1 61 Hz, 1H), 7 56 (d, J = 8 06, Hz, 1H), 6 15 (dd, J = 2 42, 0 81 Hz, 1H), 5 86 (d, J = 2 42 1H), 3 94 (s, 3H), 2 15 (s, 3H), 1 91 (s, 3H), ES-MS m/z 274 (M+H) ES-HRMS m/z 274 1066 (M+H calcd for $C_{15}H_{16}NO_4$ requires 274 1074)

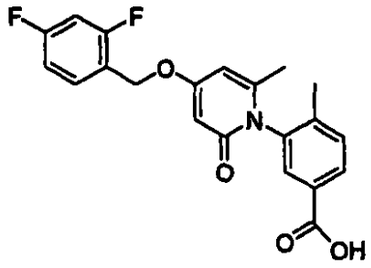
Step 2 Preparation of methyl 3-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoate




Methyl 3-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)-4-methylbenzoate ( from Step 1) (16 5 g, 60 4 mmol) 2,4-difluorobenzyl bromide (7 8 ml, 60 4 mmol) were taken up in 250 ml of N,N-dimethylformamide and the mixture was cooled to 0°C $K_2CO_3$ (8 3g, 60 4 mmol) was added and reaction stirred for 12 hours during which time the reaction was allowed to

warm to room temperature LC/MS indicated the presence of starting material after 12 hours An excess of $K_2CO_3$ was added at room temperature along with 0 50 ml of 2,4-difluorobenzyl bromide The reaction stirred for an additional two hours Saturated $NaHCO_3$ (aq ) was poured into reaction vessel The solution was extracted with ethyl acetate and the organic layers were combined then washed with water The organic layer was separated and the aqueous layer was extracted with ethyl acetate The organic layers were combined and dried over $Na_2SO_4$, and evaporated The product was carried on to the next step as a crude oil (24 1 g, quantitative yield) $^1H$ NMR (300 MHz, $CDCl_3$) δ 8 06 (dd, J = 7 85, 1 61 Hz, 1H), 7 82 (d, J = 1 61, 1H), 7 52-7 44 (m, 2H), 7 01 - 6 88 (m, 2H), 6 05 (d, J = 2 62 Hz, 1H), 5 97 (dd, J = 2 62, 0 81 Hz, 1H), 5 08 (s, 2H), 3 93 (s, 3H), 2 20 (s, 3H), 1 89 (s, 3H), ES-MS m/z 400 (M+H) ES-HRMS m/z 400 1374 (M+H calcd for $C_{22}H_{20}F_2NO_4$ requires 400 1355)

Step 3 Preparation of 3-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoic acid

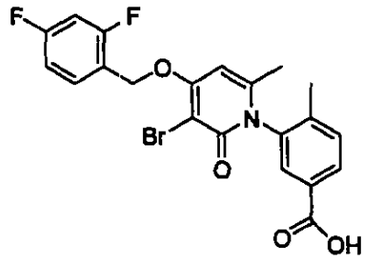



Methyl 3-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoate (14g, 35 0 mmol)(from step 2) was taken up in THF (25 ml) and $H_2O$ 2 5 N NaOH (aq ) was added and the reaction stirred for 30 minutes at room temperature The reaction was made acidic via the addition of concentrated HCl The product was extracted with ethyl acetate The ethyl acetate extraction was dried over $Na_2SO_4$,

334
337

filtered, and the solvent removed in vacuo Upon vacuum removal of the solvent, the product crashed out of the ethyl acetate This precipitate was collected on a filter pad and washed with a 50 ethyl acetate/hexanes to yield a white powder (9g, 7%) $^1$H NMR (300 MHz, $CDCl_3$) δ 8 01 (dd, J = , 1 61 Hz, 1H), 7 84 (d, J = 1 61 Hz, 1H), 7 52 - 7 47 (app q, J = 8 26, 1H), 7 43 (d, J = 8 06 Hz, 1H), 7 00 - 6 88 (m, 2H), 6 19 (d, J = 2 62 Hz, 1H), 6 05 (dd, J = 2 62, 1 81 Hz, 1H), 5 17 (s, 2H), 2 19 (s, 3H), 1 90 (s, 3H), ES-HR/MS m/z 386 12 (M+H calcd for $C_{21}H_{18}F_2NO_4$ requires 386 1198)

Step 4 Preparation of 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoic acid



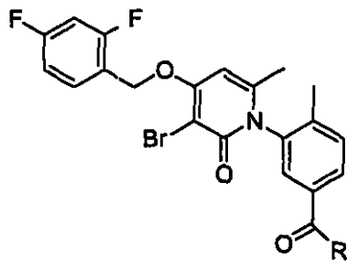

3-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoic acid (5 9 g, 15 2 mmol) (from step 3 above) was taken up in dichloromethane (25 ml) N-Bromosuccinimide was added and the reaction stirred for 14 hours The dichloromethane was removed in vacuo and the residue was taken up in acetonitrile The precipitate was collected on a filter pad and rinsed with acetonitrile to yield the desired product as a white solid (5 2 g, 74%) $^1$H NMR (300 MHz, $CD_3OD$) δ 7 87 (dd, J = 7 85, 1 61,Hz, 1H), 7 82 (d, J = 1 81 Hz, 1H), 7 69 (app q, J = 8 06 Hz 1H), 7 57 (d, J = 8 06 Hz, 1H), 7 09 (dt, J = 8 66, 2 22 Hz, 1H), 6 70 (s, 1H), 5 40 (s, 2H), 2 14 (s, 3H), 2 02 (s, 3H), ES-MS m/z 464

(M+H) ES-HRMS m/z 464 0275 (M+H calcd for $C_{21}H_{17}BrF_2NO_4$ requires 464 0304)

Step 5 Preparation of the title compound 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoic acid (from Step 4 above) (1 9g, 4 10 mmol) was dissolved in 20 ml of $CH_2Cl_2$ Ethanolamine (297 µl, 4 92 mmol) was added, followed, in order, by EDCI (0 764 g, 4 92 mmol), 1-hydroxybenzotriazole (0 665g, 4 92 mmol) and triethylamine (1 14 ml, 8 20 mmol) The reaction was stirred at room temperature overnight The reaction was quenched with $NH_4Cl$ and extracted 3 times with ethyl acetate The combined organic layer was then washed with saturated $NaHCO_3$ (aq ) and extracted 3 times with ethyl acetate The organic layers were combined and washed with $H_2O$ and extracted 3 times with ethyl acetate The organic layers were combined and dried over $Na_2SO_4$ and evaporated The resulting residue was triturated with diethyl ether/hexane to obtain a solid, which was dried in vacuo to give a white solid (1 5g, 72%) $^1H$ NMR (300 MHz, $CDCl_3$) δ 7 93 (dd, J = 7 85, 1 61 Hz, 1H), 7 65 (d, J = 1 61 Hz, 1H), 7 62 (app q, J = 8 26 Hz, 1H), 7 40 (d, J = 8 06 Hz, 1H), 7 39 - 7 30 (m, 1H), 7 03 - 6 97 (m, 1H), 6 88 - 6 81 (m, 1H), 6 25 (s, 1H), 5 20 (s, 2H), 3 70 - 3 52 (m, 1H), 3 16 - 3 12 (m, 2H), 2 10 (s, 3H), 1 98 (s, 3H), ES-MS m/z 507 (M+H) ES-HRMS m/z 507 0719 (M+H calcd for $C_{23}H_{22}BrF_2N_2O_4$ requires 507 0726)

Examples 488-491

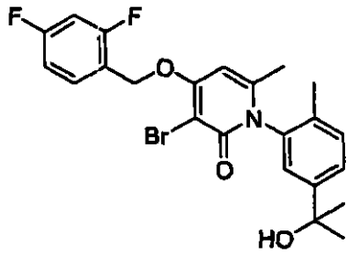
335
338



The compounds of Examples 488-491-476 are prepared essentially according to the procedures set forth for Example 487

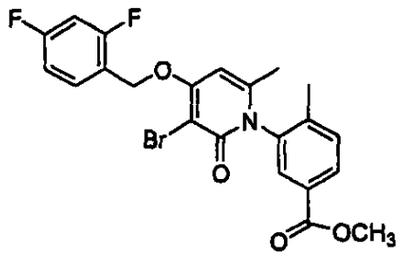
| Compound No | R | % Yield | MF | M+H Requires | ESHRMS m/z |
|---|---|---|---|---|---|
| Ex 488 | -NH(CH$_2$)$_2$OCH$_3$ | 84 | $C_{24}H_{24}BrF_2N_2O_4$ | 528 0882 | 521 0868 |
| Ex 489 | -NHCH$_3$ | 79 | $C_{22}H_{20}BrF_2N_2O_3$ | 477 0620 | 477 0602 |
| Ex 490 | -N(CH$_3$)$_2$ | 54 | $C_{23}H_{22}BrF_2N_2O_3$ | 491 0776 | 491 0753 |
| Ex 491 | -morpholine | 65 | $C_{25}H_{24}BrF_2N_2O_4$ | 533 0858 | 533 0882 |

Example 492



3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[5-(1-hydroxy-1-methylethyl)-2-methylphenyl]-6-methylpyridin-2(1H)-one

Step 1 Preparation of methyl 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoate

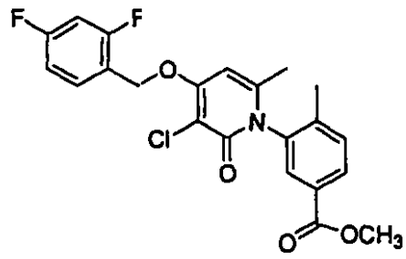


Methyl 3-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoate ( as prepared above) (1 8g, 4 51 mmol) was taken up in $CH_2Cl_2$ (10 ml) N-bromosuccinimide (0 80 g, 4 51 mmol) was added and the mixture stirred at room temperature for two hours The $CH_2Cl_2$ is removed in vacuo and the residue is taken up in $CH_3CN$ The resulting precipitate is collected on a filter pad and washed with $CH_3CN$ to yield a white solid (0 30 g, 14%, first crop) $^1H$ NMR (300 MHz, $CDCl_3$) δ 8 06 (dd, J = 8 06, 1 61 Hz, 1H), 7 80 (d, J = 1 61 Hz, 2H), 7 65 (app q, J = 8 46 Hz, 1H), 7 48 (d, J = 8 06, 1H), 7 05 - 6 99 (m, 1H), 6 96 - 6 89 (m, 1H), 6 16 (s, 1H), 5 31 (s, 2H), 3 93 (s, 3H), 2 17 (s, 3H), 1 96 (s, 3H) ES-HRMS m/z 478 0476 (M+H calcd for $C_{22}H_{19}BrF_2NO_4$ requires 478 0476)

Step 2 Preparation of the title compound Methyl 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoate (0 22 g, 0 46 mmol) was taken up in THF and cooled to 0°C MeMgCl (3 0 M in THF) (0 73 ml, 2 2 mmol) was slowly added to the 0°C solution The reaction was allowed to proceed without maintaining the 0°C bath temperature The reaction was complete within two hours At this time the mixture was quenched with saturated $NH_4Cl$ (aq ) and extracted with ethyl acetate The organic layers were combined, washed with $H_2O$, and extracted with ethyl acetate The organic layers were combined and dried over $Na_2SO_4$, filtered, and evaporated The residue was taken up in 50% ethyl acetate/hexanes The

precipitate was collected on a filter pad and washed with 50% ethyl acetate/hexanes to yield a white solid (0 10 g, 45%) $^1$H NMR (300 MHz, $CD_3OD$) δ 7 70 (app q, J = 8 26, Hz, 1H), 7 54 (dd, J = 8 06, 2 01 Hz, 1H), 7 40 (d, J = 1 81 Hz, 1H), 7 12 - 7 06 (m, 2H), 6 68 (s, 1H), 5 40 (s, 2H), 2 05 (s, 3H), 2 02 (s, 3H), 1 57 (s, 6H) ES-HRMS m/z 478 0785 (M+H calcd for $C_{23}H_{23}BrF_2NO_3$ requires 478 0824)

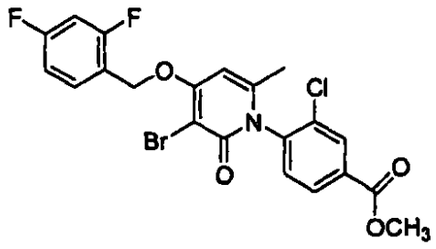
Example 493



methyl 3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoate

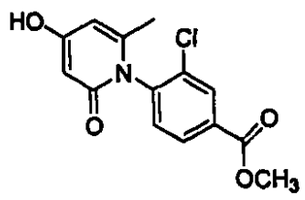
The title compound was prepared by taking up methyl 3-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoate (1 46g, 3 66 mmol) in dichloroethane (25 ml) and adding N-chlorosuccinimide (0 49g, 3 66 mmol), dichloroacetic acid (catalytic), and heating to 50°C for 6 hours At this time, the solvent was removed in vacuo and the residue taken up in diethyl ether The precipitate was collected on a filter pad $^1$H NMR (300 MHz, $CDCl_3$) δ 8 07 (dd, J = 7 85, 1 61 Hz, 1H), 7 80 (d, J = 1 81 Hz, 2H), 7 62 (app q, J = 8 46 Hz, 1H), 7 48 (d, J = 7 85, 1H), 7 05 - 6 95 (m, 1H) 6 93 - 6 89 (m, 1H,, 6 19 (s, 1H), 5 30 (s, 2H), 3 93 (s, 3H), 2 17 (s, 3H), 1 97 (s, 3H) ES-HRMS m/z 434 0932 (M+H calcd for $C_{22}H_{19}ClF_2NO_4$ requires 434 0965)

Example 494



methyl 4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-3-chlorobenzoate

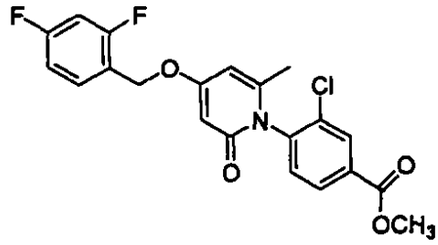
Step 1 Preparation of methyl 3-chloro-4-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)benzoate



4-Hydroxy-6-methyl-2-pyrone (24 5 g, 193 9 mmol) and methyl-3-amino-2-chlorobenzoate (30 g, 161 6 mmol) were suspended in 75 ml of 1,2-dichlorobenzene in a 250 ml, 3-necked round bottom flask equipped with a J-Kem temperature controller probe, a Dean-Stark trap, and a heating mantle The reaction was heated to 175°C for 20 minutes, during which, water and some 1,2-dichlorobenzene was collected in the Dean-Stark trap The reaction was allowed to cool to about 110°C At this point, 200 ml of toluene was added The toluene mixture was allowed to stir for 72 hours at room temperature A precipitate was collected on a filter pad The precipitate was filtered and washed 3 times with toluene, 3 times with 50°C water to remove excess pyrone, and dried in vacuo to give a tan solid (13 0 g, 27% yield) $^1$H NMR (300 MHz, $CD_3OD$) δ 8 26 (d, J = 1 81 Hz, 1H), 8 14 (dd, J = 8 26, 1 81 Hz, 1H),

7 54 (d, J = 8 26, Hz, 1H), 6 14(dd, J = 2 42, 1 0 Hz, 1H), 5 83 (d, J = 2 42 1H), 4 00 (s, 3H), 1 96 (s, 3H), LC/MS, $t_r$ = 1 81 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 294 (M+H)

Step 2 Preparation of methyl 3-cnloro-4-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoate

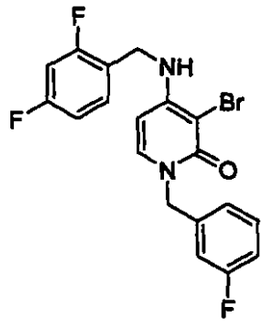


Methyl 3-chloro-4-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)benzoate ( from Step 1) (2 4g, 8 17 mmol) was taken up in DMF (10 ml) 2,4-difluorobenzylbromide (1 05 ml, 8 17 mmol) and $K_2CO_3$ (1 13 g, 8 17 mmol) were added The reaction stirred for 6 hours at room temperature At this time, the reaction was poured into water (200 ml) and extracted with ethyl acetate The ethyl acetate layer was dried over $Na_2SO_4$, filtered, and the solvent removed in vacuo to give amber oil (2 62 g, 77% crude yield) LC/MS, $t_r$ = 2 79 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 294 (M+H)

Step 3 Preparation of the title compound Methyl 3-chloro-4-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoate ( from step 2) (2 60g, 6 21 mmol) was taken up in $CH_2Cl_2$ (20 ml) N-bromcsuccinimide (1 11g, 6 21 mmol) was added and the mixture stirred at room temperature for 4 hours The $CH_2Cl_2$ is removed in vacuo and the residue is taken up in $CH_3CN$ The resulting precipitate is collected on a filter pad and washed with $CH_3CN$ to yield a white solid (0 75 g, 24%) $^1H$

NMR (300 MHz, $CDCl_3$) δ 8 22 (d, J = 1 88 Hz, 1H), 8 06 (dd, J = 8 19, 1 75 Hz, 1H), 7 59 (app q, J = 8 46 Hz, 1H), 7 33 (d, J = 8 19, 1H), 6 96 (dt, J = 8 06, 1 21 Hz, 1H), 6 89 - 6 84 (m, 1H), 6 13 (s, 1H), 5 26 (s, 2H), 3 95 (s, 3H), 1 95 (s, 3H) ES-HRMS m/z 497 9892 (M+H calcd for $C_{22}H_{16}BrClF_3NO_4$ requires 497 9914)

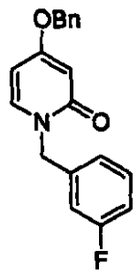
Example 495



3-bromo-4-[(2,4-difluorobenzyl)amino]-1-(3-fluorobenzyl)pyridin-2(1H)-one

Step 1

Preparation of 4-(benzyloxy)-1-(3-fluorobenzyl)pyridin-2(1H)-one

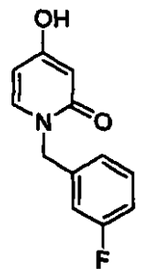


A 100 mL round bottomed flask equipped with stirbar and nitrogen inlet was charged with 4-benzyloxy-2(1H)-pyridinone (20 g, 99 6 mmol) and N,N-dimethyl formamide (50 mL) $K_2CO_3$ (13 7 g, 99 6 mmol) and KI ( 1 6 g, 9 6 mmol) were added followed by 3-fluorobenzyl bromide (14 6 mL, 119 4 mmol) The reaction mixture was heated for 18 h at 80 C The reaction

mixture was concentrated in vacuo and treated with hot ethyl acetate The solids were filtered off, the filtrate was poured into water and was extracted with ethyl acetate The organic extract was washed with brine, dried with annydrous $Na_2SO_4$, and concentrated in vacuo The residue was dissolved in hot ethyl acetate and precipitated with hexanes to give the title compound (10 g, 33%) $^1$H NMR (400 MHz, $CD_3OD$) δ 7 57 (d, J = 8 4 Hz, 1H), 7 37 (m, 5H), 7 07 (d, J = 8 4 Hz, 1H), 7 01 (app d, J = 8 4 Hz, 2H), 6 17 (d, J = 2 68 and 7 6 Hz, 1H), 6 04 (d, J = 2 68 Hz, 1H), 5 10 (s, 2H), 5 08 (s, 2H) ppm $^{19}$F NMR (400 MHz, $CD_3OD$) δ -114 88 (1 F) ppm ES-HRMS m/z 310 1271 (M+H calcd for $C_{19}H_{17}FNO_2$ requires 310 1238)

Step 2

Preparation of 1-(3-fluorobenzyl)-4-hydroxypyridin-2(1H)-one

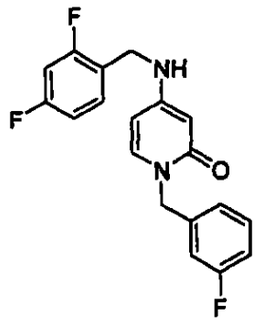



A small Parr bottle was charged with SC-82484 (10 g, 32 3 mmol), ethanol (175 mL) and10% Pd/C (0 5 g) The system was flushed twice with both nitrogen and hydrogen The reaction mixture was hydrogenated at 30 psi until no starting material was visible by LC-MS The reaction mixture was slurried with Celite and then was filtered through a pad of celite The filtrate and ensuing ethanol washes were concentrated in vacuo to give a beige solid $^1$H NMR (400 MHz, $CD_3OD$) δ 7 53 (d, J = 7 67 Hz, 1H), 7 32 (m, 1H), 7 06 (d, J = 7 6 Hz, 1H), 6 98 (d, J = 8 4 Hz, 2H), 6 05 (dd, J = 2 58 and 7 67 Hz, 1H), 5 83 (d,

J = 2 0 Hz, 2H), 5 10 (s, 2H) ppm $^{19}$F NMR (400 MHz, $CD_3OD$) δ -115 33 (1 F) ppm ES-HRMS m/z 218 0641 (M+H calcd for $C_{12}H_{11}FNO_2$ requires 218 0612)

Step 3

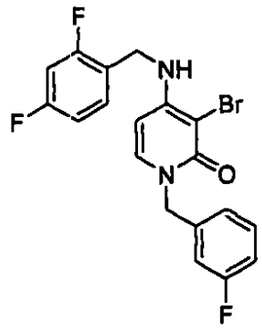
Preparation of 4-[(2,4-difluorobenzyl)amino]-1-(3-fluorobenzyl)pyridin-2(1H)-one




The product from Step 2 (0 5 g, 2 28 mmol) and 2,4-difluoro benzylamine (4 mL, 33 6 mmol) were combined in a nitrogen flushed culture tube The tube was capped and heated at 180 C for 24 h The excess amine was distilled in vacuo and the residue was chromatographed on silica (95 5 ethyl acetate methanol) The final compound was isolated as a light yellow solid (0 16 g, 36%) $^1$H NMR (400 MHz, $CD_3OD$) δ 7 33 (m, 3H), 7 03 (d, J = 8 Hz, 1H), 6 96 (m, 3H), 6 95 (m, 1H), 5 97 (dd, J = 3 2 and 8 0 Hz, 1 H), 5 48 (d, J = 2 56 Hz, 1H), 5 02 (s, 2H), 4 33 (s, 2H) ppm $^{19}$F NMR (400 MHz, $CD_3OD$) δ -113 88 (1 F), -115 33 (1F), -116 78 (1F) ppm ES-HRMS m/z 345 1221 (M+H calcd for $C_{19}H_{17}F_3N_2O$ requires 345 1209)

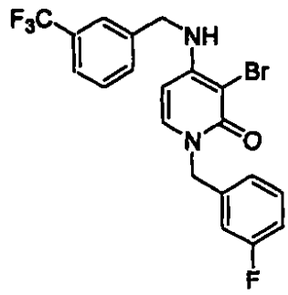
Step 4 Preparation of 3-bromo-4-[(2,4-difluorobenzyl)amino]-1-(3-fluorobenzyl)pyridin-2(1H)-one

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339



N-Bromo succinimide (81 mg, 0 46 mmol) was added to a solution of the product from Step 3 (0 15 g, 0 44 mmol) in methylene chloride (10 mL) After stirring at 25 C for 1 h, the reaction was complete by LC-MS The reaction mixture was poured into saturated aqueous $NaHCO_3$ The aqueous mixture was extracted with ethyl acetate The organic layer was washed with brine, dried with anhydrous $MgSO_4$, and concentrated in vacuo $^1H$ NMR (400 MHz, $CDCl_3$) δ 7 3-7 2 (m, 4H), 7 07 (app t, J = 7 6 Hz, 2H), 6 97 (m, 2H), 6 80 (m, 2H), 5 78 (d, J = 7 6 Hz, 1H), 5 30 (br s, 1H), 5 08 (s, 2H), 4 46 (d, J = 6 Hz, 2H) ppm $^{19}$ F NMR (400 MHz, $CDCl_3$) δ -110 64 (1 F), -112 75 (1F), -114 79 (1F) ppm ES-HRMS m/z 423 0275 (M+H calcd for $C_{19}H_{15}BrF_3N_2O$ requires 423 0314)

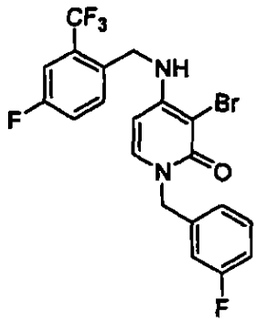
Example 496



3-bromo-1-(3-fluorobenzyl)-4-{[3-(trifluoromethyl)benzyl]amino}pyridin-2(1H)-one

The title compound was prepared essentially as in Example 495 $^1$H NMR (400 MHz, $CDCl_3$) δ 7 54 (m, 2H), 7 48 (m, 2H), 7 27 (q, J = 3 1, 9 0 Hz, 1H), 6 96 (app t, J = 8 8 Hz, 2H), 5 71 (d, J = 7 6 Hz, 1H), 5 4 (br m, 1H), 5 08 (s, 2H), 4 52 (d, J = 5 6 Hz, 2H) ppm $^{19}$ F NMR (400 MHz, $CDCl_3$) δ -63 (3 F), -112 (1 F) ppm ES-HRMS m/z 455 0388 (M+H calcd for $C_{20}H_{16}BrF_4N_2O$ requires 455 0377)

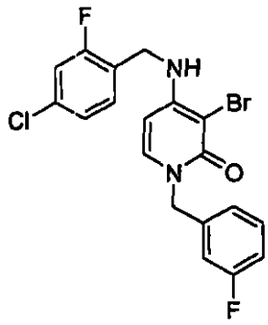
Example 497




3-bromo-1-(3-fluorobenzyl)-4-{[4-fluoro-2-(trifluoromethyl)benzyl]amino}pyridin-2(1H)-one

The title compound was prepared essentially as in Example 495 $^1$H NMR (400 MHz, $CDCl_3$) δ 7 43 (m, 2H), 7 27 (m, 3H), 7 07 (m, 2H), 6 99 (m, 2H), 5 65 (d, J = 10Hz, 1H), 5 46 (br s, 1H), 5 09 (s, 2H), 4 64 (s, 2H) ppm $^{19}$ F NMR (400 MHz, $CDCl_3$) δ -61 31 (3 F), -112 69 (1 F), 112 97 (1F) ppm ES-HRMS m/z 473 0246 (M+H calcd for $C_{20}H_{15}BrF_5N_2O$ requires 473 0282)

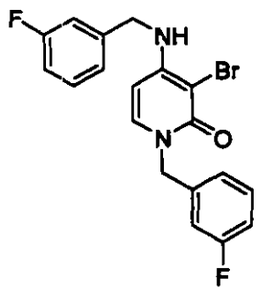
Example 498



Preparation of -bromo-4-[(4-chloro-2-fluorobenzyl)amino]-1-(3-fluorobenzyl)pyridin-2(1H)-one

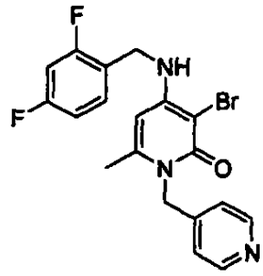
The title compound was prepared essentially as in Example 495 $^1$H NMR (400 MHz, $CDCl_3$) δ 7 27 (m, 1H), 7 19 (app t, J = 8 8 Hz, 1H), 7 10 (m, 4H), 6 95 (app t, J = 8 8 Hz, 2H), 5 74 (d, J = 8 Hz, 1H), 5 40 (br s, 1H), 5 08 (s, 2H), 4 47 (d J = 6 Hz, 2H) ppm $^{19}$ F NMR (400 MHz, $CDCl_3$) δ -112 67 (1 F), -116 39 (1 F) ppm ES-HRMS m/z 439 0047 (M+H calcd for $C_{19}H_{15}ClBrF_2N_2O$ requires 439 0019)

Example 499



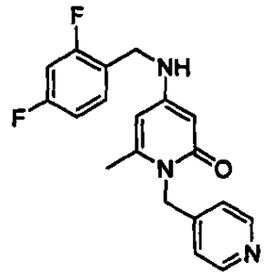
The title compound was prepared essentially as in Example 495 $^1$H NMR (400 MHz, $CDCl_3$) δ 7 35- 7 2 (m, 1H), 7 27 (dd, J = 2 5 and 8 Hz, 1H), 7 05 (app d, J = 7 2 Hz, 3H), 6 97 (m, 4H), 5 72 (d, J = 7 6 Hz, 1H), 5 41 (br s, 1H), 5 08 (s, 2H), 4 46 (d, J = 6 4 Hz, 2H) ppm $^{19}$ F NMR (400 MHz, $CDCl_3$) δ -112 5 (1 F), -113 (1 F) ppm ES-HRMS m/z 405 0431 (M+H calcd for $C_{19}H_{16}BrF_2N_2O$ requires 405 0409)

Example 500



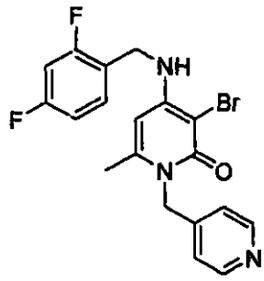
Preparation of 3-bromo-4-[(2,4-difluorobenzyl)amino]-6-methyl-1-(pyridin-4-ylmethyl)pyridin-2(1H)-one

Step 1 Preparation of 4-[(2,4-difluorobenzyl)amino]-6-methyl-1-(pyridin-4-ylmethyl)pyridin-2(1H)-one



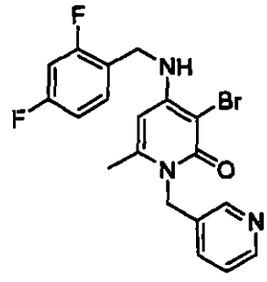
(0 3 g, 1 39 mmol) and 2,4-difluoro benzylamine (1 mL, 8 4 mmol) were combined in a nitrogen flushed culture tube The tube was capped and heated at 180 C for 24 h The excess amine was distilled in vacuo $^{1}$H NMR (400 MHz, $CD_3OD$) δ 8 44 (dd, J = 1 7 and 4 8Hz, 2H), 7 38 (q, J = 10 and 15 Hz, 1H), 7 14 (d, J = 4 8 Hz, 2H), 6 95 (m, 2H), 5 90 (dd, J = 1 and 2 5Hz, 1H), 5 47 (d, J = 2, 1H), 5 28 (s, 2H), 4 33 (s, 2H), 2 27 (s, 3H) ppm $^{19}$ F NMR (400 MHz, $CD_3OD$) δ -113 73 (1 F), -116 66 (1 F) ppm ES-HRMS m/z 342 1422 (M+H calcd for $C_{19}H_{18}F_2N_3O$ requires 342 1418)

Step 2 Preparation of 3-bromo-4-[(2,4-difluorobenzyl)amino]-6-methyl-1-(pyridin-4-ylmethyl)pyridin-2(1H)-one



N-Bromo succinimide (77 mg, 0 43 mmol) was added to a solution of the product of Step 1 (0 14 g, 0 41 mmol) in methylene chloride (10 mL) After stirring at 25 C for 1 h, the reaction was complete by LC-MS The reaction mixture was poured into saturated aqueous $NaHCO_3$ The aqueous mixture was extracted with ethyl acetate The organic layer was washed with brine, dried with anhydrous $Na_2SO_4$, filtered and concentrated in vacuo The residue was triturated with hexanes to give the title compound as a yellow solid (81 mg, 47 %) $^1H$ NMR (400 MHz, $CDCl_3$) δ 8 47 (dd, J = 1 6 and 4 8Hz, 2H), 7 24 (q, J = 6 4 and 13 6 Hz, 1H), 7 01 (d, J = 6 4 Hz, 2H), 6 83 (m, 2H), 5 68 (s, 1H), 5 25 (s, 2H), 4 45 (d, J = 6 4Hz, 2H), 2 12 (s, 3H) ppm $^{19}F$ NMR (400 MHz, $CDCl_3$) δ -110 51 (m, 1 F), -114 66 (m, 1 F) ppm ES-HRMS m/z 420 0524 (M+H calcd for $C_{19}H_{17}BrF_2N_3O$ requires 420 0523)

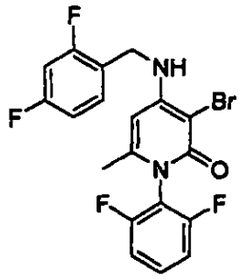
Example 501



Preparation of 3-bromo-4-[(2,4-difluorobenzyl)amino]-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one

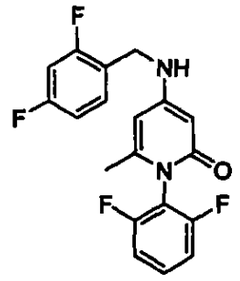
The title compound was prepared essentially as in Example 500 $^1$H NMR (400 MHz, $CDCl_3$) δ 8 45 (d, J = 4 8Hz, 2H), 7 55 (app t, J = 6 Hz, 1H), 7 21 (m, 2H), 6 83 (m, 2H), 5 65 (s, 1H), 5 34 (d, J = 5 2Hz, 1H), 5 27 (s, 2H), 4 45 (s, 2H), 2 10 (d, J = 4 8Hz, 3H) ppm $^{19}$ F NMR (400 MHz, $CDCl_3$) δ -110 74 (1 F), -114 86 (1 F) ppm ES-HRMS m/z 420 0533 (M+H calcd for $C_{19}H_{17}BrF_2N_3O$ requires 420 0523)

Example 502




Preparation of 3-bromo-4-[(2,4-difluorobenzyl)amino]-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one

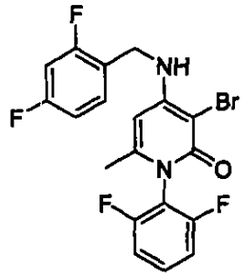
Step 1 Preparation of 4-[(2,4-difluorobenzyl)amino]-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one




1-(2,6-difluorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one (0 3 g, 1 26 mmol) and 2,4-difluoro benzylamine (1mL, 8 4 mmol) were combined in a nitrogen flushed culture tube The tube was capped and heated at 180 C for 24 h The excess amine was distilled in vacuo and the residue was

chromatographed on silica (1 1 hexanes ethyl acetate) The compound was approximately 50% pure and was carried on without further purification (0 633 g) $^1$H NMR (400 MHz, $CD_3OD$) δ 7 53 (m, 1H), 7 41 (m, 1H), 7 16 (t, J = 8 8Hz, 2H), 6 93 (m, 2H), 6 00 (s, 1H), 5 42 (s, 1H), 5 42 (s, 1H), 4 37 (s, 2H), 1 93 (s, 3H) ppm LC/MS, $t_r$ = 4 65 minutes (5 to 95% acetonitrile/water over 8 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 363 (M+H)

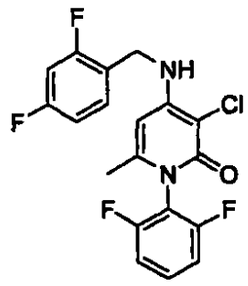
Step 2 Preparation of 3-bromo-4-[(2,4-difluorobenzyl)amino]-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one




N-Bromo succinimide (168 mg, 0 945 mmol) was added to a solution of the product of Step 1 (0 633 g) in methylene chloride (10 mL) After stirring at 25 C for 1 h, the reaction was 50 % complete by LC-MS Additional N-bromo succinimide (150 mg) was added and the reaction was stirred at 25 C for 12 h The reaction mixture was poured into saturated aqueous $NaHCO_3$ The aqueous mixture was extracted with ethyl acetate The organic layer was washed with brine, dried with anhydrous $Na_2SO_4$, and concentrated in vacuo The residue was purified by reverse phase chromatography (60 40 Acetonitrile water with 0 05% trifluoroacetic acid) The title compound was isolated as the TFA salt (0 161g, 23%) $^1$H NMR (400 MHz, $CD_3OD$) δ 7 53 (m, 1H), 7 35 (q, J = 8, 15 6Hz, 1H), 7 16 (t, J = 8 Hz, 2H), 6 96 (app q, J = 8, 16 4Hz, 2H), 6 12 (s, 1H), 4 86 (s, 2H), 1 94 (s, 3H) ppm $^{19}$ F NMR (400 MHz, $CD_3OD$) δ -

77 33 (1 F), -113 60 (1 F), -116 63 (1F), -121 50 (1F) ppm ES-HRMS m/z 441 0231 (M+H calcd for $C_{19}H_{14}BrF_4N_2O$ requires 441 0220)

Example 503



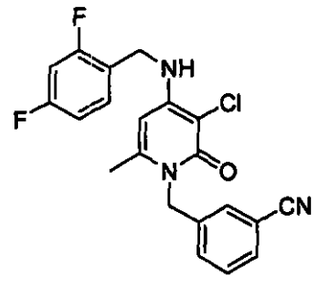

Preparation of 3-chloro-4-[(2,4-difluorobenzyl)amino]-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one

1-(2,6-difluorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one (0 3 g, 1 26 mmol) and 2,4-difluoro benzylamine (1mL, 84 mmol) were combined in an nitrogen flushed culture tube The tube was capped and heated at 180 C for 24 h The excess amine was distilled in vacuo and the residue was used without further purification N-Chloro succinimide (168 mg, 1 26 mmol) was added to a solution of the residue in methylene chloride (10 mL) After stirring at 25 C for 1 h, the reaction mixture was poured into saturated aqueous $NaHCO_3$ The aqueous mixture was extracted with ethyl acetate The organic layer was washed with brine, dried with anhydrous $Na_2SO_4$, and concentrated in vacuo The residue was chromatographed on silica (25 75 hexanes ethyl acetate) to give the title compound (32 mg, 6%) $^1H$ NMR (400 MHz, $CD_3OD$) δ 7 55 (m, 1H), 7 36 (q, J = 9 2 and 15 2Hz, 1H), 7 18 (t, J = 7 6Hz, 2H), 6 98 (m, 2H), 6 15 (s, 1H), 4 62 (s, 2H), 1 96 (s, 3H) ppm $^{19}$F NMR (400 MHz, $CD_3OD$) δ -113 78 (1 F), -116 72 (1 F), -121 57

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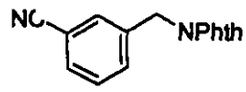
(1F) ppm ES-HRMS m/z 397 0752 (M+H calcd for $C_{19}H_{14}ClF_4N_2O$ requires 397 0725)

Example 504



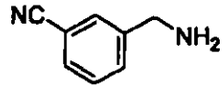

Preparation of 3-{[3-chloro-4-[(2,4-difluorobenzyl)amino]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzonitrile

Step 1 Preparation of 3-phthalimidomethyl-benzonitrile



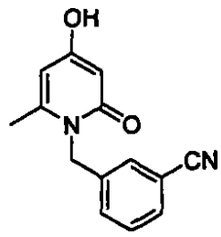

3-Phthalimidomethyl-benzonitrile was prepared as described in the literature (Bookser, B C , Bruice, T C J Am Chem Soc 1991, 113, 4208-18 )

Step 2 Preparation of 3-(aminomethyl)benzonitrile



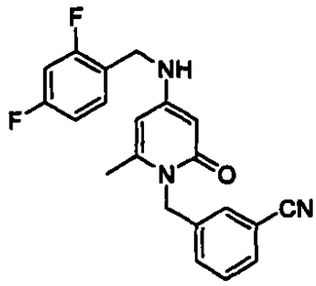

3-(Aminomethyl)benzonitrile was prepared as described in the literature (Bookser, B C , Bruice, T C J Am Chem Soc 1991, 113, 4208-18 )

Step 3 Preparation of 3-[(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)methyl]benzonitrile



A nitrogen flushed pyrex reaction tube was charged with 3-(aminomethyl)benzonitrile (1 g, 7 9 mmol), 4-hydroxy-6-methyl-2-pyrone (1 g, 7 9 mmol) and water (20 mL) The tube was capped and was heated to reflux After 1 5 h, the product precipitated from solution The reaction mixture was cooled to room temperature, filtered and washed with water The product was used without further purification (1 67g, 88 %) $^1$H NMR (400 MHz, dmso-$d_6$) δ 10 53 (s, 1H), 7 61 (d, J = 8Hz, 1H), 7 52 (t, J = 8Hz, 2H), 7 38 (d, J = 8 Hz, 1H), 5 79 (dd, J = 1 and 2 5 Hz, 1H), 5 56 (d, J = 2 7 Hz, 1H), 5 18 (s, 2H), 2 14 (s, 3H) ppm ES-HRMS m/z 241 0968 (M+H calcd for $C_{14}H_{13}N_2O_2$ requires 241 0972)

Step 5 Preparation of 3-{[4-[(2,4-difluorobenzyl)amino]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzonitrile

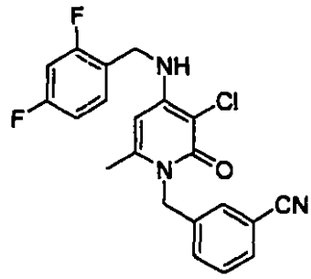


The product from Step 4 (0 5 g, 2 08 mmol) and 2,4-difluoro benzylamine (2mL, 16 8 mmol) were combined in a nitrogen flushed culture tube The tube was capped and heated at 180 C for 24 h The excess amine was distilled in vacuo and the residue was triturated with ethyl acetate/ hexanes to precipitate the starting materials The residue was

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cnromatographed on reverse phase (1 1 water acetonitrile with 0 05% trifluoroacetic acid ) The product of Step 5 was isolated as a white semi-solid (0 125g, 15%) $^1$H NMR (400 MHz, $CD_3OD$) δ 7 61(d, J = 8Hz, 1H), 7 49 (t, J = 8 Hz, 1H), 7 41 (m, 3H), 6 94 (m, 2H), 5 89 (dd, J = 0 8 and 2 7Hz, 1H), 5 47 (d, J = 2 8Hz, 1H), 5 27 (s, 2H), 4 34 (s, 2H), 2 18 (s, 3H) ppm LC/MS, $t_r$ = 4 87 minutes (5 to 95% acetonitrile/water over 8 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 366 (M+H)

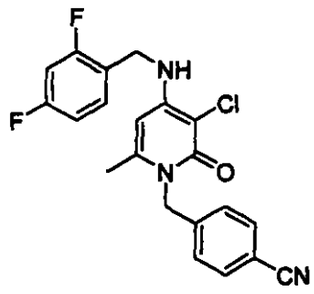
Step 6 Preparation of 3-{[3-chloro-4-[(2 4-difluorobenzyl)amino]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzonitrile




N-Chloro succinimide (36 mg, 0 27 mmol) was added to a solution of the product of Step 5 (0 125 g, 0 26 mmol) in methylene chloride (10 mL) After stirring at 25 C for 2 h, the reaction was complete by LC-MS The reaction mixture was poured into saturated aqueous $NaHCO_3$ The aqueous mixture was extracted with ethyl acetate The organic layer was washed with brine, dried with anhydrous $Na_2SO_4$, and concentrated in vacuo The residue was triturated with acetonitrile to give the title compound as a tan solid (20 mg, 13%) $^1$H NMR (400 MHz, $CD_3OD$) δ 7 61 (d, J = 8 4 Hz, 1H), 7 49 (m, 2H), 7 40 (d, J = 8 4 Hz, 1H), 7 33 (q, J = 8 4 and 14 8 Hz, 1H), 6 94 (m, 2H), 6 00 (s, 1H), 5 34 (s, 2H), 4 56 (s, 2H), 2 21 (s, 3H) ppm $^{19}$ F NMR (400 MHz, $CD_3OD$) δ -114 00 (1 F), -116 89 (1 F)

ppm LC/MS, $t_r$ = 5 49 minutes (5 to 95% acetonitrile/water over 8 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 400 (M+H)

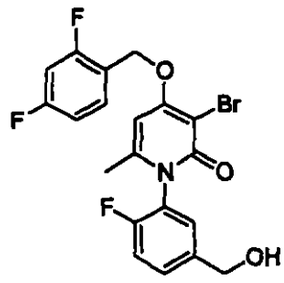
Example 505




Preparation of 4-{[3-chloro-4-[(2,4-difluorobenzyl)amino]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzonitrile

The title compound was prepared essentially as in Example 504 $^1$H NMR (400 MHz, $CD_3OD$) δ 7 66 (d, J = 8 Hz, 2H), 7 33 (q, J =8 and 15 2 Hz, 1H), 7 25 (d, J = 8 Hz, 2H), 6 94 (m, 2H), 6 01 (s, 1H), 5 36 (s, 2H), 4 55 (s, 2H), 2 19 (s, 3H) ppm $^{19}$ F NMR (400 MHz, $CD_3OD$) δ -77 52 (1F), -113 89 (1 F), -116 71 (1 F) ppm LC/MS, $t_r$ = 5 49 minutes (5 to 95% acetonitrile/water over 8 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 400 (M+H)

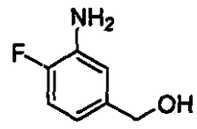
Example 506




Preparation of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[2-fluoro-5-(hydroxymethyl)phenyl]-6-methylpyridin-2(1H)-one

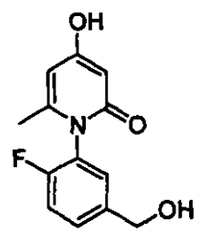
345
348

Step 1 Preparation of (3-amino-4-fluorophenyl)methanol



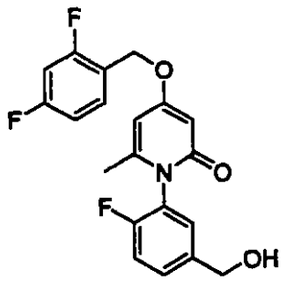
A flask equipped with overhead stirrer was charged with 4-fluoro-3-nitrobenzyl alcohol (20g, 0 117 mol) and 200 mL of 5 1 isopropanol water Ammonium chloride (62 g, 1 17 mol) was added followed by iron filings (65g, 1 17 mol) The mixture was stirred at 70 C for 1 5 H when it was shown to be complete by LC-MS The liquid was decanted and the solids were washed with additional isopropanol water The isopropanol was removed and the residue was diluted with 0 5 N HCl and was extracted with ethyl acetate The aqueous layer was brought to pH 12-14 with 2 5 N NaOH and was extracted with ethyl acetate The organic layer was dried with anhydrous $Na_2SO_4$ and concentrated in vacuo 3-Amino-4-fluorophenyl methanol was isolated as a brown solid (4 5g, 27%) and was used without further purification LC/MS, $t_r$ = 2 40 minutes (5 to 95% acetonitrile/water over 8 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 142 (M+H) ES-HRMS m/z 142 0692 (M+H calcd for $C_7H_8FNO$ requires 142 0663)

Step 2 Preparation of 1-[2-fluoro-5-(hydroxymethyl)phenyl]-4-hydroxy-6-methylpyridin-2(1H)-one



A 100 mL round bottomed flask equipped with stirbar, Dean-Stark trap and reflux condensor was charged with (3-amino-4-fluorophenyl)methanol (4 5 g, 31 9 mmol), 4-hydroxy-6-methyl-2-pyrone (4 g, 31 9 mmol) and o-dichlorobenzene (5 mL) The system was immersed in a 170 C oil bath for 10 minutes The solvent was removed in vacuo and the residue was chromatographed on reverse phase (75 25 water acetonitrile with 0 05% TFA) The product contained some starting materials after purification and was used without further purification (1 27g, 15%) $^1$H NMR (400 MHz, dmso-$d_6$) δ 7 39 (m, 1H), 7 20 (dd, J = 2 2 and 7 6 Hz, 1H), 6 74 (dd, J = 2 7 and 9 6 Hz, 1H), 5 93 (dd, J = 1 2 and 2 2 Hz, 1H), 5 22 (dd, J = 0 4 and 2 2 Hz, 1H), 2 12 (s, 3H) ppm ES-HRMS m/z 250 0862 (M+H calcd for $C_{13}H_{13}FNO_3$ requires 250 0874)

Step 3 Preparation of 4-[(2,4-difluorobenzyl)oxy]-1-[2-fluoro-5-(hydroxymethyl)phenyl]-6-methylpyridin-2(1H)-one

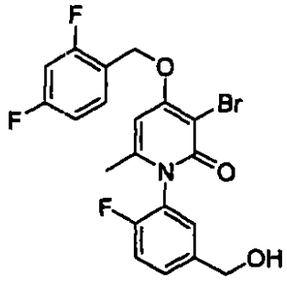



A 100 mL roundbottomed flask (nitrogen purged) was charged with 1-[2-fluoro-5-(hydroxymethyl)phenyl]-4-hydroxy-6-methylpyridin-2(1H)-one (1 2g, 4 82 mmol) and N,N-dimethyl formamide (10 mL) Potassium carbonate (0 6g, 4 4 mmol) and 2,4-difluorobenzyl bromide (0 56 mL, 4 4 mmol) was added and the reaction mixture was stirred at room temperature overnight The reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with ethyl acetate The organic

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layer was concentrated in vacuo and the residue was chromatographed on silica (9 1 methylene chloride ethanol) The impure oil (0 3g, 17%) was carried on without further purification $^1$H NMR (400 MHz, $CD_3OD$) δ 7 54 (m, 2H), 7 30 (m, 2H), 7 02 (m, 2H), 6 17 (dd, J = 1 and 2 8 Hz, 1H), 6 03 (d, J = 2 8 Hz, 1H), 5 14 (s, 2H), 4 62 (s, 2H), 2 14 (s, 3H) ppm $^{19}$ F NMR (400 MHz, $CD_3OD$) δ -111 35 (1F), -115 97 (1 F), -127 31 (1 F) ppm LC/MS, $t_r$ = 5 C5 minutes (5 to 95% acetonitrile/water over 8 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 375 (M+H)

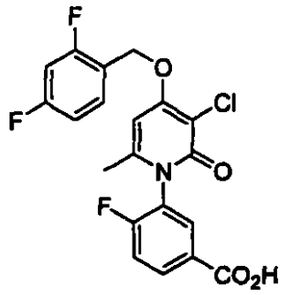
Step 4 Preparation of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[2-fluoro-5-(hydroxymethyl)phenyl]-6-methylpyridin-2(1H)-one




N-Bromo succinimide (50 mg, 0 3 mmol) was added to a solution of the product of Step 3 (0 12 g, 0 32 mmol) in N,N-dimethyl formamide (4 mL) After stirring at 25 C for 2 h, trifluoroacetic acid (50 µL) was added After 1 h, additional N-Bromo succinimide (30 mg) was added After 1 h, the reaction was complete by LC-MS The reaction mixture was poured into brine and was extracted with ethyl acetate The organic layer was washed with brine, dried with anhydrous $Na_2SO_4$, and concentrated in vacuo The residue was chromatographed on reverse phase (95 5 methylene chloride ethanol) The title compound was isolated as the TFA salt (38 mg, 26 %) $^1$H NMR (400 MHz, $CD_3OD$) δ 7 64 (q, J = 7 6 and 14 8 Hz, 1H), 7 51 (m, 1H), 7 31 (app t, J = 8 4 Hz, 1H), 7 04 (t,

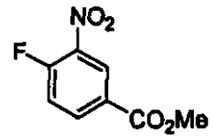
J = 8 4 Hz, 2H), 6 63 (s, 1H), 5 34 (s, 2H), 4 62 (s, 2H), 2 06 (s, 3H) ppm $^{19}$F NMR (400 MHz, $CD_3OD$) δ -111 48 (1F), -115 92 (1 F), -127 23 (1 F) ppm ES-HRMS m/z 454 0228 (M+H calcd for $C_{20}H_{16}BrF_3NO_3$ requires 454 0260)

Example 507



Preparation of 3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorobenzoic acid

Step 1 Preparation of methyl 4-fluoro-3-nitrobenzoate

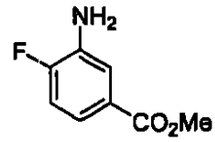


A 1 L 3-necked round bottomed flask equipped with a nitrogen inlet, stirbar, addition funnel and thermocouple was charged with 4-fluoro-3-nitrobenzoic acid (50 g, 0 27 mol) and methanol (300 mL) The system was cooled to 0 C and acetyl choride (27 mL, 0 37 mol) was added dropwise The system was warmed to room temperature, the addition funnel was replaced with a reflux condensor, and was heated to reflux for 1 5 h The reaction mixture was cooled to room temperature, quenched with saturated aqueous $NaHCO_3$, and extracted with ethyl acetate The organic extract was washed with brine, dried with $Na_2SO_4$ and concentrated in vacuo to give methyl 4-fluoro-3-nitrobenzoate as an orange solid (40 6 g, 75%) $^1$H NMR (400 MHz, $CD_3OD$) δ 8 67 ((dd, J = 2 2 and 6 8 Hz, 1H), 8 34 (dddd, J

347
350

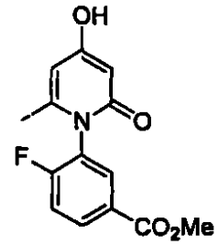
= 2 2, 4 4, 6 4 and 8 8 Hz, 1H), 7 55 (dd, J = 8 8 and 10 8 Hz, 1H), 3 94 (s, 3H) ppm ES-HRMS m/z 200 02446 (M+H calcd for $C_8H_7FNO_4$ requires 200 0354)

Step 2 Preparation of methyl 3-amino-4-fluorobenzoate




A Parr bottle was charged with the product of Step 1 (40 g, 0 2 mol), ethanol (400 mL) and10% Pd/C (1 g g) The system was flushed twice with nitrogen and hydrogen The reaction mixture was hydrogenated at 40 psi until no starting material was visible by LC-MS The reaction mixture was slurried with Celite and then was filtered through a pad of celite The filtrate and ensuing ethanol washes were concentrated in vacuo to give methyl 3-amino-4-fluorobenzoate as an orange solid (30 6 g, 91%) $^1$H NMR (400 MHz, $CD_3OD$) δ 7 54 (d, J = 8 7 Hz, 1H), 7 35 (m, 1H), 7 06 (t, J = 8 7 Hz, 1H), 3 09 (s, 3H) ppm $^{19}$ F NMR (400 MHz, $CD_3OD$) δ -131 02 (1F) ppm ES-HRMS m/z 199 0281 (M+H calcd for $C_8H_7FNO_4$ requires 199 02)

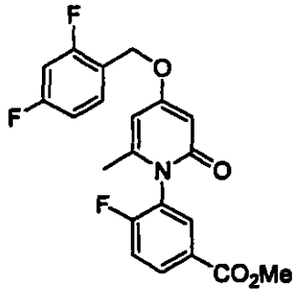
Step 3 Preparation of methyl 4-fluoro-3-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)benzoate




A 250 mL round bottomed flask equipped with stirbar, Dean-Stark trap and reflux condensor was charged with the product of Step 3 (30 g, 0 18 mol), 4-hydroxy-6-methyl-2-pyrone (22 6 g, 0 18 mol), and o-dichlorobenzene (90 mL) The

system was immersed in a 170 C oil bath for 30 minutes and was then cooled to room temperature The reaction mixture was washed with aqueous $Na_2CO_3$ (38 g, 0 36 mol, 300 mL water) The aqueous layer was washed with ethyl acetate and then was acidified to pH 1-2 with concentrated HCl This was extracted with ethyl acetate, which was then dried with $MgSO_4$ and concentrated in vacuo The viscous orange oil was used without further purification (14 4 g, 28%) $^1$H NMR (400 MHz, $CD_3OD$) δ 8 18 (dddd, J = 2 3, 5 2, 7 2 and 8 8 Hz, 1H), 7 97 (dd, J = 2 and 7 2 Hz, 1H), 7 44 (t, J = 8 8 Hz, 1H), 6 09 (d, J = 1 8 Hz, 1H), 5 78 (d, J = 2 4 Hz, 1H), 3 9 (s, 3H), 2 14 (s, 3H) ppm $^{19}$ F NMR (400 MHz, $CD_3OD$) δ -117 29 (1F) ppm ES-HRMS m/z 278 0796 (M+H calcd for $C_{14}H_{13}FNO_4$ requires 278 0823)

Step 4 Preparation of methyl 3-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorobenzoate

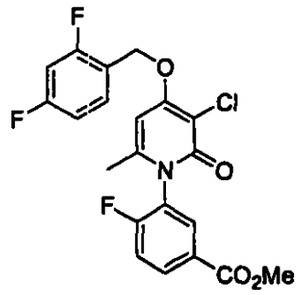



A 100 mL round bottomed flask equipped with stirbar and nitrogen inlet was charged with the product of Step 3 (14 4 g, 51 9 mmol) and N,N-dimethyl formamide (40 mL) 1,8-diazabicyclo[5 4 0]undec-7-ene (10 9 mL, 72 8 mmol) was added followed by 2,4-difluorobenzyl bromide (9 3 mL, 72 8 mmol) The reaction mixture was stirred at 65 C for 18 h, was poured into saturated aqueous $NaHCO_3$ and was extracted with ethyl acetate The organic layer was washed with brine, dried with $Na_2SO_4$ and concentrated in vacuo to give the title product, as

3458
351

an orange oil (21 5g), which was carried on to the next reaction without further purification $^1$H NMR (400 MHz, $CD_3OD$) δ 8 20 (dddd, J = 2 2, 4 8, 7 2 and 8 8 Hz, 1H), 8 00 (dd, J = 2 2 and 7 2 Hz, 1H), 7 56 (td, J = 2 4, 6 4 and 9 2 Hz, 1H), 7 46 (t, J = 9 2 Hz, 1H), 7 02 (m, 2H), 6 18 (dd, J = 0 8 and 2 6 Hz, 1H), 6 04 (d, J = 2 7 Hz, 1H), 5 14 (s, 2H), 3 90 (s, 3H), 1 98 (s, 3H) ppm $^{19}$ F NMR (400 MHz, $CD_3OD$) δ -111 34 (1F), -116 00 (1 F), -117 35 (1 F) ppm ES-HRMS m/z 404 1104 (M+H calcd for $C_{21}H_{17}F_3NO_4$ requires 404 1104)

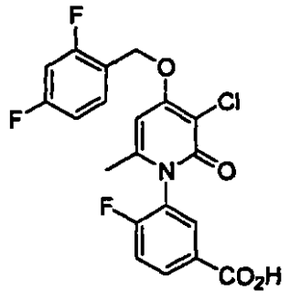
Step 5 Preparation of methyl 3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorobenzoate




A 250 mL round bottomed flask equipped with stirbar and nitrogen inlet was charged with the product of Step 4 (21 g, 52 mmol) and N-methyl-2-pyrrolidine (100 mL) N-Chloro succinimide (8 3 g, 62 mmol) was added and the reaction mixture was stirred at 65 C for 2 h The mixture was then cooled to room temperature, poured into saturated aqueous $NaHCO_3$ and extracted with ethyl acetate The organic layer was washed with brine, dried with $Na_2SO_4$, and concentrated in vacuo The residue was triturated with diethyl ether and filtered to give the title compound, as a white powder (5 9 g, 25%) $^1$H NMR (400 MHz, $CD_3OD$) δ 8 22 (dddd, J = 2, 4 8, 6 8 and 8 8 Hz, 1H), 8 03 (dd, J = 2 and 7 2 Hz, 1H), 7 62 (q, J = 8 4 and14 8 Hz, 1H), 7 48 (t, J = 14 Hz, 1H), 7 04 (m, 2H),

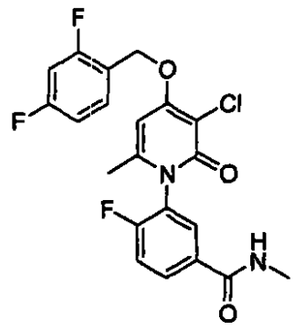
6 69 (s, 1H), 5 36 (s, 2H), 3 91 (s, 3H), 2 08 (s, 3H) ppm $^{19}$F NMR (400 MHz, $CD_3OD$) δ -111 38 (1F), -115 97 (1 F), -117 43 (1 F) ppm ES-HRMS m/z 438 0723 (M+H calcd for $C_{21}H_{16}ClF_3NO_4$ requires 438 0714)

Step 6 Preparation of 3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorobenzoic acid



A 100 mL round bottomed flask was charged with the product of Step 5 (2 5 g, 5 72 mmol), tetrahydrofuran (40 mL), methanol (10 mL), and water (10 mL) To this slurry was added 2 5 N NaOH (4 6 mL, 11 4 mmol) The reaction mixture became clear after 5 minutes and the reaction was complete in 35 minutes by LC-MS The organics were removed on the rotary evaporator and the remaining solution was acidified to pH 3 with 6N HCl The desired compound was precipitated by the addition of diethyl ether and subsequent filtration The title compound was isolated as a white powder (2 5 g, 98%) $^1$H NMR (400 MHz, dmso-$d_6$) δ 8 10 (dddd, J = 2 1, 4 8, 7 2 and 8 4 Hz, 1H), 8 00 (dd, J = 2 1 and 7 6 Hz, 1H), 7 66 (q, J = 9 2 and 15 6 Hz, 1H), 7 57 (t, J = 8 8 Hz, 1H), 7 34 (td, J = 2 4 and 10 4 Hz, 1H), 7 17 (tdd, J = 1, 2 7 and 8 4 Hz, 1H), 6 76 (s, 1H), 5 33 (s, 2H), 1 98 (s, 3H) ppm $^{19}$F NMR (400 MHz, dmso-$d_6$) δ -109 32 (1F), -113 64 (1 F), -117 22 (1 F) ppm ES-HRMS m/z 424 0575 (M+H calcd for $C_{20}H_{14}ClF_3NO_4$ requires 424 0558)

Example 508



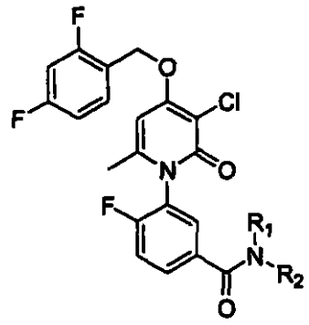
Preparation of 3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluoro-N-methylbenzamide

To a reaction vessel (borosilicate culture tube) was added 3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorobenzoic acid (0 300 g, 0 708 mmol) and 1-hydroxybenzotriazole (0 048 g, 0 45 mmol) N,N-Dimethylformamide (3 mL) was added to the reaction vessel followed by approximately 1, 2 g of the polymer bound carbodiimide resin (1 38 mmol/g) Additional N,N-dimethylformamide (2 mL) was then added to the reaction vessel The parallel reaction apparatus was then orbitally shaken (Labline Benchtop Orbital Shaker) at approximately 200 RPM at room temperature for 15 minutes N-Methyl amine (1 mL, 2 mmol) was then added to the reaction vessel and the reaction apparatus was orbitally shaken at room temperature overnight At this time the reaction was diluted with tetrahydrofuran (20 mL) and treated with approximately 2 17 g of polyamine resin (2 63 mmol/g) and approximately 2 8 g of methylisocyanate functionalized polystyrene (1 5 mmol/g) and the orbital shaking was continued at 200 RPM at room temperature for 3 hours The reaction vessel was then opened and the solution phase product was separated from the insoluble quenched byproducts by filtration and collection into a vial After partially evaporation the insoluble

byproducts were rinsed with tetrahydrofuran (2 x 10 mL) The filtrate was evaporated by blowing $N_2$ over the vial and the resulting solid was triturated with diethyl ether to give an off-white solid (0 168 g, 59%)

$^1$H NMR (400 MHz, $CD_3OD$) δ 8 02 (dddd, J = 2, 4 4, 7 2 and 8 4 Hz, 1H), 7 80 (dd, J = 2 and 6 8 Hz, 1H), 7 62 (q, J = 8 and 14 4 Hz, 1H), 7 34 (t, J = 8 8 Hz, 1H), 7 04 (m, 2H), 6 69 (s, 1H), 5 36 (s, 2H), 3 29 (s, 3H), 1 98 (s, 3H) ppm $^{19}$ F NMR (400 MHz, $CD_3OD$) δ -108 94 (1F), -113 55 (1 F), -117 76 (1 F) ppm ES-HRMS m/z 437 0861 (M+H calcd for $C_{21}H_{17}ClF_3N_2O_3$ requires 437 0874)

Examples 509-518 ,

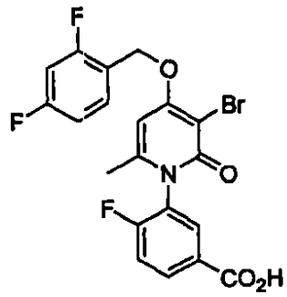


By following the method of Example 508 and replacing N-methylamine with the appropriate amine, the compounds of Examples 509-518 are prepared

| Example No | $R_1$ | $R_2$ | % Yield | MF | M+H Requires | ESHRMS m/z |
|---|---|---|---|---|---|---|
| Ex 509 | $CH_3$ | $CH_3$ | 59 | $C_{22}H_{19}ClF_3N_2O_3$ | 451 1031 | 451 1016 |
| Ex 510 | H | $CH_2CH_2OH$ | 70 | $C_{22}H_{19}ClF_3N_2O_4$ | 467 0980 | 467 0985 |
| Ex 511 | $CH_2CH_2N(CH_3)$- | $CH_2CH_2N(CH_3)$- | 70 | $C_{25}H_{24}ClF_3N_3O_3$ | 506 1453 | 506 1447 |
| Ex 512 | $CH_2CH_2O$- | $CH_2CH_2O$- | 19 | $C_{24}H_{21}ClF_3N_2O_4$ | 493 1101 | 493 1136 |
| Ex 513 | H | $CH_2CH_2OCH_3$ | 59 | $C_{23}H_{21}ClF_3N_2O_4$ | 481 1136 | 481 1136 |

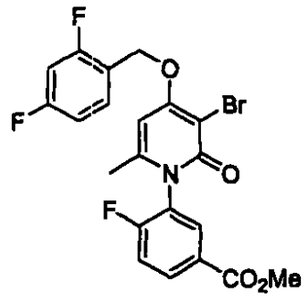
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Ex 514 | $CH_3$ | $CH_2CH_2OH$ | 63 | $C_{23}H_{21}ClF_3N_2O_4$ | 481 1136 | 481 1131 |
| Ex 515 | H | $CH_2CH_2CH_2OH$ | 51 | $C_{23}H_{21}ClF_3N_2O_4$ | 481 1136 | 481 1121 |
| Ex 516 | H | $CH_2CH(OH)CH_2OH$ | 64 | $C_{23}H_{21}ClF_3N_2O_5$ | 497 1086 | 497 1102 |
| Ex 517 | H | $C(CH_3)_2CH_2OH$- | 54 | $C_{24}H_{23}ClF_3N_2O_4$ | 495 1293 | 495 1303 |
| Ex 518 | $CH_2CH_2NH$- | $CH_2CH_2NH$- | 34 | $C_{23}H_{22}ClF_3N_3O_3$ | 491 89 | |

Example 519



Preparation of 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorobenzoic acid

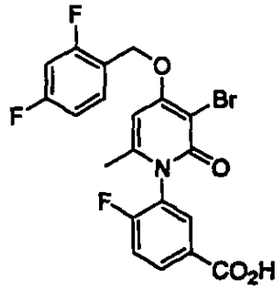
Step1 Preparation of methyl 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorobenzoate



A 100 mL round bottomed flask equipped with stirbar and nitrogen inlet was charged with methyl 3-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-

fluorobenzoate (7 3 g, 18 mmol) and N-methyl-2-pyrrolidine (20 mL) N-Bromo succinimide (3 5 g, 19 8 mmol) was added and the reaction mixture was stirred at room temperature for 30 minutes The mixture poured into saturated aqueous $NaHCO_3$ and extracted with ethyl acetate The organic layer was washed with brine, dried with $Na_2SO_4$, and concentrated in vacuo The residue was triturated with diethyl ether and filtered to give the title compound as a white powder (3 49 g) $^1H$ NMR (400 MHz, $CD_3OD$) δ 8 16 (qd, J = 3, 6 8 and 15 6 Hz, 1H), 7 84 (d, J ≈ 2 12 Hz, 1H), 7 64 (q, J = 8 4 and14 8 Hz, 1H), 7 29 (d, J = 8 4 Hz, 1H), 7 04 (m, 2H), 6 60 (s, 1H), 5 34 (s, 2H), 3 87 (s, 3H), 2 00 (s, 3H) ppm $^{19}F$ NMR (400 MHz, $CD_3OD$) δ -111 51 (1F), -115 98 (1F), -117 43 (1F) ppm ES-HRMS m/z 494 0387(M+H calcd for $C_{22}H_{19}BrF_2NO_5$ requires 494 0409)

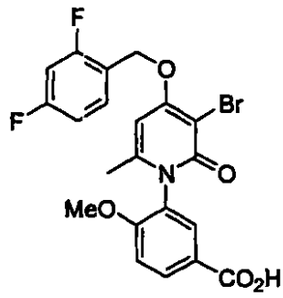
Step 2 Preparation of 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorobenzoic acid




A 100 mL round bottomed flask was charged with the product of Step 2 (3 4 g, 7 05 mmol), tetrahydrofuran (40 mL), methanol (10 mL), and water (10 mL) To this slurry was added 2 5 N NaOH (5 6 mL, 14 1 mmol) The reaction mixture became clear after 5 minutes and the reaction was complete in 1 h by LC-MS The organics were removed on the rotary evaporator and the remaining solution was acidified to pH 1-2 with 6N HCl The desired compound was precipitated by the addition of water and diethyl ether and subsequent filtration The title

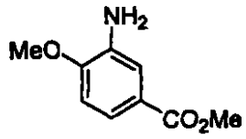
compound was isolated as a white powder (2 64 g, 80%) $^1$H NMR (400 MHz, $CD_3OD$) δ 8 21 (dddd, J = 2 4, 5 2, 7 2 and 9 2 Hz, 1H), 8 00 (dd, J = 2 0 and 7 2 Hz, 1H), 7 65 (q, J = 8 4 and 14 8 Hz, 1H), 7 45 (t, J = 8 4 Hz, 1H), 7 04 (appt, J = 9 6 Hz, 1H), 6 65 (s, 1H), 5 36 (s, 2H), 2 07 (s, 3H) ppm $^{19}$ F NMR (400 MHz, $CD_3OD$) δ -111 40 (1F), -116 00 (1 F), -118 36 (1 F) ppm *ES-HRMS* m/z 480 0259 (M+H calcd for $C_{21}H_{17}BrF_2NO_5$ requires 480 0253)

Example 520




Preparation of 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methoxybenzoic acid

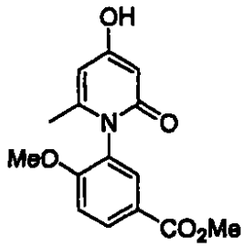
Step 1 Preparation of methyl 3-amino-4-methoxybenzoate




A 1 L 3-necked round bottomed flask equipped with a nitrogen inlet, stirbar, addition funnel and thermocouple was charged with 3-amino-4-methoxy benzoic acid (50 g, 0 299 mol) and methanol (300 mL) The system was cooled to 0 C and acetyl choride (30 mL, 0 42 mol) was added dropwise The system was warmed to room temperature, the addition funnel was replaced with a reflux condensor, and was heated to reflux for 1 5 h The reaction mixture was cooled to room temperature,

quenched with saturated aqueous $NaHCO_3$, and extracted with ethyl acetate The organic extract was washed with brine, dried with $Na_2SO_4$ and concentrated in vacuo to give methyl 3-amino-4-methoxybenzoate as a dark solid (47 9 g, 88%) $^1H$ NMR (400 MHz, $CD_3OD$) δ 7 40 (t, J = 2 68 Hz, 1H), 7 37 (t, J = 2 0 Hz, 1H), 6 86 (d, J = 8 8 Hz, 1H), 3 98 (s, 3H), 3 81 (s, 3H) ppm ES-HRMS m/z 182 0826 (M+H calcd for $C_9H_{12}ClNO_3$ requires 182 0812)

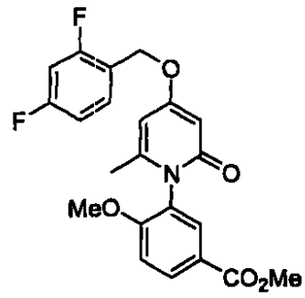
Step 2 Preparation of methyl 3-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)-4-methoxybenzoate




A 250 mL round bottomed flask equipped with stirbar, Dean-Stark trap and reflux condensor was charged with the product of Step 1 (23 5 g, 0 129 mol), 4-hydroxy-6-methyl-2-pyrone (17 8 g, 0 14 mol), and o-dichlorobenzene (200 mL) The system was immersed in a 170 C oil bath for 2 h and was then cooled to room temperature The reaction mixture was washed with aqueous $Na_2CO_3$ (28 g, 0 26 mol, 500 mL water) The aqueous layer was washed with ethyl acetate and then was acidified to pH 1-2 with concentrated HCl This was extracted with ethyl acetate, which was then dried with $Na_2SO_4$ and concentrated in vacuo The viscous orange oil was triturated with MeOH to give the title compound as a yellow solid (1 61 g, 4%) $^1H$ NMR (400 MHz, $CD_3OD$) δ 8 14 (dd, J = 2 2 and 8 8 Hz, 1H), 7 79 (d, J = 2 2 Hz, 1H), 7 27 (d, J = 8 8 Hz, 1H), 6 05 (d, J = 2 3 Hz, 1H), 5 77 (d, J = 2 3 Hz, 1H), 3 88 (s,

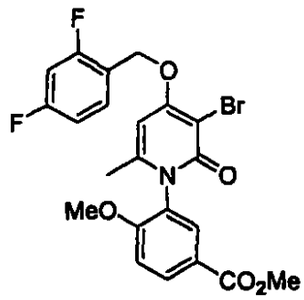
3H), 3 87 (s, 3H), 1 90 (s, 3H) ppm ES-HRMS m/z 290 0997 (M+H calcd for $C_{15}H_{16}NO_5$ requires 290 1023)

Step 3 Preparation of methyl 3-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methoxybenzoate



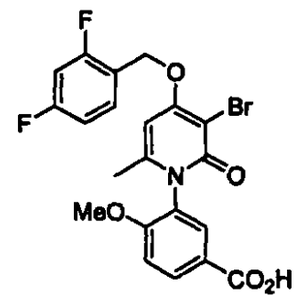

A 100 mL round bottomed flask equipped with stirbar and nitrogen inlet was charged with the product of Step 2 (1 6 g, 5 5 mmol) and N,N-dimethyl formamide (10 mL) 1,8-diazabicyclo[5 4 0]undec-7-ene (0 91 mL, 6 mmol) was added followed by 2,4-difluorobenzyl bromide (0 77 mL, 6 mmol) The reaction mixture was stirred at 60 C for 4 h, was poured into saturated aqueous $NaHCO_3$ and was extracted with ethyl acetate The organic layer was washed with brine, dried with $Na_2SO_4$ and concentrated in vacuo to give the title compound as an orange foam (2 13g, 93%), which was carried on to the next reaction without further purification $^1H$ NMR (400 MHz, $CD_3OD$) δ 8 17 (dd, J = 2 64 and 11 6 Hz, 1H), 7 82 (td, J = 2 7 and 6 8 Hz, 1H), 7 57 (m, 1H), 7 29 (d, J = 11 6 Hz, 1H), 7 02 (m, 2H), 6 16 (m, 1H), 6 03 (d, J = 3 5 Hz, 1H), 5 14 (s, 2H), 3 89 (s, 6H), 1 93 (s, 3H) ppm $^{19}F$ NMR (400 MHz, $CD_3OD$) δ -111 43(1F), -116 04 (1 F) ppm ES-HRMS m/z 416 1310 (M+H calcd for $C_{22}H_{20}F_2NO_5$ requires 416 1304)

Step 4 Preparation of methyl 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methoxybenzoate



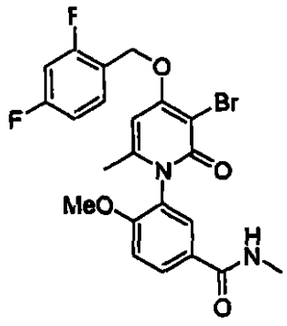
A 100 mL round bottomed flask equipped with stirbar and nitrogen inlet was charged with the product of Step 3 (2 1 g, 5 06 mmol) and N-methyl-2-pyrrolidine (10 mL) N-Bromo succinimide (1 g, 5 56 mmol) was added and the reaction mixture was stirred at room temperature for 1 h The mixture poured into saturated aqueous $NaHCO_3$ and extracted with ethyl acetate The organic layer was washed with brine, dried with $Na_2SO_4$, and concentrated in vacuo The residue was chromatographed on silica (1 1 hexanes ethyl acetate) to give the title compound as an orange oil (0 77 g, 31%) $^1H$ NMR (400 MHz, $CD_3OD$) δ 8 16 (app qd, J = 2 5 and 7 2 Hz, 1H), 7 84 (d, J = 2 6 Hz, 1H), 7 64 (m, 1H), 7 30 (d, J = 9 2 Hz, 1H), 7 04 (appt, J = 8 4 Hz, 2H), 6 60 (s, 1H), 5 33 (s, 2H), 3 80 (s, 6H), 1 99 (s, 3H) ppm $^{19}F$ NMR (400 MHz, $CD_3OD$) δ -111 56 (1F), -116 00 (1 F) ppm ES-HRMS m/z 494 0398 (M+H calcd for $C_{22}H_{19}BrF_2NO_5$ requires 494 0409)

Step 5 Preparation of 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methoxybenzoic acid



A 100 mL round bottomed flask was charged with the product of Step 4 (0 77 g, 1 55 mmol), tetrahydrofuran (10 mL), methanol (5 mL), and water (5 mL) To this slurry was added 2 5 N NaOH (1 2 mL, 3 1 mmol) The reaction mixture became clear after 30 minutes and the reaction was complete in 1 h by LC-MS The organics were removed on the rotary evaporator and the remaining solution was acidified to pH 2-3 with 6N HCl The desired compound was precipitated by the addition of water and diethyl ether and subsequent filtration The title compound was isolated as a white powder (0 60 g, 81%) $^1$H NMR (400 MHz, $CD_3OD$) δ 8 17 (dd, J = 2 2 and 8 8 Hz, 1H), 7 82 (d, J = 2 2 Hz, 1H), 7 64 (q, 1H), 7 29 (d, J = 8 8 Hz, 1H), 7 34 (t, J = 8 8 Hz, 2H), 6 60 (s, 1H), 5 34 (s, 2H), 3 87 (s, 3H), 2 01 (s, 3H) ppm ES-HRMS m/z 480 0259 (M+H calcd for $C_{21}H_{17}BrF_2NO_5$ requires 480 0253)

Example 521




Preparation of 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methoxy-N-methylbenzamide

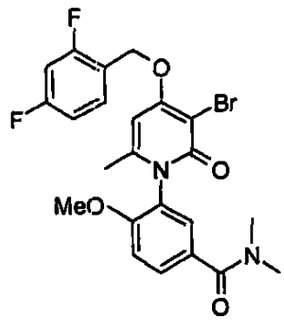
Step 1

To a reaction vessel (borosilicate culture tube) was added Example 520 (0 300 g, 0 624 mmol) and 1-hydroxybenzotriazole (0 042 g, 0 31 mmol) N,N-Dimethylformamide (3 mL) was added to the reaction vessel followed by approximately 1 06 g of the polymer bound carbodiimide resin (1 38 mmol/g) Additional

N,N-dimethylformamide (2 mL) was then added to the reaction vessel The parallel reaction apparatus was then orbitally shaken (Labline Benchtop Orbital Shaker) at approximately 200 RPM at room temperature for 15 minutes N-Methyl amine (2 mL, 4 mmol) was then added to the reaction vessel and the reaction apparatus was orbitally shaken at room temperature overnight At this time the reaction was diluted with tetrahydrofuran (20 mL) and treated with approximately 2 g of polyamine resin (2 63 mmol/g) and approximately 2 5 g of methylisocyanate functionalized polystyrene (1 5 mmol/g) and the orbital shaking was continued at 200 RPM at room temperature for 3 hours The reaction vessel was then opened and the solution phase product was separated from the insoluble quenched byproducts by filtration and collection into a vial After partially evaporation the insoluble byproducts were rinsed with tetrahydrofuran (2 x 10 mL) The filtrate was evaporated by blowing $N_2$ over the vial and the resulting solid was triturated with diethyl ether to give the desired product as an off-white solid (0 094 g, 31%) $^1$H NMR (400 MHz, $CD_3OD$) δ 7 98 (dd, J = 2 2 and 8 8 Hz, 1H), 7 64 (m, 2H), 7 28 (d, J = 9 2 Hz, 1H), 7 04 (t, J = 9 2 Hz, 2H), 6 60 (s, 1H), 5 34 (s, 2H), 3 86 (s, 3H), 2 88 (s, 3H), 2 01 (s, 3H) ppm $^{19}$ F NMR (400 MHz, $CD_3OD$) δ -111 59 (1F), -116 01 (1 F) ppm ES-HRMS m/z 493 0593 (M+H calcd for $C_{22}H_{20}BrF_2N_2O_4$ requires 493 0569)

354
357

Example 522

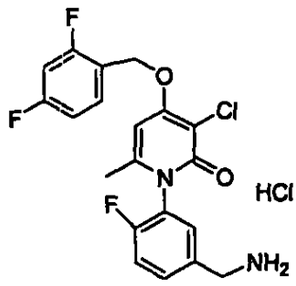


Preparation of 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methoxy-N,N-dimethylbenzamide

The title compound was prepared essentially as in Example 521 $^1$H NMR (400 MHz, $CD_3OD$) δ 7 64 (m, 1H), 7 61 (dd, J = 2 and 8 8 Hz, 1H), 7 33 (d, J = 2 2 Hz, 1H), 7 27 (d, J = 8 Hz, 1H), 7 04 (t, J = 8 Hz, 2H), 6 59 (s, 1H), 5 33 (s, 2H), 3 85 (s, 3H), 3 07 (s, 6H), 2 02 (s, 3H) ppm $^{19}$ F NMR (400 MHz, $CD_3OD$) δ -111 60 (1F), -116 01 (1 F) ppm ES-HRMS m/z 507 0716 (M+H calcd for $C_{23}H_{22}BrF_2N_2O_4$ requires 507 0726)

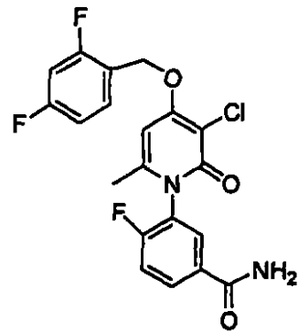
Example 523

1-[5-(aminomethyl)-2-fluorophenyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one hydrochloride



Step 1

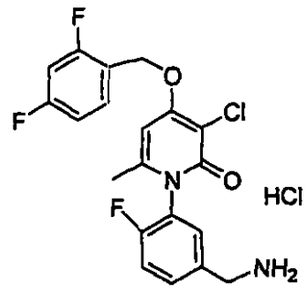
Preparation of 3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorobenzamide



A 250 mL round bottomed flask equipped with stirbar and nitrogen inlet was charged with 3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorobenzoic acid (2 58g, 6 1 mmol), 4-methylmorpholine (2 0 mL, 18 3 mmol), 2-chloro-4,6-dimethoxy-1,3,5-triazine (1 28g, 7 3 mmol) and tetrahydrofuran (30 mL) After stirring the mixture for 30 min at 25° C, $NH_4OH$ (15 0 mL) was added The mixture was stirred for 30 min and diluted with water The product precipitated from solution The precipitated was filtered and washed with water and diethyl ether to give the title compound (2 55g, 78%) as a white solid $^1H$ NMR (400 MHz, $(CD_3)_2SO$) δ 8 10 (m, 1H), 7 9 (dd, J = 2 1 and 5 2 Hz, 1H), 7 65 (q, 6 7 and 8 5 Hz, 1H), 7 56 (t, J = 9 1 Hz, 1H), 7 35 (td, J = 2 4 and 8 2 Hz, 1H) 7 17 (td, J = 2 and 6 6 Hz, 1H) 6 78 (s, 1H), 5 36 (s, 2H), 2 (s, 3H) ppm ES-HRMS m/z 423 0719 (M+H calcd for $C_{20}H_{15}ClF_3N_2O_3$ requires 423 0718)

Step 2

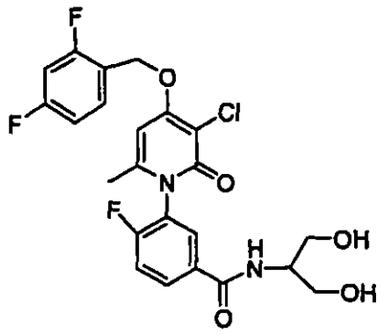
Preparation of 1-[5-(aminomethyl)-2-fluorophenyl]-3-chloro-4-[(2,4 difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one hydrochloride




A 100 mL round bottomed flask equipped with stirbar and nitrogen inlet was charged with the product from step 1 (1 5 g, 3 5 mmol), $BH_3$•THF complex (7 4 mL, 7 4 mmol), and tetrahydrofuran (15 mL) The mixture was refluxed for 6 h, allowed to cool to room temperature and quenched with HCl 6N The organics were evaporated and the remaining aqueous solution was saturated with NaOH 2 5N and extracted with dichloromethane The organic phase was dried with $Na_2SO_4$ and concentrated in vacuo HCl 6N was added, and concentrated in vacuo $^1H$ NMR (400 MHz, $(CD_3)_2SO$) δ 8 2 (m, 1H), 7 6 (m, 1H), 7 5 (m, 1H), 7 3 (t, J = 9 8 Hz, 1H), 7 16 (t, J = 8 6 Hz, 1H) 6 78 (s, 1H), 5 36 (s, 2H), 4 05 (d, J = 5 8 Hz, 2H), 2 (s, 3H) ppm ES-HRMS m/z 409 0940 (M+H calcd for $C_{20}H_{17}ClF_3N_2O_2$ requires 409 0925)

Example 524

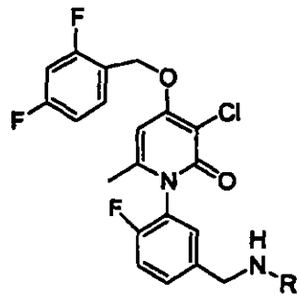
3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluoro-N-[2-hydroxy-1-(hydroxymethyl)ethyl]benzamide



Preparation of 3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluoro-N-[2-hydroxy-1-(hydroxymethyl)ethyl]benzamide

The title compound was prepared essentially as in Example 521 $^1$H NMR (400 MHz, $CD_3OD$) δ 8 1 (m, 1H), 7 8 (dd, J = 2 3 and 5 1 Hz, 1H), 7 6 (q, J = 7 4 and 7 0 Hz, 1H), 7 41 (t, J = 8 9 Hz, 1H), 7 04 (m, 2H) 6 7 (s, 1H), 5 36 (s, 2H), 4 1 (t, J = 5 8 Hz, 1H), 3 7 (d, J = 5 1 Hz, 4H) 2 1 (s, 3H) ppm ES-HRMS m/z 497 1045 (M+H calcd for $C_{23}H_{21}ClF_3N_2O_5$ requires 497 1086)

Examples 525-528



The compounds of Examples 525-528 are prepared by derivitazion of Example 523 The analytical data are shown below

| Ex No | R | MF | M+H | ESHRMS |
|---|---|---|---|---|

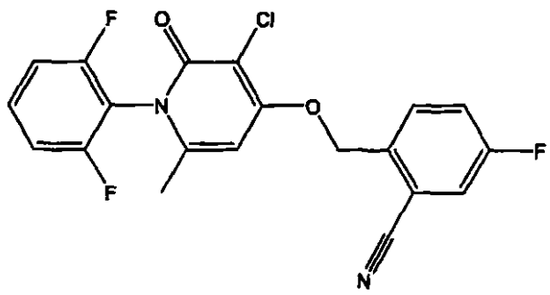
356
359

| | | | Requires | m/z |
|---|---|---|---|---|
| Ex 525 | $-C(O)CH_3$ | $C_{22}H_{18}ClF_3N_2O_3$ | 451 1031 | 451 1010 |
| Ex 526 | $-C(O)CH_2OCH_3$ | $C_{23}H_{20}ClF_3N_2O_4$ | 481 1136 | 481 1132 |
| Ex 527 | $-SO_2CH_3$ | $C_{21}H_{18}ClF_3N_2O_4S$ | 487 0701 | 487 0679 |
| Ex 528 | $-C(O)NH_2$ | $C_{21}H_{16}ClF_3N_3O_3$ | 452 0983 | 452 0987 |

NMR characterization of compounds of Examples 525-528

| Ex No | NMR Data |
|---|---|
| 525 | $^1$H NMR (400 MHz, $CD_3OD$) δ 7 6 (q, J = 7 8 and 7 0 Hz 1H), 7 5 (m 1H) 7 3 (t, J = 9 0 Hz 1H) 7 2 (dd J = 1 9 and 5 1 Hz 1H) 7 05 (m, 2H), 6 65 (s, 1H), 5 36 (s, 2H), 4 39 (s, 2H) 2 1 (s, 3H), 1 98 (s 3H) ppm |
| 526 | $^1$H NMR (400 MHz, $CD_3Cl_3$) δ 7 45 (q J = 8 6 and 6 2 Hz, 1H), 7 3 (m 1H), 7 1 (m 2H) 6 85 (q J = 6 5 and 1 9 Hz, 1H), 6 78 (td J = 2 7 and 7 8 Hz, 1H), 6 2 (s 1H), 5 2 (s 2H) 4 39 (d, J = 6 2 Hz 2H) 4 0 (s, 3H) 2 3 (s, 2H) 2 0 (s, 3H) 1 98 (s, 3H) ppm |
| 527 | $^1$H NMR (400 MHz $CD_3OD$) δ 7 49 (q J = 8 2 and 6 3 Hz 1H) 7 33 (m, 1H) 7 23(m, 1H), 7 1 (t, J = 8 9, 1H) 6 9 (td J = 0 78 and 6 6 1H), 6 8 (td J = 2 7 and 6 25 Hz 1H) 6 2 (s 1H) 5 2 (s 2H), 4 2 (s, 2H), 2 8 (s, 3H) 2 0 (s 3H) ppm |
| 528 | $^1$H NMR (400 MHz $(CD_3)_2SO$) δ 7 61 (q J = 8 9 and 6 6 Hz, 1H) 7 38(d J = 7 8 Hz 1H) 7 3 (d J = 10 2 Hz 1H) 7 21 (d J = 7 4 Hz, 1H), 7 1 (t, J = 8 6 Hz 1H), 6 71 (s 1H), 6 5 (t J = 5 8 Hz 1H) 5 56 (s 2H), 5 3 (s, 2H), 4 18 (d, J = 6 25 Hz, 2H), 3 61 (s, 1H), 1 98 (s, 3H) ppm |

Example 529

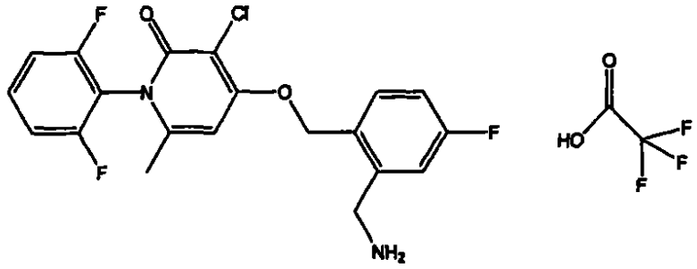



2-({[3-chloro-1-(2,6-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl]oxy}methyl)-5-fluorobenzonitrile

2-(bromomethyl)-5-fluorobenzonitrile (3 47 g, 16 2 mmol), 3-chloro-1-(2,6-difluorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one (3 15 g, 11 6 mmol), $K_2CO_3$ (2 56 g, 18 6 mmol), and 18-crown-6 (0 15 g) were dissolved in N,N-dimethylacetamide (25 mL) Reaction mixture stirred on 60°C oil bath for 4 hours Solvent removed by distillation Reaction neutralized with 5% citric acid The solid product was washed with hexane followed by 30% EtOAc/hexane Filtered a brown solid (5 2 g, 79% yield)

$^1$H NMR ($CD_3OD$ / 400MHz) δ7 82 (m, 2H), 7 61 (m, 4H), 6 75 (s, 1H), 5 49 (s, 2H), 2 13 (s, 3H) ESHRMS m/z 405 0616 (M+H $C_{20}H_{13}ClF_3N_2O_2$ requires 405 0612)

Example 530



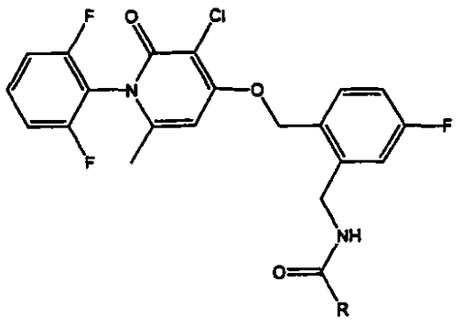

4-{[2-(aminomethyl)-4-fluorobenzyl]oxy}-3-chloro-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one trifluoroacetate

$BH_3$THF (17 8 mL, 17 8 mmol) was added dropwise to a chilled (0°C) solution of 2-({[3-chloro-1-(2,6-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl]oxy}methyl)-5-fluorobenzonitrile (3 61 g, 8 92 mmol) in THF (30 mL) Following the addition, the reaction was heated at 60°C for 1 5 hours The reaction was quenched with MeOH, the solvent evaporated, and the crude product purified by prep HPLC The product was isolated by freeze-drying and evaporation of the solvent to give a white solid (1 52 g, 32 6%) $^1$H NMR ($CD_3OD$/

360
357

400MHz) δ7 62 (m, 2H), 7 32 (m, 1H), 7 25 (tr, 2H, J = 8 00 Hz), 7 18 (m, 1H), 6 78 (s, 1H), 5 43 (s, 1h), 4 22 (s, 1H), 2 14 (s, 3H) ESHRMS m/z 409 0900 (M+H $C_{20}H_{17}N_2O_2F_3Cl$ requires 409 0925)

Examples 531-551




The compounds of Examples 531-551 are prepared by derivatization of Example 530 The analytical data are shown below

| Compound No | R | MF | M+H Requires | ESHRMS m/z |
|---|---|---|---|---|
| Ex 531 | -$OCH_3$ | $C_{22}H_{18}ClF_3N_2O_4$ | 467 0980 | 467 0985 |
| Ex 532 | -$CF_3$ | $C_{22}H_{15}ClF_6N_2O_3$ | 505 0748 | 505 0754 |
| Ex 533 | -O-isopropyl | $C_{24}H_{22}ClF_3N_2O_4$ | 495 1293 | 495 1304 |
| Ex 534 | -NH-$CH_2CH_3$ | $C_{23}H_{21}ClF_3N_3O_3$ | 480 1296 | 480 1277 |
| Ex 535 | -O-tetrahydrofuran-3-yl | $C_{25}H_{22}ClF_3N_2O_5$ | 523 1242 | 523 1282 |
| Ex 536 | -O-propyl | $C_{24}H_{22}ClF_3N_2O_4$ | 495 1293 | 495 1338 |
| Ex 537 | -O-$CH_2CH{=}CH_2$ | $C_{24}H_{20}ClF_3N_2O_4$ | 493 1136 | 493 1116 |
| Ex 538 | -O-$CH_2C{\equiv}CH$ | $C_{24}H_{18}ClF_3N_2O_4$ | 491 0980 | 491 0961 |
| Ex 539 | -O-tButyl | $C_{25}H_{24}ClF_3N_2O_4$ | 509 1449 | 509 1436 |
| Ex 540 | -NH-tButyl | $C_{25}H_{25}ClF_3N_3O_3$ | 508 1609 | 508 1574 |
| EX 541 | -$SO_2CH_2CH_2CH_3$ | $C_{23}H_{22}ClF_3N_2O_4S$ | 515 1014 | 515 0979 |

| | | | | |
|---|---|---|---|---|
| Ex 542 | $-SO_2CH_2CH_3$ | | | |
| Ex 543 | -NH-isopropyl | $C_{24}H_{23}ClF_3N_3O_3$ | 494 1453 | 494 1456 |
| Ex 544 | $-CH_2OCH_3$ | $C_{23}H_{20}ClF_3N_2O_4$ | 481 1136 | 481 1174 |
| Ex 545 | $-NHCH_3$ | $C_{22}H_{20}ClF_3N_3O_3$ | 466 1140 | 466 1141 |
| Ex 546 | $-N(CH_3)$(tButyl) | $C_{26}H_{27}ClF_3N_3O_3$ | 522 1766 | 522 1737 |
| Ex 547 | -NH(cyclopropyl) | $C_{24}H_{21}ClF_3N_3O_3$ | 492 1296 | 492 1285 |
| Ex 548 | $-NHCH_2CF_3$ | $C_{23}H_{17}ClF_6N_3O_3$ | 534 1014 | 534 1005 |
| Ex 549 | $NHCH_2$(cyclopropyl) | $C_{25}H_{23}ClF_3N_3O_3$ | 506 1453 | 506 1432 |
| Ex 550 | $-NHCH_2$(tButyl) | $C_{26}H_{27}ClF_3N_3O_3$ | 522 1766 | 522 1740 |
| Ex 551 | $-N(CH_3)_2$ | $C_{23}H_{22}ClF_3N_3O_3$ | 480 1296 | 480 1307 |

NMR characterization of compounds of Examples 531-551

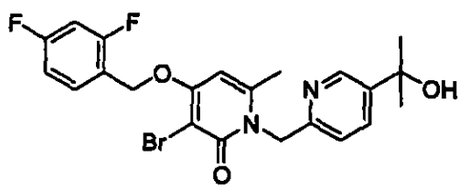
| Ex No | NMR data |
|---|---|
| 531 | $^1$H NMR ($CD_3OD$ / 400MHz) δ7 61 (m, 1H), 7 53 (m, 1H), 7 24 (t 2H J = 8 00Hz), 7 14 (m, 1H), 7 05 (m, 1H), 6 74 (s, 1H), 5 40 (s 2H), 4 42 (s, 2H), 3 63 (s 3H) 2 12 (s, 3H) |
| 532 | $^1$H NMR ($CD_3OD$ / 400MHz) δ7 59 (m, 2H), 7 24 (t, 2H, J = 8 00 Hz) 7 11 (m, 2H), 6 73 (s, 1H), 5 43 (s, 2H) 4 62 (s 2H), 2 12 (s 3H) |
| 533 | $^1$H NMR ($CD_3OD$ / 400MHz) δ7 61 (m, 1H), 7 53 (m, 1H), 7 24 (t, 2H, J = 7 60 Hz), 7 13 (m, 1H), 7 05 (m, 1H), 6 74 (s, 1H) 5 40 (s, 2H) 4 81 (m, 1H), 4 41 (s 2H), 2 12 (s, 3H), 1 21 (d, 6H, J = 6 00 Hz) |
| 534 | $^1$H NMR ($CD_3OD$ / 400MHz) δ7 61 (m, 1H), 7 52 (m, 1H), 7 24 (t, 2H, J = 0 80 Hz), 7 13 (m, 1H), 7 03 (m 1H), 6 73 (s, 1H), 5 39 (s, 2H), 4 44 (s, 2H), 3 12 (q, 2H, J = 7 20 Hz), 2 12 (s, 3H), 1 08 (t, 3H, J = 7 20 Hz) |
| 535 | $^1$H NMR ($CD_3OD$ / 300MHz) δ7 62 (m, 1H), 7 54 (m, 1H), 7 25 (t, 2H J = 8 4 Hz), 7 15 (m, 1H), 7 07 (m, 1H), 6 75 (s, 1H), 5 41 (s, 2H), 5 15 (s br, 1H), 4 44 (s, 2H), 3 82 (m, 4H), 2 13 (s, 4H), 2 03 (s br, 1H) |
| 536 | $^1$H NMR ($CD_3OD$ / 300MHz) δ7 62 (m, 1H), 7 54 (m, 1H), 7 25 (t, 2H, J = 8 1 Hz), 7 15 (m 1H), 7 06 (m, 1H), 6 74 (s, 1H), 5 41 (s, 2H), 4 43 (s, 2H), 3 98 (t, 2H, J = 6 6 Hz), 2 13 (s, 3H), 1 63 (m, 2H), 0 94 (t, 3H, J = 7 2 Hz) |
| 537 | $^1$H NMR ($CD_3OD$ / 300MHz) δ7 62 (m, 1H), 7 54 (m 1H), 7 25 (t, 2H, J = 8 4 Hz), 7 14 (m, 1H), 7 07 (m, 1H), 6 74 (s, 1H), 5 92 (m br 1H), 5 41 (s, 2H) 5 29 (d, 1H, J = 17 7 Hz), 5 17 (d, 1H, J = 10 5 Hz), 4 63 (s, 1H), 4 53 (d, 2H, J = 5 4 Hz), 4 44 (s, 2H), 2 13 (s, 3H) |
| 538 | $^1$H NMR ($CD_3OD$ / 400MHz) δ7 61 (m, 1H), 7 53 (m, 1H), 7 24 (t, 2H J = 7 6 Hz), 7 14 (m, 1H) 7 06 (m, 1H), 6 74 (s, 1H), 5 41 (s, 2H), 4 65 (d, 2H J = 2 4 Hz), 4 44 (s, 2H), 2 86 (t, 1H, J = |

| | |
|---|---|
| | 2 4 Hz), 2 12 (s 3H) |
| 539 | $^1$H NMR ($CD_3OD$ / 400MHz) δ7 61 (m 1H) 7 53 (m 1H), 7 24 (tr 2H J = 8 40), 7 12 (m 1H) 7 05 (m 1H) 6 74 (s, 1H) 5 39 (s, 2H), 4 36 (s, 2H) 2 12 (s, 3H) 1 43 (s, 9H) |
| 540 | $^1$H NMR ($CD_3OD$ / 400MHz) δ7 61 (m, 1H), 7 53 (m 1H), 7 24 (tr 2H, J = 8 00 Hz) 7 12 m 1H), 7 04 (m 1H) 6 73 (s 1H) 5 37 (s, 2H), 4 39 (s, 2H) 2 12 (s 3H) 1 28 (s, 9H) |
| 541 | $^1$H NMR ($CD_3OD$ / 300MHz) δ7 59 (m 2H), 7 26 (m, 3H) 7 11 (m 1H) 6 75 (s 1H) 5 46 (s 2H), 4 40 (s 2H), 3 02 (m, 2H) 2 12 (s, 3H) 1 80 (m 2H), 1 03 (tr 3H, J = 7 50 MHz) |
| 542 | $^1$H NMR ($CD_3OD$ / 400MHz) δ7 58 (m, 2H), 7 26 (m, 3H), 7 10 (m 1H) 6 74 (s, 1H) 5 45 (s 2H) 4 39 (s 2H) 3 06 (q 2H J = 7 60 Hz) 2 11 (s, 3H), 1 31 (t, 3H, J = 7 2 Hz) |
| 543 | $^1$H NMR ($CD_3OD$ / 400MHz) δ7 61 (m 1H) 7 52 (m, 1H), 7 24 (t 2H J = 8 40 Hz) 7 12 (m 1H), 7 04 (m 1H) 6 73 (s 1H), 5 39 (s 2H), 4 44 (s 2H) 3 77 (m, 1H), 2 12 (s, 3H) 1 10 (d, 6H, J = 6 40 Hz) |
| 544 | $^1$H NMR ($CD_3OD$ / 400MHz) δ7 61 (m, 1H), 7 54 (m, 1H), 7 24 (t 2H J = 7 6 Hz) 7 15 (m 1H) 7 06 (m 1H) 6 74 (s 1H), 5 43 (s 2H), 4 55 (s, 2H) 3 92 (s 2H) 3 40 (s, 3H), 2 12 (s 3H) |
| 545 | $^1$H NMR ($CD_3OD$ / 300MHz) δ7 63 (m, 1H), 7 54 (m 1H) 7 26 (t, 2H J = 8 7 Hz) 7 15 (m, 1H), 7 05 (m 1H), 6 75 (s 1H) 5 42 (s, 2H), 4 47 (s, 2H) 2 70 (s 3H), 2 14 (s 3H) |
| 546 | $^1$H NNMR ($CD_3OD$ / 300MHz) δ7 63 (m 1H) 7 53 (m 1H) 7 25 (t 2H J = 9 0 Hz) 7 14 (m 1H) 7 04 (m 1H) 6 76 (s, 1H), 5 41 (s, 2H), 4 44 (s, 2H) 2 90 (s 3H), 2 13 (s 3H), 1 39 (s 9H) |
| 547 | $^1$H NNMR ($CD_3OD$ / 400MHz) δ7 61 (m 1H) 7 52 (m, 1H), 7 24 (t 2H J = 7 6 Hz), 7 14 (m 1H) 7 03 (m 1H) 6 74 (s 1H) 5 41 (s 2H), 4 47 (s, 2H) 2 46 (m, 1H) 2 12 (s, 3H) 0 68 (q 2H J = 5 2 Hz), 0 46 (m 2H) |
| 548 | $^1$H NNMR ($CD_3OD$ / 400MHz) δ7 61 (m 1H) 7 53 (m, 1H) 7 24 (t, 2H J = 8 0 Hz) 7 12 (m 1H) 7 04 (m 1H), 6 73 (s 1H) 5 39 (s, 2H), 4 47 (s, 2H), 3 79 (q, 2H J = 9 6 Hz), 2 12 (s, 3H) |
| 549 | $^1$H NNMR ($CD_3OD$ / 400MHz) δ7 61 (m, 1H), 7 52 (m 1H), 7 24 (t 2H J = 8 4 Hz), 7 14 (m 1H) 7 04 (m 1H), 6 73 (s 1H) 5 39 (s 2H) 4 45 (s, 2H) 2 96 (d 2H, J = 6 8 Hz), 2 12 (s, 3H) 0 93 (m, 1H), 0 44 (m 2H) 0 16 (q 2H J = 4 8 Hz) |
| 550 | $^1$H NNMR ($CD_3OD$ / 400MHz) δ7 61 (m, 1H), 7 53 (m, 1H), 7 24 (t, 2H, J = 8 0 Hz) 7 14 (m 1H) 7 04 (m 1H) 6 73 (s 1H) 5 39 (s, 2H), 4 46 (s, 2H), 2 92 (d, 2H J = 4 8 Hz), 2 12 (s, 3H) 0 87 (s, 9H) |
| 551 | $^1$H NNMR ($CD_3OD$ / 300MHz) δ7 62 (m 1H), 7 52 (m 1H) 7 25 (t, 2H J = 8 7 Hz) 7 15 (m 1H) 7 04 (m, 1H), 6 75 (s 1H), 5 42 (s, 2H), 4 48 (s, 2H) 2 90 (s, 6H), 2 14 (s 3H) |

$^1$H NMR ($CD_3OD$ / 400MHz) δ7 58 (m, 2H), 7 26 (m, 3H), 7 10 (m, 1H), 6 74 (s, 1H), 5 45 (s, 2H), 4 39 (s, 2H), 3 06 (q, 2H, J = 7 60 Hz), 2 11 (s, 3H), 1 31 (t, 3H, J = 7 2 Hz)$^1$H NMR ($CD_3OD$ / 300MHz) δ7 63 (m, 1H), 7 54 (m, 1H), 7 26 (t, 2H, J =

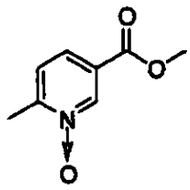
8 7 Hz), 7 15 (m, 1H), 7 05 (m, 1H), 6 75 (s, 1H), 5 42 (s, 2H), 4 47 (s, 2H), 2 70 (s, 3h), 2 14 (s, 3H) ESHRMS m/z 466 1141 (M+H $C_{22}H_{20}ClF_3N_3O_3$ requires 466 1140)

Example 552



3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-{[5-(1-hydroxy-1-methylethyl)pyridin-2-yl]methyl}-6-methylpyridin-2(1H)-one

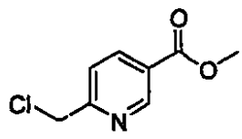
Step 1 Preparation of methyl 6-methylnicotinate 1-oxide



Methyl 6-methylnicotinate (6 0 g, 39 7 mmol) was added into dichloromethane (100 mL) in the round bottom flask under nitrogen 3-chloroperoxybenzoic acid (10 0 g, 57 9 mmol) was then added into the flask and stirred for 5 hour Saturated sodium bicarbonate solution (100 ml) was added into the reaction and the mixture was transferred to separatory funnel Additional 200mL of dichloromethane was added into the funnel and obtained the organic layer The organic layer was washed with water (150 mL) and dried over anhydrous magnesium sulfate The resulting solution was evaporated to yield white solid (6 g, 90 %) LC/MS, $t_r$ = 0 33 minutes (5 to 95%

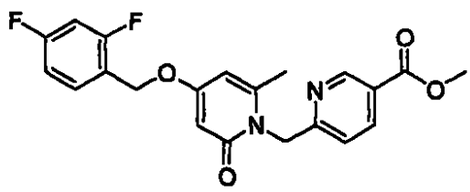
acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 168 (M+H) ES-HRMS m/z 168 0628 (M+H calcd for $C_8H_{10}NO_3$ requires 168 0655)

Step 2 Preparation of methyl 6-(chloromethyl)nicotinate



Methyl 6-methylnicotinate 1-oxide ( from Step 1) (6 0 g, 35 9 mmol) was was added into the p-toluenesulfonyl chloride (10 g, 52 4 mmol) in 100 mL of 1,4- dioxane The mixture was heated to reflux for 20 hours Saturated sodium bicarbonate solution (200 ml) was added into the reaction and the mixture was transferred to separatory funnel The compound was extracted using ethyl acetate (300ml x 2) and the combined ethyl acetate solution was dried over magnesium sulfate and evaporated to black solid (5 2 g, 78%) LC/MS, $t_r$ = 1 52 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 186 (M+H) ES-HRMS m/z 186 0314 (M+H calcd for $C_8H_9ClNO_2$ requires 186 0316)

Step 3 Preparation of methyl 6-{[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}nicotinate



Methyl 6-(chloromethyl)nicotinate ( from step 2) (2 g, 10 8 mmol) was added into 4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one in 20 mL of dimethyl formamide followed by addition of cesium carbonate (5g, 15 3 mmol) The

mixture was heated to 100 C for 20 hours It was cooled to room temperature and added 400 mL of water Brown precipitate came out of from solution It was filtered and rinsed with water (200 mL x 3) and dried to obtain 4 g of solid The product was purified using a Gilson Reversed Phase preparative chromatography to obtain white solid (1 4 g, 32%) $^1$H NMR (400 MHz, $CDCl_3$) δ 9 09 (d, J =1 48 Hz, 1H), 8 19 (dd, J = 6 04, 2 15 Hz, 1H), 7 37 (app q, J = 8 32 Hz, 1H), 7 25 (d, J = 8 33 Hz, 1H), 6 84 (m, 2H), 5 94 (d, J = 2 82Hz, 1H), 5 83 (d, J = 2 15Hz, 1H), 5 36 (s, 2H), 4 97 (s, 2H), 3 90 (s, 3H), 2 27(s, 3H), LC/MS, $t_r$ = 2 30 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 401 (M+H) ES-HRMS m/z 401 1307 (M+H calcd for $C_{21}H_{19}F_2N_2O_4$ requires 401 1307)

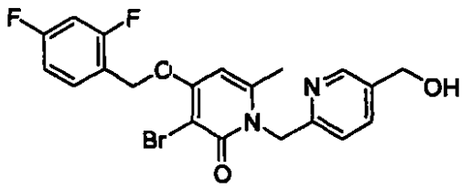
Step 4 Preparation of the title compound

3 molar solution of methyl magnesium bromide in ether (5mL, 15mmol) was added into 5 ml of anhydrous tetrahydrofuran in the round bottom flaks under nitrogen The mixture was cooled to 0°C Methyl 6-{[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}nicotinate ( from Step 3) (300mg, 0 75mmol)was dissolved in 5 ml of anhydrous tetrahydrofuran in dropper funnel and the solution was slowly added into cold methyl magnesium bromide solution in the round bottom flask After the addition, the mixture was continue stirring at 0 C for 30 minute and cold solution of saturated ammonium chloride (100 ml) was added slowly into the reaction mixture The mixture was transferred to separatory funnel and the product was extracted with ethyl acetate (200ml x2) The combined ethyl acetate solution was dried over anhydrous magnesium sulfate and evaporated to dryness The resulting residue (220 mg) was added into 10 ml of dichloromethane

followed by addition of N-bromo succinimide (100 mg, 0 56 mmol) The solution was stirred at room temperature for 3 hours Saturated sodium bicarbonate solution (100 ml) was added into the reaction mixture and it was transferred to separatory funnel The product was extracted with ethyl acetate (200ml x2) The combined ethyl acetate solution was dried over anhydrous magnesium sulfate and evaporated to dryness

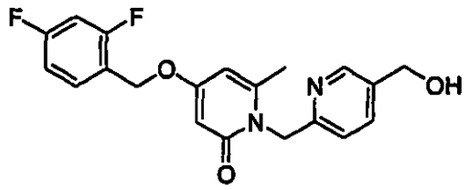
$^1$H NMR (400 MHz, $CDCl_3$) δ 8 61 (d, J =1 88 Hz, 1H), 7 73 (dd, J = 5 77, 2 42 Hz, 1H), 7 55 (app q, J = 6 31 Hz, 1H), 7 30 (d, J = 8 19b Hz, 1H), 6 93 (m, 1H), 6 84 (m, 1H), 6 00 (s, 1H), 5 37 (s, 2H), 5 19 (s, 2H), 2 48 (s, 3H), 1 56 (s, 6H), LC/MS, $t_r$ = 2 29 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 479 (M+H) ES-HRMS m/z 479 0791 (M+H calcd for $C_{22}H_{22}BrF_2N_2O_3$ requires 479 0776)

Example 553




3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-{[5-(hydroxymethyl)pyridin-2-yl]methyl}-6-methylpyridin-2(1H)-one

Step 1 Preparation of 4-[(2,4-difluorobenzyl)oxy]-1-{[5-(hydroxymethyl)pyridin-2-yl]methyl}-6-methylpyridin-2(1H)-one

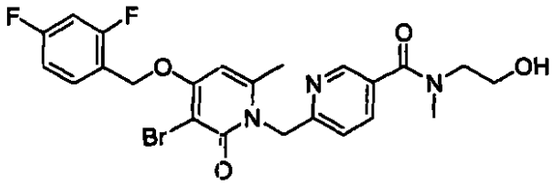


Methyl 6-{[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}nicotinate ( from preparation of step 3) (350 mg, 0 87 mmol) was added into anhydrous tetrahydrofuran (15 ml) and the solution was cooled to -78 C Into the cold solution, was added lithium aluminum hydride (100 mg, 2 6 mmol) After the addition, the reaction mixture was warm to 0 C and continue stirring for one additional hour Potassium hydrogen sulfate (1 N solution, 150 ml) was added slowly into the reaction mixture to quench the reaction The resulting mixture was transferred to a separatory funnel and the product was extracted with ethyl acetate (200ml x 2) The combine ethyl acetate solution was dried over anhydrous magnesium sulfate and evaporated to dryness LC/MS, $t_r$ = 1 88 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 373 (M+H)

Step 2 Preparation of the title compound 4-[(2,4-difluorobenzyl)oxy]-1-{[5-(hydroxymethyl)pyridin-2-yl]methyl}-6-methylpyridin-2(1H)-one ( from step 1) (230 mg, 0 62 mmol) was added into 10 ml of dichloromethane followed by addition of N-bromo succinimide (110 mg, 0 62 mmol) The solution was stirred at room temperature for 3 hours Saturated sodium bicarbonate solution (100 ml) was added into the reaction mixture and it was transferred to a separatory funnel The product was extracted with ethyl acetate (200ml x2) The combined ethyl acetate solution was dried over anhydrous magnesium sulfate and evaporated to dryness $^1$H NMR (400 MHz, $CDCl_3$) δ 8 47 (app s, 1H), 7 64 (dd, J = 5 77, 2 29

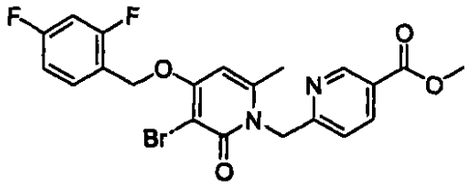
Hz, 1H), 7 55 (app q, J = 6 45 Hz, 1H), 7 33 (d, J = 6 05 Hz, 1H), 6 93 (m, 1H), 6 84 (m, 1H), 6 00 (s, 1H), 5 39 (s, 2H), 5 19 (s, 2H), 4 68 (s, 2H), 2 46 (s, 3H), LC/MS, $t_r$ = 2 01 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 451 (M+H)

Example 554



6-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-N-(2-hydroxyethyl)-N-methylnicotinamide

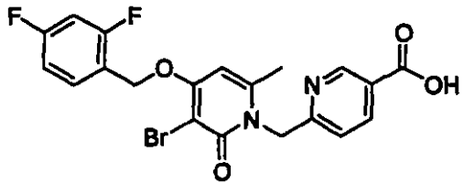
Step 1 Preparation of methyl 6-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}nicotinate



Methyl 6-{[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}nicotinate (350 mg, 0 87 mmol) (1 0 g, 2 5 mmol) was added into 150 ml of dichloromethane followed by addition of N-bromo succinimide (500 mg, 2 8 mmol) The solution was stirred at room temperature for 3 hours Saturated sodium bicarbonate solution (300 ml) was added into the reaction mixture and it was transferred to a separatory funnel The product was extracted with ethyl acetate (500ml x2) The combined ethyl acetate solution was dried over anhydrous magnesium sulfate and evaporated to dryness $^1$H NMR (400 MHz, $CDCl_3$) δ 9 08 (app d, J = 2 15 Hz, 1H), 8 21 (dd, J =

6 04, 2 15 Hz, 1H), 7 55 (app qt, J = 6 31 Hz, 1H), 7 41 (d, J = 6 31 Hz, 1H), 6 91 (m, 1H), 6 84 (m, 1H), 6 02 (s, 1H), 5 42 (s, 2H), 5 19 (s, 2H), 3 91 (s, 3H), 2 45 (s, 3H), LC/MS, $t_r$ = 2 85 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 479 (M+H) ES-HRMS m/z 479 0415 (M+H calcd for $C_{21}H_{18}BrF_2N_2O_4$ requires 479 0413)

Step 2 Preparation of 6-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}nicotinic acid



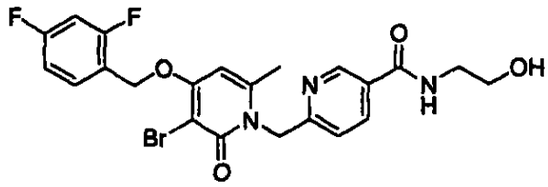
Methyl 6-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)- yl]methyl}nicotinate ( from step 1) (1 0 g, 2 1 mmol) was added into the mixture of 100 ml tetrahydrofuran and 10 ml of methanol followed by addition of 2 5 N sodium hydroxide(0 85 ml, 2 1 mmol) The solution was heated to 50 C for 2 hours After the solution was cooled to room temperature and evaporate to completely dried residue The residue was added into 50 ml of tetrahydrofuran and 4 N HCl in 1,4-dioxane (0 52 ml, 2 1 mmol) and stirred the mixture for 30 minute The mixture was evaporate to dryness The residue was added 20 ml water and the aqueous solution was neutralized to exactly ph 7 by addition of saturated sodium bicarbonate solution drop wise The resulting heterogeneous mixture was left standed for 20 hours Filtered, rinsed with water (30 ml x 3) and dried over high vacuum oven to afford white solid( 950 mg, 97%)

362
365

$^1$H NMR (400 MHz, $CDCl_3$ and $CD_3OD$) δ 8 98 (app br s, 1H), 8 15 (dd, J = 6 17, 2 02 Hz, 1H), 7 45 (app q, J = 6 58 Hz, 1H), 7 21 (d, J = 8 19 Hz, 1H), 6 84 (m, 1H), 6 76 (m, 1H), 6 04 (s, 1H), 5 35 (s, 2H), 5 12 (s, 2H), 2 32 (s, 3H), LC/MS, $t_r$ = 2 48 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 465 (M+H) ES-HRMS m/z 465 0254 (M+H calcd for $C_{20}H_{16}BrF_2N_2O_4$ requires 465 0256)

Step 3 Preparation of the title compound 6-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}nicotinic acid ( from step 2)(230 mg, 0 5 mmol) was added into the 1-hydroxybenzotriazole (101mg, 0 75 mmol) in 5 ml of N,N-dimethylforamide 4 -methyl morpholine (0 16 ml, 1 5 mmol) was added into the mixture followed by addition of 1-(3-(dimethylamino) propyl-3-ethylcarbodiimide hydrochloride (143 mg, 0 75 mmol) Stirred the mixture for 30 minute to become homogenous solution To that homogenous solution, was added 2-(methylamino) ethanol(0 06 ml, 0 75 mmol) and the mixture was stirred for 20 hours Water (150 ml) was added into the reaction mixture and the product was extracted using ethyl acetate (400ml x2) The combined ethyl acetate solution was dried over anhydrous magnesium sulfate and evaporated to dryness $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8 47 (app br s, 1H), 7 80 (br d, J = 7 92 Hz, 1H), 7 64 (app q, J = 6 58 Hz, 1H), 7 30 (m, 2H), 7 15 (m, 1H), 6 56 (s, 1H), 5 39 (s, 2H), 5 28 (s, 2H), 3 46 (m, 2H), 3 23 (m, 2H) 2 93 (m, 3H), 2 36 (s, 3H), LC/MS, $t_r$ = 2 29 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-HRMS m/z 522 0850 (M+H calcd for $C_{23}H_{23}BrF_2N_3O_4$ requires 522 0835)

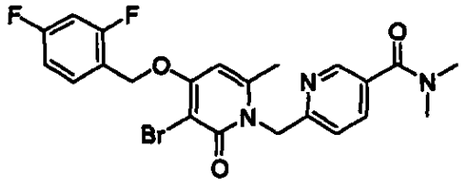
Example 555



6-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-N-(2-hydroxyethyl)nicotinamide

Following the method of Example 554 (step 3) and substituting 2-(methylamino)ethanol for the ethanolamine obtained the title compound as a white solid (79% yield) $^1$H NMR (400 MHz, $CD_3OD$) δ 8 93 (d, J = 2 01 Hz, 1H), 8 21 (dd, J = 6 04, 2 21 Hz, 1H), 7 67 (app q, J = 6 44 Hz, 1H), 7 39 (d, J = 8 06 Hz, 1H), 7 08 (m, 2H), 6 58 (s, 1H), 5 55 (s, 2H), 5 35 (s, 2H), 3 74 (app t, J = 5 73Hz, 2H), 3 53 (app t, J = 5 73Hz, 2H), 2 49 (s, 3H), LC/MS, $t_r$ = 2 26 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-HRMS m/z 508 0673 (M+H calcd for $C_{22}H_{21}BrF_2N_3O_4$ requires 508 0678)

Example 556

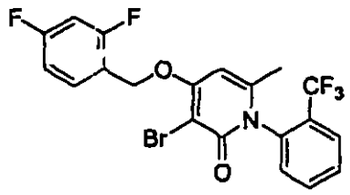


6-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-N,N-dimethylnicotinamide

Following the method of Example 554 (step 3) and substituting dimethylamine for the ethanolamine obtained the title compound as a white solid (75% yield) $^1$H NMR (400 MHz, $CDCl_3$) δ 8 55 (d, J = 1 62 Hz, 1H), 7 68 (dd, J = 5 77, 2 15 Hz, 1H), 7 55

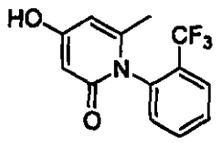
(app q, J = 6 45 Hz, 1H), 7 37 (d, J = 8 06 Hz, 1H), 6 93 (m, 1H), 6 84 (m, 1H), 6 02(s, 1H), 5 40 (s, 2H), 5 20 (s, 2H), 3 09 (s, 3H), 2 97 (s, 3H), 2 45 (s, 3H), LC/MS, $t_r$ = 2 45 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-HRMS m/z 492 0710 (*M+H calcd for* $C_{22}H_{21}BrF_2N_3O_3$ *requires* 492 0729)

Example 557



3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[2-(trifluoromethyl)phenyl]pyridin-2(1H)-one

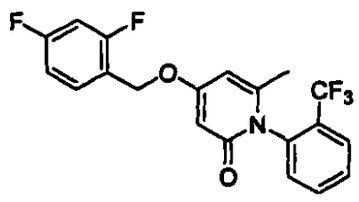
Step 1 Preparation of 4-hydroxy-6-methyl-1-[2-(trifluoromethyl)phenyl]pyridin-2(1H)-one



4-hydroxy-6-methyl-2-pyrone (10g, 79 3 mmol) was added into the 2-(trifluoromethyl) aniline (14 ml, 111 3 mmol) in 10 ml of 1,2-dichlorobenzene in a round bottom flask The mixture was then placed in a pre-heated oil bath at 165 C After 30 minute of heating, the mixture was cooled to room temperature and added 250 ml of saturated sodium bicarbonate solution The mixture was stirred at room temperature for 15 minutes and transferred to a separatory funnel Ethyl acetate (300ml) was added into the separatory funnel and partitions the layers The aqueous layer was obtained and the organic layer was added 200 ml of saturated sodium bicarbonate solution The aqueous layer was obtained again and the

combined aqueous solution was neutralized with HCl solution Upon neutralization, white solid precipitated out of the solution Filtered the solid, rinsed with water (100 ml x5) and dried over high vacuum oven to obtain the white solid (7 5 g, 35 5%) LC/MS, $t_r$ = 1 77 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 270 (M+H)

Step 2 Preparation of 4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[2-(trifluoromethyl)phenyl]pyridin-2(1H)-one

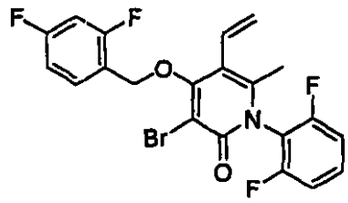



4-hydroxy-6-methyl-1-[2-(trifluoromethyl)phenyl]pyridin-2(1H)-one ( from Step 1) (7 3 g, 27 1 mmol) was added into 3,4-difluorobenzyl bromide (5 5 g, 26 5 mmol) in 60 ml of dimethyl formamide The mixture was cooled to 0 C and cesium carbonate (20g, 61 3 mmol) was added into the mixture After the addition, the mixture was warmed to room temperature and stirred for 4 hours Water (500ml) was added into the reaction mixture Yellow solid came out of solution Filtered and rinsed with water (200ml x 2) to obtain the yellow solid Dissolved the solid in ethyl acetate (500 ml) and water (300 ml) and transfer to a separatory funnel and obtained the organic layer The organic layer was washed again with water (200ml) and dried over anhydrous magnesium sulfate The organic solution was evaporated to dryness $^1$H NMR (400 MHz, $CDCl_3$) δ 7 82 (d, J =7 65 Hz, 1H), 7 7 (t, J = 7 52 Hz, 1H), 7 58 (t, J = 7 65 Hz, 1H), 7 42 (q, J = 6 45 Hz,

1H), 7 27 (d, J = 7 78 Hz, 2H), 6 89 (m, 2H), 5 95 (app d, J = 2 42Hz, 1H), 5 90 (app d, J = 2 42Hz, 1H), 5 01 (app d, J = 2 94 Hz, 2H), 1 86 (s, 3H), LC/MS, $t_r$ = 2 74 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 396 (M+H)

Step 3 Preparation of the title compound
N-bromosuccinimide (0 24g, 1 36 mmol) was added into 4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[2-(trifluoromethyl)phenyl]pyr_din-2(1H)-one (0 54g, 1 36 mmol) in 20 ml of dichloromethane The mixture was stirred at room temperature for 2 hours Saturated sodium bicarbonate solution (150 ml) was added into the reaction mixture and the combine solution was transferred to a separatory funnel The product was extracted with ethyl acetate (250ml) The ethyl acetate solution was dried over anhydrous magnesium sulfate and evaporated to dryness $^1$H NMR (400 MHz, $CDCl_3$) δ 7 82 (d, J =7 25 Hz, 1H), 7 7 (app t, J = 7 66 Hz, 1H), 7 60 (m, 2H), 7 26 (s, 1H), 6 97 (m, 1H), 6 87 (m, 1H), 6 09 (s, 1H), 5 25 (app d, J = 3 35Hz, 2H), 1 94 (s, 3H), LC/MS, $t_r$ = 2 84 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-HRMS m/z 474 0113 (M+H calcd for $C_{20}H_{14}BrF_5NO_2$ requires 474 0123)

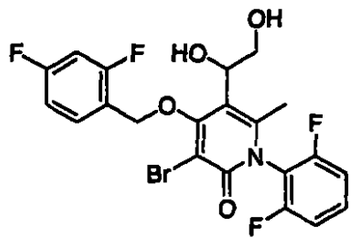
Example 558




3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-methyl-5-vinylpyridin-2(1H)-one

Step 1 To a room temperature solution of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-5-iodo-6-methylpyridin-2(1H)-one (1 00 g, 1 76 mmol) in anhydrous THF (12 mL) was added, sequentially, tributyl(vinyl)tin (1 21 g, 3 81 mmol) and tetrakis(triphenylphosphine)palladium (236 mg, 0 204 mmol) under an argon stream The reaction vessel was then equipped with a reflux condenser and the reaction system purged with an argon flow The resulting yellow solution was heated to 68 °C and stirred under a positive pressure of argon for 12 0 hours until complete disappearance of starting material by LCMS analysis The reaction mixture was concentrated in vacuo and the resulting dark residue was subjected to $SiO_2$ chromatography with ethyl acetate/hexanes (3 7) to furnish a reddish solid $^1H$ NMR (400 MHz, $CDCl_3$) δ 7 62 (app q, J = 7 8 Hz, 1H), 7 45 (app tt, J = 8 4, 6 2, 1H), 7 09 (app t, J = 8 8 Hz, 2H), 6 90 (app t, J = 8 0 Hz, 1H), 6 83 (app dt, J = 6 8, 2 5 Hz, 1H), 6 51 (dd, J = 17 7, 11 4 Hz, 1H), 5 53 (dd, J = 11 4, 1 5 Hz, 1H), 5 41 (dd, J = 17 8, 1 5 Hz, 1H), 5 09 (br s, 2H), 2 09 (s, 3H), LC/MS C-18 column, $t_r$ = 3 20 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 468 (M+H) ES-HRMS m/z 468 0210 (M+H calcd for $C_{21}H_{15}BrF_4NO_2$ requires 468 0217)

Example 560

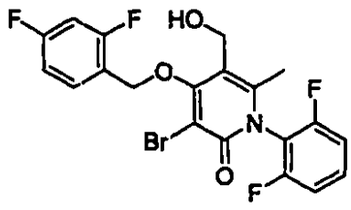


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3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-5-(1,2-dihydroxyethyl)-6-methylpyridin-2(1H)-one

Step 1 To a room temperature solution of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-methyl-5-vinylpyridin-2(1H)-one (0 970 g, 2 07 mmol) in water/acetone 1 3 (8 7 mL) was added, sequentially, osmium tetroxide (0 110 g, 0 433 mmol) and N-methyl morpholine oxide (1 32 g, 11 2 mmol) The resulting solution was stirred for one hour until complete consumption of starting material by LCMS analysis, and the reaction was concentrated in vacuo The resulting dark residue was subjected to $SiO_2$ chromatography with ethyl acetate/hexanes (3 7) to furnish a solid $^1H$ NMR (400 MHz, $CDCl_3$) δ 7 59 (app q, J = 8 2 Hz, 1H), 7 45 (ddd, J = 14 7, 8 5, 6 8 Hz, 1H), 7 08 (app t, J = 8 5 Hz, 2H), 6 94 (app t, J = 8 2 Hz, 1H), 6 88 (app t, J = 8 5 Hz, 1H), 5 31 (AB-q, J = 10 6 Hz, Δ= 38 3 Hz, 2H), 5 07 (dd, J = 9 1, 3 8 Hz, 1H), 3 83 (t, J = 10 8 Hz, 1H), 3 50 (dd, J = 11 4, 3 9 Hz, 1H), 2 94 (br s, 1H), 2 16 (s, 3H), LC/MS C-18 column, $t_r$ = 2 26 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 502 (M+H) ES-HRMS m/z 502 0276 (M+H calcd for $C_{21}H_{17}BrF_4NO_4$ requires 502 0272)

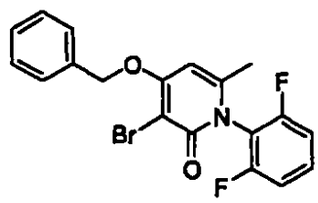
Example 561




3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-5-(hydroxymethyl)-6-methylpyridin-2(1H)-one

Step 1 To a -20 °C solution of 5-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-2-methyl-6-oxo-1,6-dihydropyridine-3-carbaldehyde (0 659 g, 1 40 mmol) in methanol (10 mL) was added, portionwise, solid sodium borohyride (3 6 g, 96 mmol) over one hour until complete consumption of starting material by LCMS analysis Next, the reaction mixture was diluted with 500 mL of ethyl acetate and washed with 3 X 200 mL of water The resulting organic extract was $Na_2SO_4$ dried, filtered, and concentrated in vacuo to approximately 100 mL volume The resulting liquid was diluted with hexanes (100 mL) to furnish an amorphous solid that was collected and dried at 1 mm Hg vacuum to furnish (620 mg, 94 %) of the desired product $^1$H NMR (400 MHz, $d_4$-MeOH) δ 7 70 (app q, J = 8 3 Hz, 1H), 7 62 (app tt, J = 10 4, 6 3 Hz, 1H), 7 25 (app t, J = 8 6 Hz, 2H), 7 03 (app t, J = 8 6 Hz, 1H), 6 88 (app t, J = 8 5 Hz, 1H), 5 31 (s, 2H), 4 58 (s, 2H), 2 17 (s, 3H), LC/MS C-18 column, $t_r$ = 2 49 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 472 (M+H) ES-HRMS m/z 472 0152 (M+H calcd for $C_{20}H_{15}BrF_4NO_3$ requires 472 0166)

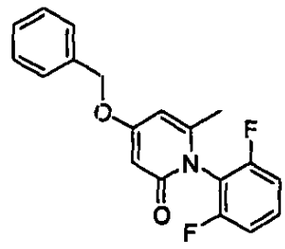
Example 562




4-(benzyloxy)-3-bromo-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one

Step 1 Preparation of 4-(benzyloxy)-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one

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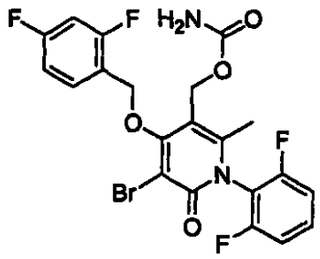


To a briskly stirred room temperature solution of 1-(2,6-difluorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one (1 43 g, 6 03 mmol) in dimethylformamide (4 6 mL) was added sequentially $K_2CO_3$ (2 01 g 14 5 mmol) and benzyl bromide (2 40 mL, 20 2 mmol) The resulting suspension was stirred for 6 5 hours until complete consumption of starting material by LCMS analysis The reaction was then diluted with ethyl acetate (200 mL) and brine washed (3 X 200 mL) The resulting organic extract was $Na_2SO_4$ dried, filtered, and concentrated in vacuo to approximately 100 mL volume The resulting mother liquor rapidly precipitated and furnished an amorphous solid that was collected and dried at 1 mm Hg vacuum to provide a solid (1 62 g, 82 %) $^1$H NMR (300 MHz, $d_4$-MeOH) δ 7 62 (app tt, J = 8 6, 6 4 Hz, 1H), 7 52-7 32 (m, 4H), 7 30-7 12 (m, 3H), 6 27 (d, J = 1 6 Hz, 1H), 6 04 (d, J = 2 6 Hz, 1H), 5 18 (s, 2H), 2 06 (s, 3H) LC/MS C-18 column, $t_r$ = 2 51 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 328 (M+H) ES-HRMS m/z 328 1179 (M+H calcd for $C_{19}H_{16}F_2NO_2$ requires 328 1144)

Step 2 To a room temperature solution of 4-(benzyloxy)-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one (1 52 g, 4 64 mmol) in methylene chloride (15 mL) was added solid N-bromosuccinimide (2 01 g, 11 3 mmol) and the resulting reddish solution was stirred for 4 0 hours At this time the reaction was diluted with ethyl acetate (400 mL) and washed with sodium sulfite (5 % aqueous solution, 100 mL) and brine

(3 X 200 mL) The resulting organic extracts were $Na_2SO_4$ dried, filtered, and concentrated in vacuo to approximately 60 mL volume The resulting mother liquor rapidly precipitated and furnished an amorphous solid that was collected and dried at 1 mm Hg vacuum to provide a solid (1 70 g, 91 %) $^1H$ NMR (300 MHz, $d_4$-MeOH) δ 7 64 (app tt, J = 8 6, 6 4 Hz, 1H), 7 57 (br d, J = 7 1 Hz, 1H), 7 50-7 34 (m, 4H), 7 27 (app t, J = 8 0 Hz, 1H), 7 26-7 21 (m, 1H), 6 66 (s, 1H), 5 40 (s, 2H), 2 12 (s, 3H), LC/MS C-18 column, $t_r$ = 2 63 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 406 (M+H) ES-HRMS m/z 406 0228 (M+H calcd for $C_{19}H_{15}BrF_2NO_2$ requires 406 0249)

Example 563

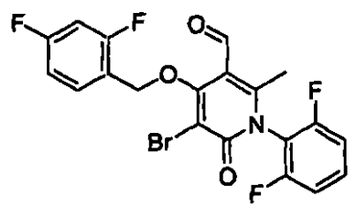


5-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-2-methyl-6-oxo-1,6-dihydropyridin-3-yl]methyl carbamate

Step 1 To a room temperature solution of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-5-(hydroxymethyl)-6-methylpyridin-2(1H)-one (76 2 mg, 0 161mmol) in methylene chloride (0 4 mL) was added a solution of trichloroacetyl isocyanate (toluene, 0 60 M, 0 5 mL, 0 30 mmol) The resulting solution was stirred for one hour until complete consumption of starting material by LCMS analysis The reaction mixture was then directly applied to $Al_2O_3$ (0 5 g of Broeckman-activity type I) and the slurry was matured for three hours At this time, the $Al_2O_3$ plug was flushed with ethyl acetate/methanol

(95 5) and the resulting mother liquor was concentrated to a residue that was subjected to $SiO_2$ chromatography using ethyl acetate/hexanes (1 1) to furnish a white solid (71 0 mg, 85 %) $^1H$ NMR (400 MHz, $d_4$-MeOH) δ 7 71-7 59 (m, 2H), 7 26 (app t, J = 8 5 Hz, 2H), 7 02 (app t, J = 9 2 Hz, 2H), 5 32 (s, 2H), 5 02 (s, 2H), 2 15 (s, 3H), LC/MS C-18 column, $t_r$ = 2 35 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 515 (M+H) ES-HRMS m/z 515 0188 (M+H calcd for $C_{21}H_{16}BrF_4N_2O_4$ requires 515 0224)

Example 564

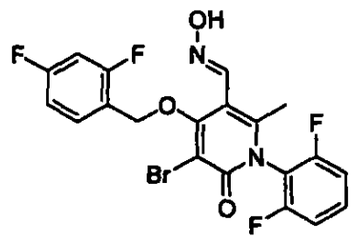


5-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-2-methyl-6-oxo-1,6-dihydropyridine-3-carbaldehyde

Step 1 To a room temperature solution of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-5-(1,2-dihydroxyethyl)- 6-methylpyridin-2(1H)-one (550 mg, 1 10 mmol) in toluene (10 0 mL) was added lead(IV) acetate (810 mg, 1 82 mmol) The resulting dark brown solution was stirred for two hours until complete consumption of starting material by LCMS analysis The reaction mixture was then diluted with ethyl acetate (400 mL), water washed (3 X 100 mL), and brine washed (3 X 300 mL) The resulting organic extract was separated, $Na_2SO_4$ dried, and concentrated The resulting dark residue was subjected to $SiO_2$ chromatography with ethyl

acetate/ hexanes (1 1) to furnish a light yellow solid (321 mg, 62 %) $^1$H NMR (400 MHz, $CDCl_3$) δ 10 08 (s, 1H), 7 56-7 48 (m, 2H), 7 12 (app t, J = 7 3 Hz, 2H), 6 94 (app t, J = 8 5 Hz, 1H), 6 88 (app t, J = 8 7 Hz, 1H), 5 33 (s, 2H), 2 45 (s, 3H), LC/MS C-18 column, $t_r$ = 2 94 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 470 (M+H) ES-HRMS m/z 469 9996 (M+H calcd for $C_{20}H_{13}BrF_4NO_3$ requires 470 0009)

Example 565



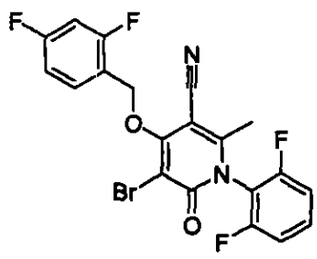
5-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-2-methyl-6-oxo-1,6-dihydropyridine-3-carbaldehyde oxime

Step 1 To a room temperature solution of 5-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-2-methyl-6-oxo-1,6-dihydropyridine-3-carbaldehyde (316 5 mg, 0 673 mmol) in methanol (10 0 mL) was added solid $NH_2OH•H_2O$(300 0 mg, 4 32 mmol) and sodium acetate (480 0 mg, 5 85 mmol) The resulting suspension was stirred for 1 5 hours until complete consumption of starting material by LCMS analysis The reaction mixture was then concentrated in vacuo and the resulting residue was diluted with methylene chloride (300 mL) and water washed (2 X 100 mL) The resulting organic extract was separated, $Na_2SO_4$ dried, and concentrated to furnish a light yellow solid (390 mg, 99 %) $^1$H NMR (400 MHz, $d_4$-MeOH with $CDCl_3$) δ 8 06 (s, 1H), 7 51-7 40 (m, 2H), 7 06 (app dd, J

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= 8 6, 7 4 Hz, 2H), 6 88 (app dt, J = 8 3, 2 4 Hz, 1H), 6 83 (app dt, J = 9 2, 2 4 Hz, 1H), 5 13 (s, 2H), 2 76 (s, 3H), LC/MS C-18 column, $t_r$ = 2 61 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 485 (M+H) ES-HRMS m/z 485 0093 (M+H calcd for $C_{20}H_{14}BrF_4N_2O_3$ requires 485 0118)

Example 566

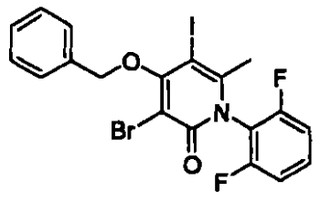



5-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-2-methyl-6-oxo-1,6-dihydropyridine-3-carbonitrile

Step 1 To a room temperature solution of 5-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-2-methyl-6-oxo-1,6-dihydropyridine-3-carbaldehyde oxime (340 0 mg, 0 701mmol) in methylene chloride (8 C mL) was added solid 1,1' carbonyl diimidazole (290 0 mg, 1 79 mmol) and sodium acetate (480 0 mg, 5 85 mmol) The resulting solution was stirred for 1 5 hours until complete consumption of starting material by LCMS analysis The reaction mixture was then concentrated in vacuo and the resulting residue was directly applied to $SiO_2$ chromatography with ethyl acetate/hexanes (3 7) to furnish a white solid (262 mg, 90 %) $^1H$ NMR (400 MHz, $CDCl_3$) δ 7 61 (app q, J = 7 4 Hz, 1H), 7 52 (app tt, J = 8 4, 6 3 Hz, 1H), 7 14 (app dd, J = 8 6, 7 4 Hz, 2H), 6 94 (app dt, J = 8 5, 2 5 Hz, 1H), 6 88 (app dt, J = 8 5, 2 4 Hz, 1H), 5 43 (s, 2H),

2 32 (s, 3H), LC/MS C-18 column, $t_r$ = 2 95 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) IR (neat) 3111, 3067, 3032, 2914, 2840, 2215 (nitrile stretch), 1678, 1587, 1470 $cm^{-1}$, ES-MS m/z 467 (M+H) ES-HRMS m/z 467 0037 (M+H calcd for $C_{20}H_{12}BrF_4N_2O_2$ requires 467 0013)

Example 567



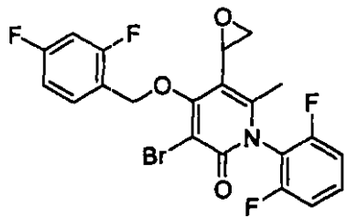
4-(benzyloxy)-3-bromo-1-(2,6-difluorophenyl)-5-iodo-6-methylpyridin-2(1H)-one

Step 1 A solution of 4-(benzyloxy)-3-bromo-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one (1 42 g, 3 50 mmol) in 1,2 dichloroethane (18 mL) was treated with solid N-iodosuccinimide (1 59 g, 7 06 mmol) and dichloroacetic acid (0 260 g, 2 01 mmol) The resulting solution was stirred and heated to 50 °C for 2 5 hours until complete consumption of starting material by LCMS At this time the reaction was diluted with ethyl acetate (400 mL) and washed with sodium sulfite (5 % aqueous solution, 100 mL) and brine (3 X 200 mL) The resulting organic extracts were $Na_2SO_4$ dried, filtered, and concentrated in vacuo to approximately 30 mL volume The resulting mother liquor rapidly precipitated and furnished an amorphous solid that was collected and dried at 1 mm Hg vacuum to provide a solid (1 49 g, 82 %) $^1H$ NMR (400 MHz, $CDCl_3$) δ 7 62 (app d, J = 6 8 Hz, 2H), 7 51-7 38 (m, 4H), 7 09 (app t, J = 8 0 Hz, 2H), 5 20 (s, 2H), 2 39 (s, 3H), LC/MS C-18 column, $t_r$ = 3 28 minutes (5 to 95% acetonitrile/water over 5

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372

minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 532 (M+H) ES-HRMS m/z 531 9196 (M+H calcd for $C_{19}H_{14}BrF_2INO_2$ requires 531 9215)

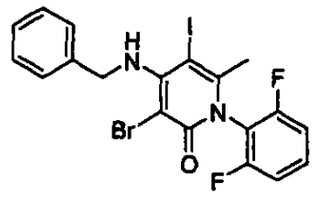
Example 568



3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-methyl-5-oxiran-2-ylpyridin 2(1H)-one

Step 1 A sample of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-methyl-5-vinylpyridin-2(1H)-one (10 0 mg, 0 0214 mmol) was treated with a solution of dimethyl dioxirane in acetone (approx 0 1 M, 5 mL, 0 5 mmol) The reaction vessel was capped and sealed, and the resulting solution was stirred 6 0 hours At this time the reaction was concentrated in vacuo and the resulting residue was subjected to $SiO_2$ chromatography with ethyl acetate/hexanes (4 6) to furnish a semi-solid (5 0 mg, 48 %) $^1H$ NMR (400 MHz, $CDCl_3$) δ 7 57 (app q, J = 7 4 Hz, 1H), 7 46 (app tt, J = 8 5, 6 2, 1H), 7 11 (app t, J = 8 0 Hz, 2H), 6 94(app t, J = 8 2 Hz, 1H), 6 83 (app t, J = 9 2 Hz, 1H), 5 31 (AB-q, J = 10 9 Hz, Δ= 29 0 Hz, 2H), 3 63 (app t, J = 3 5 Hz, 1H), 3 03 (dd, J = 9 4, 5 0, 1H), 2 85 (dd, J = 5 2, 2 7, 1H), 2 14 (s, 3H), LC/MS C-18 column, $t_r$ = 2 26 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 484 (M+H) and 502 ($M+H_3O$) ES-HRMS m/z 502 0273 ($M+H_3O$ calcd for $C_{21}H_{17}BrF_4NO_4$ requires 502 0272)

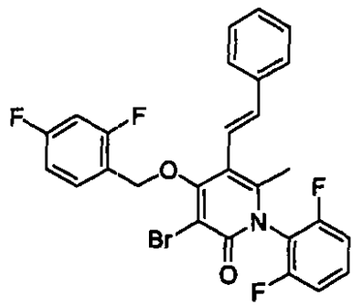
Example 569



4-(benzylamino)-3-bromo-1-(2,6-difluorophenyl)-5-iodo-6-methylpyridin-2(1H)-one

Step 1 A slurry of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-5-iodo-6-methylpyridin-2(1H)-one (80 0 mg, 0 141 mmol) and benzyl amine (300 mg, 2 80 mmol) was heated to 63 °C and stirred for 1 0 hours until complete disappearance of starting material by LCMS analysis The reaction mixture was then diluted with ethyl acetate (300 mL) and brine washed (3 X 200 mL) The resulting organic extracts were $Na_2SO_4$ dried, filtered, and concentrated in vacuo to a residue that was then subjected to $SiO_2$ chromatography with ethyl acetate/hexanes (3 7) to furnish a brown solid (60 0 mg, 81 %) $^1H$ NMR (400 MHz, $CDCl_3$) δ 7 43-7 22 (m, 6H), 7 04 (app t, J = 8 4 Hz, 2H), 5 02 (br t, J = 1 6 Hz, 1H), 4 86 (d, J = 5 5 Hz, 2H), 2 37 (s, 3H), LC/MS C-18 column, $t_r$ = 3 02 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 531 (M+H) ES-HRMS m/z 530 9344 (M+H calcd for $C_{19}H_{15}BrF_2IN_2O$ requires 530 9375)

Example 570

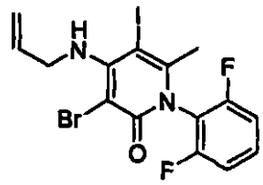


3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-methyl-5-[(E)-2-phenylethenyl]pyridin-2(1H)-one

Step 1 To an anhydrous -78 °C solution of β-bromostyrene (1 80 g, 10 0 mmol) in ether (18 mL) was added sequentially a solution of zinc chloride (10 0 mL, 1 0 M ether, 10 0 mmol) over 1 0 minute and a solution of tert-butyl lithium (15 0 mL, 1 6 M pentanes, 24 0 mmol) over 8 0 minutes The resulting solution became cloudy and the reaction mixture was allowed to warm to room temperature on its own accord (over 30 minutes) After an additional 1 0 hour, the suspension was transferred by syringe directly to a separate vessel containing a solution of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-5-iodo-6-methylpyridin-2(1H)-one (1 50 g, 2 64 mmol) and tetrakis(tripheylphosphine)palladium (294 mg, 0 254 mmol) in anhydrous THF (4 mL) This resulting suspension was heated to 55 °C for 40 minutes and cooled to room temperature, whereby it was stirred under a positive pressure of argon for an additional 4 0 hours until complete disappearance of starting material by LCMS analysis The reaction suspension was subsequently treated with $NaHCO_3$ and brine (100 and 200 mL, respectively) The resulting emulsion was extracted with ethyl acetate (3 X 300 mL) and the organic extracts were $Na_2SO_4$ dried, filtered, and concentrated in vacuo to a residue that was then subjected to $SiO_2$ chromatography with ethyl

acetate/hexanes (3 7) to furnish a reddish solid (1 25 g, 86 %) $^1$H NMR (400 MHz, $CDCl_3$) δ 7 51-7 39 (m, 2H), 7 38-7 24 (m, 5H), 7 10 (app t, J = 8 5 Hz, 2H), 6 84 (d, J = 17 2 Hz, 1H), 6 82-6 75 (m, 1H), 6 74-6 68 (m, 1H), 6 69 (d, J = 17 2, 1H), 5 11 (br s, 2H), 2 15 (s, 3H), LC/MS C-18 column, $t_r$ = 3 74 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 544 (M+H) ES-HRMS m/z 544 0565 (M+H calcd for $C_{27}H_{19}BrF_4NO_2$ requires 544 0530)

Example 574



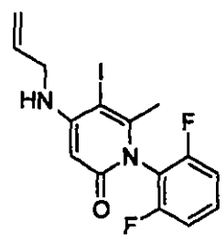
4-(allylamino)-3-bromo-1-(2,6-difluorophenyl)-5-iodo-6-methylpyridin-2(1H)-one

Step 1 A slurry of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-5-iodo-6-methylpyridin-2(1H)-one (1 40 g, 2 46 mmol) and allyl amine (1 98 mg, 34 6 mmol) was heated to 50 °C and stirred for 1 0 hours until complete disappearance of starting material by LCMS analysis The reaction mixture was then concentrated in vacuo (1 0 mm Hg) for 2 days at 50 °C to furnish a brown solid (1 18 g, 99 %) $^1$H NMR (300 MHz, $CDCl_3$) δ 7 43 (app tt, J = 8 4, 6 2, 1H), 7 09 (app t, J = 8 4 Hz, 2H), 6 02 (app dq, J = 11 0, 6 2 Hz, 1H), 5 39 (dd, J = 16 9, 1 8 Hz, 1H), 5 30 (dd, J = 11 0, 1 8 Hz, 1H), 4 84 (br s, 1H), 4 35 (br s, 2H), 2 42 (s, 3H), LC/MS C-18 column, $t_r$ =

371
374

2 71 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 481 (M+H) ES-HRMS m/z 480 9261 (M+H calcd for $C_{15}H_{13}BrF_2IN_2O$ requires 480 9219)

Example 575



4-(allylamino)-1-(2,6-difluorophenyl)-5-iodo-6-methylpyridin-2(1H)-one

Step 1 A solution of 4-(allylamino)-3-bromo-1-(2,6-difluorophenyl)-5-iodo-6-methylpyridin-2(1H)-one (1 00 g, 2 07 mmol) and tetrakis(tr_pheylphosphine)palladium (420 mg, 0 363 mmol) in anhydrous THF (10 mL) under an argon stream was heated to 64 °C and stirred for 12 hours until complete disappearance of starting material by LCMS analysis The reaction suspension was subsequently treated with brine (600 mL) The resulting emulsion was extracted with ethyl acetate (3 X 400 mL) and the organic extracts were anhy $Na_2SO_4$ dried, filtered, and concentrated in vacuo to a residue that was then subjected to $SiO_2$ chromatography with ethyl acetate/hexanes (gradient 3 7) to furnish a solid (376 mg, 45 %) $^1H$ NMR (400 MHz, $d_4$-MeOH) δ 7 55 (app tt, J = 8 7, 6 3, 1H), 7 18 (app t, J = 7 6 Hz, 2H), 5 89 (app dcd, J = 15 4, 10 3, 5 1 Hz, 1H), 5 01 (app d, J = 17 0, Hz, 1H), 5 50 (s, 1H), 5 22 (app d, J = 11 0 Hz, 1H), 4 35 (app d, J = 5 0 Hz , 2H), 2 36 (s, 3H), LC/MS C-18 column, $t_r$ = 2 33 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection

254 nm, at 50°C) ES-MS m/z 403 (M+H) ES-HRMS m/z 403 0133 (M+H calcd for $C_{15}H_{14}F_2IN_2O$ requires 403 0113)

Example 576

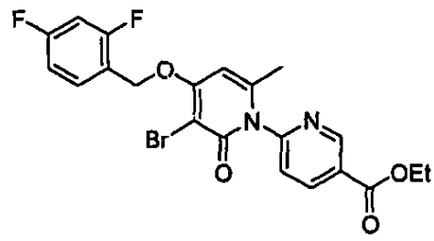


4-(allylamino)-1-(2,6-difluorophenyl)-5-iodo-6-methylpyridin-2(1H)-one

Step 1 A solution of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)- one (197 mg, 0 445 mmol) and allyl amine (1 32 mg, 23 1 mmol) in THF (6 0 mL) was heated to 68 °C and stirred for 74 0 hours The reaction mixture was then concentrated in vacuo (30 mm Hg) to furnish a residue that was subjected to $SiO_2$ chromatography with ethyl acetate/hexanes (3 7) to furnish a solid (36 0 mg, 23 %) $^1H$ NMR (400 MHz, $d_4$-MeOH) δ 7 55 (app tt, J = 8 5, 6 5, 1H), 7 18 (app t, J = 8 5 Hz, 2H), 6 14 (s, 1H), 5 91 (app dq, J = 11 5, 6 4 Hz, 1H), 5 23 (dd, J = 17 0, 1 5 Hz, 1H), 5 19 (dd, J = 11 0, 1 6 Hz, 1H), 4 00 (app d, J = 4 7 Hz , 2H), 1 98 (s, 3H), LC/MS C-18 column, $t_r$ = 2 24 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 355 (M+H) ES-HRMS m/z 355 0257 (M+H calcd for $C_{15}H_{14}F_2BrF_2N_2O$ requires 355 0252)

Example 577

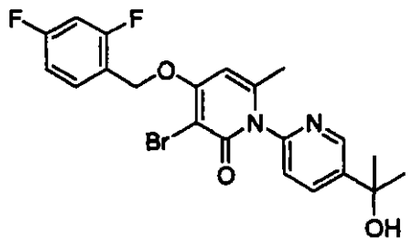
372
375



ethyl 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxo-2H-1,2'-bipyridine-5'-carboxylate

Step 1 To a room temperature suspension of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (500 0 mg, 1 51 mmol) and $Cs_2CO_3$ (1 50 g, 4 60mmol) in 1-methyl-2-pyrrolidinone (3 0 mL) was added ethyl 6-chloronicotinate (900 mg, 4 85 mmol) The resulting suspension was stirred and heated to 106 °C for 36 hours until complete consumption of starting material by LCMS analysis The reaction mixture was then diluted with ethyl acetate (400 mL), water washed (3 X 200 mL) The resulting organic extract was separated, $Na_2SO_4$ dried, and concentrated The resulting dark residue was subjected to $SiO_2$ chromatography with ethyl acetate/hexanes (3 7) to furnish a solid $^1H$ NMR (400 MHz, $d_4$-MeOH) δ 8 68 (app d, J = 2 5 Hz, 1H), 8 39 (dd, J = 8 7, 2 3 Hz, 1H), 7 62 (app q, J = 8 2 Hz, 1H), 7 15 (d, J = 8 6 Hz, 1H), 7 08 (s, 1H), 7 08-6 99 (m, 2H), 5 31 (s, 2H), 4 37 (q, J = 7 1 Hz, 2H), 2 43 (s, 3H), 1 37 (t, J = 7 1 Hz, 3H), LC/MS C-18 column, $t_r$ = 3 44 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 479 (M+H) ES-HRMS m/z 479 0401 (M+H calcd for $C_{21}H_{18}BrF_2N_2O_4$ requires 479 0431)

Example 578



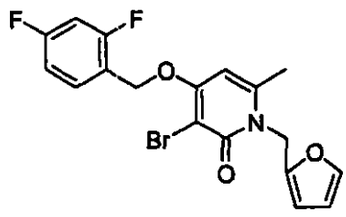
3-bromo-4-[(2,4-difluorobenzyl)oxy]-5'-(1-hydroxy-1-methylethyl)-6-methyl-2H-1,2'-bipyridin-2-one

Step 1 To a 0 °C solution of methyl magnesium bromide (3 0 M, 3 5 mL, 10 5 mmol) was added dropwise over 15 minutes a solution of ethyl 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxo-2H-1,2'-bipyridine-5'-carboxylate (500 0 mg, 1 05 mmol) in THF (4 0 mL) The internal temperature of the reaction was never allowed to exceed 0 °C The resulting solution was maintained for 30 minutes until complete consumption of starting material by LCMS analysis Next, a solution of ammonium chloride (saturated aqueous, 160 mL) was added The reaction mixture was extracted with ethyl acetate (3 X 100 mL) and the resulting organic extracts were separated, $Na_2SO_4$ dried, and concentrated in vacuo to a residue that was subjected to $SiO_2$ chromatography with ethyl acetate/hexanes (gradient 3 7 to 6 4) to furnish a solid (386 mg, 79 %) $^1H$ NMR (400 MHz, $d_4$-MeOH) δ 8 23 (app d, J = 2 8 Hz, 1H), 7 97 (dd, J = 8 6, 2 3 Hz, 1H), 7 61 (app q, J = 8 2 Hz, 1H), 7 06-7 00 (m, 3H), 7 00 (s, 1H), 5 30 (s, 2H), 2 38 (s, 3H), 1 54 (s, 6H), LC/MS C-18 column, $t_r$ = 2 75 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 465 (M+H) ES-HRMS m/z 465 0615 (M+H calcd for $C_{21}H_{20}BrF_2N_2O_3$ requires 465 0620) IR(neat) 3366, 3030, 2974, 1600, 1507, 1362, 1232 $cm^{-1}$ $^{13}C$ NMR (400 MHz, $d_4$-MeOH, visible peaks with carbon fluorine coupling present) δ 164 4, 160 7, 158 9, 157 6, 143 6, 141 6, 137 5,

373
376

131 61, 131 56, 131 51, 131 16, 119 29, 119 25, 119 15, 119 11, 112 23, 111 55, 111 52, 111 33, 111 29, 106 0, 103 9, 103 7, 103 4, 96 8, 70 3, 64 9, 64 8, 30 5, 22 6

Example 579

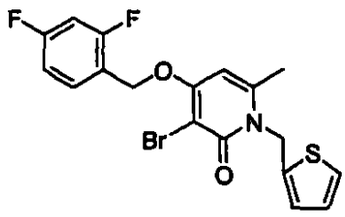


3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2-furylmethyl)-6-methylpyridin-2(1H)-one

Step 1 Preparation of the title compound To a room temperature suspension of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one 330 0 mg, 1 00 mmol)) and NaH (48 0 mg, 2 0 mmol) in THF (3 0 mL) was added 2-(chloromethyl)furan (461 mg, 3 97 mmol) The resulting suspension was stirred and heated to 68 °C for 9 hours until complete consumption of starting material by LCMS analysis The reaction mixture was then diluted with ethyl acetate (400 mL), water washed (3 X 200 mL) The resulting organic extract was separated, $Na_2SO_4$ dried, and concentrated The resulting dark residue was subjected to $SiO_2$ chromatography with ethyl acetate/hexanes (4 6) to furnish a solid $^1H$ NMR (300 MHz, $d_4$-MeOH) δ 7 62 (app q, J = 8 4 Hz, 1H), 7 46 (s, 1H), 7 06 (app t, J = 8 7 Hz, 2H), 6 51 s, 1H), 6 41-6 37 (m, 2H), 5 37 (s, 2H), 5 32 (s, 2H), 2 61 (s, 3H), LC/MS C-18 column, $t_r$ = 2 63 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 410 (M+H)

ES-HRMS m/z 410 0177 (M+H calcd for $C_{18}H_{15}BrF_2NO_3$ requires 410 0198)

Example 580

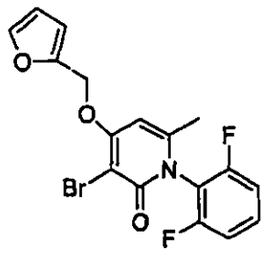


3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(thien-2-ylmethyl)pyridin-2(1H)-one

Step 1 To a room temperature suspension of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (330 0 mg, 1 00 mmol)) and NaH (48 0 mg, 2 0 mmol) in THF (3 0 mL) was added 2-(chloromethyl)thiophene (461 mg, 3 97 mmol) The resulting suspension was stirred and heated to 68 °C for 12 hours until complete consumption of starting material by LCMS analysis The reaction mixture was then diluted with ethyl acetate (400 mL), water washed (3 X 200 mL) The resulting organic extract was separated, $Na_2SO_4$ dried, and concentrated The resulting dark residue was subjected to $SiO_2$ chromatography with ethyl acetate/hexanes (4 6) to furnish a solid $^1H$ NMR (400 MHz, $d_4$-MeOH) δ 7 58 (app q, J = 8 2 Hz, 1H), 7 30 (app dd, J = 5 1, 1 2 Hz, 1H), 7 05 (d, J = 2 6 Hz, 1H), 7 01 (app t, J = 8 1 Hz, 2H), 6 93 (dd, J = 5 1, 3 4 Hz, 1H), 6 43 (s, 1H), 5 49 (s, 2H), 5 25 (s, 2H), 2 51 (s, 3H), LC/MS C-18 column, $t_r$ = 2 74 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 426 (M+H) ES-HRMS m/z 425 9936 (M+H calcd for $C_{18}H_{15}BrF_2NO_2S$ requires 425 9969)

Example 581

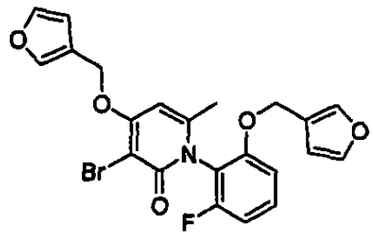
374
377



3-bromo-1-(2,6-difluorophenyl)-4-(2-furylmethoxy)-6-methylpyridin-2(1H)-one

Step 1 To a suspension of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)- one (250 mg, 0 445 mmol) and furfuryl alcohol (198 mg, 2 0 mmol) in THF (2 5 mL) was added solid NaH (46 0 mg, 1 92 mmol) Following the evolution of gas, the resulting suspension laws heated to 60 °C and stirred for 3 5 hours until complete consumption of starting material by LCMS analysis The reaction mixture was then diluted with ammonium chloride (saturated aqueous, 100 mL) and extracted with ethyl acetate (3 X 100 mL) The resulting organic extracts were separated, $Na_2SO_4$ dried, and concentrated to provide a residue that was subjected to $SiO_2$ chromatography with ethyl acetate/hexanes (3 7) to furnish a solid (110 0 mg, 49 %) $^1H$ NMR (400 MHz, $d_4$-MeOH) δ 7 63 (app tt, J = 8 5, 6 2, 1H), 7 62-7 61 (m, 1H), 7 28 (app t, J = 8 5 Hz, 2H), 6 77 (s, 1H), 6 68 (d, J = 4 1 Hz, 1H), 6 51(dd, J = 4 2, 3 9 Hz, 1H), 5 34 (s, 2H), 2 15 (s, 3H), LC/MS C-18 column, $t_r$ = 2 43 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 396 (M+H) ES-HRMS m/z 396 0044 (M+H calcd for $C_{17}H_{13}BrF_2NO_3$ requires 396 0041)

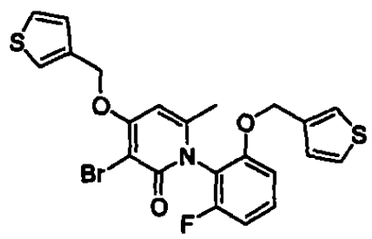
Example 582



3-bromo-1-[2-fluoro-6-(3-furylmethoxy)phenyl]-4-(3-furylmethoxy)-6-methylpyridin-2(1H)-one

By following the method of preparation of 3-bromo-1-(2,6-difluorophenyl)-4-(2-furylmethoxy)-6-methylpyridin-2(1H)-one (Example 581) and substituting 3-furylmethanol for furfuryl alcohol, the title compound was prepared in 55 % chemical yield $^1$H NMR (400 MHz, $d_4$-MeOH) δ 7 64 (s, 1H), 7 55-7 42 (m, 3H), 7 40 (app t, J = 1 4 Hz, 1H), 7 12 (d, J = 9 0 Hz, 1H), 6 92 (app t, J = 8 4 Hz, 1H), 6 58 (s, 2H), 6 34 (br s, 1H), 5 21 (s, 2H), 5 03 (AB-q, J = 14 0 Hz, Δ= 58 0 Hz, 2H), 1 99 (s, 3H), LC/MS C-18 column, $t_r$ = 2 67 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 474 (M+H) ES-HRMS m/z 474 0346 (M+H calcd for $C_{22}H_{18}BrFNO_5$ requires 474 0347)

Example 583

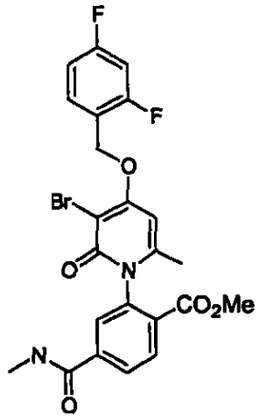


3-bromo-1-[2-fluoro-6-(thien-3-ylmethoxy)phenyl]-6-methyl-4-(thien-3-ylmethoxy)pyridin-2(1H)-one

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378

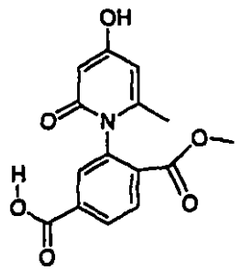
By following the method of preparation of 3-bromo-1-(2,6-difluorophenyl)-4-(2-furylmethoxy)-6-methylpyridin-2(1H)-one Example 581 and substituting thien-3-ylmethanol for furfuryl alcohol, the title compound was prepared in 38 % chemical yield $^1$H NMR (400 MHz, $d_4$-MeOH) δ 7 50-7 42 (m, 3H), 7 33 (dd, J = 5 0, 3 0 Hz, 1H), 7 26 (br d, J = 2 0 Hz, 1H), 7 19 (dd, J = 5 0, 1 2 Hz, 1H), 7 09 (d, J = 8 6 Hz, 1h), 6 98 (dd, J = 14 9, 1 3 Hz, 1H), 6 93 (dt, J = 8 7, 1 0 Hz, 1H), 6 53 (br s, 1H), 5 33 (s, 2H), 5 14 (AB-q, J = 12 1 Hz, Δ= 50 0 Hz, 2H), 1 97 (s, 3H), LC/MS C-18 column, $t_r$ = 2 93 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 506 (M+H) ES-HRMS m/z 505 9881 (M+H calcd for $C_{22}H_{18}BrFNO_3S_2$ requires 505 9890)

Example 584




methyl 2-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-[(methylamino)carbonyl]benzoate

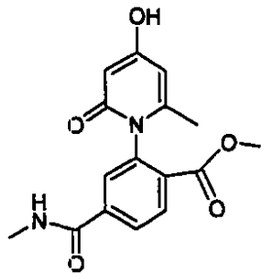
Step 1 Preparation of 3-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)-4-(methoxycarbonyl)benzoic acid



4-Hydroxy-6-methyl-2-pyrone (75 0 g, 595 mmol) and 3-amino-4-(methoxycarbonyl)benzoic acid (40 0 g, 0 205 mmol) were suspended in 56 ml of 1,2-dichlorobenzene in a 500 ml, 3-necked, round bottom flask equipped with a J-Kem temperature controller probe, a Dean-Stark trap, and a heating mantle The reaction was heated to 180 °C over a period of 26 minutes during which time all solids dissolved Upon reaching an internal temperature of 180 °C, the reaction was allowed to maintain this temperature for an additional 25 0 minutes during which time the evolution of water from the reaction mixture was evident Next, the heating apparatus was removed and the reaction was allowed to cool on its own accord to about 100 °C The reaction was then diluted with 160 ml of toluene and stirred After about 10 minutes, the reaction reached room temperature and a gummy solid had formed The precipitate was filtered, washed with EtOAc (400 mL) and water (200 mL, 55 °C), and dried in vacuo to give a tan solid (30 5 g, 49%) $^1$H NMR (400 MHz, $d_4$-MeOH) δ 8 20-8 09 (m, 2H), 7 84 (s, 1H), 6 08 (app d, J = 1 0 Hz, 1H), 5 76 (app d, J = 2 3 Hz, 1H), 3 76 (s, 3H), 1 91 (s, 3H) LC/MS, C-18 column, $t_r$ = 1 96 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50 °C) ES-MS m/z 304 (M+H) ES-HRMS m/z 304 0803 (M+H calcd for $C_{15}H_{14}NO_6$ requires 304 0816)

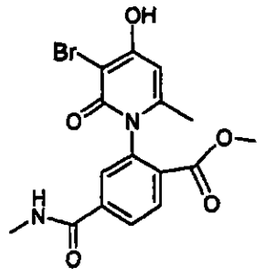
376

Step 2 Preparation of methyl 2-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)-4-[(methylamino)carbonyl]benzoate



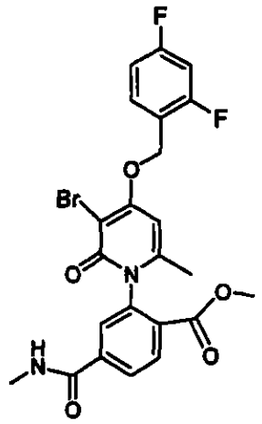
To a solution of 3-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)-4-(methoxycarbonyl)benzoic acid ( from Step 1) (1 00 g, 3 30 mmol) in dimethylformamide (10 mL) and THF (10 mL) was added *cyclohexylcarbodiimide-derivatized silica gel* (a product of Silicycle chemical division Quebec, Canada) with a loading of 0 60 mmol/g (15 2 g, 9 73 mmol) After stirring for 30 minutes, a solution of methylamine (2 0 M, THF, 2 9 mL, 5 8 mmol) was added followed by the addition of 1-hydroxy-benzotriazole (20 0 mg, 0 15 mmol) The reaction suspension was allowed to stir for 24 hours until the complete disappearance of starting material by LCMS analysis The silica suspension was filtered and washed with 300 mL ethyl acetate/methanol (9 1) and 300 mL ethyl acetate/methanol (1 1) The resulting mother liquor was concentrated to furnish a brown semi-solid (898 mg, 86 %) $^1$H NMR (300 MHz, $d_4$-MeOH) δ 8 22 (d, J = 8 0 Hz, 1H), 8 04 (dd, J = 8 3, 1 9 Hz, 1H), 7 73 (d, J = 1 6 Hz, 1H), 6 13 (d, J = 1 5, Hz, 1H), 5 80 (d, J = 2 2 Hz, 1H), 3 80 (s, 3H), 3 03 (s, 3H), 1 97 (s, 3H) LC/MS, C-18 column, $t_r$ = 1 31 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 317 (M+H) ES-HRMS m/z 317 1142 (M+H calcd for $C_{16}H_{17}N_2O_5$ requires 317 1132)

Step 3 Preparation of methyl 2-(3-bromo-4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)-4- [(methylamino)carbonyl]benzoate



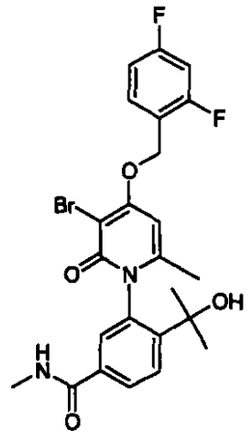
To a room temperature suspension of methyl 2-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)-4-[(methylamino)carbonyl]benzoate ( from Step 2) (406 0 mg, 1 28 mmol) in $CH_2Cl_2$ (8 mL) was added solid N-bromosuccinimide (251 mg, 1 41 mmol) and stirred for 10 minutes until complete consumption of starting material by LCMS analysis The reaction was next diluted with $CH_2Cl_2$ (5 mL), ethyl acetate (5 mL), and hexanes (1 mL) After approximately 30 minutes the resulting white precipitate was filtered and washed with ethyl acetate (5 mL) to furnish a solid (298 mg, 62%) $^1H$ NMR (400 MHz, $d_4$-MeOH) δ 8 20 (d, J = 8 2 Hz, 1H), 8 01 (d, J = 8 1 Hz, 1H), 7 69 (s, 1H), 6 18 (s 1H), 3 75 (s, 3H), 2 91 (s, 3H), 1 91 (s, 3H), LC/MS, $t_r$ = 1 27 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 395 (M+H) ES-HRMS m/z 395 0237 (M+H calcd for $C_{16}H_{16}BrN_2O_5$ requires 395 0237)

Step 4 Preparation of the title compound



To a solution of methyl 2-(3-bromo-4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)-4-[(methylamino)carbonyl]benzoate ( from Step 3) (241 mg, 0 610 mmol) in dimethylformamide (0 5 mL) was added sequentially $K_2CO_3$ (240 mg, 1 73 mmol) and 2,4 difluorobenzyl bromide (0 085 mL, 0 66 mmol) The resulting suspension was stirred for 6 5 hours until complete consumption of starting material by LCMS analysis The reaction was then diluted with ethyl acetate (200 mL) and brine washed (3 X 200 mL) The resulting organic extract was $Na_2SO_4$ dried, filtered, and concentrated in vacuo to approximately 5 mL volume The resulting mother liquor rapidly precipitated and furnished an amorphous solid that was collected $^1$H NMR (400 MHz, $d_4$-MeOH) δ 8 22 (d, J = 8 2 Hz, 1H), 8 03 (dd, J = 8 2, 1 7 Hz, 1H), 7 71 (d, J = 1 8 Hz, 1H), 7 67 (app q, J = 8 3 Hz, 1H), 7 05 (app t, J = 8 6 Hz, 2H), 6 64 (s, 1H), 5 37 (s, 2H), 3 74 (s, 3H), 2 90 (s, 3H), 2 01 (s, 3H) LC/MS C-18 column, $t_r$ = 2 87 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 521 (M+H) ES-HRMS m/z 521 0491 (M+H calcd for $C_{23}H_{20}BrF_2N_2O_5$ requires 521 0518)

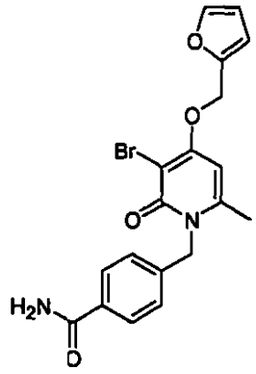
Example 585



3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-(1-hydroxy-1-methylethyl)-N-methylbenzamide

Step 1 To a -10 °C solution of methyl magnesium bromide (3 0 M, 0 60 mL, 1 8 mmol) was added dropwise over 10 minutes a solution of methyl 2-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-[(methylamino)carbonyl]benzoate (85 0 mg, 0 163 mmol) in THF (1 0 mL) The internal temperature of the reaction was never allowed to exceed 0 °C The resulting solution was maintained for 10 minutes Next, a solution of ammonium chloride (saturated aqueous, 100 mL) was added The reaction mixture was removed from the bath and resulting emulsion was extracted with ethyl acetate (3 X 100 mL) and the resulting organic extracts were separated, $Na_2SO_4$ dried, and concentrated in vacuo to a residue that was subjected to $SiO_2$ chromatography with ethyl acetate/hexanes (gradient 3 7 to 6 4) to furnish a solid (16 mg, 19 %) $^1H$ NMR (400 MHz, $d_4$-MeOH) δ 7 89 (d, J = 8 5 Hz, 1H), 7 78 (d, J = 8 4 Hz, 1H), 7 61 (app q, J = 8 2 Hz, 1H), 7 41 (s, 1H), 7 03-6 99 (m, 2H), 6 57 (s, 1H), 5 30 (s, 2H), 2 83 (s, 3H), 2 05 (s, 3H), 1 51 (s, 3H), 1 39 (s, 3H), LC/MS C-18 column, $t_r$ = 2 28 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 521 (M+H) ES-HRMS m/z 521 0860 (M+H calcd for $C_{24}H_{24}BrF_2N_2O_4$ requires 521 0882)

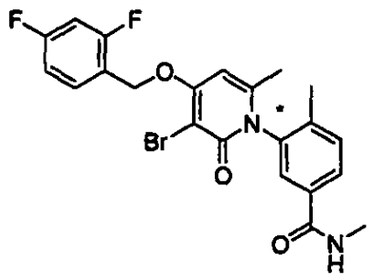
Example 586



3-bromo-1-[2-fluoro-6-(thien-3-ylmethoxy)phenyl]-6-methyl-4-(thien-3-ylmethoxy)pyridin-2(1H)-one

By following the method of preparation of 3-bromo-1-(2,6-difluorophenyl)-4-(2-furylmethoxy)-6-methylpyridin-2(1H)-one Example 581 and substituting 4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzamide for 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)- one , the title compound was prepared in 76 % chemical yield $^1$H NMR (400 MHz, $d_4$-MeOH) δ 7 83 (d, J = 8 1 Hz, 2H), 7 54 (app d, J = 1 1 Hz, 1H), 7 19 (d, J = 8 1 Hz, 2H), 6 57 (d, J = 3 2 Hz, 1H), 6 53 (s, 1H), 6 43 (dd, J = 3 1, 1 8 Hz, 1H), 5 45 (br s, 2H), 5 22 (s, 2H), 2 34 (s, 3H), LC/MS C-18 column, $t_r$ = 1 98 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 417 (M+H) ES-HRMS m/z 417 0469 (M+H calcd for $C_{19}H_{18}BrN_2O_4$ requires 417 0444)

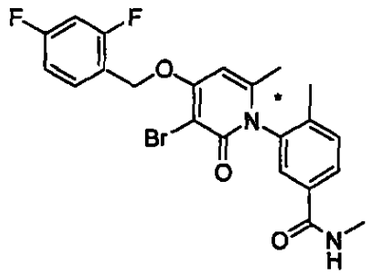
Example 587



(-)-3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-N,4-dimethylbenzamide

Example 489 (1 78 g, 4 36 mmol) were separated using a Chiral Technologies Chiralpak AD column (21 mm x 250 mm, 20 μm) eluting with 100% ethanol (isocratic, 20 ml/min), loading 10 mg per injection Fractions of the early-eluting atropisomer were pooled and concentrated in vacuo to the title compound (718 mg, 80%) Analytical chiral LC (Chiralpak AD, 4 6 mm x 50 mm, 10μm particle size, 0 5 ml/min ethanol) Retention time 1 70 min, ee 94% $[\alpha]_D$ = -23 8° (5 mg/ml DMSO, 22 °C) $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8 42 (br qr, J = 4 51 Hz, 1H), 7 82 (dd, J = 7 92, 1 70 Hz, 1H), 7 68 (dt, J = 8 24, 6 58 Hz, 1H), 7 58 (d, J = 1 59 Hz, 1H), 7 48 (d, J = 7 98 Hz, 1H), 7 34 (dt, J = 9 90, 2 50 Hz, 1H), 7 18 (dt, J = 8 53, 2 57 Hz, 1H), 6 71 (s, 1H), 5 33 (s, 2H), 2 74 (s, 3H), 1 98 (s, 3H), 1 88 (s, 3H) $^{19}$F-NMR (400 MHz, DMSO-$d_6$) δ -109 58 (quintet, J = 7 49 Hz, 1F), -113 65 (quartet, J = 9 11 Hz, 1F) ES-HRMS m/z 477 0612 (M+H calcd for $C_{22}H_{20}BrF_2N_2O_3$ requires 477 0620)

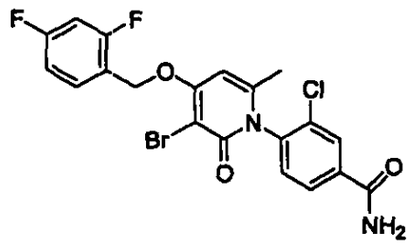
Example 588



(+)-3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-N,4-dimethylbenzamide

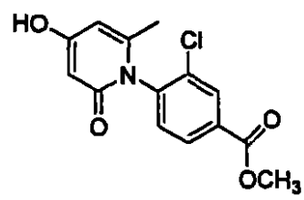
The title compound was prepared as in Example 587 , pooling the late-eluting atropisomer (722 mg, 81%) Analytical chiral LC (Chiralpak AD, 4 6 mm x 50 mm, 10μm particle size, 0 5 ml/min ethanol) Retention time 2 00 min, ee 98% $[\alpha]_D$ = +28 2° (5 mg/ml DMSO, 22 °C) $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8 42 (br qr, J = 4 51 Hz, 1H), 7 82 (dd, J = 7 92, 1 70 Hz, 1H), 7 68 (dt, J = 8 24, 6 58 Hz, 1H), 7 58 (d, J = 1 59 Hz, 1H), 7 48 (d, J = 7 98 Hz, 1H), 7 34 (dt, J = 9 90, 2 50 Hz, 1H), 7 18 (dt, J = 8 53, 2 57 Hz, 1H), 6 71 (s, 1H), 5 33 (s, 2H), 2 74 (s, 3H), 1 98 (s, 3H), 1 88 (s, 3H) $^{19}$F-NMR (400 MHz, DMSO-$d_6$) δ -109 58 (quintet, J = 7 49 Hz, 1F), -113 65 (quartet, J = 9 11 Hz, 1F) ES-HRMS m/z 477 0614 (M+H calcd for $C_{22}H_{20}BrF_2N_2O_3$ requires 477 0620)

Example 589



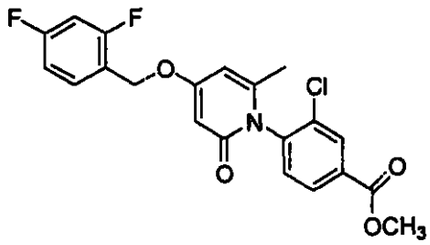
4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-3-chlorobenzamide

Step 1 Preparation of methyl 3-chloro-4-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)benzoate



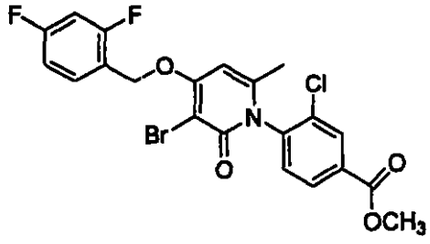

4-Hydroxy-6-methyl-2-pyrone (24 5 g, 193 9 mmol) and methyl-3-amino-2-chlorobenzoate (30 g, 161 6 mmol) were suspended in 75 ml of 1,2-dichlorobenzene in a 250 ml, 3-necked round bottom flask equipped with a J-Kem temperature controller probe, a Dean-Stark trap, and a heating mantle The reaction was heated to 175°C for 20 minutes, during which, water and some 1,2-dichlorobenzene was collected in the Dean-Stark trap The reaction was allowed to cool to about 110°C At this point, 200 ml of toluene was added The toluene mixture was allowed to stir for 72 hours at room temperature A precipitate was collected on a filter pad The precipitate was filtered and washed 3 times with toluene, 3 times with 50°C water to remove excess pyrone, and dried in vacuo to give a tan solid (13 0 g, 27% yield) $^1$H NMR (300 MHz, $CD_3OD$) δ 8 26 (d, J = 1 81 Hz, 1H), 8 14 (dd, J = 8 26, 1 81 Hz, 1H), 7 54 (d, J = 8 26, Hz, 1H), 6 14(dd, J = 2 42, 1 0 Hz, 1H), 5 83 (d, J = 2 42 1H), 4 00 (s, 3H), 1 96 (s, 3H), LC/MS, $t_r$ = 1 81 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 294 (M+H)

Step 2 Preparation of methyl 3-chloro-4-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoate



Methyl 3-chloro-4-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)benzoate ( from Step 1) (2 4g, 8 17 mmol) was taken up in DMF (10 ml) 2,4-difluorobenzylbromide (1 05 ml, 8 17 mmol) and $K_2CO_3$ (1 13 g, 8 17 mmol) were added The reaction stirred for 6 hours at room temperature At this time, the reaction was poured into water (200 ml) and extracted with ethyl acetate The ethyl acetate layer was dried over $Na_2SO_4$, filtered, and the solvent removed in vacuo to give amber oil (2 62 g, 77% crude yield) LC/MS, $t_r$ = 2 79 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 294 (M+H)

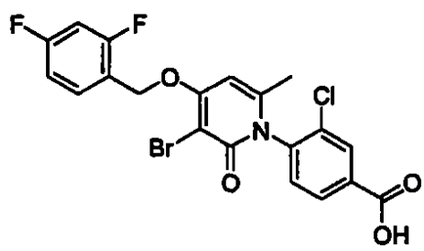
Step 3 Preparation of methyl 4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-3-chlorobenzoate



Methyl 3-chloro-4-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoate ( from step 2) (2 60g, 6 21 mmol) was taken up in $CH_2Cl_2$ (20 ml) N-bromosuccinimide (1 11g, 6 21 mmol) was added and the mixture stirred at room temperature for 4 hours The $CH_2Cl_2$ is removed in vacuo and

the residue is taken up in $CH_3CN$ The resulting precipitate is collected on a filter pad and washed with $CH_3CN$ to yield a white solid (0 75 g, 24%) $^1H$ NMR (300 MHz, $CDCl_3$) δ 8 22 (d, J = 1 88 Hz, 1H), 8 06 (dd, J = 8 19, 1 75 Hz, 1H), 7 59 (app q, J = 8 46 Hz, 1H), 7 33 (d, J = 8 19, 1H), 6 96 (dt, J = 8 06, 1 21 Hz, 1H), 6 89 - 6 84 (m, 1H), 6 13 (s, 1H), 5 26 (s, 2H), 3 95 (s, 3H), 1 95 (s, 3H), ES-MS m/z 478 (M+H) ES-HRMS m/z 497 9892 (M+H calcd for $C_{22}H_{16}BrClF_2NO_4$ requires 497 9914)

Step 4 Preparation of 4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-3-chlorobenzoic acid

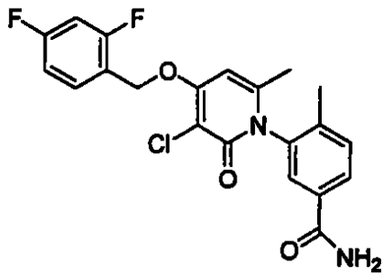



Methyl-4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-3-chlorobenzoate (2 30g, 4 61 mmol) was taken up in THF (20 ml) and $H_2O$ (4 ml) 2 5 N NAOH (9 2 ml) was added to the vessel and the reaction stirred overnight to completion Concentrated HCl was added dropwise until reaction was made acidic (pH = 1) $H_2O$ (100 ml) and THF (100 ml) were added to the mixture The contents were poured into a separatory funnel and the aqueous layer was extracted with ethyl acetate The organic layer was dried over $Na_2SO_4$, the solvent removed in vacuo, and the residue was taken up in a 50% mixture of ethyl acetate/hexane The precipitate was collected on a filter pad to yield a white powder (1 5g, 67%) $^1H$ NMR (300 MHz, DMSO) δ 13 59 (1H), 8 16 (d, J = 1 81 Hz, 1H),

8 06 (dd, J = 6 24, 1 81 Hz, 1H), 7 73 (app q, J = 8 46, 1H), 7 68 (d, J = 8 26 Hz, 1H), 7 38 (dt, J = 9 48, 2 62 Hz, 1H) 7 26 - 7 18 (m, 1H), 6 80 (s, 1H), 5 39 (s, 2H), 3 93 (s, 3H), 1 96 (s, 3H), ES-MS m/z 483 (M+H) ES-HRMS m/z 483 9749 (M+H calcd for $C_{20}H_{14}BrClF_2NO_4$ requires 483 9757)

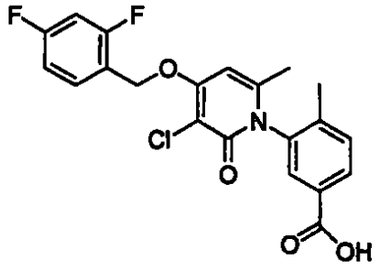
Step 5 4-[3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-3-chlorobenzoic acid (0 5 g, 1 03 mmol) was taken up in THF (10 ml) 2-Chloro-4,6-dimethoxy-1,3,5-triazine (0 22 g, 1 24 mmol) and N-methyl morpholine (0 34 ml, 3 09 mmol) were added The mixture stirred at room temperature for 1 hour At this time, $NH_4OH$ (2 5 ml) was added and the reaction stirred at room temperature for one more hour To the reaction mixture was added more THF (50 ml) and water (200 ml) The mixture was extracted with ethyl acetate The ethyl acetate extraction was washed with saturated brine solution The brine layer was extracted with ethyl acetate The organic layers were combined, dried over $Na_2SO_4$, filtered and the solvent was removed in vacuo The residue was taken up in ethyl acetate and the resulting precipitate was collected on a filter pad to yield a white powder (0 38 g, 76%) $^1H$ NMR (300 MHz, $CD_3OD$) δ 8 18 (d, J = 1 81 Hz, 1H), 8 02 (dd, J = 8 26, 2 01 Hz, 1H), 7 69 (app q, J = 8 26 Hz, 1H), 7 55 (d, J = 8 06 Hz, 1 H) 7 12 - 7 06 (m, 2H), 6 71 (s, 1H), 5 40 (s, 2H), 2 07 (s, 3H) ES-MS m/z 482 (M+H) ES-HRMS m/z 482 9919 (M+H calcd for $C_{20}H_{15}BrClF_2N_2O_3$ requires 482 9917)

Example 590



3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(H)-yl]-4-methylbenzamide

Step1 Preparation of 3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoic acid



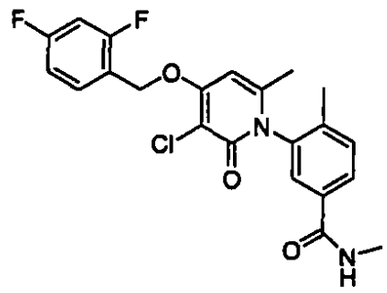
3-[4-[(2,4-Difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoic acid ( from above) (7 5g,19 4 mmol) and NCS (2 6 g, 19 4 mmol) were taken up in 65°C dichloroethane (100 ml) A catalytic amount of dichloroacetic acid (2 drops) was added After two hours the solvent was removed in vacuo and the residue was taken up in diethyl ether The precipitate was collected on a filter pad and then taken up in 50% ethyl acetate/hexanes to remove residual succinimide The precipitate was collected on a filter pad and then dried in vacuo to produce a white powder (4 2 g, 52%) $^1$H NMR (300 MHz, $CD_3OD$) δ 8 10 (dd, J = 7 85, 1 81 Hz, 1H), 7 83 (d, J = 8 26, 1 81 Hz, 1H), 7 40 (app q, J = 8 26 Hz, 1H), 7 58 (d, J = 7 85 Hz, 1H), 7 13 - 7 06 (m, 2H), 6 74 (s, 1H), 5 40 (s, 2H), 2 14

385
382

(s, 3H), 2 04 (s, 3H), ES-MS m/z 420 (M+H) ES-HRMS m/z 420 0786 (M+H calcd for $C_{21}H_{17}ClF_2NO_4$ requires 420 0809)

Step 2 3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoic acid ( 1 5g, 3 57 mmol) was taken up in THF (30 ml) 2-Chloro-4,6-dimethoxy-1,3,5-triazine (0 75 g, 4 28 mmol) and N-methyl morpholine (1 18 ml, 10 72 mmol) were added The mixture stirred at room temperature for 1 hour At this time, $NH_4OH$ (7 5 ml) was added and the reaction stirred at room temperature for one more hour To the reaction mixture was added more THF (100 ml) and water (150 ml) The mixture was extracted with ethyl acetate The ethyl acetate extraction was washed with saturated brine solution The brine layer was extracted with ethyl acetate The organic layers were combined, dried over $Na_2SO_4$, filtered and the solvent was removed in vacuo The residue was taken up in ethyl acetate and the resulting precipitate was collected on a filter pad to yield a white powder (1 32 g, 88%) $^1H$ NMR (300 MHz, $CD_3OD$) δ 7 96 (dd, J = 7 85, 1 81 Hz, 1H), 7 71 (d, J = 1 81 Hz, 1H), 7 67 (app q, J = 8 06 Hz, 1H), 7 56 (d, J = 8 06 Hz, 1H), 7 12 - 7 06 (m, 2H), 6 74 (s, 1H), 5 40 (s, 2H), 2 13 (s, 3H) 2 05 (s, 3H) ES-MS m/z 419 (M+H) ES-HRMS m/z 419 0979 (M+H calcd for $C_{21}H_{18}ClF_2N_2O_3$ requires 419 0969)

Example 591

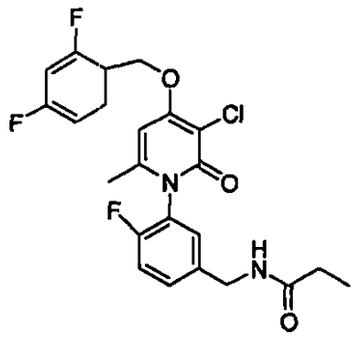


3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-N,4-dimethylbenzamide

The title compound was prepared from 3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoic acid ( from step 1 above) (1 5 g, 3 57 mmol) in dichloromethane (35 ml) To this mixture, 2 0 M methyl amine in THF (3 6 ml, 7 14 mmol) was added, followed, in order, by EDCI (0 67 g, 4 28 mmol), 1-hydroxybenzotriazole (0 58 g, 4 28 mmol) and tr chylamine (0 99 ml, 7 14 mmol) The reaction was stirred at room temperature overnight The reaction was quenched with $NH_4Cl$ and extracted 3 times with ethyl acetate The combined organic layer was then washed with saturated $NaHCO_3$ (aq ) and extracted 3 times with ethyl acetate The organic layers were combined and washed with $H_2O$ and extracted 3 times with ethyl acetate The organic layers were combined and dried over $Na_2SO_4$ and evaporated The resulting residue was triturated with diethyl ether/hexane to obtain a solid, which was dried in vacuo to give a white solid (1 5g, 72%) $^1H$ NMR (300 MHz, $CD_3OD$) δ 7 90 (dd, J = 8 06, 1 81 Hz, 1H), 7 67 (app q, J = 6 44 Hz, 1H), 7 55 (d, J = 8 06 Hz, 1H), 7 13 - 7 06 (m, 2H), 6 74 (s, 1H), 5 40 (s, 2H), 2 93 (s, 3H), 2 13 (s, 3H), 2 04 (s, 3H) ES-MS m/z 433 (M+H) ES-HRMS m/z 433 1153 (M+H calcd for $C_{22}H_{20}ClF_2N_2O_3$ requires 433 1125)

386
383

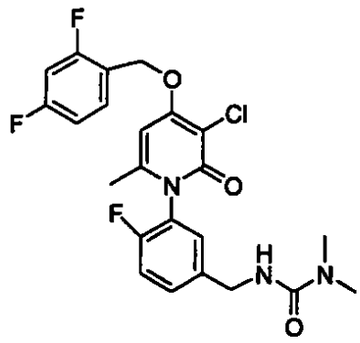
Example 592



N-{3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorobenzyl}propanamide

A 10 mL round bottomed flask equipped with stirbar and nitrogen inlet was charged with 1-[5-(aminomethyl)-2-fluorophenyl]-3-chloro-4-[(2,4 difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one hydrochloride (250 mg, 0 56 mmol), propionyl chloride (49 µL, 0 56 mmol), triethylamine (195 µL, 1 4 mmol) and tetrahydrofuran (4 0 mL) After stirring at 25° C for 5 min the reaction was completed by LC-MS The reaction mixture was poured into a saturated aqueous $NH_4Cl$ solution The aqueous mixture was extracted with ethyl acetate The organic phase was dried with $Na_2SO_4$ and concentrated in vacuo to obtain (240 mg, 91%) as a yellow solid $^1H$ NMR (400 MHz, $(CD_3)_2SO$) δ 8 3 (t, J = 5 8 Hz, 1H), 7 6 (q, J = 8 7 and 6 58 Hz, 1H), 7 38 (d, J = 7 78 Hz, 1H), 7 3 (dd, J = 2 6 and 7 6 Hz, 1H), 7 22 (d, J = 7 51 Hz, 1H), 7 12 (td, J = 2 0 and 6 5 Hz, 1H), 6 65 (s, 1H), 5 3 (s, 2H), 4 23 (d, J = 3 6 Hz, 2H), 2 1 (q, J = 7 7 Hz 2H), 1 98 (s, 3H), 0 98 (t, J = 7 5 Hz, 3H) ppm ES-HRMS m/z 465 1203 (M+H calcd for $C_{23}H_{21}ClF_3N_2O_3$ requires 465 1187)

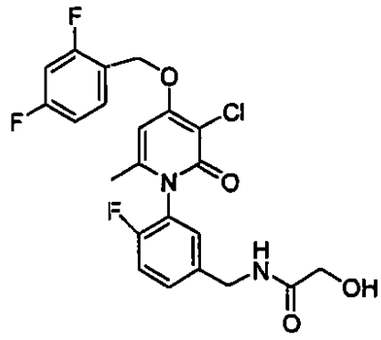
Example 593



N-{3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorobenzyl} dimethylurea

A 10 mL round bottomed flask equipped with stirbar and nitrogen inlet was charged with 1-[5-(aminomethyl)-2-fluorophenyl]-3-chloro-4-[(2,4 difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one hydrochloride (250 mg, 0 56 mmol), dimethylcarbamyl chloride (52 µL, 0 56 mmol), triethylamine (195 µL, 1 4 mmol) and tetrahydrofuran (4 0 mL) After stirring at 25° C for 5 min the reaction was completed by LC-MS The reaction mixture was poured into a saturated aqueous $NH_4Cl$ solution The aqueous mixture was extracted with ethyl acetate The organic phase was dried with $Na_2SO_4$ and concentrated in vacuo to obtain the desired product (245 mg, 86%) as a white solid $^1H$ NMR (400 MHz, ($CD_3OD$) δ 7 61 (q, J = 7 9 and 6 7 Hz, 1H), 7 4(m, 1H), 7 3 (d, J = 9 3 Hz, 1H), 7 21 (m, 1H), 7 1 (m, 2H), 6 65 (s, 1H), 5 35 (s, 2H), 4 38 (s, 2H), 2 9 (s, 6H), 2 1 (s, 3H) ppm ES-HRMS m/z 480 1269 (M+H calcd for $C_{23}H_{22}ClF_3N_3O_3$ requires 480 1296)

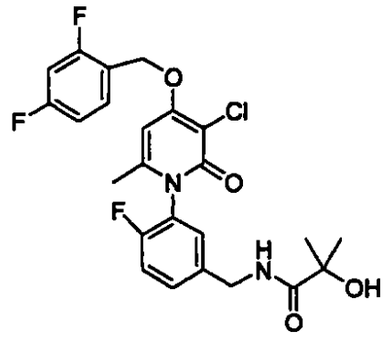
Example 594



N-{3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorobenzyl}-2-hydroxyacetamide

A 10 mL round bottomec flask equipped with stirbar and nitrogen inlet was charged with 1-[5-(aminomethyl)-2-fluorophenyl]-3-chloro-4-[(2,4 difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one hydrochloride (250 mg, 0 56 mmol), acetoxyacetyl chloride (66 µL, 0 62 mmol), triethylamine (195 µL, 1 4 mmol) and tetrahydrofuran (4 0 mL) After stirring at 25° C for 5 min the reaction was completed by LC-MS NaOH (2 5M, 2 24 mmol, 1 0 mL) and MeOH (2 0mL) was added and stirred for 10 min to give the title compound The reaction mixture was acidified with concentrated HCl and extracted with ethyl The organic phase was dried with $Na_2SO_4$ and concentrated in vacuo to obtain (217 mg, 78%) of the desired product as a yellow solid $^1H$ NMR (400 MHz, ($CD_3OD$) δ 7 6 (q, J = 7 6 and 6 9 Hz, 1H), 7 44 (m, 1H), 7 34 (m, 2H), 7 22 (m, 2H), 6 63 (s, 1H), 5 35 (s, 2H), 4 41 (s, 2H), 4 0 (s, 2H), 2 05 (s, 3H) ppm ES-HRMS m/z 467 0957 (M+H calcd for $C_{22}H_{19}ClF_3N_2O_4$ requires 467 0980)

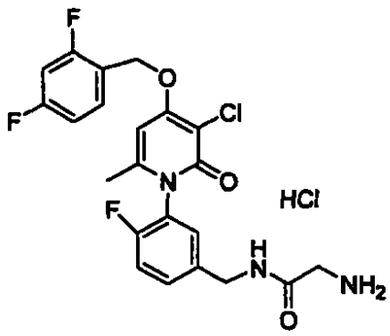
Example 595



N-{3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorobenzyl}-2-hydroxy-2-methylpropanamide

The title compound was prepared essentially as described in Example 594, with 1-chlorocarbonyl-1-methylethyl acetate substituting acetoxyacetyl chloride $^1$H NMR (400 MHz, ($CDCl_3$) δ 9 9 (q, J = 8 2 and 6 5 Hz, 1H), 9 7 (t, J = 2 6 Hz, 1H), 9 5 (t, J = 8 9 Hz, 2H), 9 3 (m, 1H), 9 2 (m, 1H), 8 6 (s, 1H) 7 6 (s, 2H), 6 8 (d, J = 15 Hz, 1H), 6 63 (d, J = 15 Hz, 1H), 4 42 (d, J = 3 2 Hz, 6H), 3 99 (s, 3H) ppm ES-HRMS m/z 495 1271 (M+H calcd for $C_{24}H_{23}ClF_3N_2O_4$ requires 495 1293)

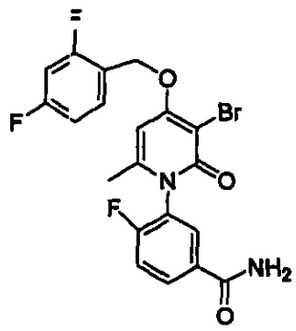
Example 596



$N^1$-{3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorobenzyl}glycinamide hydrochloride

A 25 mL round bottomed flask equipped with stirbar and nitrogen inlet was charged with boc-glycine (105 mg, 0 6 mmol) and 8 mL of DMF The mixture was cooled to 0° C and isboutylchloroformate (77 5 µL, 0 6 mmol) was added and stirred for 20 min 1-[5-(aminomethyl)-2-fluorophenyl]-3-chloro-4-[(2,4 difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one hydrochloride (250 mg, 0 6 mmol) was added and stirred for 3h After completion of the reaction by LC-MS, concentrated HCl (2 mL) and 2 mL of methanol was added to remove the boc group The reaction was stirred for 24 h, neutralized with 2M NaOH and extracted with ethyl acetate The organic phase was dried with $Na_2SO_4$ and concentratec in vacuo to obtain (196 mg, 66%) of the desired product as a the HCl salt $^1$H NMR (400 MHz, ($CD_3OD$) δ 7 6 (q, J = 8 and 6 5 Hz, 1H), 7 5 (m, 1H), 7 3 (m, 2H), 7 0 (m, 2H), 6 63 (s, 1H), 5 35 (s, 2H), 4 4 (q, J = 15 and 13 6 Hz, 2H), 3 7 (s, 2H), 2 05 (s, 3H) ppm ES-HRMS m/z 466 1157 (M+H calcd for $C_{22}H_{20}ClF_3N_3O_3$ requires 466 1140)

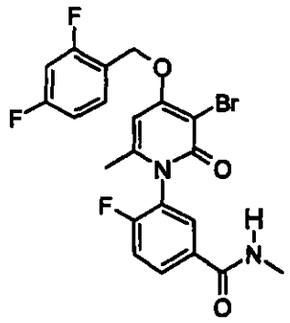
Example 597




3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorobenzamide

A 250 mL round bottomed flask equipped with stirbar and nitrogen inlet was charged with 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorobenzoic acid (3 65g, 7 8 mmol), 4-methylmorpholine (2 6 mL, 23 4 mmol), 2-chloro-4,6-dimethoxy-1,3,5-triazine (1 64g, 9 36 mmol) and tetrahydrofuran (40 mL) After stirring the mixture for 30 min at 25° C, $NH_4OH$ (20 0 mL) was added The mixture was stirred for 30 min and diluted with water The product precipitated from solution The precipitated was filtered and washed with water and diethyl ether to give the title compound (2 37g, 65%) as a white solid $^1H$ NMR (400 MHz, $(CD_3)_2SO$) δ 7 9 (d, J = 7 3 Hz, 1H), 7 61 (q, J = 8 6 and 6 7 Hz, 1H), 7 5 (m, 2H), 7 3 (t, J = 9 6 Hz, 1H), 7 15 (t, J = 8 7 Hz, 1H), 6 7 (s, 1H), 5 36 (s, 2H), 2 (s, 3H) ppm ES-HRMS m/z 469 0172 (M+H calcd for $C_{20}H_{15}BrF_3N_2O_3$ requires 469 0195)

Example 598

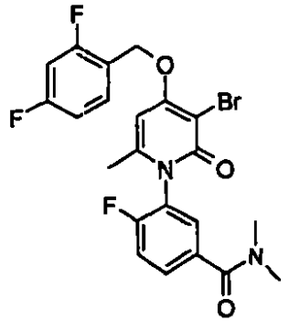


3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluoro-N-methylbenzamide

A solution of 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorobenzoic acid (1 g, 2 1 mmol) in N,N-dimethylformamide (20 mL) was cooled to -10 C Isobutyl chloroformate (0 27 mL, 2 1 mmol) and N-methyl morpholine (0 23 mL, 2 1 mmol) were added to the reaction

vessel After stirring at -10 C for 20 minutes, a solution of N-methyl amine (2 1 mL, 4 2 mmol, 2 M in THF) was added and the reaction mixture was warmed to room temperature as it stirred for 18 hours The reaction mixture was concentrated in vacuo, suspended in water, filtered and washed with water, ethyl acetate and diethyl ether $^{1}$H NMR (400 MHz, $CD_3OD$) δ 8 03 (dddd, J = 3 0, 6 4, 9 2 and 11 6 Hz, 1H), 7 81 (dd, J = 3 0 and ( 2 Hz, 1H), 7 66 (c, J = 10 4 Hz, 1H), 7 47 (t, J = 12 Hz, 1H), 7 06 (t, J = 12 Hz, 2H), 6 67 (s, 1H), 5 38 (s, 2H), 2 91 (s, 3H), 2 10 (s, 3H) ppm $^{19}$ F NMR (400 MHz, $CD_3OD$) δ -111 50 (1F), -115 97 (1 F), -120 16 ppm ES-HRMS m/z 481 0346 (M+H calcd for $C_{21}H_{17}BrF_3N_2O_3$ requires 481 0369)

Example 599

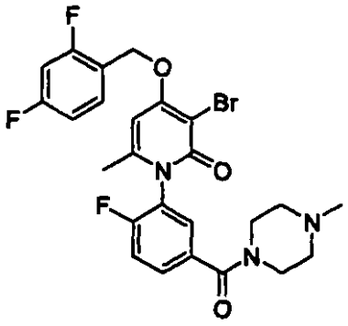


3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluoro-N,N-dimethylbenzamide

A solution of 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorobenzoic acid (1 g, 2 1 mmol) in N,N-dimethylformamide (20 mL) was cooled to -10 C Isobutyl chloroformate (0 27 mL, 2 1 mmol) and N-methyl morpholine (0 23 mL, 2 1 mmol) were added to the reaction vessel After stirring at -10 C for 20 minutes, a solution of N-methyl amine (2 1 mL, 4 2 mmol, 2 M in THF) was added and the reaction mixture was warmed to room temperature as it

stirred for 18 hours The reaction mixture was concentrated in vacuo and partitioned between water and ethyl acetate The organic layer was washed with brine and concentrated in vacuo The solid was chromatographed on silica (95 5 methylene chloride isopropyl alcohol) to give the desired product as a white powder (0 31 g, 30 %) $^1$H NMR (400 MHz, $CD_3OD$) δ 7 64 (m, 1H), 7 50 (dd, J = 2 4 and 7 2 Hz, 1H), 7 45 (t, J = 9 6 Hz, 1H), 7 04 (t, J = 9 2 Hz, 2H), 6 65 (s, 1H), 5 36 (s, 2H), 3 09 (s, 3H), 3 05 (s, 3H), 2 10 (s, 3H) ppm $^{19}$ F NMR (400 MHz, $CD_3OD$) δ -111 51 (1F), -115 88 (1 F), -121 90 (1F) ppm ES-HRMS m/z 495 0508 (M+H calcd for $C_{22}H_{19}BrF_3N_2O_3$ requires 495 0526)

Example 600

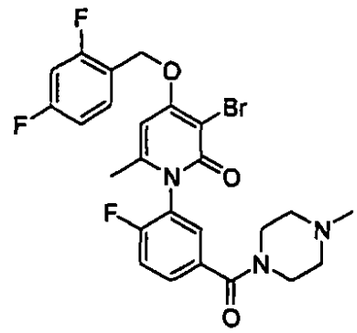


3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-{2-fluoro-5-[(4-methylpiperazin-1-yl)carbonyl]phenyl}-6-methylpyridin-2(1H)-one

Step 1 Preparation of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-{2-fluoro-5-[(4-methylpiperazin-1-yl)carbonyl]phenyl}-6-methylpyridin-2(1H)-one

387

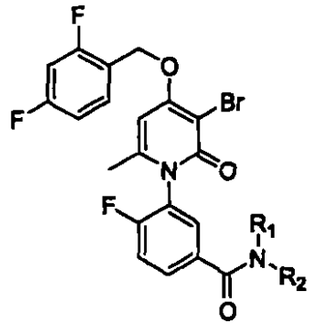
390



To a reaction vessel (borosilicate culture tube) was added 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorobenzoic acid (0 300 g, 0 623 mmol) and 1-hydroxybenzotriazole (0 042 g, 0 45 mmol) N,N-Dimethylformamide (3 mL) was added to the reaction vessel followed by approximately ~ 1 g of the polymer bound carbodiimide resin (1 38 mmol/g) Additional N,N-dimethylformamide (2 mL) was then added to the reaction vessel The parallel reaction apparatus was then orbitally shaken (Labline Benchtop Orbital Shaker) at approximately 200 RPM at room temperature for 15 minutes N-Methyl amine (1 mL, 2 mmol) was then added to the reaction vessel and the reaction apparatus was orbitally shaken at room temperature overnight At this time the reaction was diluted with tetrahydrofuran (20 mL) and treated with approximately 2 0 g of polyamine resin (2 63 mmol/g) and approximately 2 5 g of methylisocyanate functionalized polystyrene (1 5 mmol/g) and the orbital shaking was continued at 200 RPM at room temperature for 3 hours The reaction vessel was then opened and the solution phase product was separated from the insoluble quenched byproducts by filtration and collection into a vial After partially evaporation the insoluble byproducts were rinsed with tetrahydrofuran (2 x 10 mL) The filtrate was evaporated by blowing $N_2$ over the vial and the resulting solid was triturated with diethyl ether to give an off-white solid (0 14g, 41%)

$^1$H NMR (400 MHz, $CD_3OD$) δ 7 63 (m, 1H), 7 51 (dd, J = 2 2 and 7 2 Hz, 1H), 7 45 (t, J = 8 4 Hz, 1H), 7 03 (m, 2H), 6 65 (s, 1H), 5 34 (s, 2H), 3 74 (s, 2H), 3 51 (s, 2H), 2 80 (s, 4H), 2 08 (s, 3H) ppm $^{19}$ F NMR (400 MHz, $CD_3OD$) δ -111 31 (1F), -115 72 (1 F), -121 41 (1 F) ppm ES-HRMS m/z 550 0946 (M+H calcd for $C_{25}H_{24}ClF_3N_3O_3$ requires 550 0948)

Example 601-603

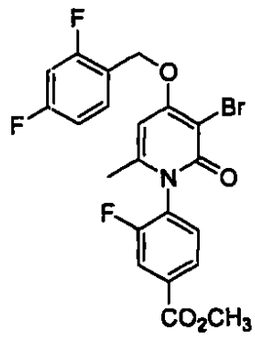


By following the method of Example 600 and replacing N-methylamine with the appropriate amine, the compounds of Examples 601-603 are prepared

| Compound No | $R_1$ | $R_2$ | % Yield | MF | M+H Requires | ESHRMS m/z |
|---|---|---|---|---|---|---|
| Ex 601 | $CH_2CH_2O$- | $CH_2CH_2$- | 98 | $C_{24}H_{21}BrF_3N_2O_4$ | 537 0631 | 537 0620 |
| Ex 602 | $CH_3$ | $CH_2CH_2OH$ | 43 | $C_{23}H_{21}BrF_3N_2O_4$ | 525 0631 | 525 0618 |
| Ex 603 | H | $CH_2C(CH_3)_2OH$ | 65 | $C_{24}H_{23}BrF_3N_2O_4$ | 539 0783 | 539 0788 |

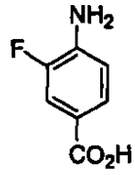
388
391

Example 604



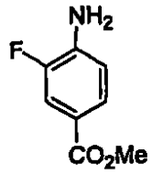
methyl 4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-3-fluorobenzoate

Step 1 Preparation of 4-amino-3-fluorobenzoic acid



3-Fluoro-4-aminobenzoic acid was prepared as described in the literature (Schmelkes, F C , Rubin, M J Am Chem Soc 1944, 66, 1631-2 )

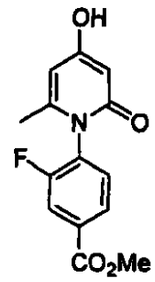
Step 2 Preparation of methyl 4-amino-3-fluorobenzoate



A 250 mL 3-necked round bottomed flask equipped with a nitrogen inlet, stirbar, addition funnel and thermocouple was charged with 4-amino-3-fluorobenzoic acid (11 8 g, 76 mol) and methanol (100 mL) The system was cooled to 0 C and acetyl choride (7 6 mL, 107 mol) was added dropwise The system was warmed to room temperature, the addition funnel was replaced with a reflux condensor, and was heated to reflux for 6 h The reaction mixture was cooled to room temperature, quenched

with saturated aqueous $NaHCO_3$, and extracted with ethyl acetate The organic extract was washed with brine and concentrated in vacuo to give methyl methyl 4-amino-3-fluorobenzoate as an tan solid (8 2 g, 64%) $^1H$ NMR (400 MHz, $CD_3OD$) δ 7 56 (dd, J = 1 6 and 8 0 Hz, 1H), 7 52 (dd, J = 1 9 and 12 Hz, 1H), 6 76 (t, J = 8 4 Hz, 1H), 3 81 (s, 3H) ppm $^{19}F$ NMR (400 MHz, $CD_3OD$) δ -139 05 (1F) ppm ES-HRMS m/z 170 0565 (M+H calcd for $C_8H_9FNO_2$ requires 170 0612)

Step 3 Preparation of methyl 3-fluoro-4-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)benzoate

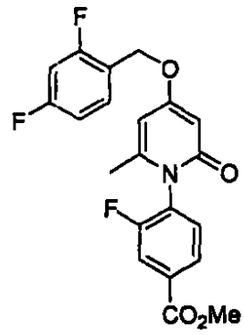



A 250 mL round bottomed flask equipped with stirbar, Dean-Stark trap and reflux condensor was charged with the product of Step 2 (8 g, 47 3 mmol), 4-hydroxy-6-methyl-2-pyrone (12 g, 84 6 mmol), and N-methyl-2-pyrrolidine (8 mL) The system was immersed in a 150 C oil bath for 2 hours and was then cooled to room temperature The reaction mixture was washed with aqueous $K_2CO_3$ (8 5 g, 200 mL water) The aqueous layer was washed with ethyl acetate and then was acidified to pH 4-5 with glacial HOAc This was extracted with ethyl acetate, which was then concentrated in vacuo The viscous oil was triturated with acetonitrile and filtered to the title compound as a tan solid (2 3 g, 17%) $^1H$ NMR (400 MHz, $CD_3OD$) δ 7 98 (dd, J = 1 8 and 8 0 Hz, 1H), 7 91 (dd, J = 1 7 and 10 Hz, 1H), 7 46 (t, J = 8Hz, 1H), 6 09 (dd, J = 0 9 and 2 4 Hz, 1H), 5 77 (d, J = 2 7 Hz, 1H), 3 94 (s, 3H), 1 97 (s, 3H) ppm

389
392

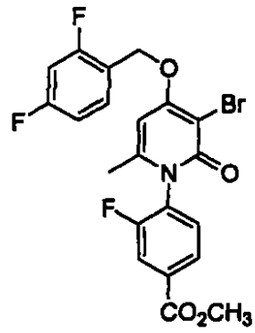
$^{19}$F NMR (400 MHz, $CD_3OD$) δ -123 00 (1F) ppm ES-HRMS m/z 278 0781 (M+H calcd for $C_{14}H_{13}FNO_4$ requires 278 0823)

Step 4 Preparation of methyl 4-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-3-fluorobenzoate




A 100 mL round bottomed flask equipped with stirbar and nitrogen inlet was charged with the product of Step 4 (2 3 g, 8 3 mmol) and N,N-dimethyl formamide (20 mL) 1,8-diazabicyclo[5 4 0]undec-7-ene (1 4 mL, 9 1 mmol) was added followed by 2,4-difluorobenzyl bromide (1 2 mL, 9 1 mmol) The reaction mixture was stirred at 60 C for 3 h, was poured into saturated aqueous $NaHCO_3$ and was extracted with ethyl acetate The organic layer was washed with brine and concentrated in vacuo The solid was triturated with acetonitrile and filtered to give the title compound (2 15 g, 64%) $^1$H NMR (400 MHz, $CD_3OD$) δ 7 99 (dd, J = 1 7 and 8 4 Hz, 1H), 7 93 (dd, J = 1 8 and 10 4 Hz, 1H), 7 55 (m, 1H), 7 48 (t, J = 6 8 Hz, 1H), 7 02 (m, 2H), 6 18 (dd, J = 1 3 and 2 76 Hz, 1H), 6 02 (d, J = 2 7 Hz, 1H), 5 14 (s, 2H), 3 94 (s, 3H), 1 98 (s, 3H) ppm $^{19}$F NMR (400 MHz, $CD_3OD$) δ -111 34 (1F), -115 97 (1 F), -122 98 (1 F) ppm ES-HRMS m/z 404 1133 (M+H calcd for $C_{21}H_{17}F_3NO_4$ requires 404 1104)

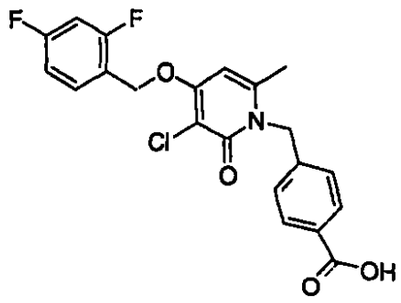
Step 5 Preparation of methyl 4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-3-fluorobenzoate




A 100 mL round bottomed flask equipped with stirbar and nitrogen inlet was charged with the product of Step 4 (2 15 g, 5 3 mmol) and N-methyl-2-pyrrolidine (15 mL) After cooling to 0 C, a solution of N-bromo succinimide (1 03 g, 5 8 mmol) in 10 mL of N-methyl-2-pyrrolidine was added over 15 minutes After 15 additional minutes, the reaction mixture was warmed to room temperature and was stirred for 1 hour The mixture was then poured into saturated aqueous $NaHCO_3$ and extracted with ethyl acetate The organic layer was washed with brine and concentrated in vacuo The residue was triturated with acetonitrile and filtered to give the title compound as a white powder (1 5 g, 59%) $^1H$ NMR (400 MHz, $CD_3OD$) δ 8 00 (dd, J = 2 0 and 8 4 Hz, 1H), 7 95 (dd, J = 1 7 and 10 Hz, 1H), 7 64 (q, J = 8 8 and 14 4 Hz, 1H), 7 51 (t, J = 7 6 Hz, 1H), 7 04 (t, J = 8 4 Hz, 2H), 6 66 (s, 1H), 5 36 (s, 2H), 3 95 (s, 3H), 2 01 (s, 3H) ppm $^{19}F$ NMR (400 MHz, $CD_3OD$) δ -111 50 (1F), -115 97 (1 F), -123 01 (1 F) ppm ES-HRMS m/z 484 0169 (M+H calcd for $C_{21}H_{16}BrF_3NO_4$ requires 484 0192)

390
393

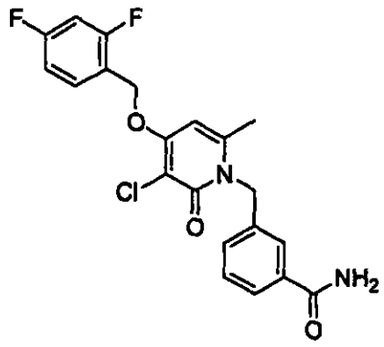
Example 605



4-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzoic acid

Preparation of 4-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzoic acid Methyl-4-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzoate (30 4 g, 70 1 mmol) was suspended in methanol (150 mL) and dioxane (150 mL) 2 5N NaOH (30 8 mL, 77 08 mmol) was added The resulting mixture was heated to 50 °C for 8 0 hours The reaction was partially concentrated and the heterogenous mixture was acidified (pH 2) with 1N HCl The precipitate was collected by filtration washing with $H_2O$ and diethyl ether to afford a white solid (29 2 g, 99 %) $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 7 88 (d, J = 8 3 Hz, 2H), 7 63 (app q, J = 7 9 Hz, 1H), 7 31 (dt, J = 2 4, 9 9 Hz, 1H), 7 18 (app d, J = 8 3 Hz, 2H), 7 17-7 12 (m, 1H), 6 60 (s, 1H), 5 35 (s, 2H), 5 27 (s, 2H), 2 28 (s, 3H) ES-HRMS m/z 420 0821 (M+H calcd for $C_{21}H_{17}ClF_2NO_4$ requires 420 0809)

Example 606

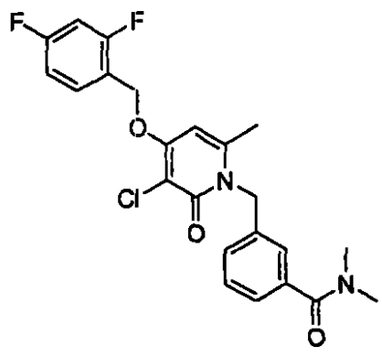


4-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzamide

Preparation of 4-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzamide 4-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzoic acid (12 0 g, 28 58 mmol) was suspended in tetrahydrofuran (100 mL) 2-Chloro-4,6-dimethoxy-1,3,5-triazine (6 02 g, 34 3 mmol) was added followed by 4-methylmorpholine (9 43 mL, 85 74 mmol) The resulting mixture was stirred at room temperature for 1 5 hours at which time $NH_4OH$ (50 0 mL) was added The resulting mixture was stirred at room temperature for 1 hour and then partially concentrated The precipitate was collected by filtration washing with $H_2O$ and diethyl ether to provide an off-white solid (12 11 g, >100 %) $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 7 91 (br s, 1H), 7 80 (d, J = 8 3 Hz, 2H), 7 63 (app q, J = 7 9 Hz, 1H), 7 31 (dt, J = 2 6, 10 5 Hz, 1H), 7 17-7 12 (m, 1H), 7 13 (app d, J = 8 3 Hz, 2H), 6 59 (s, 1H), 5 32 (s, 2H), 5 27 (s, 2H), 2 28 (s, 3H) ES-HRMS m/z 419 0968 (M+H calcd for $C_{21}H_{18}ClF_2N_2O_3$ requires 419 0969)

Example 607

391
394

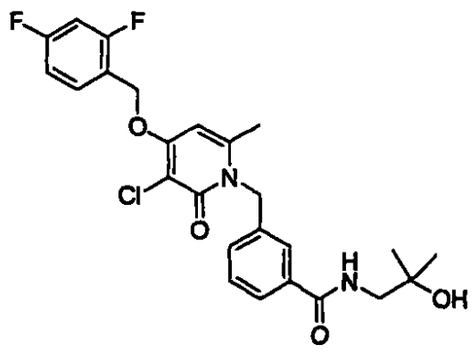


4-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-N,N-dimethylbenzamide

Preparation of 4-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}}-N,N-dimethylbenzamide 4-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzoic acid (2 00 g, 4 76 mmol) was suspended in N,N-dimethylformamide (20 mL) 1-Hydroxybenzotriazole (0 773 g, 5 72 mmol) was added followed by 4-methylmorpholine (1 57mL, 14 28 mmol), dimethylamine (7 14 mL, 2 0 M in tetrahydrofuran, 14 28 mmol) and then 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1 28 g, 6 66 mmol) The resulting mixture was stirred at room temperature for 3 hours at which time the reaction was diluted with $H_2O$ (75 mL) The reaction mixture was then extracted with ethyl acetate The combined organic extracts were washed with saturated $NaHCO_3$, brine, dried over $Na_2SO_4$, filtered and concentrated The resulting solid was washed with ethyl acetate to provide the title compound as a white solid (1 67 g, 78%) $^1H$ NMR (400 MHz, $CDCl_3$) δ 7 53 (app q, J = 7 8 Hz, 1H), 7 33 (d, J = 8 3 Hz, 2H), 7 16 (d, J = 8 3 Hz, 2H), 6 95-6 90 (m, 1H), 6 84 (app dt, J = 2 5, 9 4 Hz, 1H), 6 02 (s, 1H), 5 35 (s, 2H), 5 19 (s, 2H), 2 97-2 93 (br m, 6H),

2 26 (s, 3H) ES-HRMS m/z 447 1246 (M+H calcd for $C_{23}H_{22}ClF_2N_2O_3$ requires 447 1282)

Example 608



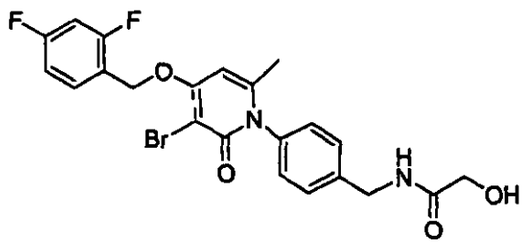
4-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-N-(2-hydroxy-2-methylpropyl)benzamide

Preparation of 4-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-N-(2-hydroxy-2-methylpropyl)benzamide 4-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzoic acid (2 00 g, 4 76 mmol) was suspended in N,N-dimethylformamide (10 mL) 1-Hydroxybenzotriazole (0 772 g, 5 71 mmol) was added followed by 4-methylmorpholine (1 57mL, 14 28 mmol), 1-amino-2-methyl-2-propanol hydrochloride (1 49 g, 11 90 mmol) and then 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1 28 g, 6 66 mmol) The resulting mixture was stirred at room temperature for 2 days at which time the reaction was diluted with $H_2O$ (50 mL) The reaction mixture was then extracted with ethyl acetate The combined organic extracts were washed with saturated $NaHCO_3$, brine, dried over $Na_2SO_4$, filtered and

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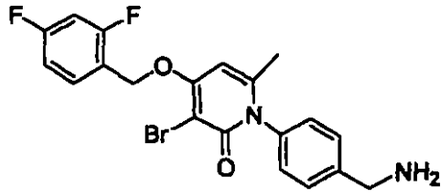
concentrated The resulting solid was washed with diethyl ether to provide the title compound as a tan solid (2 08 g, 89%) $^1$H NMR (400 MHz, $CDCl_3$) δ 7 72 (d, J = 8 2 Hz, 2H), 7 51 (app q, J = 7 7 Hz, 1H), 7 25-7 21 (m, 1H), 7 10 (d, J = 8 2 Hz, 2H), 6 93 (app dt, J = 1 6, 8 3, 9 4 Hz, 1H), 6 87-6 82 (m, 1H), 6 01 (s, 1H), 5 32 (s, 2H), 5 19 (s, 2H), 3 42 (d, J = 5 9 Hz, 2H), 2 26 (s, 3H), 1 23 (s, 6H) ES-HRMS m/z 491 1522 (M+H calcd for $C_{25}H_{26}ClF_2N_3O_4$ requires 491 1544)

Example 609



N-{4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzyl} 2-hydroxyacetamide

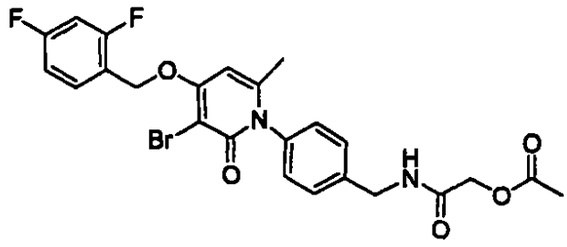
Step 1 Preparation of 1-[4-(aminomethyl)phenyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one



Example 244 (0 250 g, 0 556 mmol) was suspended in tetrahydrofuran (2 0 mL) and cooled in an ice-bath Borane dimethyl sulfide (0 500 mL, 2 0 M in tetrahydrofuran, 1 00 mmol) was added The resulting mixture was heated to reflux overnight and then cooled in an ice-bath The reaction was quenched by the addition of 6 0 N HCl (5 0 mL) then washed

with ethyl acetate The aqueous layer was made alkaline with 2 5 N NaOH and extracted with ethyl acetate The combined organic layers were washed with brine, dried over $Na_2SO_4$, filtered and concentrated to provide an off-white solid (0 180 g, 74 %) $^1H$ NMR (400 MHz, $CDCl_3$) δ 7 58 (app q, J = 7 8 Hz, 1H), 7 44 (app d, J = 8 2 Hz, 2H), 7 10 (d, J = 8 2 Hz, 2H), 6 95 (app dt, J = 1 5, 8 5 Hz, 1H), 6 88-6 83 (m, 1H), 6 06 (s, 1H), 5 24 (s, 2H), 3 93 (s, 2H), 1 96 (s, 3H)

Step 2 Preparation of 2-({4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzyl}amino)-2-oxoethyl

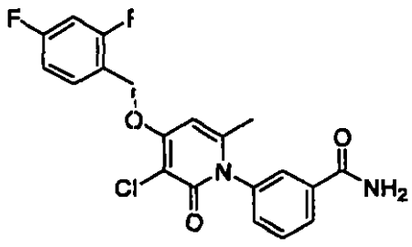


Acetoxyacetic acid (0 037 g, 0 310 mmol) was dissolved in dichloromethane (2 0 mL) 1-hydroxybenzotriazole (0 021 g, 0 155 mmol) was added followed by 3-(1-cyclohexylcarbodiimide)propyl-functionalized silica gel (1 00 g, 0 620 mmol, loading = 0 64 mmol/g) After stirring at room temperature for 15 minutes, 1-[4-(aminomethyl)phenyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (Step 1) (0 180 g, 0 310 mmol) in dichloromethane (2 0 mL) was added The resulting mixture was stirred at room temperature overnight, at which time the reaction mixture wasfiltered and concentrated Chromatography (silica gel, hexanes/ethyl acetate with 10% methanol) provided a white solid (0 130 g, 78%) $^1H$ NMR (400 MHz, $CDCl_3$) δ 7 58 (app q, J = 7 8 Hz, 1H),

7 33 (d, J = 8 3 Hz, 2H), 7 05 (app d, J = 8 3 Hz, 2H), 6 97-6 92 (m, 1H), 6 88-6 83 (m, 1H), 6 08 (s, 1H), 5 24 (s, 2H), 4 58 (s, 2H), 4 44 (d, J = 6 0 Hz, 2H), 2 13 (s, 3H), 1 95 (s, 3H)

Step 3 Preparation of N-{4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzyl}-2-hydroxyacetamide 2-({4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzyl}amino)-2-oxoethyl (Step 2) (0 130 g, 0 243 mmol) was dissolved in methanol (5 mL) and $H_2O$ (1 mL) $K_2CO_3$ (0 055 g, 0 398 mmol) was added and the resulting mixture was stirred at room temperature for 2 hours The mixture was then concentrated and the residue was partitioned between $H_2O$ and ethyl acetate The organic layer was removed and the aqueous layer was further extracted with ethyl acetate The combined organic layer were washed with brine, dried over $Na_2SO_4$, filtered and concentrated to provide an off-white solid (0 100 g, 84%) $^1H$ NMR (400 MHz, $CDCl_3$) δ 7 56 (app q, J = 7 7 Hz, 1H), 7 43 (t, J = 5 8 Hz, 1H), 7 33 (d, J = 8 2 Hz, 2H), 7 04 (app d, J = 8 3 Hz, 2H), 6 98-6 93 (m, 1H), 6 88-6 83 (m, 1H), 6 11 (s, 1H), 5 24 (s, 2H), 4 41 (d, J = 6 0 Hz, 2H), 3 87 (s, 2H), 1 96 (s, 3H) ES-HRMS m/z 493 0575 (M+H calcd for $C_{22}H_{20}BrF_2N_2O_4$ requires 493 0569)

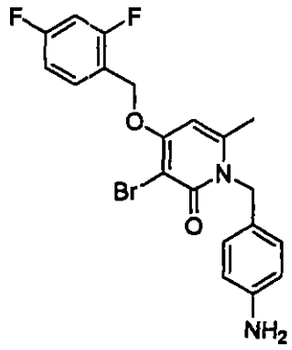
Example 610



3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzamide

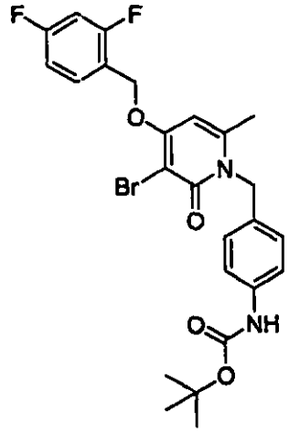
Example 291 (2 00 g, 4 93 mmol) and 2-chloro-4,6-dimethoxy-1,3,5-triazine (1 04 g, 5 91 mmol) were suspended in tetrahydrofuran (20 mL) 4-Methylmorpholine (1 6 mL, 14 79 mmol) was added The resulting mixture was stirred for 1 5 hours at room temperature $NH_4OH$ (10 mL, 148 00 mmol) was added and the reaction was stirred for 0 5 hours at room temperature $H_2O$ (50 mL) and tetrahydrofuran (50 mL) were added and the organic layer was separated The aqueous phase was extracted with ethyl acetate (75 mL) and the combined organics were washed with saturated $Na_2CO_3$ (50 mL), 1N HCl (50 mL), and brine (50 mL) The organic phase was dried over $Na_2SO_4$ and evaporated The resulting solid was washed with diethyl ether to give a white solid (1 96 g, 98%) $^1H$ NMR (400 MHz, DMF-$d_6$) δ 8 24 (br s, 1H), 8 10 (dt, J = 1 21, 7 79 Hz, 1H), 7 90 (t, J = 1 88 Hz, 1H), 7 79 (app dt, J = 6 58, 8 59 Hz, 1H), 7 66 (t, J = 7 79 Hz, 1H), 7 57-7 55 (m, 1H), 7 46 (br s, 1H), 7 33 (ddd, J = 2 55, 9 26, 11 82 Hz, 1H) 7 24-7 19 (m, 1H), 6 78 (s, 1H), 5 44 (s, 2H), 2 04 (s, 3H) ES-HRMS m/z 405 0835 (M+H calcd for $C_{20}H_{16}BrF_2N_2O_3$ requires 405 0812)

Example 611



1-(4-aminobenzyl)-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one

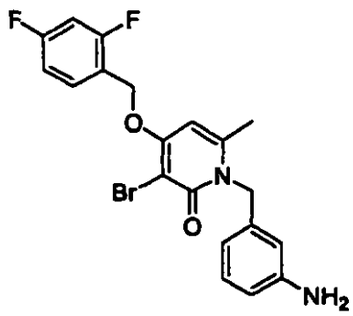
Step 1 Preparation of 1-tert-butyl-4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}phenylcarbamate



4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzoic acid (8 00 g, 17 23 mmol) was suspended in 1 1 acetonitrile t-butanol (172 mL) Diphenylphosphoryl azide (5 69 g, 20 68 mmol) and triethylamine (2 08 g, 20 68 mmol) were added The reaction was heated to reflux for 1 5 hours The reaction mixture was cooled to room temperature, concentrated and subjected to chromatography (on silica, ethyl acetate with 10% methanol/hexanes) to afforc an off-white solid (6 14 g, 66%)

Step 2 1-tert-butyl-4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}phenylcarbamate (Step 1) (6 14 g, 11 47 mmol) was suspended in 4N HCl in dioxane (5 74 mL, 22 94 mmol) The reaction mixture was stirred at room temperature for 1 hour then diluted with diethyl ether The precipitate was collected by filtration and washed with diethyl ether (3 x 30 mL) to afford a tan solid (3 45 g, 69%) $^1$H NMR (400 MHz, DMF-$d_6$) δ 7 64 (app dt, J = 6 58, 8 59 Hz, 1H), 7 31 (ddd, J = 2 55, 9 53, 10 61 Hz, 1H) 7 29-7 12 (m, 5H), 6 56 (s, 1H), 5 28 (s, 2H), 5 27 (s, 2H), 2 28 (s, 3H) ES-HRMS m/z 435 0516 (M+H calcd for $C_{20}H_{18}BrF_2N_2O_2$ requires 435 0514)

Example 612

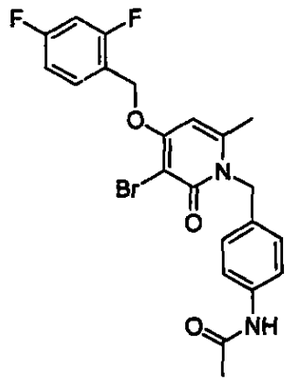


1-(3-aminobenzyl)-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one

By following the method for Example 611 and substituting 3-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzoic acid for 4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzoic acid , the title compound was prepared (2 65 g, 67%) $^1$H NMR (400 MHz, DMF-$d_6$) δ 7 64 (app dt, J = 6 58, 8 59 Hz, 1H), 7 39 (t, J = 7 79 Hz, 1H), 7 32 (ddd, J = 2 55,

9 53, 10 61 Hz, 1H) 7 18-7 08 (m, 3H), 6 96 (s, 1H), 6 58 (s, 1H), 5 30 (s, 2H), 5 27 (s, 2H), 2 29 (s, 3H) ES-HRMS m/z 435 0513 (M+H calcd for $C_{20}H_{18}BrF_2N_2O_2$ requires 435 0514)

Example 613

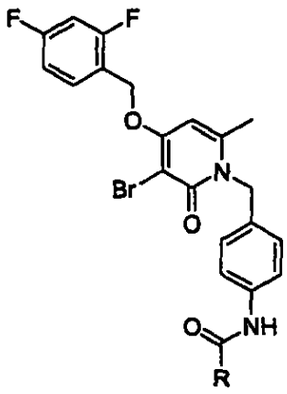


N-(4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}phenyl)acetamide

To a reaction vessel (borosilicate culture tube) was added Example 611 (0 300 g, 0 689 mmol) and dichloromethane (3 0 mL) A stock solution of N-methylmorpholine (0 30 M, 3 0 mL) was added and the parallel reaction apparatus was then orbitally shaken (Labline Benchtop Orbital Shaker) at approximately 200 RPM at room temperature for 10 minutes Acetyl chloride (0 074 mL, 1 033 mmol) was then added to the reaction vessel and the reaction apparatus was orbitally shaken at room temperature for 1 5 hours At this time the reaction was diluted with dichloromethane (15 mL) and treated with approximately 2 1 g of polyamine resin (2 63 mmol/g) and approximately 3 8 g of methylisocyanate functionalized polystyrene (1 10 mmol/g) and the orbital shaking was continued at 200 RPM at room temperature overnight The reaction vessel was then opened and the solution phase products were separated from the insoluble quenched byproducts

by filtration and collection into a vial After partial evaporation the insoluble byproducts were rinsed with dichloromethane (2 x 10 mL) The filtrate was evaporated by blowing $N_2$ over the vial to afford a white solid (0 135 g, 41%) $^1$H NMR (400 MHz, DMF-$d_6$) δ 7 75 (app dt, J = 6 58, 8 59 Hz, 1H), 7 63 (d, J = 8 59 Hz, 1H), 7 30 (ddd, J = 2 55, 9 53, 10 61 Hz, 1H), 7 22-7 14 (m, 3H), 6 60 (s, 1H), 5 37 (s, 4h), 2 40 (s, 3H), 2 06 (s, 3H) ES-HRMS m/z 477 0600 (M+H calcd for $C_{22}H_{21}BrF_2N_2O_3$ requires 477 0620)

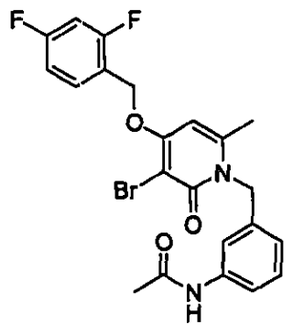
Preparation of Examples 614-616




By following the method for Example 613 and replacing acetyl chloride with the appropriate acid chloride or sulfamoyl chloride, the compounds of Examples 614-616 are prepared The deprotection of the protected intermediate was accomplished with 1M $K_2CO_3$ in methanol to afford the title compound

| Compound No | R | % Yield | MF | M+H Requires | ES-HRMS m/z |
|---|---|---|---|---|---|
| Ex 614 | $CH_2OH$ | 65 | $C_{22}H_{20}BrF_2N_2O_4$ | 493 0569 | 493 0593 |
| Ex 615 | $CH_2OCOCH_3$ | 43 | $C_{24}H_{22}BrF_2N_2O_5$ | 535 0675 | 535 0702 |
| Ex 616 | $SO_2N(CH_3)_2$ | 43 | $C_{22}H_{23}BrF_2N_3O_4S$ | 542.0555 | 542 0572 |

Example 617

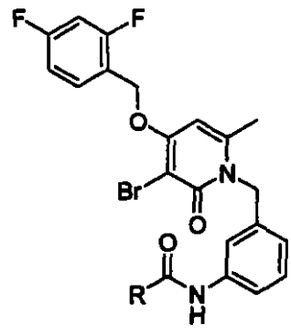


N-(3-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}phenyl)acetamide

To a reaction vessel (borosilicate culture tube) was added Example 612 (0 300 g, 0 689 mmol) and dichloromethane (3 0 mL) A stock solution of N-methylmorpholine (0 30 M, 3 0 mL) was added and the parallel reaction apparatus was then orbitally shaken (Labline Benchtop Orbital Shaker) at approximately 200 RPM at room temperature for 10 minutes Acetyl chloride (0 074 mL, 1 033 mmol) was then added to the reaction vessel and the reaction apparatus was orbitally shaken at room temperature for 1 5 hours At this time the reaction was diluted with dichloromethane (15 mL) and treated with approximately 2 1 g of polyamine resin (2 63 mmol/g) and approximately 3 8 g of methylisocyanate functionalized polystyrene (1 10 mmol/g) and the orbital shaking was continued at 200 RPM at room temperature overnight The reaction vessel was then opened and the solution phase products were separated from the insoluble quenched byproducts by filtration and collection into a vial After partial evaporation the insoluble byproducts were rinsed with dichloromethane (2 x 10 mL) The filtrate was evaporated by

blowing $N_2$ over the vial to afford a white solid (0 167 g, 51%) $^1$H NMR (400 MHz, DMF-$d_6$) δ 7 77 (app dt, J = 6 58, 8 59 Hz, 1H), 7 69 (d, J = 8 32 Hz, 1H), 7 41 (br s, 1H), 7 34-7 17 (m, 3H), 6 88 (d, J = 7 65 Hz, 1H), 6 63 (s, 1H), 5 39 (s, 3H), 5 38 (s, 2H), 2 40 (s, 3H), 2 06 (s, 3H) ES-HRMS m/z 477 0620 (M+H calcd for $C_{22}H_{21}BrF_2N_2O_3$ requires 477 0620)

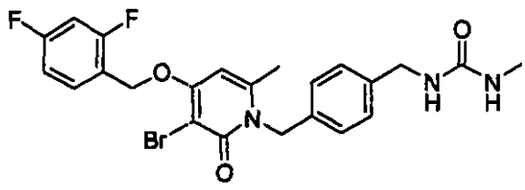
Preparation of Example 618-620



By following the method for Example 617 and replacing acetyl chloride with the appropriate acid chloride or sulfamoyl chloride, the compounds of Examples 618-620 are prepared The deprotection of the protected intermediate was accomplished with 1M $K_2CO_3$ in methanol to afford the title compound

| Compound No | R | % Yield | MF | M+H Requires | ES-HRMS m/z |
|---|---|---|---|---|---|
| Ex 618 | $CH_2OH$ | 72 | $C_{22}H_{20}BrF_2N_2O_4$ | 493 0569 | 493 0604 |
| Ex 619 | $CH_2OCOCH_3$ | 53 | $C_{24}H_{22}BrF_2N_2O_5$ | 535 0675 | 535 0692 |
| Ex 620 | $SO_2N(CH_3)_2$ | 21 | $C_{22}H_{23}BrF_2N_3O_4S$ | 542 0555 | 542 0567 |

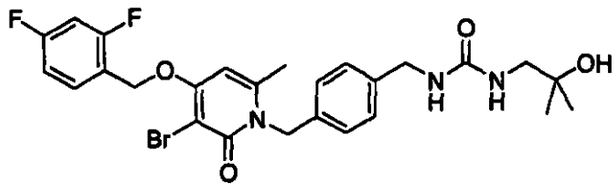
Example 621



N-(4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzyl)-N'-methylurea

Preparation of (4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzyl)-N'-methylurea EXAMPLE 159 (150 mg, 0 33 mmol) was dissolved in N,N-dimethylacetamide (5 mL) and cooled to 0° C 4-Nitrophenyl chloroformate (100 mg, 0 5 mmol) was added, followed by N,N-diisopropylethylamine (0 15 mL, 0 85 mmol) and the reaction was stirred at 0° C for 5 minutes N-Methylamine (0 5 mL, 1 0 mmol, 2M in tetrahydrofuran) was added and the reaction was allowed to reach ambient temperature and stirred for 1 hour The reaction was then diluted with tetrahydrofuran (40 mL) and polyamine resin (1 3 g, 2 81 mmol/g) and methylisocyanate functionalized polystyrene (1 g, 1 38 mmol/g) were added The mixture was shaken for 16 hours at ambient temperature, filtered, and the resulting filtrate concentrated to an oil that was triturated with ether The resulting white solid was collected, washed with ether, and dried (87 mg, 52%) $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 7 61 (app q, J = 8 4 Hz, 1H), 7 24 (d, J = 8 0 Hz, 2H), 7 07 (d, J = 8 0 Hz, 2H), 7 02 (app t, J = 8 4 Hz, 2 H), 6 47 (s, 1H), 5 39 (s, 2H), 5 28 (s, 2H), 4 26 (s, 2H), 2 68 (s, 3H), 2 34 (s, 3H) ES-HRMS m/z 506 0862 (M+H calcd for $C_{23}H_{23}BrF_2N_3O_3$ requires 506 0885)

Example 622

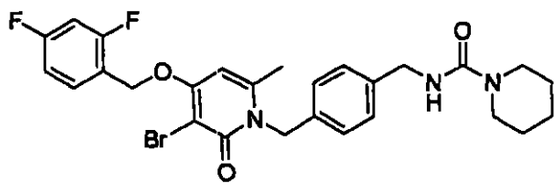


N-(4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzyl)-N'-(2-hydroxy-2-methylpropyl)urea

Preparation of N-(4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzyl)-N'-(2-hydroxy-2-methylpropyl)urea EXAMPLE 159 (300 mg, 0 67 mmol) was dissolved in N,N-dimethylacetamide (5 mL) and cooled to 0° C 4-Nitrophenyl chloroformate (200 mg, 1 0 mmol) was added, followed by N,N-diisopropylethylamine (0 3 mL, 1 7 mmol) and the reaction was stirred at 0° C for 5 minutes 3-Amino-2-methyl-2-propanol (248 mg, 2 0 mmol) was added and the reaction was allowed to reach ambient temperature and stirred for 3 h The reaction was then diluted with tetrahydrofuran (40 mL) and polyamine resin (1 3 g, 2 81 mmol/g) and methylisocyanate functionalized polystyrene (1 g, 1 38 mmol/g) were added The mixture was shaken for 16 hours at ambient temperature, filtered, and the resulting filtrate concentrated to an oil that was triturated with ether The resulting white solid was purified by chromatography (silica gel, hexane/ethyl acetate/methanol) followed by reversed phase chromatography ($C_{18}$, 0 1% aqueous trifluoroacetic acid/acetonitrile) to yield an off-white solid (43 mg, 11%) $^1$H NMR (400 MHz, $CDCl_3$) δ 7 56 (app q, J = 8 0 Hz, 1H), 7 12 (d, J = 8 4 Hz, 2H), 6 97 (d, J = 8 0 Hz, 2H), 7 02 (app dt, J = 1 6, 8 0 Hz, 2H), 6 83-6 88 (m, 1H), 6 06 (s, 1H), 5 26 (s, 2H), 5 21 (s, 2H), 4 22 (s, 2H), 3 09 (s, 2H), 2 30 (s, 3H),

1 14 (s, 6H) ES-HRMS m/z 564 1279 (M+H calcd for $C_{26}H_{29}BrF_2N_3O_4$ requires 564 1304)

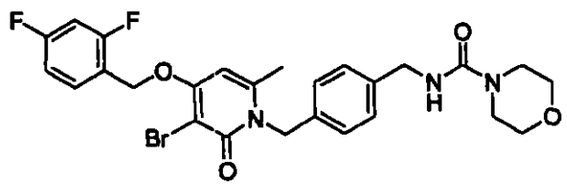
Example 623



N-(4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzyl)piperidine-1-carboxamide

By following the general method for Example 622 and substituting piperidine (170 mg, 2 0 mmol) for 3-amino-2-methyl-2-propanol the title compound was prepared and purified by chromatography (silica gel, hexane/ethyl acetate/methanol) yielding an oil that was triturated with ether to afford a white solid (107 mg, 28%) $^1$H NMR (400 MHz, $CDCl_3$) δ 7 56 (app q, J = 8 0 Hz, 1H), 7 23 (d, J = 8 4 Hz, 2H), 7 11 (d, J = 8 0 Hz, 2H), 7 02 (app t, J = 8 0 Hz, 2H), 6 81-6 88 (m, 1H), 5 97 (s, 1H), 5 32 (s, 2H), 5 19 (s, 2H), 4 37 (s, 2H), 3 34-3 28 (m, 4H), 2 29 (s, 3H), 1 68-1 50 (m, 6H) ES-HRMS m/z 560 1365 (M+H calcd for $C_{27}H_{29}BrF_2N_3O_3$ requires 560 1355)

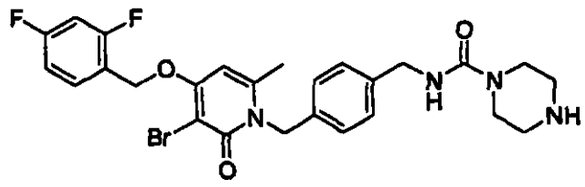
Example 624



N-(4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzyl)morpholine-4-carboxamide

By following the general method for Example 622 and substituting morpholine (175 mg, 2 0 mmol) for 3-amino-2-methyl-2-propanol the title compound was prepared and purified by chromatography (silica gel, hexane/ethyl acetate/methanol) followed by reversed phase chromatography ($C_{18}$, 0 1% aqueous trifluoroacetic acid/acetonitrile) to yield an off-white solid (51 mg, 13%) $^1$H NMR (400 MHz, $CDCl_3$) δ 7 55 (app q, J = 8 0 Hz, 1H), 7 17 (d, J = 8 4 Hz, 2H), 7 01 (d, J = 8 0 Hz, 2H), 6 94(app dt, J = 2 4, 8 0 Hz, 2H), 6 82-6 87 (m, 1H), 6 02 (s, 1H), 5 27 (s, 2H), 5 19 (s, 2H), 4 33 (s, 2H), 3 65-3 62 (m, 4H), 3 34-3 36 (m, 4H), 2 28 (s, 3H) ES-HRMS m/z 562 1152 (M+H calcd for $C_{26}H_{27}BrF_2N_3O_4$ requires 562 1148)

Example 625

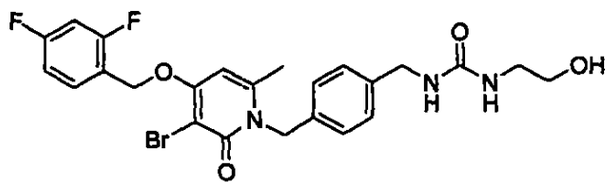


N-(4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzyl)piperazine-1-carboxamide hydrochloride

By following the general method for Example 622 and substituting 1-Boc-piperazine (372 mg, 2 0 mmol) for 3-amino-2-methyl-2-propanol the title compound was prepared from its N-t-butoxycarbonyl protected intermediate that was purified by chromatography (silica gel, hexane/ethyl acetate/methanol) Deprotection was accomplished with 4N HCl in dioxane to afford the title compound as its hydrochloride salt (78 mg, 19%) $^1$H NMR (400 MHz, $CD_3OD$) δ 7 61 (app q, J = 7 6 Hz, 1H), 7 26 (d, J = 8 4 Hz, 2H), 7 07 (d, J = 8 4 Hz, 2H), 7 08-7 00 (m, 2H), 6 48 (s, 1H), 5 41 (s, 2H), 5 28 (s, 2H), 4 31 (s, 2H), 3 65-

3 62 (m, 4H), 3 21-3 17 (m, 4H), 2 35 (s, 3H) ES-HRMS m/z 561 1318 (M+H calcd for $C_{26}H_{28}BrF_2N_4O_3$ requires 561 1307)

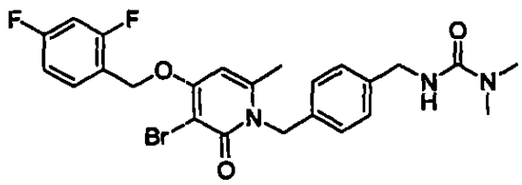
Example 626



N-(4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzyl)-N'-(2-hydroxyethyl)urea

By following the gereral method for Example 622 and substituting ethanolamine (121 mg, 2 0 mmol) for 3-amino-2-methyl-2-propanol the title compound was prepared and purified by chromatography (silica gel, hexane/ethyl acetate/methanol) to yield an off-white solid (130 mg, 36%) $^1$H NMR (400 MHz, $CDCl_3$) δ 7 54 (app q, J = 7 6 Hz, 1H), 7 13 (d, J = 8 4 Hz, 2H), 6 95 (d, J = 8 0 Hz, 2H), 6 96-6 92 (m, 1H), 6 83-6 88 (m, 1H), 6 09 (s, 1H), 5 '6 (s, 2H), 5 21 (s, 2H), 4 24 (s, 2H), 3 56 (t, J = 4 8 Hz, 2H), 3 21 (t, J = 4 8 Hz, 2H), 2 31 (s, 3H) ES-HRMS m/z 536 0948 (M+H calcd for $C_{24}H_{25}BrF_2N_3O_4$ requires 536 0991)

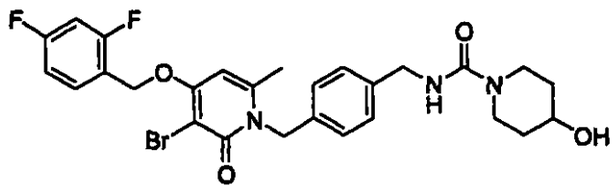
Example 627



N'-(4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzyl)-N,N-dimethylurea

By following the general method for Example 622 and substituting N,N-dimethylamine (1 0 mL, 2 0 mmol, 2M in tetrahydrofuran) for 3-amino-2-methyl-2-propanol the title compound was prepared and purified by chromatography (silica gel, hexane/ethyl acetate/methanol) yielding an oil that was triturated with ether to afford a white solid (65 mg, 19%) $^1$H NMR (400 MHz, $CDCl_3$) δ 7 56 (app q, J = 8 0 Hz, 1H), 7 22 (d, J = 8 0 Hz, 2H), 7 10 (d, J = 8 0 Hz, 2H), 6 93 (app dt, J = 2 0, 8 0 Hz, 1H), 6 87-6 81 (m, 1H), 5 97 (s, 1H), 5 31 (s, 2H), 5 19 (s, 2H), 4 36 (s, 2H), 2 89 (s, 6H), 2 28 (s, 3H) ES-HRMS m/z 520 1072 (M+H calcd for $C_{24}H_{25}BrF_2N_3O_3$ requires 520 1042)

Example 628

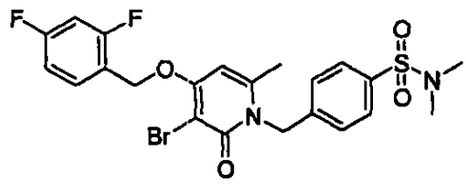


N-(4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzyl)-4-hydroxypiperidine-1-carboxamide

By following the general method for Example 622 and substituting 4-Hydroxypiperidine (202 mg, 2 0 mmol) for 3-amino-2-methyl-2-propanol the title compound was prepared and purified by chromatography (silica gel, hexane/ethyl acetate/methanol) yielding an oil that was triturated with ether to afford a white solid (41 mg, 11%) $^1$H NMR (400 MHz, $CDCl_3$) δ 7 56 (app q, J = 8 0 Hz, 1H), 7 20 (d, J = 7 6 Hz, 2H), 7 06 (d, J = 8 0 Hz, 2H), 6 94 (app t, J = 8 0 Hz, 1H), 6 84 (app t, J = 8 0 Hz, 1H), 5 99 (s, 1H), 5 29 (s, 2H), 5 19 (s, 2H), 4 34 (s, 2H), 3 84-3 70 (m, 3H), 3 04-2 92 (m, 3H),

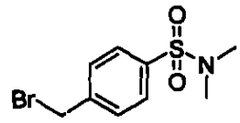
2 28 (s, 3H), 1 84-1 81 (m, 2H), 1 47-1 44 (m, 2H) ES-HRMS m/z 576 1348 (M+H calcd for $C_{27}H_{29}BrF_2N_3O_4$ requires 576 1304)

Example 629



4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-N,N-dimethylbenzenesulfonamide

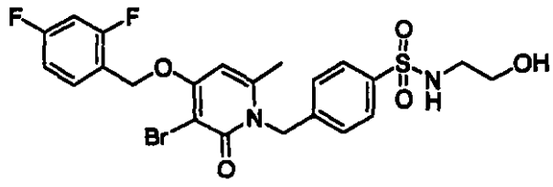
Step 1 Preparation of 4-Bromomethyl-N,N-dimethylbenzenesulfonamide



4-(Bromomethyl)benzenesulfonyl chloride (5 0 g, 18 6 mmol) was dissolved in tetrahydrofuran N,N-dimethylamine (7 7 mL, 15 5 mmol, 2M in tetrahydrofuran) and and N,N-diisopropylethylamine (3 5 mL, 20 1 mmol) were added, and the reaction was allowed to stir at ambient temperature for 2 hours The reaction was concentrated to an oil that was partitioned between water and ethyl acetate and extracted with ethyl acetate The organic extracts were combined, washed with brine, dried over $Na_2SO_4$, and filtered The resulting filtrate was concentrated to an oil which deposited needles that were a mixture of the title compound and 4-chloromethyl N,N-dimethylbenzenesulfonamide The resulting needles were collected and dried (2 3 g, 44 %) ES-MS m/z 534 (M+H) and 578 (M+H)

Step 2 Preparation of 4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-N,N-dimethylbenzenesulfonamide 3-bromo-4-(2,4-difluorophenoxy)-6-methylpyridin-2(1H)-one (300 mg, 0 91 mmol) was suspended in 1,4-dioxane (50 mL) 4-(Bromomethyl)-N,N-dimethylbenzenesulfonamide ( from step1) (300 mg, 1 09 mmol) was added followed by sodium hydride (45 mg, 1 09 mmol, 60% in mineral oil) The reaction was heated to 80 C and stirred for 16 hours after which more sodium hydride (45 mg, 1 09 mmol, 60% in mineral oil) and sodium iodide (150 mg, 1 0 mmol) were added The reaction was allowed to stir at 80 C for 4 hours more The reaction was then filtered through Celite® and the filtrate was concentrated to an oil that was purified by chromatography (silica gel, hexane/ethyl acetate) followed by reversed phase chromatography ($C_{18}$, 0 1% aqueous trifluoroacetic acid/acetonitrile) to yield an off-white solid (41 mg, 8%) $^1$H NMR (400 MHz, $CDCl_3$) δ 7 71(d, J = 8 4 Hz, 2H), 7 57 (app q, J = 7 6 Hz, 1H), 7 29 (d, J = 8 0 Hz, 2H), 6 95 (app dt, J = 2 0, 8 0 Hz, 1H), 6 88-6 83 (m, 1H), 6 05 (s, 1H), 5 42 (s, 2H), 5 22 (s, 2H), 2 69 (s, 6H), 2 29 (s, 3H) ES-HRMS m/z 527 0439 (M+H calcd for $C_{22}H_{22}Br_2F_2N_2O_4S$ requires 527 0446)

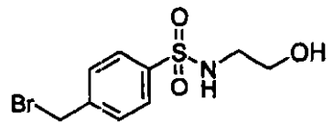
Example 630




4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-N-(2-hydroxyethyl)benzenesulfonamide

401
404

Step 1 Preparation of 4-Bromomethyl-N-(2-hydroxyethyl)benzenesulfonamide

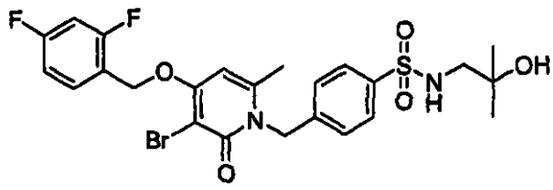


4-(Bromomethyl)benzenesulfonyl chloride (5 0 g, 18 6 mmol) was dissolved in tetrahydrofuran Ethanolamine (1 1 mL, 18 6 mmol) and and N,N-diisopropylethylamine (3 9 mL, 22 3 mmol) were added, and the reaction was allowed to stir at ambient temperature for 30 minutes The reaction was concentrated to an oil that was partitioned between water and ethyl acetate and extracted with ethyl acetate The organic extracts were combined, washed with brine, dried over $Na_2SO_4$, and filtered The resulting filtrate was concentrated to an oil that was a mixture of the title compound and 4-chloromethyl N-(2-hydroxyethyl)benzenesulfonamide The resulting oil was dried in vacuo (3 7 g, 68 %) ES-MS m/z 250 (M+H) and 294 (M+H)

Step 2 Preparation of 4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-N-(2-hydroxyethyl)benzenesulfonamide

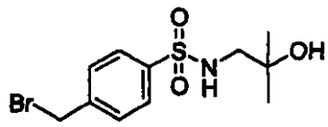
The title compound was prepared essentially according to the procedure described in Step 2 of Example 629, using 4-Bromomethyl-N-(2-hydroxyethyl) benzenesulfonamide ( from step 1) $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7 81 (d, J = 8 4 Hz, 2H), 7 61 (app q, J = 7 6 Hz, 1H), 7 30 (d, J = 8 4 Hz, 2H), 6 95 (app t, J = 8 4 Hz, 2H), 6 53 (s, 1H), 5 49 (s, 2H), 5 30 (s, 2H), 3 50 (t, J = 6 0 Hz, 2H), 2 92 (t, J = 6 0 Hz, 2H), 2 36 (s, 3H) ES-HRMS m/z 543 0453 (M+H calcd for $C_{22}H_{22}Br_2F_2N_2O_5S$ requires 543 0395)

Example 631



4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-N-(2-hydroxy-2-methylpropyl)benzenesulfonamide

Step 1 Preparation of 4-Bromomethyl-N-(2-hydroxy-2-methylpropyl) benzenesulfonamide



4-(Bromomethyl)benzenesulfonyl chloride (2 0 g, 7 3 mmol) was dissolved in tetrahydrofuran 3-Amino-2-methyl-2-propanol (1 0 g, 8 mmol) and and N,N-diisopropylethylamine (1 5 mL, 8 8 mmol) were added, and the reaction was allowed to stir at ambient temperature for 30 minutes The reaction was concentrated to an oil that was partitioned between water and ethyl acetate and extracted with ethyl acetate The organic extracts were combined, washed with brine, dried over $Na_2SO_4$, and filtered The resulting filtrate was concentrated to an oil that was a mixture of the title compound and 4-chloromethyl-N-(2-hydroxy-2-methylpropyl) benzenesulfonamide The resulting oil was dried in vacuo (1 9 g, 81 %)

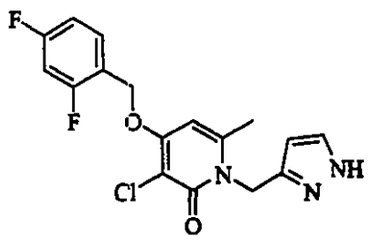
Step 2 Preparation of 4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-N-(2-hydroxy-2-methylpropyl)benzenesulfonamide

The title compound was prepared essentially according to the procedure described in Step 2 of Example 629, using 4-Bromomethyl-N-(2-hydroxy-2-methylpropyl) benzenesulfonamide (

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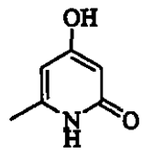
from step 1) $^1$H NMR (400 MHz, $CDCl_3$) δ 7 78 (a, J = 8 4 Hz, 2H), 7 56 (app q, J = 7 6 Hz, 1H), 7 26 (d, J = 8 4 Hz), 6 95 (app t, J = 8 4 Hz, 1H), 6 86-6 83 (m, 1H), 6 07 (s, 1H), 5 41 (s, 2H), 5 22 (s, 2H), 4 98 (t, J = 6 4 Hz, 1H), 2 84 (d, J = 6 4 Hz, 2H), 2 29 (s, 3H), 1 21 (s, 6H) ES-HRMS m/z 571 0684 (M+H calcd for $C_{24}H_{26}Br_2F_2N_2O_5S$ requires 571 0708)

Example 632




3-Chloro-4-(2,4-difluorobenzyloxy)-6-methyl-1-(1*H*-pyrazol-3-ylmethyl) 1*H*-pyridin-2-one

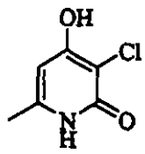
Step 1 Preparation of 4-Hydroxy-6-methyl-1*H*-pyridin-2-one




4-Hydroxy-6-methyl-pryan-2-one (25 8 g, 0 2 mol) was dissolved in 180 ml of concentrated ammonium hydroxide The reaction was heated at refluxed for 4 hours The reaction was cooled to room temperature and evaporated on a rotary evaporator to a quarter of the original volume The resulting solid was filtered, washed with cold water, hexanes, and dried in a vacuum oven overnight to give a white solid (25 g, 98%) $^1$H NMR

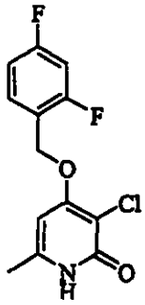
(300 MHz, DMSO-$d_6$) $\delta$ 10 94 (br s, 1H), 10 34 (s, 1H), 5 59 (d, $J$ = 1 4 Hz, 1H), 5 32 (d, $J$ = 2 0 Hz, 1H), 2 07 (s, 3H)

Step 2 Preparation of 3-Chloro-4-hydroxy-6-methyl-1*H*-pyridin-2-one



4-Hydroxy-6-methyl-1*H*-pyridin-2-one (25g, 0 2 mol) and *N*-chlorosuccinimide (29 4 g, 0 22 mol) were dissolved in 200 mL of acetic acid The reaction was heated at 115 °C for 6 hours The reaction was cooled to room temperature, the solid was filtered, and washed with acetic acid and hexanes The solid was dried in a vacuum oven overnight to give a white solid (19 2 g, 60%) $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 11 46 (br s, 1H), 11 04 (s, 1H), 5 79 (s, 1H), 2 09 (s, 3H)

Step 3 Preparation of 3-Chloro-4-(2,4-difluorobenzyloxy)-6-methyl-1*H*-pyridin-2-one

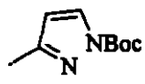


3-Chloro-4-hydroxy-6-methyl-1*H*-pyridin-2-one (19 2 g, 0 12 mol) and DBU (19 9 mL, 0 13 mol) were dissolved in 70 mL of NMP 2,4-Difluorobenzylbromide (17 mL, 0 13 mol) was added

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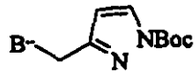
dropwise and the reaction was heated at 80 °C for 6 hours The reaction was cooled to room temperature, the solid was filtered, and washed with NMP and hexanes The solid was dried in a vacuum oven overnight to give a white solid (4 4 g, 13%) $^1$H NMR (300 MHz, DMSO-$d_6$) δ 11 88 (br s, 1H), 7 63 (app q, $J$ = 9 Hz, 1H), 7 33 (app t, $J$ = 10 Hz, 1H), 7 16 (app t, $J$ = 9 Hz, 1H), 6 37 (s, 1H), 5 24 (s, 2H), 2 20 (s, 3H)

Step 4 Preparation of 3-Methylpyrazole-1-carboxylic acid tert-butyl ester




3-Methyl-1H-pyrazole (5 3 g, 65 mmol), DMAP (0 79 g, 6 5 mmol), and di-tert-butyl dicarbonate (2 8 g, 13 mmol) were at room temperature in 90 mL of $CH_3CN$ for 1 hour The reaction was evaporated on a rotary evaporator, and the resulting solid dissolved in EtOAc, washed with 1 N HCl, water and brine, dried ($MgSO_4$), filtered, and evaporated on a rotary evaporator to give a light yellow oil (11 4 g, 96%) $^1$H NMR (300 MHz, $CDCl_3$) δ 7 96 (d, $J$ = 2 7 Hz, 1H), 6 17 (d, $J$ = 2 7 Hz, 1H), 2 32 (s, 3H), 1 63 (s, 9H)

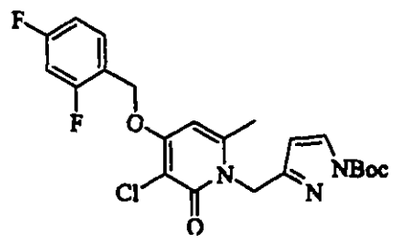
Step 5 Preparation of 3-Bromomethylpyrazole-1-carboxylic acid tert-butyl ester




3-Methylpyrazole-1-carboxylic acid tert-butyl ester (6 0 g, 33 mmol), N-bromosuccinimide (1 0 g, 5 6 mmol) and benzoyl peroxide (50 mg) were dissolved in 20 mL of carbon

tetrachloride The reaction was heated at reflux for 16 h The reaction was cooled to room temperature, filtered, and concentrated under reduced pressure Purification by flash column chromatography (silica, 1 4 EtOAc/hexanes) gave a light yellow oil (4 5 g, 53%) $^1$H NMR (300 MHz, $CDCl_3$) δ 8 03 (d, $J$ = 2 6 Hz, 1H), 6 47 (d, $J$ = 2 6 Hz, 1H), 4 48 (s, 2H), 1 64 (s, 9H)

Step 6 Preparation of 3-[3-Chloro-4-(2,4-difluorobenzyloxy)-6-methyl-2-oxo-2*H*-pyridin-1-ylmethyl]pyrazole-1-carboxylic acid *tert*-butyl ester

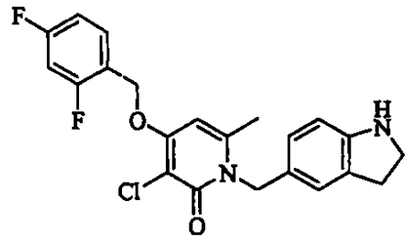



3-[3-Chloro-4-(2,4-difluorobenzyloxy)-6-methyl-2-oxo-2*H*-pyridin-1-ylmethyl]pyrazole-1-carboxylic acid *tert*-butyl ester was prepared by a procedure similar to the one described for Example 401 gave a yellow solid (1 4 g, 39%) $^1$H NMR (300 MHz, $CDCl_3$) δ 7 53 - 7 49 (m, 2H), 6 97 - 6 81 (m, 2H), 6 35 (d, $J$ = 2 0 Hz, 1H), 6 01 (s, 1H), 5 32 (s, 2H), 5 26 (s, 2H), 2 52 (s, 3H), 1 62 (s, 9H)

Step 7 Preparation of the title compound Example 632 3-[3-Chloro-4-(2,4-difluorobenzyloxy)-6-methyl-2-oxo-2*H*-pyridin-1-ylmethyl]pyrazole-1-carboxylic acid *tert*-butyl ester (0 16 g, 0 34 mmol) was heated to 140 °C for 16 h The reaction mixture was cooled to room temperature Recrystallization from methylene chloride/hexanes provided an off-white solid (1 0 g, 91%) $^1$H NMR (300 MHz, DMSO-$d_6$) δ 12 67 (br s, 1H),

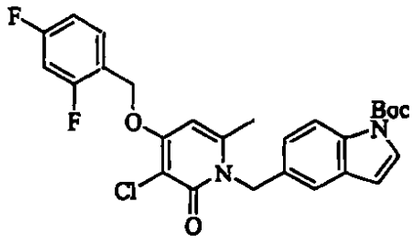
7 67 - 7 60 (m, 2H), 7 34 (dt, $J$ = 10 5, 2 5 Hz, 1H), 7 17 (dt, $J$ = 8 5, 1 6 Hz, 1H), 6 52 (s, 1H), 6 10 (d, $J$ = 1 9 Hz, 1H), 5 27 (s, 2H), 5 20 (s, 2H), 2 48 (s, 2H)

Example 633



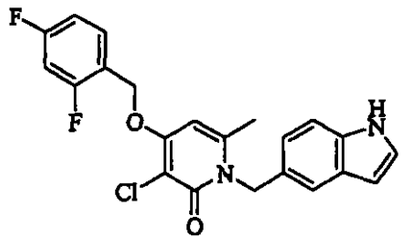
3-Chloro-4-(2,4-difluorobenzyloxy)-6-methyl-1-(2,3-dihydro-1H-indol-5-ylmethyl)-1H-pyridin-2-one

Step 1 Preparation of 5-[3-Chloro-4-(2,4-difluorobenzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]indole-1-carbamic acid tert-butyl ester



5-[3-Chloro-4-(2,4-difluorobenzyloxy)-2-oxo-2H-pyridin-1-ylmethyl]indole-1-carbamic acid tert-butyl ester was prepared by a procedure similar to the one described for Example 632 as an off-white solid (2 5 g, 61%) $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8 00 (d, J = 8 5 Hz, 1H), 7 70 - 7 62 (m, 2H), 7 39 - 7 32 (m, 2H), 7 21 - 7 13 (m, 2H), 6 70 (d, J = 3 8 Hz, 1H), 6 66 (s, 1H), 5 40 (s, 2H), 5 29 (s, 2H), 2 33 (s, 3H), 1 62 (s, 9H)

Step 2 Preparation of 3-Chloro-4-(2,4-difluorobenzyloxy)-6-methyl-1-(1H-indol-5-ylmethyl)-1H-pyridin-2-one

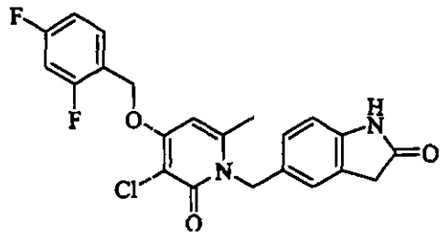


5-[3-Chloro-4-(2,4-difluorobenzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]indole-1-carbamic acid tert-butyl ester (1 08g, 2 1 mmol) dissolved in 40 mL of DMSO was stirred at 120 °C for 20 hours The reaction was cooled to room temperature, diluted with water, and washed 5 times with ethyl acetate The combined organics were washed 1 time with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure $^1H$ NMR (300 MHz, DMSO-$d_6$) $\delta$ 11 1 (br s, 1H), 7 67 (d, J = 6 7 Hz, 1H), 7 36 - 7 32 (m, 2H), 7 23 (s, 1H), 7 18 (d, J = 2 3 Hz, 1H), 6 93 (dd, J = 8 4, 1 2 Hz, 1H) 6 57 (s, 1H), 6 38 (s, 1H), 5 37 (s, 2H), 5 29 (s, 2H), 2 35 (s, 3H)

Step 3 3-Chloro-4-(2,4-difluorobenzyloxy)-6-methyl-1-(1H-indol-5-ylmethyl)-1H-pyridin-2-one (, from Step 2) (1 7 g, 4 1 mmol) was stirred in 26 mL of acetic acid and $NaCNBH_3$ (0 27 g, 4 3 mmol) was added portionwise The reaction was stirred for 1 hour The reaction was diluted water, and washed 5 times with ethyl acetate The combined organics were washed 1 time with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure Purification by flash column chromatography (silica, 100% EtOAc) gave a white solid (1 2 g, 71%) $^1H$ NMR (300 MHz, DMSO-$d_6$) $\delta$ 7 64 (app q, J = 8 5 Hz, 1H), 7 34 (dt, J = 9 5, 2 6 Hz, 1H), 7 17 (app t, J = 8 5, 1H), 6 82 (s, 1H), 6 72 (d, J = 8 0 Hz, 1H), 6 53 (s, 1H), 6 42 (d, J = 8 0 Hz, 1H), 5 48 (br s, 1H), 5 27 (s, 2H), 5 13 (s, 2H), 3 37 (t, J = 8 3 Hz, 2H), 2 82 (t, J = 8 3 Hz, 2H), 2 35 (s, 3H)

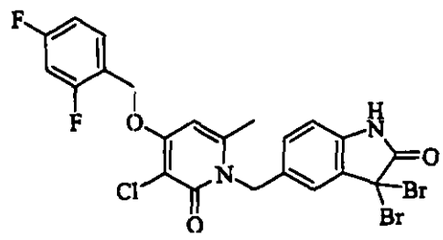
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Example 634



5-[3-Chloro-4-(2,4-difluorobenzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-1,3-dihydro-indol-2-one

Step 1 Preparation of 5-[3-Chloro-4-(2,4-difluorobenzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-3,3-dibromo-1H-indol-2-one

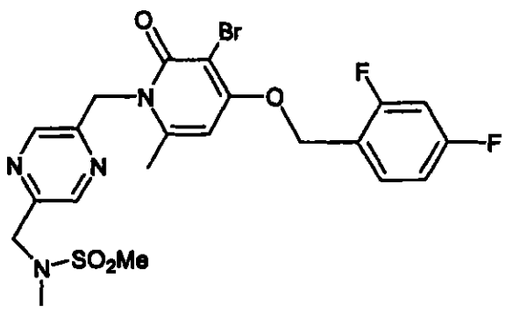


3-Chloro-4-(2,4-difluorobenzyloxy)-6-methyl-1-(1H-indol-5-ylmethyl)-1H-pyridin-2-one (0 45 mg, 1 1 mmol)(example 633, step 2) was suspended in 11 mL of tert-butanol and pyridinium bromide perbromide (1 04 g, 3 3 mmol) was added portionwise The reaction was stirred for 16 hours The reaction was diluted with water, and washed 4 times with ethyl acetate The combined organics were washed 1 time with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure Trituration with methylene chloride gave an off-white solid (0 25 g, 39%) $^1H$ NMR (300 MHz, DMSO-$d_6$) $\delta$ 11 26 (br s, 1H), 7 66 (app q, J = 8 6 Hz, 1H), 7 48 (s, 1H), 7 35 (dt, J = 10 5, 2 5 Hz, 1H), 7 18 (dt, J = 8 7, 1 9, 1H), 7 05 (dd, J =

8 2, 1 5, 1H), 6 88 (d, J = 8 1 Hz, 1H), 6 61 (s, 1H), 5 29 (s, 4H), 2 36 (s, 3H)

Step 2 5-[3-Chloro-4-(2,4-difluorobenzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-3,3-dibromo-1H-indol-2-one (0 2 g, 0 34 mmol) was suspended in 5 mL of acetic acid, and zinc metal (0 22 g, 3 4 mmol) was added The reaction was stirred for 48 hours The reaction was diluted with water, and washed 2 times with ethyl acetate The combined organics were washed 1 time with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure Purification by flash column chromatography (silica, 100% EtOAc) gave a white solid (0 12 g, 82%) $^1H$ NMR (300 MHz, DMSO-$d_6$) $\delta$ 10 37 (br s, 1H), 7 65 (app q J = 6 9 Hz, 1H), 7 34 (dt, J = 8 2, 2 5 Hz, 1H), 7 18 (dt, J = 7 1, 1 9, 1H), 6 98 (br s, 2H), 6 77 (d, J = 8 4 Hz, 1H), 6 57 (s, 1H), 5 28 (s, 2H), 5 23 (s, 2H), 3 44 (s, 2H), 2 34 (s, 3H)

Example 635



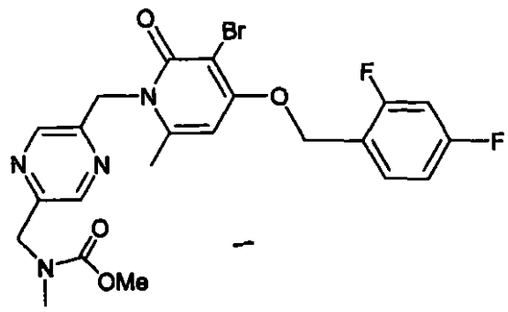

N-[(5-{[3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrazin-2-yl)methyl]-N-methylmethanesulfonamide

To a suspension of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-({5-[(methylamino)methyl]pyrazin-2-yl}methyl)pyridin-2(1H)-one (0 16 g, 0 34 mmol) in acetonitrile at 0 °C was

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409

added triethylamine (0 043 g, 0 42 mmol), followed by the addition of methane sulfonylchloride (0 047 g, 0 41 mmol) and stirred at room temperature for 1 h under argon atmosphere The solvents were removed in vacuo and the residue was triturated with water and filtered It was washed with water an, acetonitrile and dried in vacuo to afford 0 11 g of material $^1$H NMR ($CD_3OD$/ 400 MHz) δ 8 62 (s, 1H), 8 55 (s, 1H), 7 61 (m, 1H), 7 0 (m, 2H), 6 53 (s, 1H), 5 47 (s, 2H), 5 29 (s, 2H), 4 49 (s, 2H), 2 95 (s, 3H), 2 85 (s, 3H), and 2 55 (s, 3H), $^{19}$F NMR($CD_3OD$/ 400 MHz) -111 70(m) and -116 07 (m), ES-HRMS m/z 543 0515(M+H calcd for $C_{21}H_{22}BrF_2N_4O_4S$ requires 543 0508)

Example 636

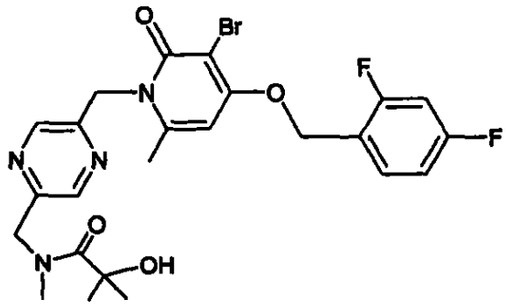



Methyl (5-{[3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrazin-2-yl)methyl(methyl)carbamate

To a cold (5 °C) solution of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-({5-[(methylamino)methyl]pyrazin-2-yl}methyl)pyridin-2(1H)-one (0 20 g, 0 4 mmol) in DMF (2 0 ml), was added methylchloroformate (0 049 g, 0 52 mmol), followed by the addition of triethylamine (0 072 g, 0 71 mmol) The mixture was stirred at 5 °C for 30 min and at room temperature for an additional 30 min and concentrated in vacuo The residue was

partitioned between water (5 0 mL) and EtOAc (10 0 mL) The organic extract was washed with water, dried ($Na_2SO_4$), and concentrated to dryness The resulting material was purified by reverse-phase HPLC using 10 -90 % $CH_3CN$/ Water gradient (60 min) at a flow rate of 70 mL/min The appropriate fractions (m/z = 523 M+H ) were combined and freeze dried to give a white powder This was partitioned between 5% $NaHCO_3$ (10 mL) and EtOAc (15 mL) The organic layer was washed with water, dried ($Na_2SO_4$), and concentrated to dryness to afford the title compound (0 12 g, 53%) as a white powder $^1H$ NMR ($CD_3OD$/ 400 MHz) δ 8 59 (s, 1H), 8 41(m, 1H), 7 60 (m, 1H), 7 05 (m, 2H), 6 52 (s, 1H), 5 45 (s, 2H), 5 29 (s, 2H), 4 58 (s, 2H), 3 69 and 3 64 (s, 3H), 2 97 (s, 3H), 2 85 (s, 3H), and 2 55 (s, 3H), $^{19}F$ NMR($CD_3OD$/ 400 MHz) -111 69(m) and -116 09 (m), ES-HRMS m/z 523 0775(M+H calcd for $C_{22}H_{22}BrF_2N_4O_4$ requires 523 0787)

Example 637

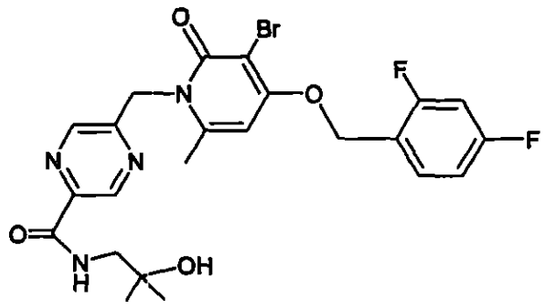



N-[(5-{[3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrazin-2-yl)methyl]-2-hydroxy-N,2-dimethylpropanamide

To a cold (5 °C) solution of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-({5-[(methylamino)methyl]pyrazin-2-yl}methyl)pyridin-2(1H)-one (0 24 g, 0 52 mmol) in DMF (2 0 ml), was added 2-

acetoxyisobutyryl chloride (0 093g, 0 56 mmol), followed by the addition of triethylamine (0 072 g, 0 71 mmol) The mixture was stirred at room temperature for an additional 2 h and concentrated in vacuo The residue was partitioned between water (5 0 mL) and EtOAc (15 0 mL) The EtOAc extract was washed with water, dried ($Na_2SO_4$), and concentrated to dryness The resulting material (0 2 g) was stirred with 1M LiOH (0 5 mL, MeOH,/Water 1 1v/v) at room temperature for 3h, cooled, acidified with trifluoroacetic acid and the product was purified by reverse-phase HPLC using 10 -90 % $CH_3CN$/ Water gradient (60 min) at a flow rate of 70 mL/min The appropriate fractions (m/z = 551 M+H ) were combined and freeze dried to give a white powder This was partitioned between 5% $NaHCO_3$ (10 mL) and EtoAc (15 mL) The organic layer was washed with water, dried ($Na_2SO_4$), and concentrated to dryness to afford the title compound (0 075 g) as a white powder $^1H$ NMR ($CD_3OD$/ 400 MHz) δ 8 59 (s, 1H), 8 41(br, 1H), 7 60 (m, 2H), 7 01 (m, 2H), 6 52 (s, 1H), 5 45 (s, 2h), 5 29 (s, 2H),

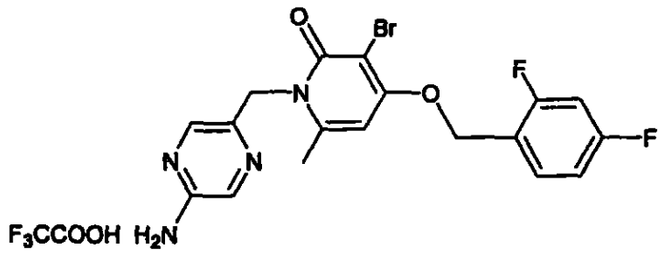
Example 638




5-{[3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-N-(2-hydroxy-2-methylpropyl)pyrazine-2-carboxamide

To a solution of 5-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrazine-2-carboxylic acid (0 42 g, 0 9 mmol) in DMF (3 0 mL) was added isobutylchloroformate (0 126 g, 0 13 mmol) followed by the addition of N-methylmorpholine (0 11 g, 1 1 mmol ) and stirred at -10 °C, under argon atmosphere After 20 min, added a solution of 1,1 dimethyl-2-aminoethanol hydrochloride (0 135g, 1 1 mmol) in DMF (2 0 mL) containing N-methylmorpholine (0 11 g, 1 1 mmol) The mixture was stirred at room temperature for 1 h, and concentrated to dryness in vacuo The resulting residue was purified by reverse-phase HPLC using 10 -90 % $CH_3CN$/ Water gradient (60 min) at a flow rate of 70 mL/min The appropriate fractions (m/z = 537 M+H ) were combined and freeze dried to give a white powder This was partitioned between 5% $NaHCO_3$ (10 mL) and EtOAc (15 mL) The organic layer was washed with water, dried ($Na_2SO_4$), and concentrated to dryness to afford the title compound (0 35 g, 75%) as a white powder $^1H$ NMR ($CD_3OD$/ 400 MHz) δ 9 1 (d, 1H, J = 1 6 Hz), 8 71 (d, 1H, J = 1 6 Hz), 7 61 (m 1H), 7 02 (m, 2H), 6 54 (s, 1H), 5 54 (s, 2H), 5 30 (s, 2h) 3 30 (s, 2h), 2 55 (s, 3H), and 1 21 (s, 6H), $^{19}F$ NMR($CD_3OD$/ 400 MHz) -111 67(m) and -116 05 (m), ES-HRMS m/z 537 0948 (M+H calcd for $C_{23}H_{24}BrF_2N_4O_4$ requires 537 0943)

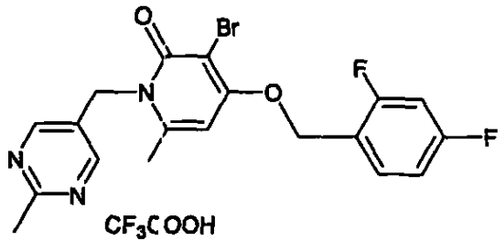
Example 639



1-[(5-Aminopyrazin-2-yl)methyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one trifluoroacetate

A mixture of 5-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrazine-2-carboxylic acid (0 70g, 1 5 mmol) diphenylphosphoryl azide (0 51 g, 1 8 mmol) in dimethylacetamide (15 0 mL) and t-butanol (5 0 mL) containing triethylamine (0 18 g, 1 8 mmol) was heated at 90 °C for 6 h under argon atmosphere The reaction mixture was cooled, filtered the precipitate It was washed with acetonitrile and dried to obtain 0 22 g of the unreacted acid The combined filtrate and the washings were concentrated in vacuo and the resulting material was purified by reverse-phase HPLC using 10 -90 % $CH_3CN$/ Water gradient (60 min) at a flow rate of 70 mL/min The appropriate fractions (m/z = 437 M+H ) were combined and freeze dried to give the title compound (0 21g, 37%) as a white powder $^1H$ NMR (DMSO-$d_6$/ 400 MHz) δ 7 88 (d, 1H, J = 1 2 Hz), 7 75 (d, 1H, J = 1 2 Hz), 7 61 (m 1H), 7 34 (m, 1H), 7 18 (m,1H), 6 49 (s, 1H), 5 25 (s, 2H), 5 10 (s, 2H), and 2 49 (s, 3H), $^{19}F$ NMR($CD_3OD$/ 400 MHz) -111 72(m) and -116 11 (m), ES-HRMS m/z 437 0402(M+H calcd for $C_{18}H_{16}BrF_2N_4O_2$ requires 437 0419)

Example 640




3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[(3-methyl-1,2,4-triazin-6-yl)methyl]pyridin-2(1H)-one trifluoroacetate

Step 1 Preparation of (2-methylpyrimidin-5-yl)methanol trifluoroacetate



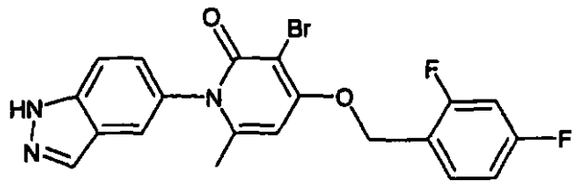

To solution of methyl 2-methylpyrimidinecarboxylate (2 6 g, 17 1 mmol) in THF was added dropwise diisobutylaluminumhydride (39 5 mL, 1M solution in THF) and stirred at -20 °C under argon atmosphere for 1 5 h, and at room temperature for 2 h The reaction was quenched by the addition of powdered sodiumsulphate decahydrate (25 g), added THF (25 mL) and stirred at room temperature for 1h This mixture was allowed to stand in the refrigerator overnight and filtered through a celite pad The precipitate was thoroughly with warm THF (100 mL) containing 10% ethanol The combined washings and the filtrate were concentrated to afford ayellow syrup, which was purified
by reverse-phase HPLC using 10 -90 % $CH_3CN$/ Water gradient (60 min) at a flow rate of 70 mL/min The appropriate fractions (m/z = 125 M+H) were combined and lyophilized to give the title compound (0 67 g, 32%) as its trifluoroacetate salt $^1H$ NMR ($CD_3OD$/ 400 MHz) δ 8 65 (s, 2H ) 4 62 (s, 2H), and 2 66 (s, 3H), ES-HRMS m/z 125 0678 (M+H calcd for $C_6H_9N_2O$ requires 125 0709)

Step 2 Preparation of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[(3-methyl-1,2,4-triazin-6-yl)methyl]pyridin-2(1H)-one trifluoroacetate

To a solution of (2-methylpyrimidin-5-yl)methanol trifluoroacetate (0 9 g, 3 76 mmol) in dichloromethane (10 mL) at 0 °C, was added triethylamine (0 95 g, 9 41 mmol), followed by the addition of methanesulfonyl chloride (0 59 g, 5 17 mmol) and stirred at 0 °C for 1 h After stirring for 1 h at room temperature, additional triethylamine ( 0 22 g) and methanesulfonyl chloride (0 15 g)were added and the mixture was stirred at room temperature for another hour under argon atmosphere The reaction was quenched by the addition of cold water (15 mL) and stirred for 15 min The organic layer was washed with water, followed by 5% sod bicarbonate (2 x 15 mL), water, and dried ($Na_2SO_4$) After the removal of the solvent under reduced pressure, the residue was dried in a desiccator under vacuum for 4 h This material was suspended in THF (10 mL) and DMF (5 0 mL), added 3-bromo-4-(2,4-difluorophenoxy)-6-methylpyridin-2(1H)-one (0 5 g, 1 52 mmol) and NaH (0 04 g) The resulting mixture was heated at 65 °C for 16 h under argon atmosphere The solvents were distilled under vacuum and the residue was purified by reverse-phase HPLC using 10 -90 % $CH_3CN$/ Water gradient (60 min) at a flow rate of 70 mL/min The appropriate fractions (m/z = 436 M+H) were combined and freeze dried to give the title compound (0 045 g,) as its trifluoroacetate salt $^1H$ NMR ($CD_3OD$/ 400 MHz) δ 8 58 (s, 2H) 7 61 (m, 1H), 7 01 (m, 2H), 6 53 (s, 1H), 5 37 (s, 2h), 5 29 (s, 2H), 2 65 (s, 3H), and 2 46 (s, 3H), $^{19}F$ NMR($CD_3OD$/ 400 MHz)

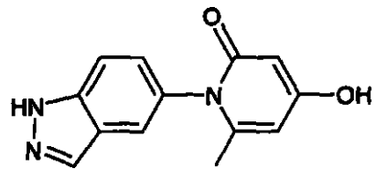
-111 62 (m), and -116 08 (m), ES-HRMS m/z 436 0433(M+H calcd for $C_{19}H_{17}BrF_2N_3O_2$ requires 436 0467)

Example 641



3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-(1H-indazol-5-yl)-6-methylpyridin-2(1H)-one

Step 1 Preparation of 4-hydroxy-1-(1H-indazol-5-yl)-6-methylpyridin-2(1H)-one



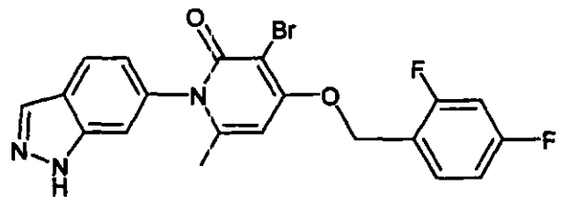
A mixture of 4- hydoxy-6-methyl-2-pyrone (3 75 g, 0 029 mol) and 5-aminoindazole (4 0 g, 0 03 mol) in water (70 ml) was heated at 90 °C under argon for 1 h The mixture was cooled, decanted the supernatant and residue was triturated with ethanol, cooled and filtered the solid It was washed with cold ethanol, and dried $^1$H NMR ($CD_3OD$/ 400 MHz) δ 8 11 (s, 1H), 7 64 (m, 2H), 7 18 (d, 1H, J = 2 0 Hz ), 7 16 (d, 1H, J = 2 0 Hz) 6 07 (m, 1H), 5 81 (d, 1H, J = 2 8 Hz), and 1 94 (s, 3H), ES-HRMS m/z 242 0962(M+H calcd for $C_{13}H_{12}N_3O_2$ requires 242 0924)

Step 2

A mixture of 4-hydroxy-1-(1H-indazol-5-yl)-6-methylpyridin-2(1H)-one (0 2g, 0 83 mmol), N- bromosuccinmide (0 15 g, 0 84 mmol) in dichloromethane (4 0 mL) and acetic acid (1 0 mL) was stirred at room temperature under argon atmosphere for 2 5 h After the removal of the solvents, the

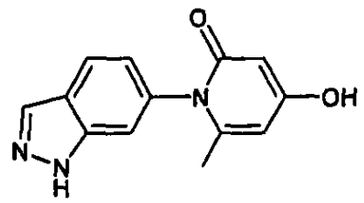
residue was dried in vacuo for 4 h in a desiccator It was then suspended in DMF (3 0 mL), potassium carbonate (0 1g), and 2,4 difluorobenzyl bromide were added and mixture was stirred at room temperature for 3 h DMF was distilled in vacuo and the residue was purified by reverse-phase HPLC using 10 -90 % $CH_3CN$/ Water gradient (60 min) at a flow rate of 70 mL/min The appropriate fractions (m/z = 537 M+H ) were combined and freeze dried to give a white powder This was partitioned between 5% $NaHCC_3$ (10 mL) and EtOAc (15 mL) The organic layer was washed with water, dried ($Na_2SO_4$), and concentrated to dryness to afford the title compound (0 075 g) as a white powder $^1H$ NMR ($CD_3OD$/ 400 MHz) δ 8 13 (s, 1H ), 7 68 (m, 3H), 7 20 (2d, 1H, J = 1 2 Hz), 7 05 (m, 2H), 6 61 (s, 1H), 5 35 (s, 2H), and 2 05 (s, 3H), $^{19}F$ NMR($CD_3OD$/ 400 MHz) -111 62 (m) and -116 02 (m), ES-HRMS m/z 446 0305(M+H calcd for $C_{20}H_{15}BrF_2N_3O_2$ requires 446 0310)

Example 642




3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(1H-indazol-6-yl)-6-methylpyridin-2(1H)-one

Step 1 Preparation of 4-hydroxy-1-(1H-indazol-6-yl)-6-methylpyridin-2(1H)-one

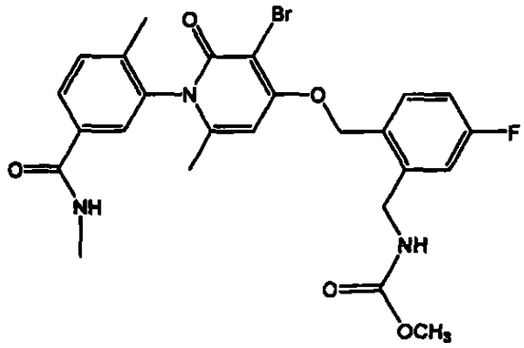


The title compound was prepared by a similar procedure described for 4-hydroxy-1-(1H-indazol-5-yl)-6-methylpyridin-2(1H)-one Yield = 12%, $^1$H NMR ($CD_3OD$/ 400 MHz) δ 8 12 (s, 1H), 7 90 (d, 1H, J = 8 0 Hz), 7 42 (s, 1H), 6 94 (d, 1H, J = 8 8 Hz) 6 08 (br s, 1H), 5 81 (d, 1H, J = 2 4 Hz), and 1 96 (s, 3H), ES-HRMS m/z 242 0946(M+H calcd for $C_{13}H_{12}N_3O_2$ requires 242 0924)

Step 2

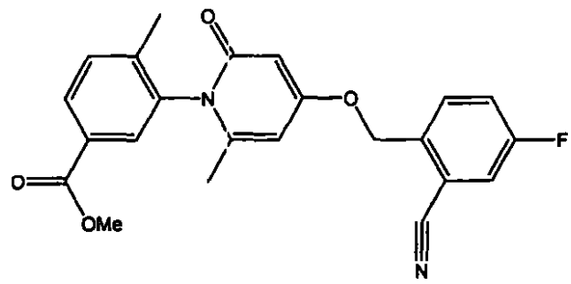
The title was prepared by a similar procedure described for 3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-(1H-indazol-5-yl)-6-methylpyridin-2(1H)-one $^1$H NMR ($CD_3OD$/ 400 MHz) δ 8 14 (s, 1H), 7 93 (d, 1H, J = 8 4Hz), 7 61 (m 1H), 7 46 (s, 1H), 7,04 (m, 2H), 6 98 (m, 1H) 6 62 (s, 1H), 5 36 (s, 2H), and 2 06 (s, 3H), $^{19}$F NMR($CD_3OD$/ 400 MHz) -111 62 (m) and -116 03 (m), ES-HRMS m/z 446 0302(M+H calcd for $C_{13}H_{12}N_3O_2$ requires 446 0310)

Example 643



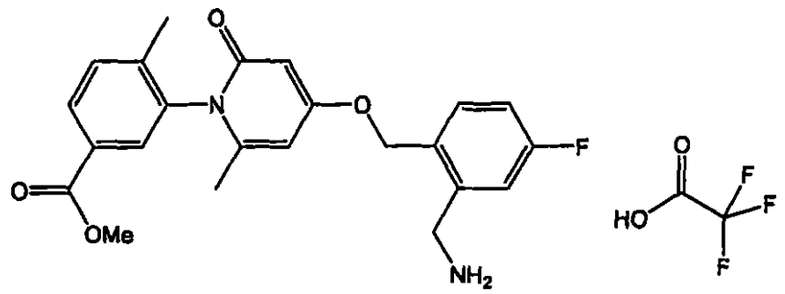
methyl 2-{[(3-bromo-6-methyl-1-{2-methyl-5-[(methylamino)carbonyl]phenyl}-2-oxo-1,2-dihydropyridin-4-yl)oxy]methyl}-5-fluorobenzylcarbamate

Step 1 Preparation of methyl 3-[4-[(2-cyano-4-fluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoate



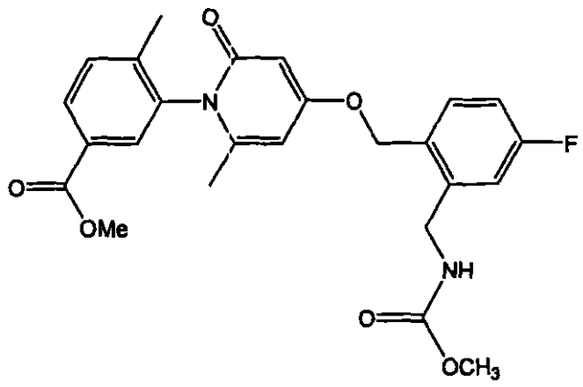
To a cooled (0°C) solution of 2-(bromomethyl)-5-fluorobenzonitrile (4 31 g, 20 1 mmol) and methyl 3-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)-4-methylbenzoate (5 00 g, 18 3 mmol) in DMF (20 mL) was added $K_2CO_3$ (3 00 g, 22 0 mmol) The reaction was allowed to warm to RT and stirred overnight Additional 2-(bromomethyl)-5-fluorobenzonitrile (0 39 g, 1 83 mmol) and $K_2CO_3$ (0 25 g, 1 83 mmol) were added and the reaction heated at 60°C for 2h Solvent removed by distillation Reaction neutralized with 5% citric acid (50 mL) Organic products were extracted in DCM (3 x 25 mL), dried over $Na_2SO_4$, filtered, and concentrated to a thick dark brown oil Purified by silica gel flash column chromatography using EtOAc as the eluent to give the product as a brown solid, dried in vacuo (6 18 g, 76%) $^1H$ NMR ($CD_3OD$/ 400MHz) δ8 03 (m, 1H), 7 76 (m, 2H), 7 66 (m, 1H), 7 52 (m, 2H), 6 24 (s, 1H), 6 09 (s, 1H), 5 27 (s, 2H), 3 89 (s, 3H), 2 12 (s, 3H), 1 90 (s, 3H) ESHRMS m/z 407 1408 (M+H calculated for $C_{23}H_{20}FN_2O_4$ requires 407 1402)

Step 2 Preparation of methyl 3-[4-{[2-(aminomethyl)-4-fluorobenzyl]oxy}-6-methyl 2-oxopyridin-1(2H)-yl]-4-methylbenzoate trifluoroacetate



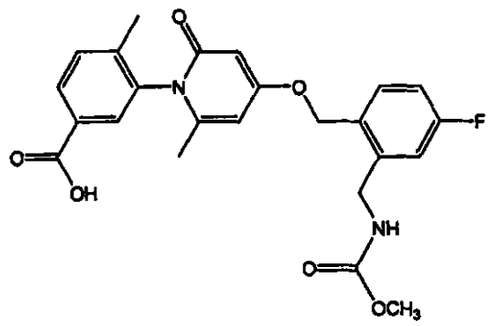
To a cooled (0°C) solution of methyl 3-[4-[(2-cyano-4-fluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoate ( from Step 1) (0 510 g, 1 25 mmol) in THF (5 mL) was added dropwise $BH_3THF$ (2 51 mL, 2 51 mmol) The reaction was then stirred at RT for 2 5h Reaction cooled (0°C), quenched by the slow addition of MeOH, concentrated, and purified by preparatory HPLC The product was isolated by freeze-drying and evaporation of the solvent to give a white solid, dried in vacuo (0 39 g, 76%) $^1H$ NMR ($CD_3OD$/ 400MHz) δ8 04 (m, 1H), 7 75 (s, 1H), 7 63 (m, 1H), 7 55 (d, 1H, J = 8 4 Hz), 7 32 (m, 1H), 7 24 (m, 1H), 6 25 (s, 1H), 6 12 (s, 1H), 5 23 (s, 2H), 4 25 (s, 2H), 3 90 (s, 3H), 2 11 (s, 3H), 1 90 (s, 3H) ESHRMS m/z 411 1691 (M+H calculated for $C_{23}H_{24}FN_2O_4$ requires 411 1715)

Step 3 Preparation of methyl 3-[4-[(4-fluoro-2-{[(methoxycarbonyl)amino]methyl}benzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoate



To a cooled (0°C) solution of methyl 3-[4-{[2-(aminomethyl)-4-fluorobenzyl]oxy}-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoate trifluoroacetate ( from Step 2) (0 50 g, 0 95 mmol) in DMA (4 mL) was added 4-methylmorpholine (0 21 mL, 1 9 mmol) and methyl chloroformate (0 08 mL, 1 0 mmol) Reaction was stirred at RT for 1h Solvent removed by distillation Crude product purified by preparatory HPLC Acetonitrile was evaporated and the solution washed with 5% $NaHCO_3$ (30 mL) and extracted in DCM (3 x 25 mL) The organic extracts were dried over $Na_2SO_4$, filtered, and concentrated to a white solid, dried in vacuo (0 36 g, 81%) $^1H$ NMR ($CD_3OD$/ 400MHz) δ8 03 (m, 1H), 7 77 (s, 1H), 7 53 (d, 1H, J = 7 6 Hz), 7 47 (m, 1H), 7 12 (m, 1H), 7 03 (m, 1H), 6 21 (s, 1H), 6 08 (s, 1H), 5 18 (s, 2H), 4 38 (s, 2H), 3 89 (s, 3H), 3 65 (s, 3H), 2 12 (s, 3H), 1 89 (s, 3H) ESHRMS m/z 469 1767 (M+H calculated for $C_{25}H_{26}FN_2O_6$ requires 469 1769)

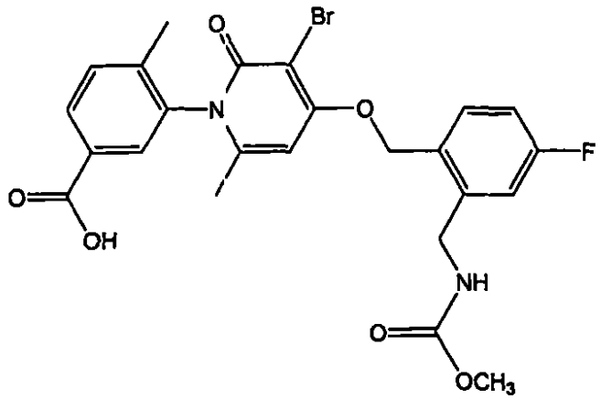
Step 4 Preparation of 3-[4-[(4-fluoro-2-{[(methoxycarbonyl)amino]methyl}benzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoic acid



To methyl 3-[4-[(4-fluoro-2-{[(methoxycarbonyl)amino]methyl}benzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoate ( from Step 3) (0 17 g, 0 36 mmol) was added 1 5 N NaOH solution in 1 1 MeOH water (0 39 mL, 0 59 mmol) The reaction mixture was stirred at 60°C for 2 5h The solution was cooled (0°C), neutralized by the slow addition of 5% citric acid, and organic products extracted in DCM A white solid suspended in the organic layer was filtered, washed with DCM and water, dried in vacuo, and found to be the desired product (0 090 g, 55%) $^1$H NMR ($CD_3OD$/ 400MHz) δ8 03 (m, 1H), 7 75 (s, 1H), 7 52 (d, 1H, J = 8 0 Hz), 7 47 (m, 1H), 7 12 (m, 1H), 7 03 (m, 1H), 6 21 (s, 1H), 6 08 (s, 1H), 5 18 (s, 2H), 4 38 (s, 2H), 3 65 (s, 3H), 2 12 (s, 3H), 1 90 (s, 3H) ESHRMS m/z 455 1632 (M+H calculated for $C_{24}H_{24}FN_2O_6$ requires 455 1613)

Step 5 Preparation of 3-[3-bromo-4-[(4-fluoro-2-{[(methoxycarbonyl)amino]methyl}benzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoic acid

413
416



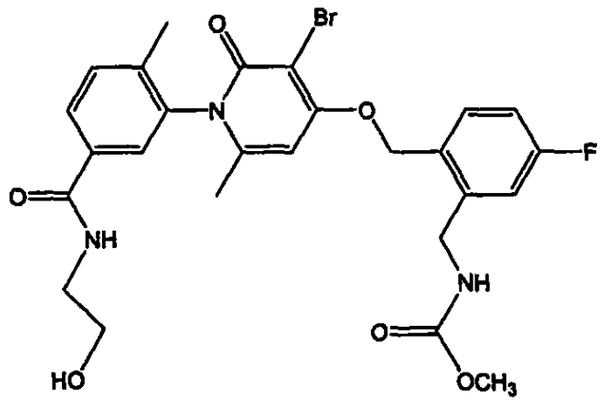
NBS (0 69 g, 3 85 mmol) was added to a solution of 3-[4-[(4-fluoro-2-{[(methoxycarbonyl)amino]methyl}benzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoic acid ( from Step 4) (1 75 g, 3 85 mmol) in DCM (45 mL) After 1 5h, solvent removed on rotary evaporator Solid dissolved in EtOAc and hexane added, resulting in a solid precipitate Solid filtered Solid subsequently dissolved in DCM and washed with water Organic layer dried over $Na_2SO_4$, filtered, and concentrated Pale yellow solid dried in vacuo (1 47 g, 72%) $^1H$ NMR ($CD_3OD$/ 400MHz) δ8 04 (m, 1H), 7 77 (s, 1H), 7 54 (m, 2H), 7 13 (m, 1H), 7 05 (m, 1H), 6 68 (s, 1H), 5 40 (s, 2H), 4 44 (s, 2H), 3 64 (s, 3H), 2 09 (s, 3H), 1 99 (s, 3H) ESHRMS m/z 533 0700 and 535 0677 (M+H calculated for $C_{24}H_{23}BrFN_2O_6$ requires 533 0718 and 535 0701)

Step 6 Preparation of the title compound

To a cooled (-10°C) solution of 3-[3-bromo-4-[(4-fluoro-2-{[(methoxycarbonyl)amino]methyl}benzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoic acid (0 07 g, 0 13 mmol) in DMF (2 0 mL) was added isobutyl chloroformate (0 02 mL, 0 16 mmol) and 4-methylmorpholine (0 02 mL, 0 16 mmol) After 15min, 2 0M methylamine in THF (0 01 mL, 0 20 mmol) was added Solvent removed by distillation after 30min Crude product purified by preparatory HPLC Acetonitrile was evaporated and

the solution washed with 5% $NaHCO_3$ (30 mL) and extracted in DCM (3 x 25 mL) The organic extracts were dried over $Na_2SO_4$, filtered, concentrated, and dried in vacuo to give a white foam, (0 061 g, 86%) $^1H$ NMR ($CD_3OD$/ 400MHz) δ7 85 (m, 1H), 7 54 (m, 3H), 7 14 (m, 1H), 7 05 (m, 1H), 6 68 (s, 1H), 5 40 (s, 2H), 4 43 (s, 2H), 3 64 (s, 3H), 2 89 (s, 3H), 2 08 (s, 3H), 1 99 (s, 3H) ESHRMS m/z 546 0987 and 548 1018 (M+H calculated for $C_{25}H_{26}BrFN_3O_5$ requires 546 1034 and 548 1018)

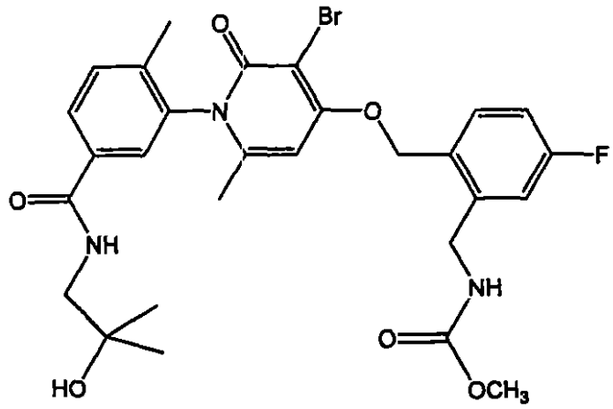
Example 644




methyl 2-({[3-bromo-1-(5-{[(2-hydroxyethyl)amino]carbonyl}-2-methylphenyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl]oxy}methyl)-5-fluorobenzylcarbamate

The title compound was prepared using a procedure similar to that used in the preparation of Example 643 $^1H$ NMR ($CD_3OD$/ 400MHz) δ7 88 (m, 1H), 7 61 (s, 1H), 7 53 (m, 2H), 7 13 (m, 1H), 7 04 (m, 1H), 6 68 (s, 1H), 5 41 (s, 2H), 4 43 (s, 2H), 3 68 (t, 2H, J = 5 6 Hz), 3 64 (s, 3H), 3 48 (t, 2H, J = 5 6Hz), 2 08 (s, 3H), 2 00 (s, 3H) ESHRMS m/z 576 1101 and 578 1072 (M+H calculated for $C_{26}H_{28}BrFN_3O_6$ requires 576 1140 and 578 1124)

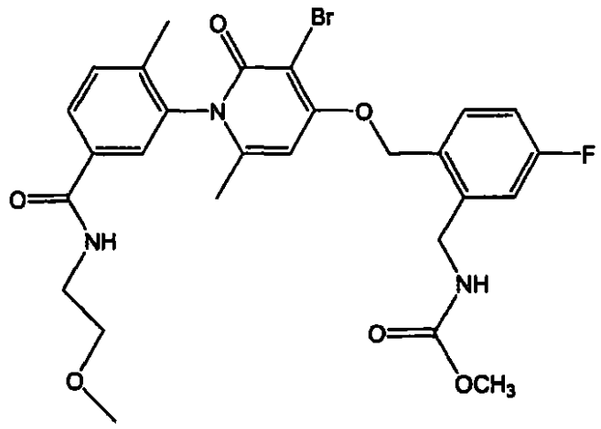
Example 645




methyl 2-({[3-bromo-1-(5-{[(2-hydroxy-2-methylpropyl)amino]carbonyl}-2-methylphenyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl]oxy}methyl)-5-fluorobenzylcarbamate

The title compound was prepared using a procedure similar to that used in the preparation of Example 643 $^1$H NMR ($CD_3OD$/400MHz) δ7 89 (m, 1H), 7 63 (s, 1H), 7 54 (m, 2H), 7 13 (m, 1H), 7 04 (m, 1H), 6 69 (s, 1H), 5 41 (s, 2H), 4 43 (s, 2H), 3 64 (s, 3H), 3 38 (s, 2H), 2 09 (s, 3H), 2 01 (d, 6H, J = 3 2 Hz), 1 21 (s, 3H) ESHRMS m/z 604 1412 and 606 1418 (M+H calculated for $C_{28}H_{32}BrFN_3O_6$ requires 604 1453 and 606 1438)

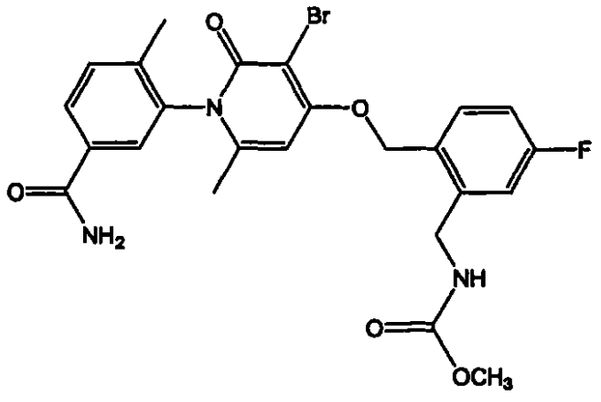
Example 646



methyl 2-({[3-bromo-1-(5-{[(2-methoxyethyl)amino]carbonyl}-2-methylphenyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl]oxy}methyl)-5-fluorobenzylcarbamate

The title compound was prepared using a procedure similar to that used in the preparation of Example 643 $^1$H NMR ($CD_3OD$/400MHz) δ7 87 (m, 1H), 7 59 (s, 1H), 7 53 (m, 2H), 7 14 (m, 1H), 7 05 (m, 1H), 6 68 (s, 1H), 5 41 (s, 2H), 4 44 (s, 2H), 3 64 (s, 3H), 3 54 (s, 4H), 3 35 (s, 3H), 2 08 (s, 3H), 2 00 (s, 3H) ESHRMS m/z 590 1267 and 592 1219 (M+H calculated for $C_{27}H_{30}BrFN_3O_6$ requires 590 1297 and 592 1281)

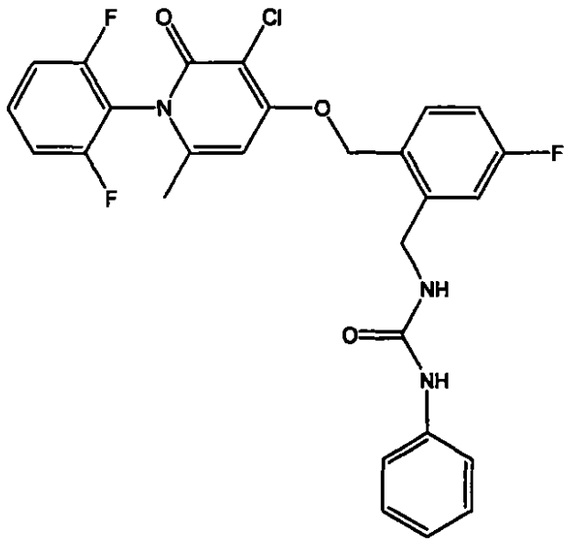
Example 647



methyl 2-[({1-[5-(aminocarbonyl)-2-methylphenyl]-3-bromo-6-methyl-2-oxo-1,2-dihydropyridin-4-yl}oxy)methyl]-5-fluorobenzylcarbamate

The title compound was prepared using a procedure similar to that used in the preparation of Example 643 $^1$H NMR ($CD_3OD$/400MHz) δ7 91 (m, 1H), 7 64 (s, 1H), 7 54 (m, 2H), 7 14 (m, 1H), 7 05 (m, 1H), 6 68 (s, 1H), 5 40 (s, 2H), 4 44 (s 2H), 3 64 (s, 3H), 2 09 (s, 3H), 2 00 (s, 3H) ESHRMS m/z 532 0836 and 534 0787 (M+H calculated for $C_{24}H_{24}BrFN_3O_5$ requires 532 0878 and 534 0861)

Example 648

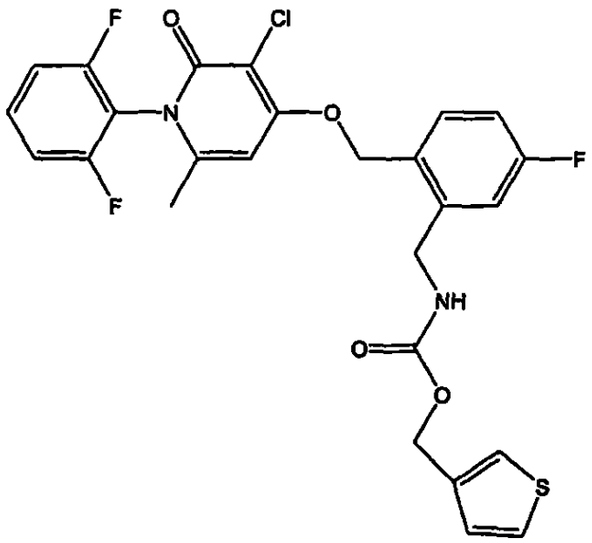



N-[2-({[3-chloro-1-(2,6-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl]oxy}methyl)-5-fluorobenzyl]-N'-phenylurea

To a cooled (0°C) solution of 4-{[2-(aminomethyl)-4-fluorobenzyl]oxy}-3-chloro-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one trifluoroacetate (0 25 g, 0 48 mmol)

in DMA (2 0 mL) was added 4-methylmorpholine (0 06 mL, 0 53 mmol) and phenyl isocyanate (0 06 mL, 0 53 mmol) The reaction was stirred at RT for 1 5h Solvent distilled and crude product purified by preparatory HPLC Acetonitrile was evaporated and the solution washed with 5% $NaHCO_3$ (30 mL) and extracted in DCM (3 x 25 mL) The organic extracts were dried over $Na_2SO_4$, filtered, and concentrated to a white solid, dried in vacuo (0 18 g, 71%) $^1H$ NMR ($CD_3OD$/ 400MHz) δ7 60 (m, 1H), 7 54 (m, 1H), 7 33 (d, 2H, J = 7 6 Hz), 7 22 (m, 5H), 7 06 (m, 1H), 6 95 (t, 1H, J = 7 2 Hz), 6 73 (s, 1H), 5 44 (s, 2H), 4 53 (s, 2H), 2 07 (s, 3H) ESHRMS m/z 528 1304 (M+H calculated for $C_{27}H_{22}ClF_3N_3O_3$ requires 528 1296)

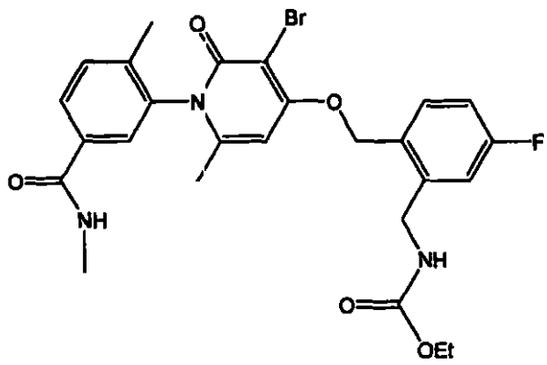
Example 649




thien-3-ylmethyl 2-({[3-chloro-1-(2,6-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl]oxy}methyl)-5-fluorobenzylcarbamate

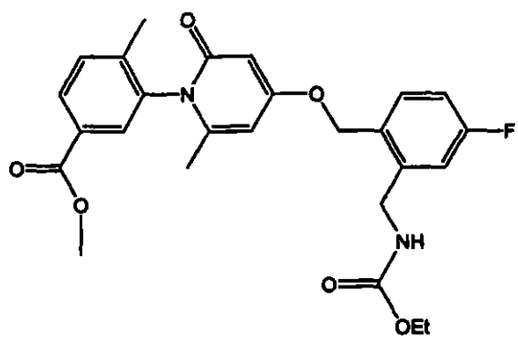
To a cooled (0°C) solution of 4-{[2-(aminomethyl)-4-fluorobenzyl]oxy}-3-chloro-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one trifluoroacetate (0 26 g, 0 50 mmol) and 1, 1-carbonyldiimidazole (0 10 g, 0 60 mmol) in DMA (2 0 mL) was added 4-methylmorpholine (0 06 mL, 0 55 mmol) After 1h at RT, 3-thiophenemethanol (0 09 mL, 0 99 mmol) was added No product was observed after 2h at RT NaH (0 01 g, 0 50 mmol) was added and the reaction stirred at 60°C Reaction was complete after 20min The reaction mixture was cooled (0°C) and acetic acid added to quench the reaction Solvent removed by distillation Crude product purified by preparatory HPLC Acetonitrile was evaporated and the solution washed with 5% $NaHCO_3$ (30 mL) and extracted in DCM (3 x 25 mL) The organic extracts were dried over $Na_2SO_4$, filtered and concentrated to a white foam, dried in vacuo (0 20 g, 73%) $^1H$ NMR ($CD_3OD$/ 400MHz) δ7 61 (m, 1H), 7 52 (m, 1H), 7 34 (s, 2H), 7 23 (t, 3H, J = 8 4 Hz), 7 10 (m, 2H), 6 71 (s, 1H), 5 40 (s, 2H), 5 07 (s, 2H), 4 43 (s, 2H), 2 10 (s, 3H) ESHRMS m/z 549 0858 (M+H calculated for $C_{26}H_{21}ClF_3N_2O_4S$ requires 549 0857)

Example 650



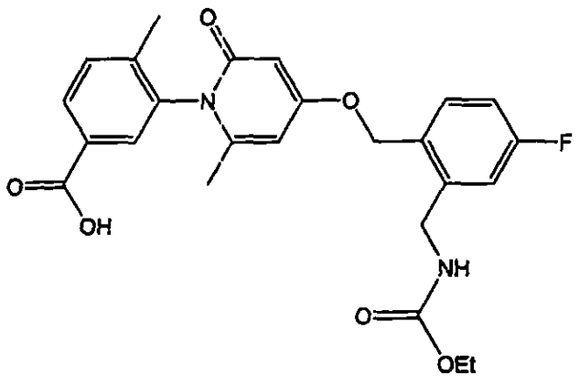

ethyl 2-{[(3-bromo-6-methyl-1-{2-methyl-5-[(methylamino)carbonyl]phenyl}-2-oxo-1,2-dihydropyridin-4-yl)oxy]methyl}-5-fluorobenzylcarbamate

Step 1 Preparation of methyl 3-[4-[(2-{[(ethoxycarbonyl)amino]methyl}-4-fluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoate



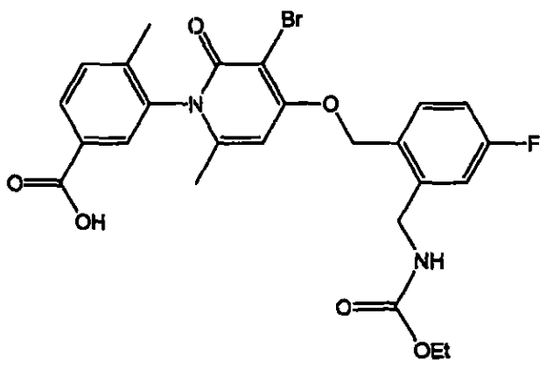
Prepared using a procedure similar to that used in the preparation of methyl 3-[4-[(4-fluoro-2-{[(methoxycarbonyl)amino]methyl}benzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoate $^1$H NMR ($CD_3OD$/ 400MHz) δ8 03 (m, 1H), 7 76 (s, 1H), 7 53 (d, 1H, J = 8 0 Hz), 7 47 (m, 1H), 7 12 (m, 1H), 7 03 (m, 1H), 6 21 (s, 1H), 6 08 (s, 1H), 5 18 (s, 2H), 4 38 (s, 2H), 4 08 (q, 2H, J = 6 8 Hz), 3 89 (s, 3H), 2 12 (s, 3H), 1 89 (s, 3H), 1 23 (t, 3H, J = 6 8 Hz) ESHRMS m/z 483 1900 (M+H calculated for $C_{26}H_{28}FN_2O_6$ requires 483 1926)

Step 2 Preparation of 3-[4-[(2-{[(ethoxycarbonyl)amino]methyl}-4-fluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoic acid



Prepared using a procedure similar to that used in the preparation of 3-[4-[(4-fluoro-2-{[(methoxycarbonyl)amino]methyl}benzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoic acid $^1$H NMR ($CD_3OD$/ 400MHz) δ8 03 (m, 1H), 7 74 (s, 1H), 7 48 (m, 2H), 7 11 (m, 1H), 7 03 (m, 1H), 6 21 (s, 1H), 6 08 (s, 1H), 5 18 (s, 2H), 4 38 (s, 2H), 4 08 (q, 2H, J = 7 2 Hz), 2 11 (s, 3H), 1 90 (s, 3H), 1 23 (t, 3H, J = 7 2 Hz) ESHRMS m/z 469 1738 (M+H calculated for $C_{25}H_{26}FN_2O_6$ requires 469 1769)

Step 3 Preparation of 3-[3-bromo-4-[(2-{[(ethoxycarbonyl)amino]methyl}-4-fluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoic acid



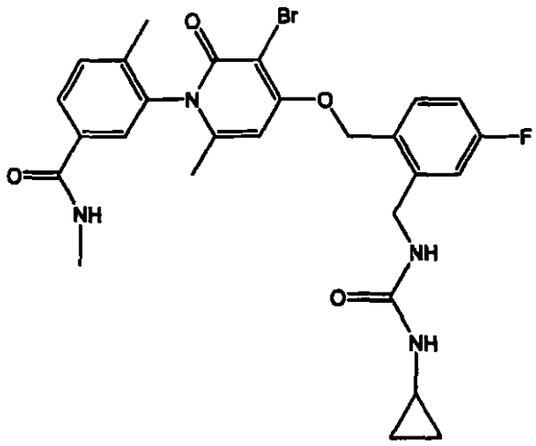
Prepared using a procedure similar to that used in Step 5 of the synthesis of Example 643 $^1$H NMR ($CD_3OD$/ 400MHz) δ8 04

(m, 1H), 7 76 (s, 1H), 7 55 (m, 2H), 7 13 (m, 1H), 7 05 (m, 1H), 6 68 (s, 1H), 5 40 (s, 2H), 4 43 (s, 2H), 4 07 (m, 2H), 2 09 (s, 3H), 1 99 (s, 3H), 1 22 (t, 3H, J = 7 2 Hz) ESHRMS m/z 547 0842 and 549 0818 (M+H calculated for $C_{25}H_{25}BrFN_2O_6$ requires 547 0875 and 549 0858)

Step 4

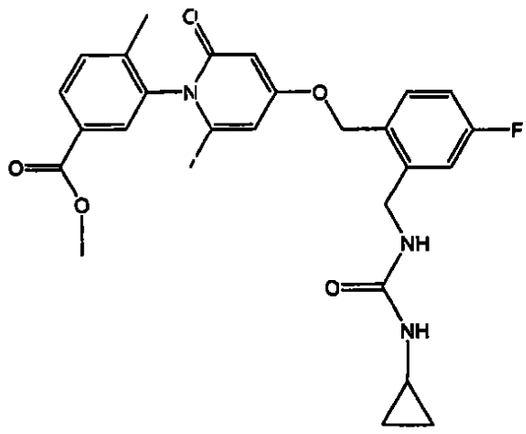
Prepared using a procedure similar to that used in the preparation of Example 643 $^1$H NMR ($CD_3OD$/ 400MHz) δ7 85 (m, 1H), 7 54 (m, 3H), 7 13 (m, 1H), 7 04 (m, 1H), 6 68 (s, 1H), 5 40 (s, 2H), 4 43 (s, 2H), 4 07 (q, 2H), 2 89 (s, 3H), 2 08 (s, 3H), 1 99 (s, 3H), 1 23 (t, 3H, J = 7 2 Hz) ESHRMS m/z 560 1215 and 562 1193 (M+H calculated for $C_{26}H_{28}BrFN_3O_5$ requires 560 1191 and 562 1175)

Example 651



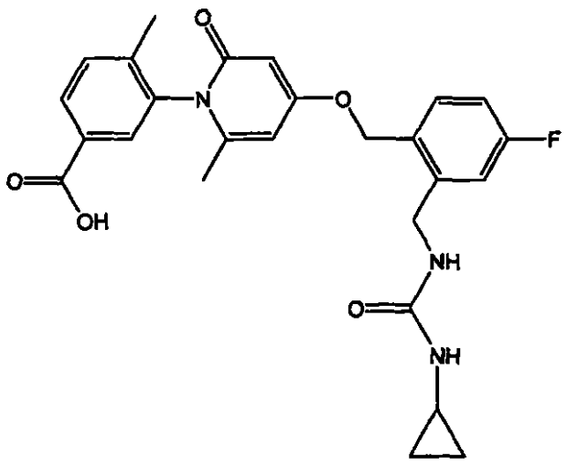

3-[3-bromo-4-{[2-({[(cyclopropylamino)carbonyl]amino}methyl)-4-fluorobenzyl]oxy}-6-methyl-2-oxopyridin-1(2H)-yl]-N,4-dimethylbenzamide

Step 1 Preparation of methyl 3-[4-{[2-({[(cyclopropylamino)carbonyl]amino}methyl)-4-fluorobenzyl]oxy}-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoate



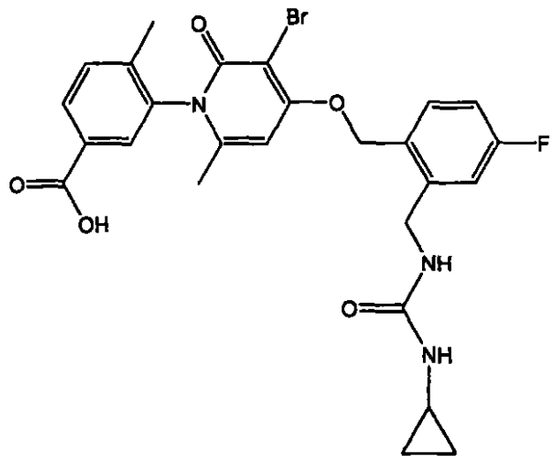
To a cooled (0°C) solution of methyl 3-[4-{[2-(aminomethyl)-4-fluorobenzyl]oxy}-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoate trifluoroacetate () (1 13 g, 2 16 mmol) and 1,1-carbonyldiimidazole (0 42 g, 2 59 mmol) in DMA (8 0 mL) was added 4-methylmorpholine (0 36 mL, 3 2 mmol) Reaction was stirred at RT for 2h DMA removed by distillation Crude product purified by preparatory HPLC Acetonitrile was evaporated and the solution washed with 5% $NaHCO_3$ (30 mL) and extracted in DCM (3 x 25 mL) The organic extracts were dried over $Na_2SO_4$, filtered, concentrated, and dried in vacuo (0 78 g, 73%) $^1H$ NMR ($CD_3OD$/ 400MHz) δ8 03 (m, 1H), 7 76 (s, 1H), 7 53 (d, 1H, J = 8 0 Hz), 7 46 (m, 1H), 7 12 (m, 1H), 7 01 (m, 1H), 6 22 (s, 1H), 6 08 (s, 1H), 5 19 (s, 2H), 4 44 (s, 2H), 3 89 (s, 3H), 2 48 (m, 1H), 2 12 (s, 3H), 1 89 (s, 3H), 0 70 (m, 2H), 0 47 (m, 2H) ESHRMS m/z 494 2076 (M+H calculated for $C_{27}H_{29}FN_3O_5$ requires 494 2086)

Step 2 Preparation of 3-[4-{[2-({[(cyclopropylamino)carbonyl]amino}methyl)-4-fluorobenzyl]oxy}-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoic acid



Prepared using a procedure similar to that used in the preparation of 3-[4-[(4-fluoro-2-{[(methoxycarbonyl)amino]methyl}benzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoic acid $^1$H NMR ($CD_3OD$/400MHz) δ8 02 (m, 1H), 7 74 (s, 1H), 7 48 (m, 2H), 7 12 (m, 1H), 7 01 (m, 1H), 6 22 (s, 1H), 6 08 (s, 1H), 5 19 (s, 2H), 4 44 (s, 2H), 2 48 (m, 1H), 2 11 (s, 3H), 1 90 (s, 3H), 0 69 (m, 2H), 0 47 (m, 2H) ESHRMS m/z 480 1921 (M+H calculated for $C_{26}H_{27}FN_3O_5$ requires 480 1929)

Step 3 Preparation of 3-[3-bromo-4-{[2-({[(cyclopropylamino)carbonyl]amino}methyl)-4-fluorobenzyl]oxy}-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoic acid

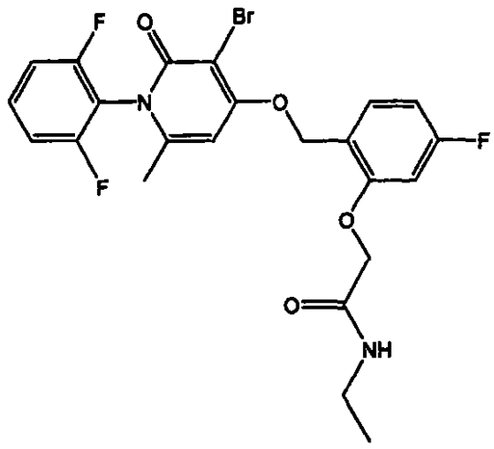


Prepared using a procedure similar to that used in Step 5 of the synthesis of Example 643 $^1$H NMR (DMSO-$d_6$/ 400MHz) δ7 92 (m, 1H), 7 67 (s, 1H), 7 54 (m, 2H), 7 12 (m, 2H), 6 71 (s, 1H), 5 37 (s, 2H), 4 31 (d, 2H, J = 6 4 Hz), 2 40 (m, 1H), 2 00 (s, 3H), 1 88 (s, 3H), 0 56 (m, 2H), 0 33 (m, 2H) ESHRMS m/z 558 0988 and 560 0981 (M+H calculated for $C_{26}H_{26}BrFN_3O_5$ requires 558 1034 and 560 1018)

Step 4

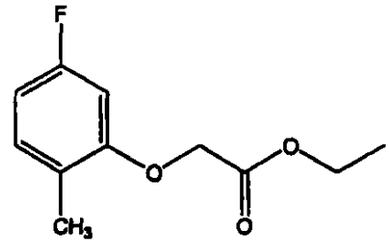
Prepared using a procecure similar to that used in the preparation of Example 643 $^1$H NMR ($CD_3OD$/ 400MHz) δ7 85 (m, 1H), 7 54 (m, 3H), 7 14 (m, 1H), 7 03 (m, 1H), 6 69 (s, 1H), 5 41 (s, 2H), 4 48 (s, 2H), 2 89 (s, 3H), 2 48 (m, 1H), 2 08 (s, 3H), 1 99 (s, 2H), 0 70 (m, 2H), 0 47 (m, 2H) ESHRMS m/z 571 1348 and 573 1355 (M+H calculated for $C_{27}H_{29}BrFN_4O_4$ requires 571 1351 and 573 1335)

Example 652



3-[3-bromo-4-{[2-({[(cyclopropylamino)carbonyl]amino}methyl)-4-fluorobenzyl]oxy}-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoic acid

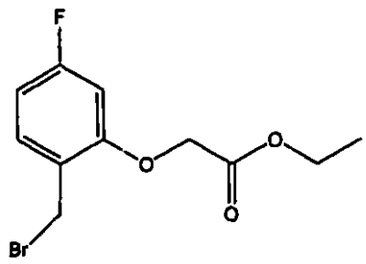
Step 1 Preparation of ethyl (5-fluoro-2-methylphenoxy)acetate



To a solution of 5-fluoro-2-methylphenol (1 00 g, 7 93 mmol) and ethylbromoacetate (1 59 g, 9 51 mmol) in DMF (15 mL) was added $K_2CO_3$ (1 10 g, 7 93 mmol) After 30min at RT, DMF was removed by distillation The crude product was washed with 5% citric acid (30 mL) and water (30 mL), extracted in DCM (3 x 20 mL), dried over $Na_2SO_4$, filtered, concentrated, and dried in vacuo Desired product obtained as yellow oil (1 30 g, 77%) $^1H$ NMR ($CD_3OD$/ 400MHz) δ7 09 (t, 1H, J = 8 8 Hz), 6 58 (m, 1H), 6 56 (m, 1H), 4 71 (s, 2H), 4 23 (q, 2H, J = 7 2

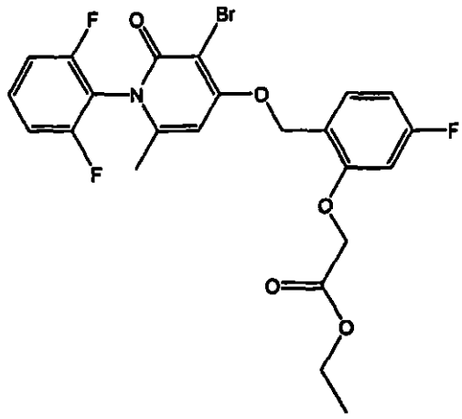
Hz), 2 18 (s, 3H), 1 27 (t, 3H, J = 7 2 Hz) ESHRMS m/z 212 0847 (M+H calculated for $C_{11}H_{13}FO_3$ requires 212 0849)

Step 2 Preparation of etnyl [2-(bromomethyl)-5-fluorophenoxy]acetate



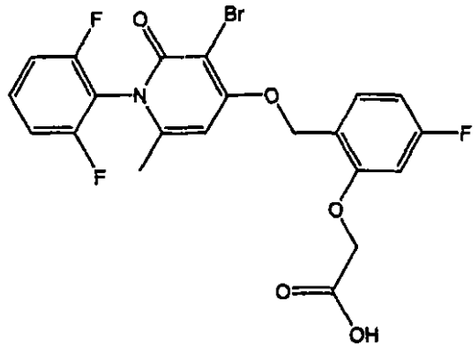

A solution of ethyl (5-fluoro-2-methylphenoxy)acetate (from Step 1) (0 65 g, 3 06 mmol), NBS (0 65 g, 3 68 mmol), and benzoyl peroxide (0 05 g, 0 21 mmol) in CCl4 (7 0 mL) were refluxed at 90°C for 2 5h Additional NBS (0 16 g, 0 92 mmol) added, and reaction continued overnight Solid filtered and filtrate concentrated onto silica gel Purified by flash column chromatography using hexane and 2 5% EtOAc/hexane as eluent Product obtained as yellow liquid (0 27 g, 30%) $^1$H NMR ($CD_3OD$/ 400MHz) δ7 37 (m, 1H), 6 69 (m, 2H), 4 80 (s, 2H), 4 60 (s, 2H), 4 23 (q, 2H, J = 7 2 Hz), 1 27 (t, 3H, J = 7 2 Hz)

Step 3 Preparation of ethyl [2-({[3-bromo-1-(2,6-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl]oxy}methyl)-5-fluorophenoxy]acetate



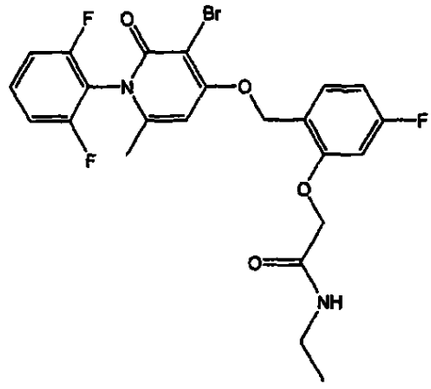
To a solution of ethyl [2-(bromomethyl)-5-fluorophenoxy]acetate (from Step 2) (0 59 g, 2 03 mmol) and 3-bromo-1-(2,6-difluorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one (0 61 g, 1 93 mmol) in DMF (3 0 mL) was added $K_2CO_3$ (0 34 g, 2 43 mmol) After 2h at RT, DMF was removed by distillation The crude product was washed with 5% citric acid, extracted in DCM, dried over $Na_2SO_4$, filtered, and concentrated onto silica gel Purified by flash column chromatography using 50% EtOAc/hexane as the eluent Obtained product as a pale yellow solid (0 45 g, 42%) $^1H$ NMR ($CD_3OD$/ 400MHz) δ7 21 (q, 3H, J = 8 4 Hz), 6 80 (m, 2H), 6 69 (s, 1H), 6 15 (s, 1H), 5 40 (s, 2H), 4 84 (s, 2H), 4 23 (q, 2H, J = 6 8 Hz), 2 08 (s, 3H), 1 26 (t, 3H, J = 6 8 Hz) ESHRMS m/z 526 0446 and 528 0414 (M+H calculated for $C_{23}H_{20}BrF_3NO_5$ requires 526 0471 and 528 0454)

Step 4 Preparation of [2-({[3-bromo-1-(2,6-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl]oxy}methyl)-5-fluorophenoxy]acetic acid



A solution of ethyl [2-({[3-bromo-1-(2,6-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl]oxy}methyl)-5-fluorophenoxy]acetate (from Step 3) (0 62 g, 1 18 mmol), 1 5 N NaOH solution in 1 1 MeOH water (1 2 mL, 1 77 mmol), and THF (1 2 mL) were refluxed at 60°C for 1h The solution was concentrated on a rotary evaporator, cooled, and 5% citric acid added The solid precipitate was filtered and dried in vacuo Product obtained as a pale yellow solid (0 35 g, 60%) $^1H$ NMR ($CD_3OD$/ 400MHz) δ7 59 (m, 1H), 7 49 (m, 1H), 7 22 (m, 2H), 6 75 (m, 2H), 6 72 (s, 1H), 5 43 (s, 2H), 4 66 (s, 2H), 2 07 (s, 3H) ESHRMS m/z 498 0143 and 500 0186 (M+H calculated for $C_{21}H_{16}BrF_3NO_5$ requires 498 0158 and 500 0141)

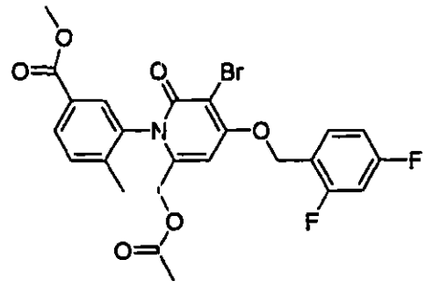
Step 5 Preparation of 2-[2-({[3-bromo-1-(2,6-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl]oxy}methyl)-5-fluorophenoxy]-N-ethylacetamide



To a cooled (-10°C) solution of [2-({[3-bromo-1-(2,6-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl]oxy}methyl)-5-fluorophenoxy]acetic acid (from Step 4) (0 15 g, 0 30 mmol) in DMA (2 0 mL) was added 4-methylmorpholine (0 04 mL, 0 36 mmol) and isobutyl chloroformate (0 05 mL, 0 36 mmol) Ethylamine (0 04 mL, 0 45 mmol) was added after 20 minutes DMF removed by distillation after 1h Crude product purified by preparatory HPLC Acetonitrile was evaporated and the solution washed with 5% $NaHCO_3$ (30 mL) and extracted in DCM (3 x 25 mL) The organic extracts were dried over $Na_2SO_4$, filtered, concentrated, and dried in vacuo to give a white solid (0 080 g, 51%) $^1H$ NMR ($CD_3OD$/ 400MHz) δ7 60 (m, 1H), 7 53 (t, 1H, J = 8 0 Hz), 7 23 (t, 2H, J = 8 4 Hz), 6 82 (m, 2H), 6 71 (s, 1H), 5 42 (s, 2H), 4 61 (s, 2H), 3 31 (q, 2H, J = 6 4 Hz), 2 10 (s, 3H), 1 09 (t, 3H, J = 7 2 Hz) ESHRMS m/z 525 0616 and 527 0568 (M+H calculated for $C_{23}H_{21}BrF_3N_2O_4$ requires 525 0631 and 527 0614)

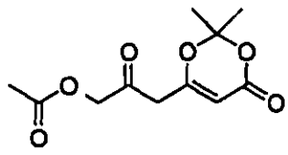
Example 653

422
425



methyl 3-[6-[(acetyloxy)methyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-4-methylbenzoate

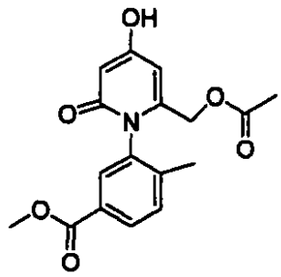
Step 1 Preparation of 3-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)-2-oxopropyl acetate



A solution of 2,2,6-trimethyl-4H-1,3-dioxin-4-one (20g, 141 mmol) in dry THF (400 mL) was cooled to -78 °C To this solution was slowly added a LiHMDS (1M-THF, 160 mL, 160 mmol) The resulting solution was maintained at -78°C with stirring for 30 min To the reaction mixture was added acetoxy acetylchloride (17 mL, 160 mmol) and the resulting mixture was maintained at -78 °C for at 1h The reaction was then allowed to slowly warm to rt and stir for an additional 1h The reaction was then quenched with addition of a 1N solution of ammonium chloride The layers were sperated and the aqueous layer was extracted with ethyl acetate (5x) The organics were combined, dried, and concentrated in vacuo The crude product was purified using a medium pressure liquid chromatography biotage system Elution with hexanes-ethyl acetate (3 1) gave 13 1 g (38%) of a red-brown oil The

product looks clean by NMR $^1$H NMR (300 MHz, $CDCl_3$) δ 5 42 (s, 1H), 4 75 (s, 2H), 3 41 (s, 2H), 2 22 (s, 3H), 1 75 (s, 6H)

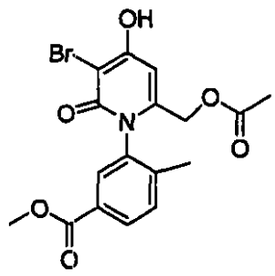
Step 2 Preparation of methyl 3-[6-[(acetyloxy)methyl]-4-hydroxy-2-oxopyridin-1(2H)-yl]-4-methylbenzoate



To a 100 mL RBF containing methyl 3-amino,4-methylbenzoate (1 65g, 10 mmol) was added the enone from Step 1 (2 6g, 10 7 mmol) The mixture was then dissolved in toluene (40 mL), fitted with a reflux condenser, and placed in an oil bath preset to 115 °C The mixture was heated to reflux for 1 5h The reaction flask was removed from the oil bath and a catalytic amount of TFA (5-6 drops) was added The reaction was placed back in the oil bath and heated to reflux for an additional 2h The reaction was then allowed to cool to 0°C The toluene was then removed under vacuum to give a thick brown residue The residue was then dissolved in acetonitrile (10-15 mL) and allowed to stand After 20-30 min a precipitate results which was filtered and washed with diethyl ether After drying, an off-white solid (1 9g, 57% yield) was obtained $^1$H NMR (300 MHz, $DMSO_{-d6}$) δ 7 94 (dd, J = 7 8,1 5 Hz, 1H), 7 73 (s, 1H), 7 54 (d, J = 8 1 Hz, 1H), 6 19 (s, 1H), 5 73-5 71 (m, 1H), 4 47 (AB quar, J = 10 5 Hz, 2H), 3 87 (s, 3H), 2 09 (s, 3H), 1 91 (s, 3H) ES-HRMS m/z 332 1096 (M+H calcd for $C_{17}H_{18}NO_6$ requires 332 1129)

423
426

Step3 Preparation of methyl 3-[6-[(acetyloxy)methyl]-3-bromo-4-hydroxy-2-oxopyridir-1(2H)-yl]-4-methylbenzoate

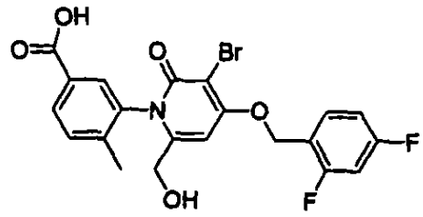


To a slurry of the phenol (2 5g, 7 5 mmol) in dry acetonitrile (50 mL), at rt, was added n-bromosuccinimide (1 33g, 7 5 mmol) The resulting homogeneous mixture was stirred at rt for 3h The resulting precipitate was filtered and washed sequentially with acetonitrile and the diethyl ether The product was dried in a vacuum oven to yield an off-white solid (2 5g, 81%) $^1$H NMR (300 MHz, DMSO $_{d6}$) δ 11 82 (s, 1H), 7 97 (dd, J = 7 8,1 5 Hz, 1H), 7 80 (d, J = 1 5 Hz, 1H), 7 57 (d, J = 8 1 Hz, 1H), 6 38 (s, 1H), 4 49 (AB quar, J = 13 8 Hz, 2H), 3 87 (s, 3H), 2 08 (s, 3H), 1 92 (s, 3H) ES-HRMS m/z 410 0225 (M+H calcd for $C_{17}H_{17}NBrO_6$ requires 410 0234)

Step 4 Preparation of the title compound To a solution of the above phenol (2 5g, 6 C mmol) in dry DMF (25 mL) was added solid potassium carbonate (804 mg, 6 0 mmol) To this mixture was then added, via syringe, 2,4-diflourobenzyl bromide (783 µL, 6 0 mmol) The resulting mixture was allowed to stir at rt overnight The reaction was then poured into ice water and stirred vigorously The resulting precipitate was filtered and washed sequentially with water and diethyl ether The solid was dried in a vacuum oven to yield an off-white solid (3 3g, 99%) $^1$H NMR (400 MHz, DMSO-$_{d6}$) δ 7 97 (dd, J = 7 6,1 2

Hz, 1H), 7 83 (d, J = 1 6 Hz, 1H), 7 71 (q, J = 8 8 Hz, 1H), 7 57 (d, J = 8 0 Hz, 1H), 7 37 (dt, J = 10 4, 2 4 Hz, 1H), 7 21 (dt, J = 8 4, 2 0 Hz, 1H), 6 90 (s, 1H), 5 40 (s, 2H), 4 57 (AB quar, J = 13 6 Hz, 2H), 3 86 (s, 3H), 2 07 (s, 3H), 1 90 (s, 3H) ES-HRMS m/z 536 0484 (M+H calcd for $C_{24}H_{21}NF_2BrO_6$ requires 536 0515)

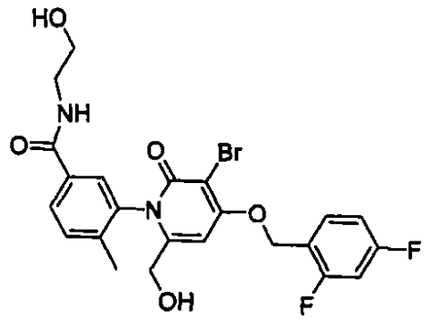
Example 654



3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-(hydroxymethyl)-2-oxopyridin-1(2H)-yl]-4-methylbenzoic acid

To a stirred suspension, at rt, of the Example 643 (2 0g, 3 7 mmol) in THF (10 mL) was added a solution of 2 5N NaOH (3mL, 7 5 mmol) The resulting homogeneous solution was stirred for 2h The reaction was judged complete and 1N HCl was added dropwise until a pH ~ 4 was obtained The reaction was then diluted with $CH_2Cl_2$ (10 mL) The resulting precipitate was filtered with additional washing from $CH_2Cl_2$ The solid was dried in a vacuum oven to yield a pure white solid (1 8g, 99%) $^1H$ NMR (300 MHz, DMSO $_{d6}$) δ 7 95 (dd, J = 7 8,1 8 Hz, 1H), 7 74-7 66 (m, 2H), 7 54 (d, J = 8 1 Hz, 1H), 7 37 (dq, J = 7 8, 2 7 Hz, 1H), 7 24-7 17 (m, 1H), 6 72 (s, 1H), 5 39 (s, 2H), 3 83 (AB quar, J = 15 6 Hz, 2H), 2 02 (s, 3H) ES-HRMS m/z 480 0253 (M+H calcd for $C_{21}H_{17}NF_2BrO_5$ requires 480 0253)

Example 655

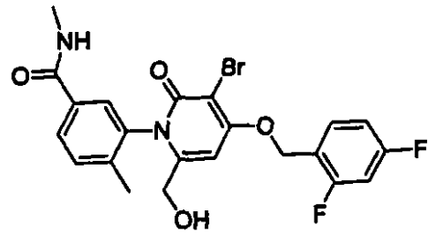


3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-(hydroxymethyl)-2-oxopyridin-1(2H)-yl]-N-(2-hydroxyethyl)-4-methylbenzamide

To a slurry of Example 654 (500mg, 1 04 mmol) in anhydrous $CH_2Cl_2$ was added $Et_3N$ (218 µL, 1 56 mmol) and the resulting homogeneous mixture was stirred at rt To this mixture was then added ethanolamine (70 µL, 1 14 mmol) via syringe HOBt (155mg, 1 14 mmol) was then added followed by addition of EDC (217 mg, 1 14 mmol) The reaction was allowed to stir overnight at rt The reaction was quenched by addition of a solution of 1N $NH_4Cl$ The biphasic mixture was separated and the aqueous layer was extracted with $CH_2Cl_2$ (4X) The organics were combined, dried, and concentrated in vacuo The resulting residue was purified by flash chromatography on a 16g Michele-Miller column Elution with $CH_2Cl_2$-MeOH (10 1 → 12 1) resulted in obtaining the desired product as a viscous oil The oil was then dissolved in a $CH_3CN$-$Et_2O$ combination After 5-10 minutes, a precipitate resulted which upon filtration and drying yielded a pure white solid (210 mg, 40%) $^1H$ NMR (300 MHz, $DMSO_{-d6}$) δ 8 46 (t, J = 5 2 Hz, 1H), 7 88 (dd, J = 8 0, 2 0 Hz, 1H), 7 72-7 65 (m, 2H), 7 50 (d, J = 8 4 Hz, 1H), 7 37 (dq, J = 9 6, 2 4 Hz, 1H), 7 20 (dq, J = 7 6, 1 6 Hz, 1H), 6 71 (s, 1H), 5 68 (t, J = 5 6 Hz, -OH), 5 40 (s, 2H), 4 73 (t, J = 5 6 Hz, -OH), 4 02 (dd, J = 16 4,

5 6 Hz, 1H), 3 70 (dd, J = 16 4, 5 6 Hz, 1H), 3 52-3 48 (m, 2H), 3 39-3 25 (m, 2H), 2 00 (s, 3H) ES-HRMS m/z 523 0674 (M+H calcd for $C_{23}H_{22}N_2F_2BrO_5$ requires 523 0675)

Example 656

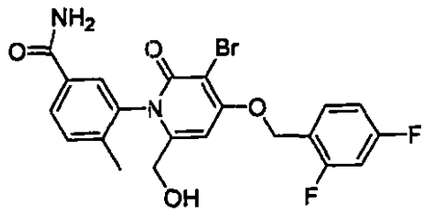


3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-(hydroxymethyl)-2-oxopyridin-1(2H)-yl]-N,4-dimethylbenzamide

The titled compound was prepared from the acid Example 654 (550 mg, 1 07 mmol) in a similar manner to the amide described above using EDC (245 mg, 1 28 mmol), HOBt (171 µL, 1 28 mmol), $Et_3N$ (225 mL, 1 6 mmol), and 2 0M $MeNH_2$-THF (1 2 µL, 2 48 mmol) Following work-up with 1N $NH_4Cl$ the product was precipitated out of the biphasic mixture after dilution with additional $CH_2Cl_2$ to give a white solid (250 mg, 51% yield) ¹H NMR (300 MHz, $DMSO_{d6}$) δ 8 48 (quar, J = 4 5 Hz, 1H), 7 88 (dd, J = 8 1, 1 8 Hz, 1H), 7 72 (app quar, J = 6 6 Hz, 1H), 7 63 (d, J = 1 8 Hz, 1H), 7 52 (d, J = 8 1 Hz, 1H), 7 37 (dt, J = 10 2, 2 4 Hz, 1H), 7 20 (app dt, J = 8 4, 1 8 Hz, 1H), 6 74 (s, 1H), 5 71 (t, J = 5 4 Hz, 1H), 5 42 (s, 2H), 4 03 (dd, J = 13 8, 5 1 Hz, 1H), 3 72 (dd, J = 16 4, 5 1 Hz, 1H), 2 78 (d, J = 4 5 Hz, 3H), 2 02 (s, 3H) ES-HRMS m/z 493 0575 (M+H calcd for $C_{22}H_{20}N_2F_2BrO_4$ requires 493 0569)

425
428

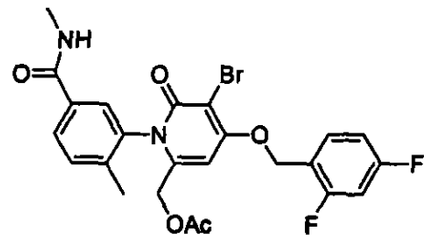
Example 657



3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-(hydroxymethyl)-2-oxopyridin-1(2H)-yl]-4-methylbenzamide

To a stirred suspension, at rt, of the carboxylic acid Example 654 (400 mg, 0 80 mmol) in anhydrous THF (4 mL) was added 4-methylmorpholine (274 µL, 2 5 mmol) To the resulting heterogeneous solution was then added 2-Chloro-4,6-dimethyltriazine (170 mg, 1 0 mmol) and the mixture was allowed to stir for 1h at rt Ammonium hydroxide solution (28-32%, 2 mL) was then added to the reaction and it was allowed to stir at rt overnight The reaction was then worked up by diluting with $H_2O$ (2-3 mL) and stirring vigorously The resulting precipitate was filtered and washed with H2O and then diethyl ether After drying with a vacuum oven an off-white solid (140 mg, 32%) was obtained %) $^1$H NMR (300 MHz, DMSO-$_{d6}$) δ 7 99-7 80 (m, 2H), 7 76 (m, 3H), 7 52 (d, J = 8 1 Hz, 1H), 7 43-7 39 (m, 2H), 7 52 (d, J = 8 1 Hz, 1H), 7 43-7 36 (m, 2H), 7 20 (dt, J = 8 7, 1 8 Hz, 1H), 6 74 (s, 1H), 5 41 (s, 2H), 4 02-3 62 (m, 2H), 2 03 (s, 3H) ES-HRMS m/z 479 0411 (M+H calcd for $C_{21}H_{18}N_2F_2BrO_4$ requires 479 0413)

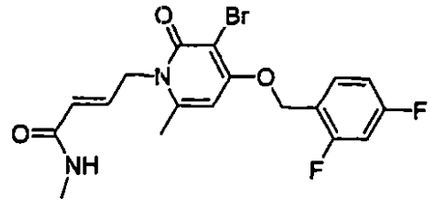
Example 658



(5-bromo-4-[(2,4-difluorobenzyl)oxy]-1-{2-methyl-5-[(methylamino)carbonyl]phenyl}-6-oxo-1,6-dihydropyridin-2-yl)methyl acetate

To a solution of 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-(hydroxymethyl)-2-oxopyridin-1(2H)-yl]-N,4-dimethylbenzamide, (225 mg, 0 50 mmol) stirred in $CH_2Cl_2$ was added pyridine (55 µL, 0 69 mmol) To the resulting homogeneous solution was then added acetic anhydride (47 µL, 0 51 mmol) The mixture was stirred at rt for 3h Additional pyridine (150 µL, 1 8 mmol) and acetic anhydride (100 µL, 1 05 mmol) were then added and the reaction was allowed to stir overnight at rt The reaction was then quenched with 1N $NHCl_4$ and diluted with $CH_2Cl_2$ The layers were separated and the organic layer was then extracted with $CH_2Cl_2$ (3X) The organics were then combined, dried, and concentrated in vacuo The residue was then triturated with $Et_2O$ and filtered to give (150 mg, 61%) an off-white solid $^1H$ NMR (300 MHz, $DMSO_{d6}$) δ 8 48 (br s, 1H), 7 87 (app d, J = 7 8 Hz, 1H), 7 74-7 69 (m, 2H), 7 52 (d, J = 7 5 Hz, 1H), 7 40 (app t, J = 8 1 Hz, 1H), 7 28-7 19 (m, 1H), 6 91 (s, 1H), 5 43 (s, 2H), 4 60 (s, 2H), 2 79 (s, 3H), 2 06 (s, 3H), 1 94 (s, 3H) ES-HRMS m/z 535 0676 (M+H calcd for $C_{24}H_{22}N_2F_2BrO_5$ requires 535 0675)

Example 659



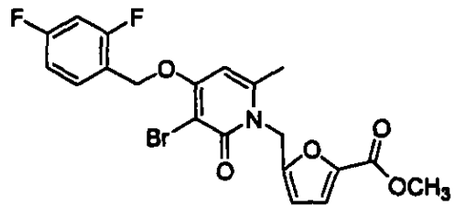
(2E)-4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-N-methylbut-2-enamide

Step 1, (2E)-4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]but-2-enoic acid The carboxylic acid compo was prepared by stirring the ester (900 mg, 2 1 mmol) in THF (10 mL) To this solution was added 1N NaOH (1 mL) and the resulting mixture was stirred at rt After 2 h, additional NaOH (1 mL) was added to the reaction and then allowed to stir at rt overnight The THF was then concentrated under vacuum The remaining aqueous layer was then acidified to pH ~ 4 after which a white precipitate resulted Filtration and drying under vacuum gave rise to a white solid (900 mg) that was used as in the next step

The titled compound was prepared by stirring the above acid (480 mg, 1 16 mmol) in $CH_2Cl_2$ at rt To this mixture was added sequentiallyEt$_3$N (244 µL), HOBt (188 mg, 1 4 mmol), MeNH$_2$ (2 0M-THF, 700 mL, 1 4 mmol), and finally EDC (266 mg, 1 4 mmol) The homogeneous mixture was then allowed to stir at rt overnight The reaction was quenched with 1N HCl The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (4x) The organics were combined, dried, and concentrated in vacuo The crude residue was triturated in $CH_3CN$-$Et_2O$ combination and filtered to give a pure white solid (330 mg, 67%) $^1$H-NMR (DMSO$_{d6}$/300 MHz) δ 8 20-7 90 (m, 1H), 7 68 (q, J = 8 4 hz, 1H), 7 37 (dt, J = 10 2, 2 4 Hz, 1H), 7 20 (dt, J = 15 6, 4 2 Hz, 1H), 6 60 (s, 1H), 5 63 (d, J = 15 6 Hz, 1H),

5 31 (s, 2H), 4 81 (d, J = 2 7 Hz, 2H), 3 33 (d, J = 6 9 Hz, 1H), 2 61 (d, J = 4 8 Hz, 3H), 2 37 (s, 3H) ES-HRMS m/z 427 0493 (M + H calcd for $C_{18}H_{18}BrF_2N_2O_3$ = 427 0463)

Example 660

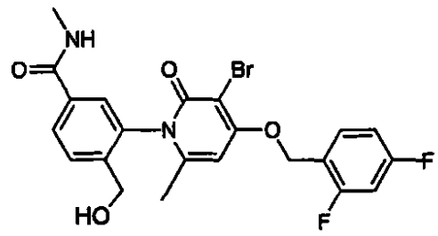


methyl 5-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-2-furoate

Step 1 To a room temperature suspension of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (330 1 mg, 1 00 mmol)) and NaH (48 0 mg, 2 0 mmol) in THF (1 6 mL) was added methyl-5-chloromethyl-2-furate (400 mg, 2 30 mmol) The resulting suspension was stirred and heated to 68 °C for 8 hours until complete consumption of starting material by LCMS analysis The reaction mixture was then diluted with ammonium chloride (saturated aqueous solution, 10 mL) and water (100 mL) This resulting emulsion was then extracted with with ethyl acetate (3 X 300 mL) The resulting organic extract was separated, $Na_2SO_4$ dried, and concentrated The resulting dark residue was subjected to $SiO_2$ chromatography with ethyl acetate/hexanes (3 7) to furnish a solid $^1H$ NMR (400 MHz, $CDCl_3$) δ 7 53 (app q, J = 8 2 Hz, 1H), 7 07 (d, J = 3 5 Hz, 1H), 6 93 (app dt, J = 8 4, 1 5 Hz, 1H), 6 84 (app ddd, J = 10 2, 8 7, 2 4 Hz, 1H), 6 53 (d, J = 3 4 Hz, 1H), 6 00 (s, 1H), 5 27 (s, 2H), 5 18 (s, 2H), 3 85 (s, 3H), 2 54 (s, 3H), LC/MS C-18 column, $t_r$ = 2 64 minutes (5 to 95%

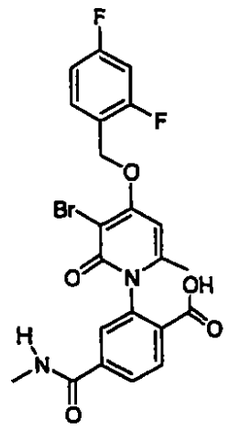
acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 468 (M+H) ES-HRMS m/z 468 0276 (M+H calcd for $C_{20}H_{17}BrF_2NO_5$ requires 468 0253)

Example 661



3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-(hydroxymethyl)-N-methylbenzamide

Step 1 Preparation of 2-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-[(methylamino)carbonyl] benzoic acid



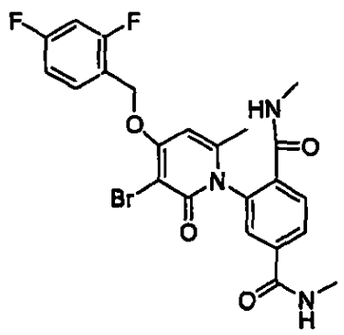
To a room temperature solution of methyl 2-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-[(methylamino)carbonyl]benzoate (1 05 g, 2 02 mmol) in THF

(10 0 mL) was added dropwise an aqueous solution of sodium hydroxide (3 0 M, 3 5 mL, 10 mmol) The reaction was then heated to 60 °C for 8 0 hours The resulting suspension was then diluted with 500 mL of ethyl acetate and neutralized with an aqueous solution of hydrochloric acid (2 0 N, 5 0 mL, 10 mmol) The resulting biphasic solution was separated and the resulting aqueous layer was further extracted with ethyl acetate (2 X 200 mL) The resulting combined organic extracts were $Na_2SO_4$ dried, filtered and concentrated in vacuo to a volume of 50 mL At this time a white solid began to form and the resulting solid suspension was allowed to sit until precipitation appeared to stop (approximately 1 0 hour) The precipitate was collected and dried in vacuo (1 0 mm Hg) to furnish the solid acid as an intermediate (806 mg, 78 %) $^1H$ NMR (400 MHz, $d_7$-DMF) δ 13 19 (s, 1H), 8 63 (app d, J = 4 5 Hz, 1H), 8 09 (d, J = 8 0 Hz, 1H), 8 00 (dd, J = 8 0, 1 6 Hz, 1H), 7 71-7 67 (m, 2H), 7 34 (app dt, J = 9 6, 1 6 Hz, 1H), 7 16 (app dt, J = 8 7, 1 8 Hz, 1H), 6 66 (s, 1H), 5 33 (s, 2H), 3 29 (s, 3H), 1 92 (s, 3H), LC/MS C-18 column, $t_r$ = 2 15 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 507 (M+H) ES-HRMS m/z 507 0344 (M+H calcd for $C_{22}H_{18}BrF_2N_2O_5$ requires 507 0362)

Step 2 Preparation of the title compound To a 0 °C solution of 2-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-[(methylamino)carbonyl] benzoic acid (500 mg, 0 986 mmol) in THF (6 8 mL) was added dropwise a solution of borane-dimethyl sulfide complex (THF solution, 2 0 M, 2 0 mL, 4 0 mmol) The internal temperature of the reaction was never allowed to exceed 0 °C The resulting solution was maintained for 4 0 hours, at which time the

cooling bath was removed and the reaction was maintained at room temperature for an additional two hours Next, a solution of ammonium chloride (saturated aqueous, 300 mL) was added The resulting emulsion was extracted with ethyl acetate (3 X 300 mL) and the resulting organic extracts were separated, $Na_2SO_4$ dried, and concentrated in vacuo to a residue that was subjected to $SiO_2$ chromatography with ethyl acetate/hexanes (6 4) to furnish a solid (392 mg, 81 %) $^1H$ NMR (400 MHz $d_4$-MeOH) δ 7 96 (dd, J = 8 0, 1 9 Hz, 1H), 7 75 (d, J = 8 1 Hz, 1H), 7 65 (app q, J = 8 0 Hz, 1H), 7 58 (d, J = 1 7 Hz, 1H), 7 05 (app t, J = 8 5 Hz, 2H), 6 64 (s, 1H), 5 36 (s, 2H), 4 35 (AB-q, J = 14 1 Hz, Δ= 60 8 Hz, 2H), 2 90 (s, 3H), 2 03 (s, 3H), LC/MS C-18 column, $t_r$ = 2 16 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 493 (M+H) ES-HRMS m/z 493 0590 (M+H calcd for $C_{22}H_{20}BrF_2N_2O_4$ requires 493 0596)

Example 662

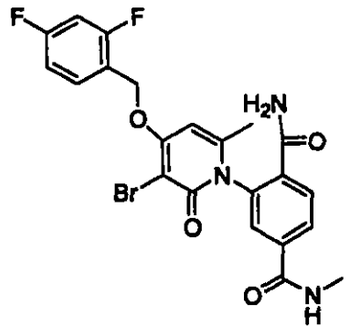



2-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-N,N'-dimethylterephthalamide

Step 1 To a room temperature solution of 2-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-

[(methylamino)carbonyl] benzoic acid (500 mg, 0 986 mmol) in DMF (5 0 mL) was added 1-(3-dimethylaminopropyl)-ethylcarbodiimide hydrochloride (EDC-HCl, 350 0 mg, 1 83 mmol) and 1-hydroxy-benzotriazole (HOBT, 100 0 mg, 0 74 mmol) sequentially To this resulting suspension was then added a solution of methylamine (2 0 M THF, 1 0 mL, 2 0 mmol) The reaction was stirred for 16 0 hours, at which time the reaction was diluted with ethyl acetate (600 mL) The mixture was washed with (3 X 200 mL) of water and the organic extract was separated, $Na_2SO_4$ dried, and concentrated in vacuo to a volume of approximately 60 mL At this time a solid precipitate formed and was collected to furnish (289 mg, 56 %) $^1H$ NMR (300 MHz, $d_4$-MeOH) δ 8 06 (br d, J = 8 0 Hz, 1H), 7 81 (d, J = 8 1 Hz, 1H), 7 73 (s, 1H), 7 70 (app q, J = 7 4 Hz, 1H), 7 09 (app t, J = 8 0 Hz, 2H), 6 65 (s, 1H), 5 39 (s, 2H), 2 96 (s, 3H), 2 79 (s, 3H), 2 13 (s, 3H), LC/MS C-18 column, $t_r$ = 2 13 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 520 (M+H) ES-HRMS m/z 520 0700 (M+H calcd for $C_{23}H_{21}BrF_2N_3O_4$ requires 520 0678)

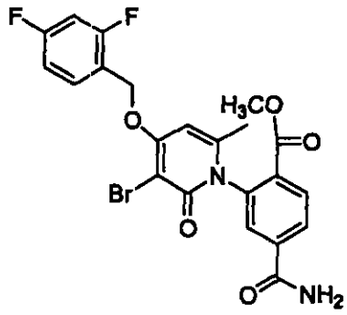
Example 663



2-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-N-4-methylterephthalamide

Step 1 To a room temperature suspension of 2-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2h)-yl]-4-[(methylamino)carbonyl] benzoic acid (302 mg, 0 595 mmol) in THF (1 8 mL) was added 2-chloro-4,6 dimethoxy-1,3,5 triazine (140 5 mg, 0 800 mmol) and N-methyl morpholine (NMM, 184 mg, 1 824 mmol) sequentially The resulting solution was matured for 2 hours and then a saturated aqueous solution of ammonium hydroxide (0 60 mL) was added The reaction was allowed to continue for 1 additional hour at which time a precipitate formed which was collected, washed with 20 mL of diethyl ether, and dried in vacuo to furnish a solid (201 mg, 66 %) $^1$H NMR (400 MHz, $d_6$-DMSO) δ 8 59 (br d, J = 8 0, 1H), 7 96 (d, J = 8 0 Hz, 1H), 7 83 (s, 1H), 7 72 (d, J = 9 0, 1H), 7 69-7 64 (m, 2H), 7 39-7 31 (m, 1H), 7 19 (app t, J = 8 0 Hz, 1H) 6 60 (s, 1H), 5 31(s, 2H), 3 85 (s, 1H), 2 78 (br d, J = 8 0 Hz, 3H), 1 96 (s, 3H), LC/MS C-18 column, $t_r$ = 2 20minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 506 (M+H) ES-HRMS m/z 506 0550 (M+H calcd for $C_{22}H_{19}BrF_2N_3O_4$ requires 506 0522)

Example 664

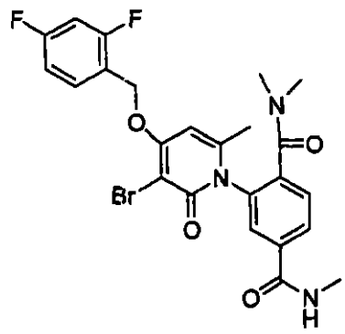


methyl 4-(aminocarbonyl)-2-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoate

Step 1 To a room temperature solution of 3-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)-4-(methoxycarbonyl)benzoic acid (3 01 g, 9 93 mmol) in DMF (20 mL) was added 1-(3-dimethylaminopropyl)-ethylcarbodiimide hydrochloride (EDC-HCl, 2 00 g, 10 4 mmol) and 1-hydroxy-benzotriazole (HOBT, 50 0 mg, 0 367 mmol) sequentially To this resulting suspension was then added a solution of ammonia (0 5 M 1,4 dioxane, 30 0 mL, 15 0 mmol) The reaction was stirred for 16 0 hours until complete consumption of starting material was seen by LCMS analysis At this time the reaction vessel was placed on a roto-evaporator at 30 mm Hg vacuum and maintained at 30 °C for 30 minutes to strip off any residual ammonia from the reaction mixture The reaction vessel was removed from the roto-evaporator and subsequently charged with solid N-bromosuccinimide (1 790 g, 10 06 mmol) and the resulting reddish solution was stirred for 3 0 hours At this time the reaction was charged with $K_2CO_3$ (3 00 g, 21 7 mmol) and 2,4 difluorobenzyl bromide (1 95 mL, 15 2 mmol) The resulting suspension was stirred for 16 0 hours At this time the reaction suspension was diluted with water (400 mL) and extracted with ethyl acetate (3 X 300 mL) The organic extracts were separated, $Na_2SO_4$ dried, and concentrated to a residue that was subjected to $SiO_2$ chromatography using ethyl acetate/hexanes/methanol (6 3 5 0 5) to furnish an off white solid (1 09 g, 21%) $^1H$ NMR (400 MHz, $d_4$-MeOH) δ 8 21 (dd, J = 8 5, 1 5 Hz, 1H), 8 09 (dd, J = 7 6, 2 0 Hz, 1H), 7 78 (br s, 1H), 7 65 (app q, J = 7 9 Hz, 1H), 7 03 (app t, J = 8 0 Hz, 2H), 6 63 (s, 1H), 5 37 (s, 2H), 3 75 (s, 3H), 2 02 (s, 3H), LC/MS C-18 column, $t_r$ = 2 28 minutes (5 to 95%

acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 507 (M+H) ES-HRMS m/z 507 0385 (M+H calcd for $C_{22}H_{18}BrF_2N_2O_5$ requires 507 0362)

Example 665

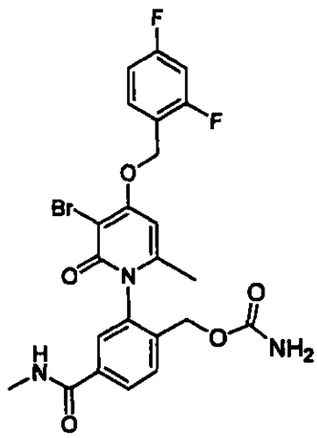


2-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-$N^1$,$N^1$,$N^4$-trimethylterephthalamide

Step 1 To a room temperature solution of 2-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-[(methylamino)carbonyl] benzoic acid (300 mg, 0 591 mmol) in DMF (1 8 mL) was added 1-(3-dimethylaminopropyl)-ethylcarbodiimide hydrochloride (EDC-HCl, 190 0 mg, 1 0 mmol) and 1-hydroxy-benzotriazole (HOBT, 26 0 mg, 0 191 mmol) sequentially To this resulting suspension was then added a solution of dimethylamine (2 0 M THF, 0 50 mL, 1 0 mmol) The reaction was stirred for 16 0 hours, at which time the reaction mixture was directly applied to $SiO_2$ chromatography with ethyl acetate/hexanes (6 4) to furnish a solid (206 mg, 65 %) $^1$H NMR (400 MHz, $d_4$-MeOH) δ 8 01 (dd, J = 8 2, 1 5 Hz, 1H), 7 73 (app d, J = 8 1 Hz, 1H), 7 61 (app q, J = 7 2 Hz, 1H), 7 60 (app d, J = 9 5 Hz, 1H), 7 04 (app t, J = 8 0 Hz, 2H), 6 65 (s, 1H), 5 32 (s, 2H), 3 64 (s, 3H), 2 92 (s, 6H), 2 13 (s, 3H), LC/MS C-18 column, $t_r$ = 2 20 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection

254 nm, at 50°C) ES-MS m/z 534 (M+H) ES-HRMS m/z 534 0820 (M+H calcd for $C_{24}H_{23}BrF_2N_3O_4$ requires 534 0835)

Example 666

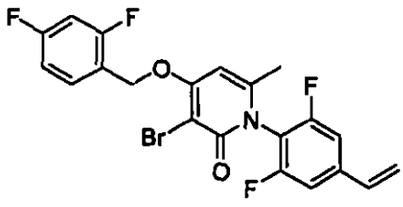


2-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-[(methylamino)carbonyl]benzyl carbamate

Step 1 To a room temperature solution of 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-(hydroxymethyl)-N-methylbenzamide (493 mg, 1 00 mmol) in methylene chloride (5 0 mL) was added a solution of trichloroacetyl isocyanate (toluene, 0 53 M, 1 9 mL, 1 0 mmol) The resulting solution was stirred for one hour until complete consumption of starting material by LCMS analysis The reaction mixture was then directly applied to $Al_2O_3$ (0 5 g of activity type I) and the slurry was matured for three hours At this time, the $Al_2O_3$ plug was flushed with ethyl acetate/methanol (95 5) and the resulting mother liquor was concentrated to a residue that was subjected to $SiO_2$ chromatography using ethyl acetate/hexanes/methanol (6 3 5 0 5) to furnish a white solid (396 mg, 74 %) $^1H$ NMR (300 MHz, $d_4$-MeOH) δ 8 00 (dd, J = 8 0, 1 7 Hz, 1H), 7 75 (d, J

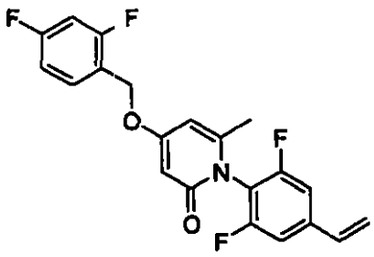
= 8 2 Hz, 1H), 7 72-7 64 (m, 2H), 7 09 (app t, J = 8 5 Hz, 2H), 6 69 (s, 1H), 5 40 (s, 2H), 4 85 (m, 2H), 2 90 (s, 3H), 2 10 (s, 3H), LC/MS C-18 column, $t_r$ = 2 15 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 536 (M+H) ES-HRMS m/z 536 0617 (M+H calcd for $C_{23}H_{21}BrF_2N_3O_5$ requires 536 0627)

Example 667



3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluoro-4-vinylphenyl)-6-methylpyridin-2(1H)-one

Step 1 Preparation of 4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluoro-4-vinylphenyl)-6-methylpyridin-2(1H)- one



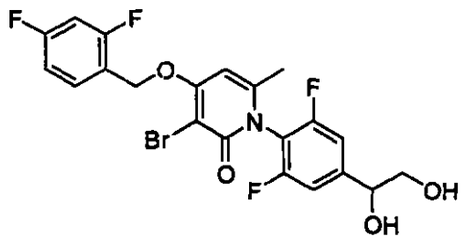
To a room temperature solution of 1-(4-bromo-2,6-difluorophenyl)-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)- one (4 01 g, 9 06 mmol) in anhydrous THF (30mL) was added, sequentially, tributyl(vinyl)tin (5 00 g, 15 7 mmol) and tetrakis(tripheylphosphine)palladium (1 00 g, 0 865 mmol) under an argon stream The reaction vessel was then equipped with a reflux condenser and the reaction system purged with an

argon flow The resulting yellow solution was heated to 68 °C and stirred under a positive pressure of argon for 12 0 hours until complete disappearance of starting material by LCMS analysis The reaction mixture was diluted with 300 mL of brine and extracted with ethyl acetate (3 X 300 mL) The organic extracts were separated, $Na_2SO_4$ dried, and concentrated in vacuo and the resulting dark residue was subjected to $SiO_2$ chromatography with ethyl acetate/hexanes (1 1) to furnish a yellowish solid (3 18 g, 90 %) $^1H$ NMR (400 MHz, $CDCl_3$) δ 7 41 (app q, J = 8 0 Hz, 1H), 7 08 (app d, J = 8 3 Hz, 2H), 6 90 (app t, J =7 2 Hz, 1H), 6 85 (app t, J = 7 4 Hz, 1H), 6 63 (dd, J = 17 5, 10 9 Hz, 1H), 5 96 (app d, 15 8 Hz, 1H), 5 94 (app d, J = 15 8 Hz, 1H), 5 79 (d, J = 17 4 Hz, 1H), 5 43 (d, J = 10 9 Hz, 1H), 5 01 (br s, 2H), 1 99 (s, 3H), LC/MS C-18 column, $t_r$ = 2 93 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 390 (M+H) ES-HRMS m/z 390 1095 (M+H calcd for $C_{21}H_{16}F_4NO_2$ requires 390 1112)

Step 2 To a briskly stirred room temperature solution of 4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluoro-4-vinylphenyl)-6-methylpyridin-2(1H)- one (721 mg, 1 85 mmol) in methylene chloride (10 mL) was added solid N-bromosuccinimide (330 mg, 1 86 mmol) and the resulting reddish solution was stirred for 10 minutes At this time the reaction was diluted with ethyl acetate (100 mL) and washed with sodium sulfite (5 % aqueous solution, 50 mL) The resulting organic extracts were $Na_2SO_4$ dried, filtered, and concentrated in vacuo to approximately 50 mL volume The resulting mother liquor rapidly precipitated and furnished an amorphous solid that was collected and dried at 1 mm Hg vacuum to provide a solid (610 mg, 70 %) $^1H$ NMR (400 MHz, $CDCl_3$) δ 7 59 (app q, J = 8 0 Hz, 1H), 7 09 (app d, J

= 8 3 Hz, 2H), 6 95 (app t, J =7 2 Hz, 1H), 6 87(app t, J = 7 4 Hz, 1H), 6 62 (dd, J = 17 5, 10 9 Hz, 1H), 6 12 (s, 1H), 5 81 (d, J = 17 4 Hz, 1H), 5 43 (d, J = 10 9 Hz, 1H), 5 25 (br s, 2H), 2 07 (s, 3H), LC/MS C-18 column, $t_r$ = 3 17 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 468 (M+H) ES-HRMS m/z 468 0249 (M+H calcd for $C_{21}H_{15}BrF_4NO_2$ requires 468 0217)

Example 668

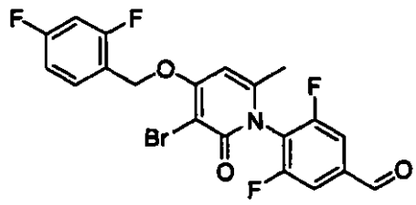



3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[4-(1,2-dihydroxyethyl)-2,6-difluorophenyl]-6-methylpyridin-2(1H)-one

Step 1 Preparation of the title compound To a room temperature solution of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluoro-4-vinylphenyl)-6-methylpyridin-2(1H)-one (408 0 mg, 0 871 mmol) in water/acetone 1 3 (8 0 mL) was added, sequentially, N-methyl morpholine oxide (268 0 mg, 2 29 mmol) and osmium tetroxide (4 % water solution, 0 25 mL or approximately 10 mg, 0 039 mmol) The resulting solution was stirred for 8 hours until complete consumption of starting material by LCMS analysis, and the reaction was concentrated in vacuo to one-fourth original volume The resulting solution was diluted with ethyl acetate (300 mL) and washed with water (2 X 100 mL) The organic extract was separated, $Na_2SO_4$ dried, and concentrated in vacuo and the resulting dark residue was subjected to $SiO_2$ chromatography with ethyl acetate/hexanes/

methanol (6 3 5 0 5) to furnish a solid (389 mg, 88 %) $^1$H NMR (400 MHz, $d_4$-MeOH) δ 7 62 (app q, J = 8 0 Hz, 1H), 7 26 (dd, J = 9 6, 4 5 Hz, 2H), 7 04 (app t, J = 8 6 Hz, 2H), 6 67 (s, 1H), 5 36 (s, 2H), 4 75 (app t, J = 5 6 Hz, 1H), 3 68-3 61 (m, 2H), 2 11 (s, 3H), LC/MS C-18 column, $t_r$ = 2 26 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 502 (M+H) ES-HRMS m/z 502 0247 (M+H calcd for $C_{21}H_{17}BrF_4NO_4$ requires 502 0272)

Example 669

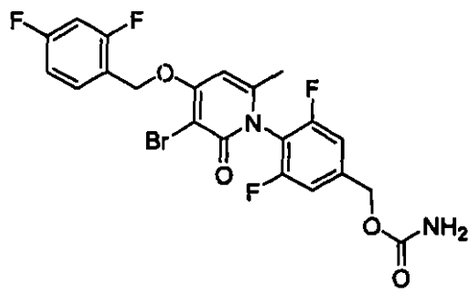


4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzaldehyde

Step 1 Preparation of the title compound To a room temperature solution of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[4-(1,2-dihydroxyethyl)-2,6-difluorophenyl]- 6-methylpyridin-2(1H)-one (310 mg, 0 615 mmol) in toluene (3 0 mL) was added lead(IV) acetate (443 mg, 1 63 mmol) The resulting dark brown solution was stirred for one hour until complete consumption of starting material by LCMS analysis The reaction mixture was then diluted with ethyl acetate (100 mL), water washed (3 X 100 mL), and brine washed (3 X 30 mL) The resulting organic extract was separated, $Na_2SO_4$ dried, and concentrated The resulting dark residue was subjected to $SiO_2$ chromatography with ethyl acetate/ hexanes (1 1) to furnish a light yellow solid (269 mg, 93 %) Caution, product is easily air oxidized $^1$H NMR (300 MHz, $d_4$-MeOH) δ 10 05 (s, 1H), 7 68 (app q, J = 7 2 Hz, 1H), 7 38 (d, J = 8 0 Hz, 2H), 7 05 (app t, J =

8 2 Hz, 2H), 6 73 (s, 1H), 5 40 (s, 2H), 2 15 (s, 3H), LC/MS C-18 column, $t_r$ = 2 72 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 470 (M+H) ES-HRMS m/z 470 0049 (M+H calcd for $C_{20}H_{13}BrF_4NO_3$ requires 470 0009)

Example 670



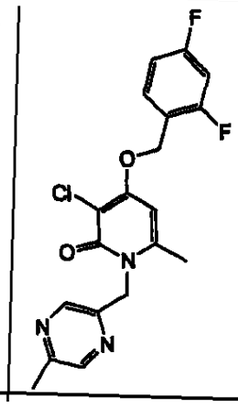
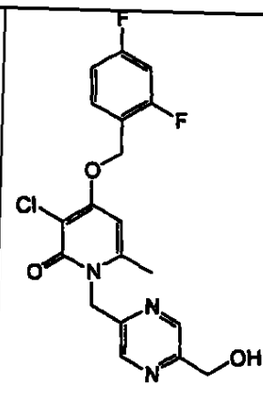
4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzyl carbamate

Step 1 To a room temperature solution of 4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzaldehyde (220 mg, 0 468 mmol) in methanol (10 mL) was added solid sodium borohydride (60 0 mg, 1 58 mmol) The resulting solution evolved gas for approximately 0 5 minute and was stirred for 10 additional minutes until complete consumption of starting material by LCMS analysis The reaction was then diluted with saturated aqueous solution of ammonium chloride (10 mL) and extracted with ethyl acetate (4 X 50 mL) The organic extract was separated, $Na_2SO_4$ dried, and concentrated to a residue This resulting residue was then diluted with methylene chloride (5 0 mL) and a solution of trichloroacetyl isocyanate (toluene, 0 53 M, 1 0 mL, 0 53 mmol) was added The resulting solution was stirred for one hour until complete consumption of starting material by LCMS

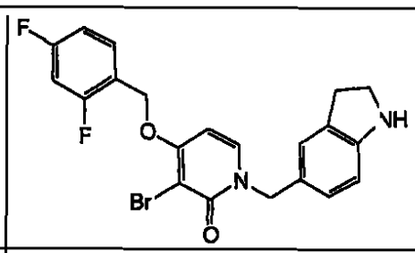
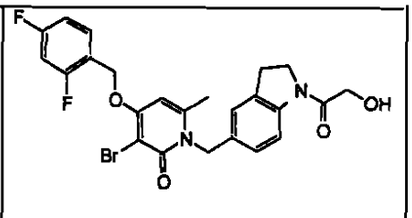
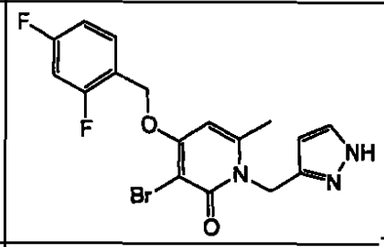
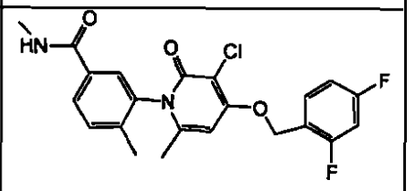
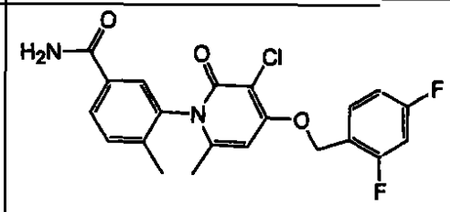
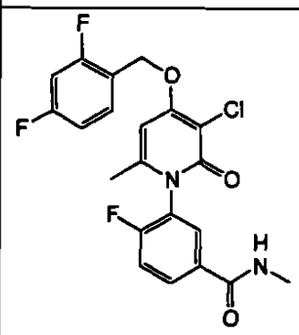
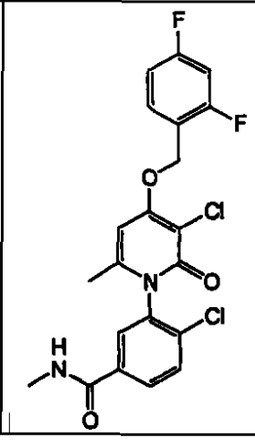
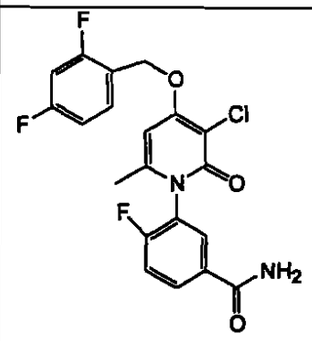
analysis The reaction mixture was then directly applied to $Al_2O_3$ (0 5 g of activity type I) and the slurry was matured for three hours At this time, the $Al_2O_3$ plug was flushed with ethyl acetate/methanol (95 5) and the resulting mother liquor was concentrated to a residue that was subjected to $SiO_2$ chromatography using ethyl acetate/hexanes/methanol (6 3 8 0 2) to furnish a white solid (181 mg, 75 %) $^1H$ NMR (400 MHz, $d_4$-MeOH) δ 7 63 (app q, J = 8 0 Hz, 1H), 7 43 (d, J = 8 2 Hz, 2H), 7 04 (app t, J = 8 1 Hz, 2H), 6 68 (s, 1H), 5 37 (s, 2H), 5 12 (m, 2H), 2 11 (s, 3H), LC/MS C-18 column, $t_r$ = 2 54 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS m/z 515 (M+H) ES-HRMS m/z 515 0232 (M+H calcd for $C_{21}H_{16}BrF_4N_2O_4$ requires 515 0234)

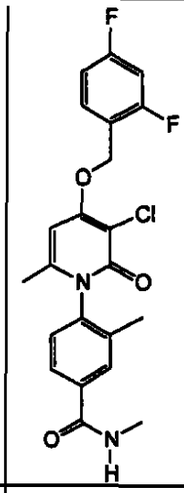
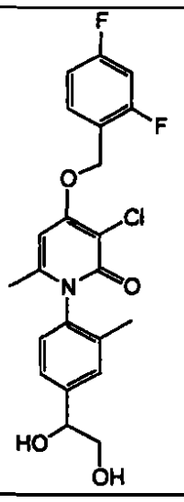
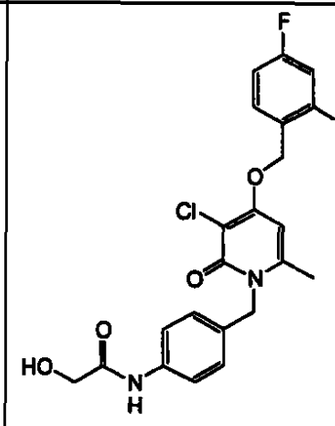
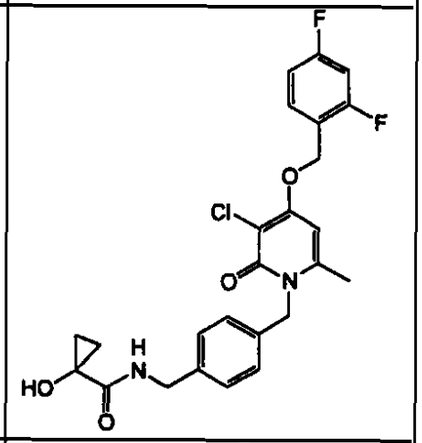
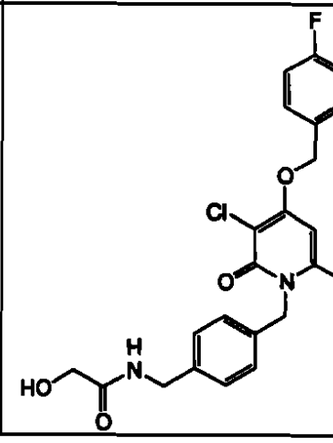
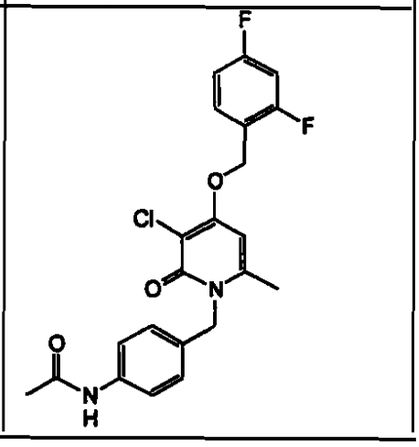
Example 671-687

The following compounds are prepared essentially according to the procedures outlined in the schemes and the above examples

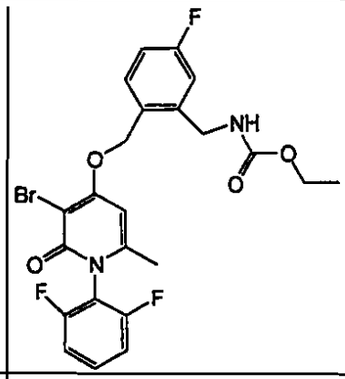
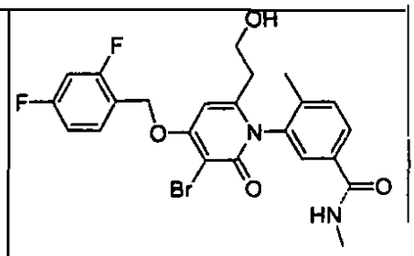
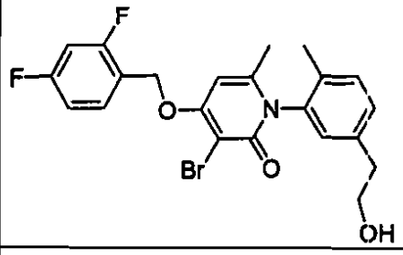
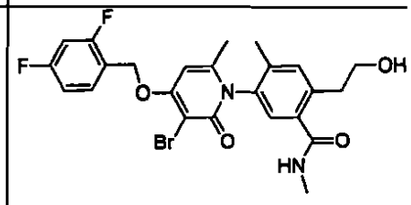
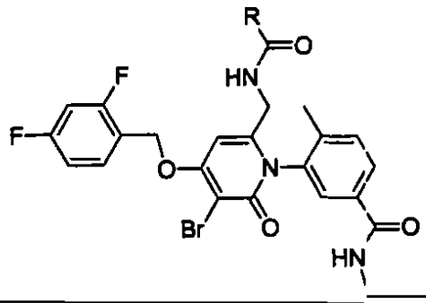
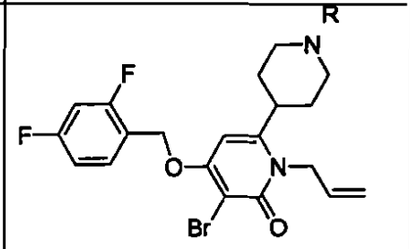
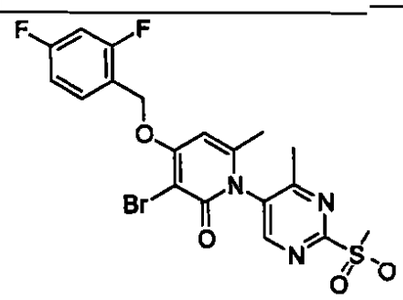
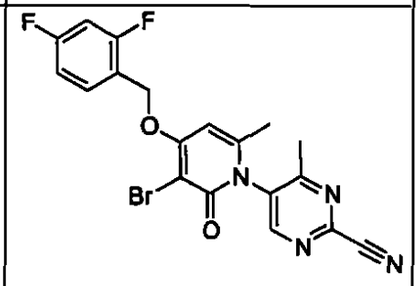
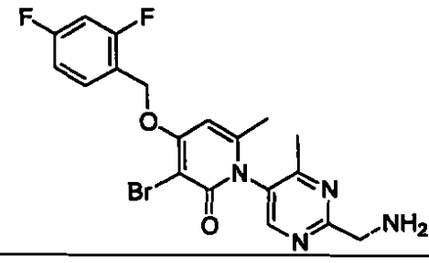
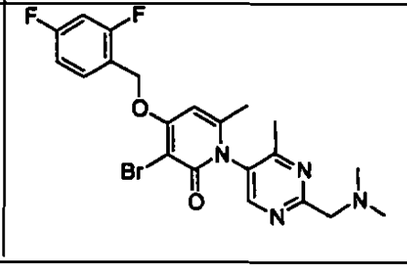
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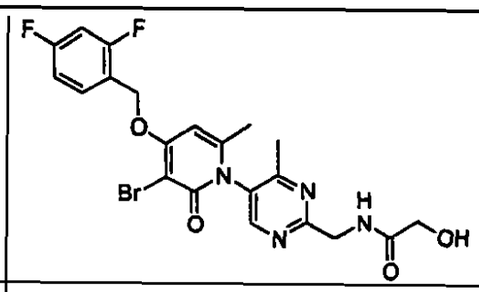
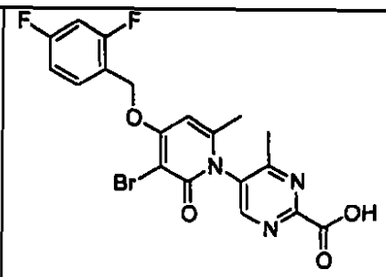
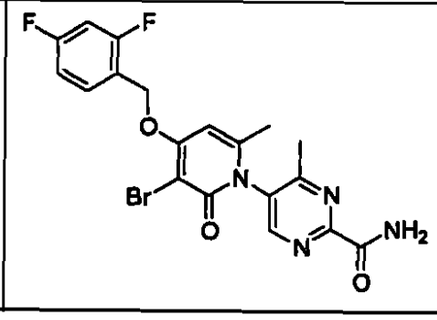
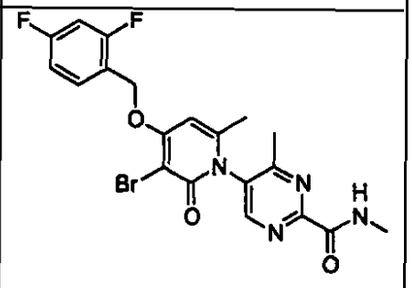
434
437

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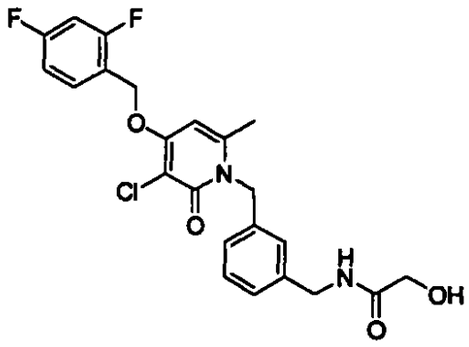
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485
438

| | | | |
|---|---|---|---|
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| 691 |  | 692 |  |
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| 695 |  | 696 |  |

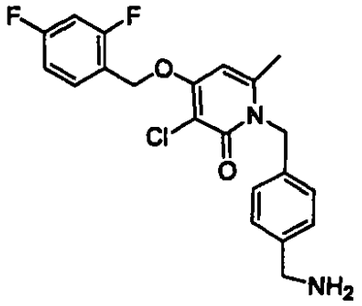
| | | | |
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| 699 |  | 700 |  |

Example 701



N-(4-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzyl)-2-hydroxyacetamide

Step 1 Preparation of 1-[4-(aminomethyl)benzyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one



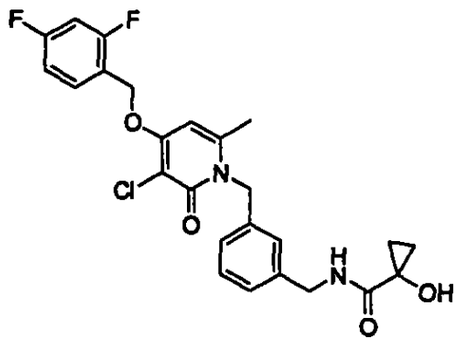
The compound of Example 606 (10 0 g, 23 38 mmol) was suspended ın tetrahydrofuran (100 mL) and cooled ın an ıce-bath Borane dımethyl sulfıde (29 9 mL, 2 0 *M* ın tetrahydrofuran, 59 7 mmol) was added The resultıng mıxture was heated to reflux overnight and then cooled ın an ıce-bath Additıonal borane dımethyl sulfıde (5 85 mL, 2 0 *M* ın tetrahydrofuran, 11 7 mmol) was added The resultıng mıxtue was heated to reflux overnight and the cooled to room temperature The flask was fıtted wıth a dıstıllatıon head and the reactıon was partıally concentrated Additıonal borane dımethyl sulfıde (5 85 mL, 2 0 *M* ın tetrahydrofuran, 11 7 mmol) was added The mıxture was heated to reflux overnight and the cooled ın an ıce-bath The reactıon was quenched by the addıtıon of 1 0 *N* HCl (75 0 mL) then partıally concentrated The aqueous layer was made alkalıne wıth 2 5 *N* NaOH and a precıpıtate developed The solıd was collected by fıltratıon washıng wıth dıethyl ether to gıve a pale purple solıd (3 00 g, 32 %) $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7 64 (*app* q, *J* = 7 9 Hz, 1H), 7 44 (d, *J* = 7 9 Hz, 2H), 7 32 (*app* dt, *J* = 2 4, 9 9 Hz, 1H), 7 14 (*app* dt, *J* = 1 9, 8 5 Hz, 1H), 7 13 (d, *J* = 7 9 Hz, 2H), 6 61 (s, 1H), 5 27 (s, 4H), 3 90 (s, 2H), 2 29 (s, 3H)

Step 2 Preparatıon of N-(4-{[3-chloro-4-[(2,4-dıfluorobenzyl)oxy]-6-methyl-2-oxopyrıdın-1(2*H*)-yl]methyl}benzyl)-2-hydroxyacetamıde

Acetoxyacetıc acıd (1 46 g, 12 35 mmol) was dıssolved ın *N*,*N*-dımethylformamıde (30 mL) and 1-Hydroxybenzotrıazole (1 84 g, 13 59 mmol) was added followed by 4-methylmorpholıne (2 04 mL, 18 53 mmol), 1-[4-(amınomethyl)benzyl]-3-chloro-4-[(2,4-dıfluorobenzyl)oxy]-6-methylpyrıdın-2(1H)-one (compound of step 1) (2 50 g, 6 18 mmol) and then 1-[3-(dımethylamıno)propyl]-3-ethylcarbodıımıde hydrochlorıde (2 84 g, 14 83 mmol) The resultıng mıxture was stırred at room

temperature for 1 hour at which time the reaction was diluted with $H_2O$ (100 mL) The reaction mixture was then extracted with ethyl acetate The combined organic extracts were washed with saturated $NaHCO_3$, brine, dried over $Na_2SO_4$, filtered and concentrated Chromatography (silica gel, hexanes/ethyl acetate with 10% methanol) provided a white foam The resulting foam was dissolved in 10% aqueous methanol (20 mL) $K_2CO_3$ (0 653 g, 4 73 mmol) was added and the mixture was stirred at room temperature for 2 hours The reaction mixture was concentrated and H2O (50 mL) was added The resulting precipitate was collected by filtration washing with diethyl ether to give an off-white solid (1 34 g, 47%) $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7 50 (*app* q, $J$ = 7 7 Hz, 1H), 7 27 (app t, $J$ = 5 8 Hz, 1H), 7 12 (d, $J$ = 8 1 Hz, 2H), 6 97 (d, $J$ = 8 1 Hz, 2H), 6 94-6 89 (m, 1H), 6 86-6 81 (m, 1H), 6 09 (s, 2H), 5 23 (s, 2H), 5 18 (s, 2H), 4 53 (t, $J$ = 5 8 Hz, 1H), 4 33 (d, $J$ = 5 9 Hz, 2H), 3 85 (d, $J$ = 5 6 Hz, 2H), 2 30 (s, 3H) ES-HRMS $m/z$ 463 1256 (M+H calcd for $C_{23}H_{22}ClF_2N_2O_4$ requires 463 1231)

Example 702

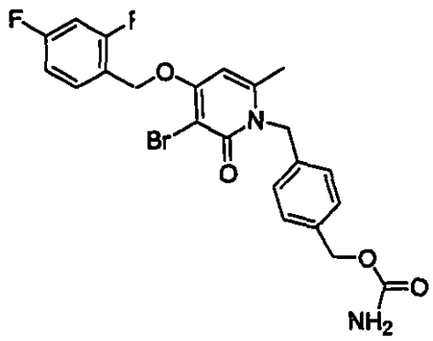


N-(4-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzyl)-1-hydroxycyclopropanecarboxamide

Preparation of N-(4-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}benzyl)-1-hydroxycyclopropanecarboxamide 1-Hydroxy-1-cyclopropane-

carboxylic acid (1 26 g, 12 35 mmol) was dissolved in *N,N*-dimethylformamide (30 mL) 1-Hydroxybenzotriazole (1 84 g, 13 59 mmol) was added followed by 4-methylmorpholine (2 04 mL, 18 53 mmol), 1-[4-(aminomethyl)benzyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (Example 701, step 1) (2 50 g, 6 18 mmol) and then 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (2 84 g, 14 83 mmol) The resulting mixture was stirred at room temperature for 24 hours at which time the reaction was diluted with $H_2O$ (100 mL) The reaction mixture was then extracted with ethyl acetate The combined organic extracts were washed with saturated $NaHCO_3$, brine, dried over $Na_2SO_4$, filtered and concentrated Chromatography (silica gel, hexanes/ethyl acetate with 10% methanol) provided a white foam The resulting foam was dissolved in 10% aqueous methanol (20 mL) to provide an white foam (1 45 g, 48%) $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7 52-7 46 (m, 1H) 7 34 (t, $J$ = 5 9 Hz, 1H), 7 08 (d, $J$ = 8 2 Hz, 2H), 6 92 (*app* d, $J$ = 8 2 Hz, 2H), 6 92-6 89 (m, 1H), 6 86-6 81 (m, 1H), 6 11 (s, 1H), 5 22 (s, 2H), 5 18 (s, 2H), 4 30 (d, $J$ = 5 9 Hz, 2H), 2 28 (s, 3H), 1 11 (*app* q, $J$ = 4 1 Hz, 2H), 0 90 (*app* q, $J$ = 4 1 Hz, 2H) ES-HRMS *m/z* 489 1420 (M+H calcd for $C_{25}H_{24}ClF_2N_2O_4$ requires 489 1387)

Example 703

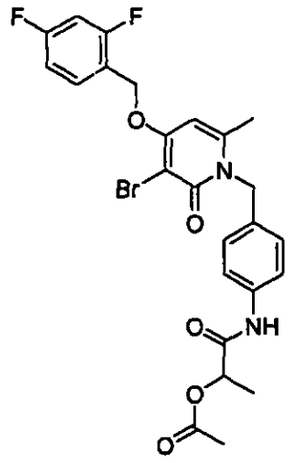


4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}benzyl carbamate

Preparation of 4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}benzyl carbamate

Compourd of Example 206 (0 868 g, 1 93 mmol) was suspended in dichloromethane (7 0 mL) Trichloroacetyl isocyanate (4 00 mL, 0 53 *M* in toluene, 2 12 mmol) was added The resulting mixture was stirred at room temperature for 3 hours then diluted with tetrahydrofuran (50 mL) and Al2O3 (5 0 g) was added and the mixture was stirred at room temperature overnight The reaction mixture was filtered through a pad of Celite® washing with methonal The filtrate was then concentrated and the residue was redissolved in tetrahydrofuran (30 mL) $Al_2O_3$ (5 0 g) was added and the mixture was heated to 40 oC for 3 hours After cooling to room temperature, the reaction was filtered through a pad of Celite ® washing with methanol The filtrate was concentrated and the resulting solid was washed with diethyl ether to give an off-white solid (0 831 g, 87%) $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7 54 (*app* q, *J* = 7 7 Hz, 1H), 7 25 (d, *J* = 8 2 Hz, 2H), 7 13 (d, *J* = 8 2 Hz, 2H), 6 25 (*app* dt, *J* = 2 0, 8 3 Hz, 1H), 6 86-6 30 (m, 1H), 5 97 (s, 1H), 5 32 (s, 2H), 5 18 (s, 2H), 5 02 (s, 2H), 4 81 (br s, 2H), 2 25 (s, 3H) ES-HRMS *m/z* 493 0580 (M+H calcd for $C_{22}H_{20}BrF_2N_2O_4$ requires 493 0569)

Example 704

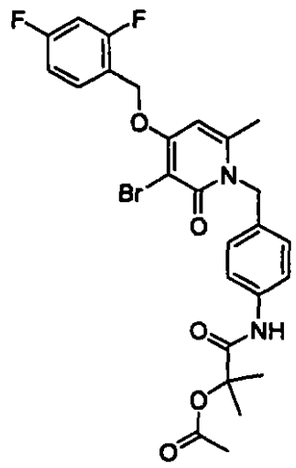


2-[(4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}phenyl)amino]-1-methyl-2-oxoethyl acetate

To a reaction vessel (borosilicate culture tube) was added compound of Example 611 (0 300 g, 0 69 mmol) and dichloromethane (3 0 mL) A stock solution of *N*-methylmorpholine (0 30 M, 3 0 mL) was added and the parallel reaction apparatus was then orbitally shaken (Labline Benchtop Orbital Shaker) at approximately 200 RPM at room temperature for 10 minutes (S)-(-) 2-Acetoxypropionyl chloride (0 131 mL, 1 04 mmol) was then added to the reaction vessel and the reaction apparatus was orbitally shaken at room temperature for 1 5 hours At this time the reaction was diluted with dichloromethane (20 mL) and treated with approximately 2 1 g of polyamine resin (2 63 mmol/g) and approximately 3 8 g of methylisocyanate fucntionalized polystyrene (1 10 mmol/g) and the orbital shaking was continued at 200 RPM at room temperature overnight The reaction vessel was then opened and the solution Phase products were separated from the insoluble quenched byproducts by filtration and collection into a vial After partial evaporation the insoluble byproducts were rinsed with dichloromethane (2 x 10 mL) The

filtrate was evaporated by blowing $N_2$ over the vial to afford an off-white solid (0 375 g, 99%) $^1$H NMR (400 MHz, DMF-$d_6$) δ 10 14 (s, 1H), 7 75 (*app* dt, *J* = 6 98, 8 59 Hz, 1H), 7 67-7 64 (m, 2H), 7 30 (ddd, *J* = 2 55, 9 26, 11 81 Hz, 1H), 7 21-7 17 (m, 3H), 6 61 (s, 1H), 5 37 (s, 4H), 5 11 (q, *J* = 6 85 Hz, 1H), 2 40 (s, 3H), 2 10 (s, 3H), 1 46 (d, *J* = 6 85 Hz, 3H) ES-HRMS *m/z* 549 0790 (M+H calcd for $C_{25}H_{23}BrF_2N_2O_5$ requires 549 0831)

Example 705

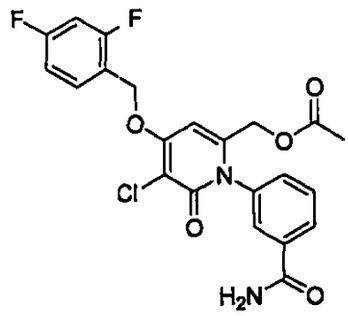



2-[(4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}phenyl)amino]-1,1-dimethyl-2-oxoethyl acetate

By the method for Example 704 and substituting (S)-(-)-2-acetoxypropionyl chloride with 2-acetoxy-2-methylpropionyl chloride, the title compound was prepared (0 380 g, 98%) $^1$H NMR (400 MHz, DMF-$d_6$) δ 9 68 (s, 1H), 7 75 (*app* dt, *J* = 6 72, 8 60 Hz, 1H), 7 71-7 68 (m, 2H), 7 30 (ddd, *J* = 2 55, 9 40, 11 95 Hz, 1H), 7 21-7 15 (m, 3H), 6 61 (s, 1H), 5 37 (s, 4H), 2 41 (s, 3H), 2 04 (s, 3H), 1 59 (s, 6H) ES-HRMS *m/z* 563 1027 (M+H calcd for $C_{26}H_{25}BrF_2N_2O_5$ requires 563 0988)

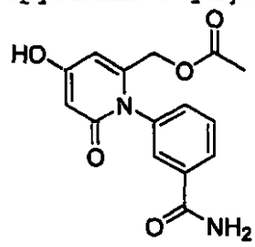
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Example 706



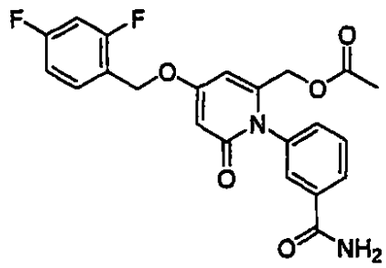
{1-[3-(aminocarbonyl)phenyl]-5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxo-1,6-dihydropyridin-2-yl}methyl acetate

Step 1 Preparation of {1-[3-(aminocarbonyl)phenyl]-4-hydroxy-6-oxo-1,6-dihydropyridin-2-yl}methyl acetate



3-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)-2-oxopropyl acetate (4 00 g, 16 52 mmol) was dissolved in 1,4-dioxane (160 mL) and 3-aminobenzamide (1 73 g, 12 71 mmol) was added The reaction was heated to reflux for 1 hour then cooled to 70 °C Methanesulfonic acid (1 22 g, 12 71 mmol) was added and the reaction brought back to reflux for 1 hour The reaction was cooled to room temperature, concentrated and used as crude product for the next step

Step 2 Preparation of {1-[3-(aminocarbonyl)phenyl]-4-[(2,4-difluorobenzyl)oxy]-6-oxo-1,6-dihydropyridin-2-yl}methyl acetate



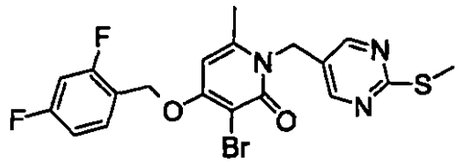
{1-[3-(aminocarbonyl)phenyl]-4-hydroxy-6-oxo-1,6-dihydropyridin-2-yl}methyl acetate (crude from step 1) (3 61 g, 11 94 mmol) was dissolved in *N,N*-dimethylformamide (40 mL) $K_2CO_3$ (3 80 g, 27 46 mmol) was added followed by 2,4-difluorobenzyl bromide (5 44 g, 26 27 mmol) The reaction mixture was stirred for 48 hours at room temperature The reaction mixture was then partially concentrated and the residue taken up in dichloromethane/tetrahydrofuran 1 1 and filtered The filtrate was collected, concentrated and the residue tritrated with dichloromethane to afford a tan solid (1 64 g, 32%) $^1$H NMR (400 MHz, DMF-$d_6$) δ 8 19 (br s, 1H), 8 07 (*app* dt, *J* = 1 35, 7 66 Hz, 1H), 7 91 (*app* t, *J* = 1 81 Hz, 1H), 7 76 (*app* dt, *J* = 6 58, 8 59 Hz, 1H) 7 62 (t, *J* = 7 79 Hz, 1H), 7 55 (ddd, *J* = 1 21, 2 01, 7 79 Hz, 1H), 7 46 (br s, 1H), 7 34 (ddd, *J* = 2 55, 9 40, 10 47 Hz, 1H), 7 23-7 18 (m, 1H), 6 26 (d, *J* = 2 55 Hz, 1H), 6 11 (d, *J* = 2 69 Hz, 1H), 5 23 (s, 2H), 4 62 (AB q, $J_{AB}$ = 14 97 Hz, 2H), 1 96 (s, 3H) ES-HRMS *m/z* 429 1280 (M+H calcd for $C_{22}H_{18}F_2N_2O_5$ requires 429 1257)

Step 3 Preparation of the title compound

{1-[3-(aminocarbonyl)phenyl]-4-[(2,4-difluorobenzyl)oxy]-6-oxo-1,6-dihydropyridin-2-yl}methyl acetate (from step 2) (1 02 g, 2 39 mmol) was suspended in dichloromethane (15 mL) and *N*-chlorosuccinimide (0 37 g, 2 75 mmol) was added Dichloroacetic acid (0 10 ml, 1 22 mmol) was added and the reaction mixture was stirred at 40 °C for 1 5 hours The

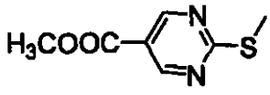
reaction was cooled to room temperature and a precipitate formed The reaction mixture was diluted with diethyl ether and the precipitate was collected by filtration and washed with diethyl ether (3 x 15 mL) to afford a tan solid (0 940 g, 85%) $^1$H NMR (400 MHz, DMF-$d_6$) δ 8 21 (*br* s, 1H), 8 11 (*app* dt, *J* = 1 48, 7 52 Hz, 1H), 7 95 (*app* t, *J* = 1 61 Hz, 1H), 7 80 (*app* dt, *J* = 6 72, 8 59 Hz, 1H) 7 69-7 60 (m, 2H), 7 48 (*br* s, 1H), 7 35 (ddd, *J* = 2 55, 9 53, 10 61 Hz, 1H), 7 24-7 19 (m, 1H), 6 97 (s, 1H), 5 49 (s, 2H), 4 71 (AB q, $J_{AB}$ = 15 04 Hz, 2H), 1 98 (s, 3H) ES-HRMS *m/z* 463 0883 (M+H calcd for $C_{22}H_{17}ClF_2N_2O_5$ requires 463 0867)

Example 707



3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-{[2-(methylthio)pyrimidin-5-yl]methyl}pyridin-2(1*H*)-one

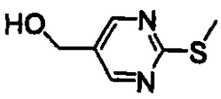
Step 1 Preparation of methyl 2-(methylthio)pyrimidine-5-carboxylate



A solution of the sodium salt of 3,3-dimethoxy-2-methoxycarbonylpropen-1-ol (5 0g, 25 mmol), 2-methyl-2-thiopseudourea sulfate (3 5g, 25 mmol) in anhydrous methanol (25 mL) was refluxed for 3 hours under anhydrous conditions The reaction mixture was cooled and diluted with ethyl acetate The reaction mixture was filtered and the residue was washed with ethyl acetate The filtrate was concentrated and the residue was purified by flash chromatography (silica

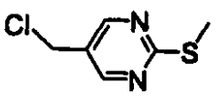
gel) using 25% ethyl acetate in hexane to afford the desired product (3 5g, 75%) as a white powder $^1$H-NMR ($d_6$-DMSO, 400 MHz) δ 9 0 (s, 2H), 3 92 (s, 3H), 2 58 (s, 3H), ES-HRMS *m/z* 185 041 (M+H $C_7H_8N_2O_2S$ requires 185 0379)

Step 2 Preparation of [2-(methylthio)pyrimidin-5-yl]methanol



To a cold suspension of methyl 2-(methylthio)pyrimidine-5-carboxylate (1 74g, 9 4 mmol) in dichloromethane (20 mL, -70° C) was added DIBAL (20 8 mL, 20 mmol) dropwise via an addition funnel The mixture was stirred under nitrogen at -70° C for 1 hour and then at -50° C for 3 hours The reaction was diluted with dichloromethane (50 mL) and quenched with a suspension of sodium sulfate decahydrate (10g) in water (50 mL) The slurry was filtered through celite and the filtrate was concentrated The residue was purified by flash chromatography (silica gel) using 100% ethyl acetate to afford the desired compound (0 7813 g, 39%) as a yellow solid $^1$H-NMR ((CD$_3$OD, 400 MHz) δ 8 53 (s, 2H), 4 56 (s, 2H), 2 54 (s, 3H), ES-HRMS *m/z* 157 0409 (M+H $C_6H_8N_2OS$ requires 157 0430)

Step 3 Preparation of 5-(chloromethyl)-2-(methylthio)pyrimidine



To a cold solution of [2-(methylthio)pyrimidin-5-yl]methanol (0 7813g, 5 0 mmol) in anhydrous dichloromethane (10 mL, 0° C) was added triethylamine (0 836 mL, 8 2 mmol) followed by the addition of methanesulfonyl chloride (0 465mL, 6 0 mmol) The reaction mixture stirred at 0° C under a

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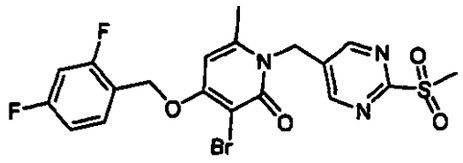
nitrogen atmosphere for 30 minutes then at room temperature for 3 5 hours The reaction was quenched with sodium bicarbonate (5%, 100 mL)) and extracted with dichloromethane (50 mL) The organic extracts were concentrated and the residue was purified by flash chromatography (silica gel) using 15% ethyl acetate in hexane to afford the desired compound (0 720 g, 82%) as a white solid $^1$H-NMR ($CD_3OD$, 400 MHz) δ 8 60 (s, 2H), 4 64 (s, 2H), 2 54 (s, 3H), ES-HRMS *m/z* 175 0106 (M+H $C_6H_7N_2ClS$ requires 175 0091)

Step 4 Preparation of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-{[2-(methylthio)pyrimidin-5-yl]methyl}pyridin-2(1*H*)-one

To a solution of 5-(chloromethyl)-2-(methylthio)pyrimidine (0 62g, 3 56 mmol) in anhdrous DMF (10 mL) was added KBr (0 424, 3 56 mmol) After the suspension stirred at room temperature for 30 minutes, 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (1 05g, 3 19 mmol) was added followed by NaH (0 102g, 4 25 mmol) The reaction mixture stirred at 70° C under a nitrogen atmosphere for 3 5 hours The solvent was distilled and the residue was washed with water and extracted with ethyl acetate The organic extracts were concentrated and the residue was purified by reverse phase HPLC using a 10-90% acetonitrile/water (30 minute gradient) at a 70mL/min flow rate to afford the desired TFA salt (0 32 g, 15%) as a white powder The TFA compound was washed with sodium bicarbonate (5%) and extracted with dichloromethane The organic extract was concentrated to afford the desired compound (0 295g, 18 %) as a yellow solid $^1$H-NMR ($CD_3OD$, 400 MHz) δ 8 47 (s, 2H), 7 62 (q, 1H, J= 8Hz), 7 03 (m, 2H), 6 51 (s, 1H), 5 31 (s 2H), 5 29 (s, 2H), 2 52 (s, 3H), 2 47 (s, 2H), ES-HRMS *m/z*

468 0174/470 0156 (M+H $C_{19}H_{16}N_3O_2F_2BrS$ requires 468 0187/470 0168)

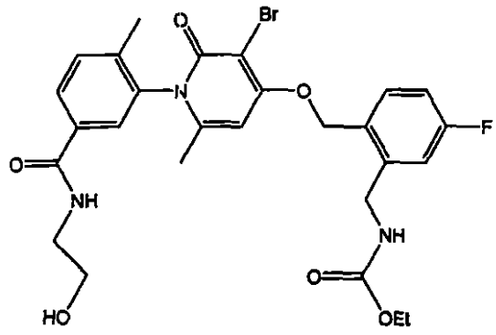
Example 708



3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-{[2-(methylsulfonyl)pyrimidin-5-yl]methyl}pyridin-2(1*H*)-one

To a solution of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-{[2-(methylthio)pyrimidin-5-yl]methyl}pyridin-2(1H)-one (example 707) (0 26g, 0 55 mmol) in acetonitrile water (4 1 v/v, 10 mL) was added MMPP (0 549g, 1 1 mmol) The reaction stirred at room temperature for 30 hours The reaction mixture was diluted with ethyl acetate and filtered The filtrate was concentrated and the residue was purified by reverse phase HPLC using a 10-90% acetonitrile/water (30 minute gradient) at a 70mL/min flow rate to afford the desired TFA salt of the title copmound (0 13 g, 38%) as a white powder $^1$H-NMR ((CD$_3$OD, 400 MHz) δ 8 86 (s, 2H), 7 62 (q, 1H, J= 8Hz), 7 02 (m, 2H), 6 56 (s, 1H), 5 48 (s, 2H), 5 31 (s, 2H), 3 34 (s, 3H), 2 49 (s, 2H), ES-HRMS *m/z* 500 0109/502 0066 (M+H $C_{19}H_{16}N_3O_4F_2BrS$ requires 500 0086/502 0067)

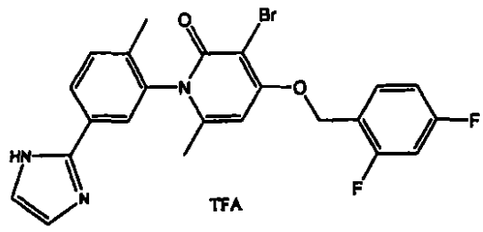
Example 709



Ethyl 2-({[3-bromo-1-(5-{[(2-hydroxyethyl)amino]carbonyl}-2-methylphenyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl]oxy}methyl)-5-fluorobenzylcarbamate

To a cooled (-10°C) solution of 3-[3-bromo-4-[(2-{[(ethoxycarbonyl)amino]methyl}-4-fluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-4-methylbenzoic acid (0 25 g, 0 46 mmol) and 4-methylmorpholine (0 06 mL, 0 55mmol) in DMF was added isobutyl chloroformate (0 07 mL, 0 55 mmol) The colorless solution gradually turned dark brown After 30 min, ethaolamine (0 04 mL, 0 69 mmol) was added and the solution warmed to RT After 1h, solvent was removed and the crude product was purified by preparatory HPLC Acetonitrile was evaporated and the solution washed with 5% $NaHCO_3$ (20 mL) and extracted in DCM (3 x 15 mL) The organic extracts were dried over $Na_2SO_4$, filtered, and concentrated to a white solid, dried *in vacuo* (0 09 g, 33%) $^1H$ NMR ($CD_3OD$/ 400MHz) δ 7 88 (m, 1H), 7 61 (s, 1H), 7 53 (m, 2H), 7 13 (m, 1H), 7 05 (m, 1H), 6 68 (s, 1H), 5 40 (s, 2H), 4 43 (s, 2H), 4 07 (q, 2H, *J* = 7 2 Hz), 3 68 (t, 2H, *J* = 5 6 Hz), 3 48 (t, 2H, *J* = 5 6 Hz), 2 09 (s, 3H), 2 00 (s, 3H), 1 22 (t, 3H , *J* = 7 2 Hz) ESHRMS *m/z* 590 1266 and 592 1254 (M+H calculated for $C_{27}H_{30}BrFN_3O_6$ requires 590 1297 and 592 1281)

Example 710

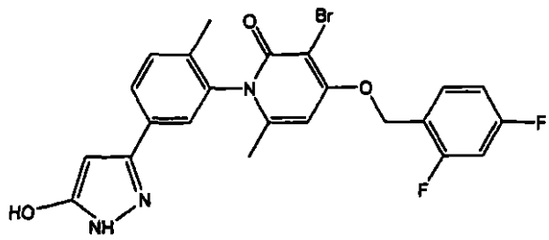



3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[5-(1H-imidazol-2-yl)-2-methylphenyl]-6-methylpyridin-2(1*H*)-one trifluoroacetate

An oven-dried flask was alternately evacuated and flushed with argon Toluene (2 18 mL) and trimethyl aluminum (1 25 mL, 2 51 mmol) were added sequentially and the solution cooled to -5°C Ethylene diamine (0 17 mL, 2 51 mmol) was added dropwise Methyl 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-4-methylbenzoate (0 75 g, 1 57 mmol) was added portionwise to the cooled solution The reaction mixture was then refluxed at 110°C for 4h The solution was cooled and water (0 7 mL), DCM (2 2 mL), and MeOH (2 2 mL) were added The solution was refluxed for 15 min following this addition and then dried over $Na_2SO_4$, filtered, and concentrated The residue was dissolved in EtOAc (20 mL), refluxed 15 min, dried over $Na_2SO_4$, filtered, and concentrated The crude product was purified by preparatory HPLC The product was isolated by freeze-drying and evaporation of the solvent to give a white solid, dried *in vacuo* (0 30 g, 31%) $^1H$ NMR ($CD_3OD$/ 400MHz) δ 7 88 (m, 1H), 7 71 (d, 1H, $J$ = 8 0 Hz), 7 64 (m, 2H), 7 05 (m, 2H), 6 70 (s, 1H), 5 37 (s, 2H), 4 09 (s, 4H), 2 16 (s, 3H), 2 01 (s, 3H) ESHRMS *m/z* 488 0750 and 490 0774 (M+H calculated for $C_{23}H_{21}BrF_2N_3O_2$ requires 488 0780 and 490 0762)

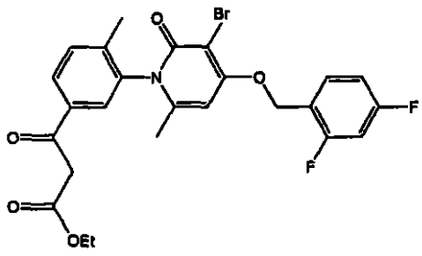
Example 711

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3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[5-(5-hydroxy-1H-pyrazol-3-yl)-2-methylphenyl]-6-methylpyridin-2(1*H*)-one

Step 1 Preparation of ethyl 3-{3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-4-methylphenyl}-3-oxopropanoate



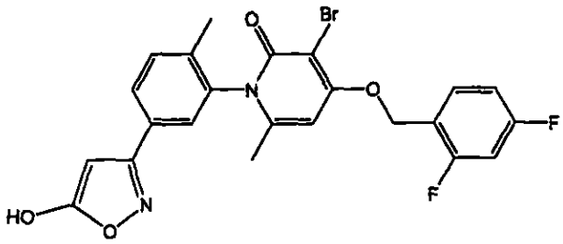
In an oven-dried round bottom flask, 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-4-methylbenzoic acid (see Example 487) (0 75 g, 1 62 mmol), DCM (2 00 mL), and oxalyl chloride (0 97 mL, 1 94 mmol) were combined under argon DMF (3-5 drops) was added to aid in dissolution Stirred at RT overnight Solvent was removed and the crude acid chloride was coevaporated with DCM (3-5 mL x 3) and dried in vacuo to give an orange solid In a separate oven-dried flask, in an argon atmosphere, a solution of monoethyl malonate (0 38 mL, 3 23 mmol) in THF (3 00 mL) was cooled to -78°C Isopropyl magnesium chloride (3 23 mL, 6 46 mmol) was added dropwise The solution was stirred for 30 min at -78°C The acid chloride prepared as described above was added dropwise as a solution in THF The reaction was warmed to RT After 30 min, the reaction was cooled (0°C) and 10% citric acid (5 0 mL) added The crude product was extracted in EtOAc, washed with 5% $NaHCO_3$, dried over $Na_2SO_4$, filtered,

and concentrated to a crude brown oil Recrystallization from DCM and hexane Filtered a beige solid, dried *in vacuo* (0 41 g, 47%) $^1$H NMR ($CD_3OD$/ 400MHz) δ 8 02 (m, 1H), 7 79 (s, 1H), 7 65 (m, 2H), 7 05 (t, 2H, *J* = 9 2 Hz), 6 66 (s, 1H), 5 36 (s, 2H), 4 16 (q, 2H, *J* = 7 2 Hz), 2 11 (s, 3H), 2 07 (s, 2H), 1 99 (s, 3H), 1 23 (t, 3H, *J* = 7 2 Hz) ESHRMS *m/z* 534 0744 and 536 0746 (M+H calculated for $C_{25}H_{23}BrF_2NO_5$ requires 534 0722 and 536 0706)

Step 2 Preparation of the title compound
To a mixture of ethyl 3-{3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-4-methylphenyl}-3-oxopropanoate (from Step 1) (0 20 g, 0 37 mmol) in EtOH (5 00 mL) was added hydrazine hydrate (0 01 mL, 0 41 mmol) The reaction mixture was heated at 60°C with a condensere After 1h, additional hydrazine hydrate (0 01 mL) was added After 2h, acetic acid (2 drops) was added At 4h, additional hydrazine was added (0 1 mL) At 5h, the reaction appeared to be complete Left in fridge overnight
Precipitate filtered, washed with hexane, found to be product, a white solid (0 10 g, 54%) $^1$H NMR ($CD_3OD$/ 400MHz) δ 7 66 (m, 2H), 7 45 (m, 2H), 7 05 (t, 2H, *J* = 9 6 Hz), 6 65 (s, 1H), 5 36 (s, 2H), 2 04 (s, 3H), 2 02 (s, 3H) ESHRMS *m/z* 502 0552 and 504 0569 (M+H calculated for $C_{23}H_{19}BrF_2N_3O_3$ requires 502 0572 and 504 0555)

Example 712

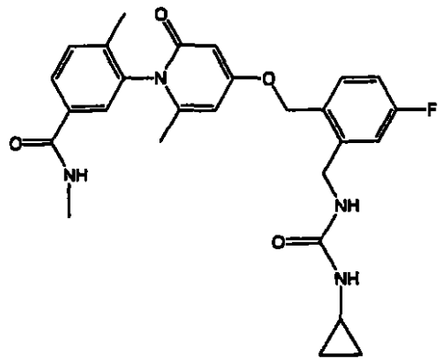
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3-bromo-4-[(2,4-difluoroben yl)oxy]-1-[5-(5-hydroxyisoxazol-3-yl)-2-methylphenyl]-6-methyipyridin-2(1*H*)-one

A solution of ethyl 3-{3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-4-methylphenyl}-3-oxopropanoate (0 20 g, 0 37 mmol), triethylamine (0 06 mL, 0 41 mmol), and hydroxylamine hydrochloride (0 03 g, 0 41 mmol) in EtOH (3 00 mL) was heated overnight at 60°C with a condenser Additional triethylamine (0 06 mL) and hydroxylamine hydrochloride (0 03 g) were added After 2 5h, the additions of triethylamine and hydroxylamine hydrochloride were repeated After 1h, the reaction was concentrated and purified by preparatory HPLC The product was isolated by freeze-drying and evaporation of the solvent to give a white solid Dissolved solid in DCM Upon addition of 5% $NaHCO_3$, solution became a milky emulsion Added additional DCM and some brine Organic extracts were dried over $Na_2SO_4$, filtered, and concentrated to a pink solid, dried in vacuo (120 mg, 64%) $^1H$ NMR ($CD_3OD$/ 400MHz) δ 7 66 (m, 2H), 7 44 (m, 2H), 7 04 (t, 2H, $J$ = 8 8 Hz), 6 64 (s, 1H), 5 36 (s, 2H), 2 04 (s, 3H), 2 01 (s, 3H) ESHRMS m/z 503 0415 and 505 0402 (M+H calculated for $C_{23}H_{18}BrF_2N_2O_4$ requires 503 0413 and 505 0395)

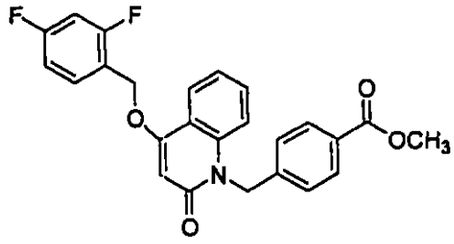
Example 713



3-[4-{[2-({[(cyclopropylamino)carbonyl]amino}methyl)-4-fluorobenzyl]oxy}-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*,4-dimethylbenzamide

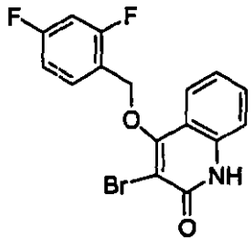
To a cooled (-15°C) solution of 3-[4-{[2-({[(cyclopropylamino)carbonyl]amino}methyl)-4-fluorobenzyl]oxy}-6-methyl-2-oxopyridin-1(2*H*)-yl]-4-methylbenzoic acid (see Example 651) (0 30 g, 0 63 mmol) and isobutyl chloroformate (0 10 mL, 0 75 mmol) in DMF (3 00 mL) was added 4-methylmorpholine (0 08mL, 0 75 mmol) The solution instantly turned yellow and was dark brown within minutes After 20 min, methylamine (0 47 mL of 2 0M solution in THF, 0 94 mmol) was added The reaction was carried out at RT After 2 5h, a catalytic amount of DMAP and additional methylamine (0 47 mL, 0 94 mmol) were added After an additional 2 5h, the reaction was concentrated to a dark red oil The crude product was purified by preparatory HPLC Acetonitrile was evaporated and the solution washed with 5% $NaHCO_3$ (20 mL) and extracted in DCM (3 x 15 mL) The organic extracts were dried over $Na_2SO_4$, filtered, and concentrated to an off-white solid, dried *in vacuo* (0 06 g, 19%) $^1H$ NMR ($CD_3OD$/ 400MHz) δ 7 85 (m, 1H), 7 58 (s, 1H), 7 48 (m, 2H), 7 14 (m, 1H), 7 02 (m, 1H), 6 23 (s, 1H), 6 09 (s, 1H), 5 20 (s, 2H), 4 45 (s, 2H), 2 90 (s, 3H), 2 49 (m, 1H), 2 11 (s, 3H), 1 91 (s, 3H), 0 71 (m, 2H), 0 48 (m, 2H) ESHRMS *m/z* 493 2260 (M+H calculated for $C_{27}H_{30}N_4O_4F$ requires 493 2246)

Example 714



Methyl 4-{[4-[(2,4-difluorobenzyl)oxy]-2-oxoquinolin-1(2*H*)-yl]methyl}benzoate

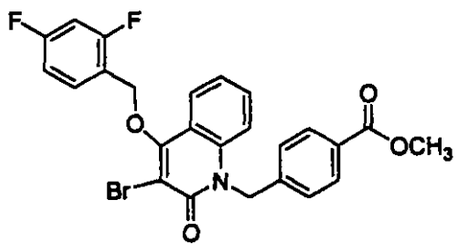
Step 1 Preparation of 3-bromo-4-[(2,4-difluorobenzyl)oxy]quinolin 2(1*H*)-one



To a room temperature solution of 4-hydroxy-1,2-dihydroquinolin-2-one (500 mg, 3 10 mmol) in $CH_2Cl_2$ (10 0 mL) was added portion-wise solid *N*-bromosuccinimide (551 5 mg, 3 10 mmol) The reaction was stirred vigorously for 1 0 h, followed by the sequential addition of $K_2CO_3$ (540 mg, 3 90 mmol), DMF (4 0 mL), and 2,4 difluorobenzyl bromide (0 430 mL, 3 30 mmol) The resulting suspension was stirred for 4 5 hours until complete formation of desired product was seen by LCMS analysis The reaction was then diluted with ethyl acetate (400 mL) and brine washed (3 X 200 mL) The resulting organic extract was $Na_2SO_4$ dried, filtered, and concentrated *in vacuo* to a residue that was subjected to $SiO_2$ chromatography with ethyl acetate/hexanes/methanol (60 35 5) to furnish a

solid (529 mg, 47 %) $^1$H NMR (300 MHz, $d_6$-DMSO) δ 12 23 (s, 1H), 7 68 (*app* q, *J* = 7 5 Hz, 1H), 7 64 (*app* q, *J* = 8 5 Hz, 1H), 7 54 (*app* q, *J* = 8 3 Hz, 1H), 7 38-7 27 (m, 2h), 7 20 (*app* t, *J* = 7 4 Hz, 1H), 7 13 (*app* dt, *J* = 8 4, 2 6 Hz, 1H), 5 25 (s, 2H), LC/MS C-18 column, $t_r$ = 2 64 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS *m/z* 366 (M+H) ES-HRMS *m/z* 365 9967 (M+H calcd for $C_{16}H_{11}BrF_2NO_2$ requires 365 9936)

Step 2 Preparation of methyl 4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-2-oxoquinolin-1(2*H*)- yl]methyl}benzoate



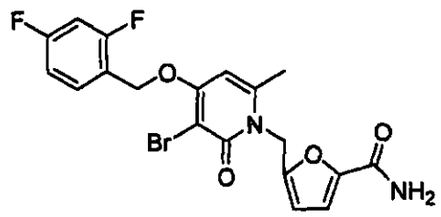
To a room temperature solution of 3-bromo-4-[(2,4-difluorobenzyl)oxy]quinolin-2(1*H*)-one (400 mg, 1 09 mmol) in THF (4 5 mL) was added portion-wise solid sodium hydride (95 % oil-free, 60 0 mg, 2 49 mmol) The reaction was vigorously stirred for 30 minutes followed by addition of methyl-4-(bromomethyl)-benzoate (400 mg, 1 75 mmol) This resulting suspension was then heated to 60 °C for 12 0 hours The resulting solution was then treated with saturated aqueous ammonium chloride (400 mL) and extracted with ethyl acetate (3 X 300 mL) The resulting organic extracts were $Na_2SO_4$ dried, filtered, and concentrated *in vacuo* to a residue that was subjected to $SiO_2$ chromatography with ethyl acetate/hexanes (60 40) to furnish a solid (396 mg, 71 %) $^1$H NMR (400 MHz, $CDCl_3$) δ 7 97 (*app* d, *J* = 8 0 Hz, 2H), 7 87 (d, *J* = 7 5 Hz, 1H), 7 60 (*app* q, *J* = 8 4 Hz, 1H), 7 49-7 42 (m, 1H), 7 30-7 15 (m, 4H), 6 94 (*app* t, *J* = 6 3 Hz, 1H), 6 88 (*app* t, *J* =

447
449

9 4 Hz, 1H), 5 64 (s, 2H), 5 33 (s, 2H), 3 88 (s, 3H), LC/MS C-18 column, $t_r$ = 3 46 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS *m/z* 514 (M+H) ES-HRMS *m/z* 514 0451 (M+H calcd for $C_{25}H_{19}BrF_2NO_4$ requires 514 0460)

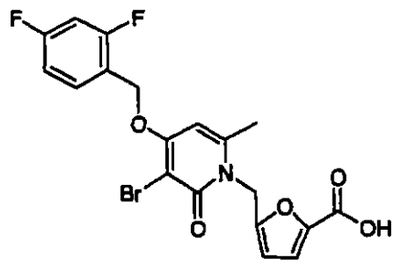
Step 3 Preparation of the title compound In a 25 mL round bottom flask was added, at room temperature, a solution of methyl 4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-2-oxoquinolin-1(2H)- yl]methyl}benzoate (step 2) (120 mg, 0 233 mmol) in MeOH (3 0 mL) Next, a combination of Pd on carbon (10 % Pd, weight by weight 50 % water, 100 mg, 0 047 mmol) and $Pd(OAc)_2$ (15 mg, 0 067 mmol) was added to the reaction vessel that purged with argon and then fitted with a septum The vessel was then equipped with a 2 0 L hydrogen balloon (*c a* 20 psi) The resulting suspension was allowed to stir of 12 0 hours and was then directly applied to $SiO_2$ chromatography using ethyl acetate/ hexanes (3 7) to furnish the desired title compound as a solid (52 mg, 51 %) $^1H$ NMR (300 MHz, $CDCl_3$) δ 8 05-7 98 (m, 3H), 7 55 (*app* q, *J* = 8 3 Hz, 1H), 7 48 (app t, *J* = 7 5 Hz, 1H), 7 30 (d, *J* = 8 0 Hz 2H), 7 19 (*app* q, *J* = 8 5, 2H), 7 05-6 90 (m, 2H), 6 28 (s, 1H), 5 60 (s, 2H), 5 26 (s, 2H), 3 91 (s, 3H), LC/MS C-18 column, $t_r$ = 3 71 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS *m/z* 436 (M+H) ES-HRMS *m/z* 436 1371 (M+H calcd for $C_{25}H_{20}BrF_2NO_4$ requires 436 1355)

Example 715



5-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}-2-furamide

Step 1 Preparation of 5-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}-2-furoic acid

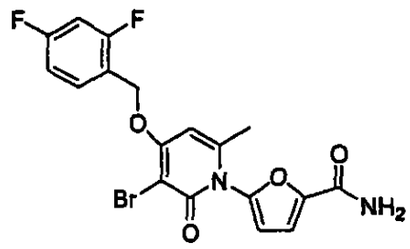


To a room temperature solution of methyl 5-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)- yl]methyl}-2-furoate (Example 660) (608 g, 1 30 mmol) in THF (8 0 mL) was added dropwise an aqueous solution of sodium hydroxide (3 0 M, 0 50 mL, 1 50 mmol) The reaction was then heated to 60 °C for 12 0 hours The resulting suspension was then diluted with 500 mL of ethyl acetate and neutralized with an aqueous solution of hydrochloric acid (1 0 N, 1 5 mL, 10 mmol) The resulting biphasic solution was then concentrated *in vacuo* to a volume of 50 mL At this time a white solid began to form and the resulting solid suspension was allowed to sit until precipitation appeared to stop (approximately 1 0 hour) The precipitate was collected and dried *in vacuo* (1 0 mm Hg) to furnish the solid acid as an intermediate (500 mg, 85 %) $^1$H NMR (300 MHz, $d_4$-MeOH) δ 7 64 (*app* q, *J* = 8 3 Hz, 1H), 7 18 (d, *J* = 3 4 Hz, 1H), 7 10-7 02 (m, 2H), 6 54 (s, 1H), 6 50 (d, *J* =

3 5 Hz, 1H), 5 42 (s, 2H), 5 37 (s, 2H), 2 64 (s, 3H), LC/MS C-18 column, $t_r$ = 2 38 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS *m/z* 454 (M+H) ES-HRMS *m/z* 454 0070 (M+H calcd for $C_{19}H_{15}BrF_2NO_5$ requires 454 0096)

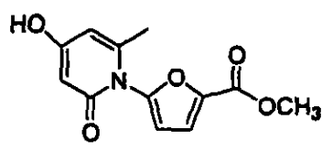
Step 2 Preparation of the title compound To a room temperature suspension of 5 {[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}-2-furoic acid (500 mg, 1 10 mmol) in THF (6 0 mL) was added 2-chloro-4,6 dimethoxy-1,3,5 triazine (307 mg, 1 75 mmol) and N-methyl morpholine (NMM, 184 mg, 1 82 mmol) sequentially The resulting solution was matured for 2 hours and then a saturated aqueous solution of ammonium hydroxide (0 70 mL) was added The resulting suspension was allowed to continue for 1 additional hour The reaction mixture was diluted with 400 mL of brine and extracted with ethyl acetate (3 X 400 mL) The organic extracts were separated, $Na_2SO_4$ dried, and concentrated *in vacuo* and the resulting residue was subjected to $SiO_2$ chromatography with ethyl acetate/hexanes/methanol (57 38 5) to provide the title compound (370 g, 74 %) $^1$H NMR (300 MHz, $d_4$-MeOH) δ 7 64 (*app* q, *J* = 8 1 Hz, 1H), 7 10-7 00 (m, 3H), 6 53 (s, 1H), 6 52 (d, *J* = 3 4 Hz, 1H), 5 43 (s, 2H), 5 32 (s, 2H), 2 61 (s, 3H), LC/MS C-18 column, $t_r$ = 2 15 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS *m/z* 453 (M+H) ES-HRMS *m/z* 453 0249 (M+H calcd for $C_{19}H_{16}BrF_2N_2O_4$ requires 453 0256)

Example 716



5-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-2-furamide

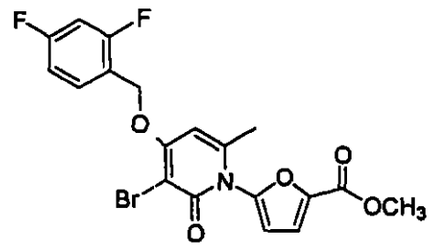
Step 1 Preparation of methyl 5-(4-hydroxy-6-methyl-2-oxopyridin-1(2*H*)-yl)-2-furoate



To a room temperature solution of methyl-2-amino-5-furoate (4 85 g, 34 4 mmol) in 1,4 dioxane (28 0 mL) was added 5-(1-hydroxy-3-oxobutylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (8 16 g, 44 3 mmol) The reaction was stirred vigorously and heated quickly (within 8 minutes) to an internal temperature of 98 °C Upon reaching temperature, the reaction was maintained for 1 0 hour At this time, the reaction was cooled to room temperature rapidly using an ice-bath and methane sulfonic acid (3 30 g, 34 4 mmol) was added The reaction mixture was once again brought to an internal temperature of approximately 100 °C After 1 0 hour the reaction was diluted with 10 mL of toluene and allowed to cool to room temperature on its own accord A solid formed after 3 0 hours that was collected and subsequently recrystallized from methanol/ ethyl acetate (1 1) The developing crystals were allowed to form and stand for 12 0 hours prior to collection to furnish the desired product as a solid (3 78 g, 44 %) $^1$H NMR (400 MHz, $d_7$-DMF) δ 11 34 (s, 1H), 7 43 (*app* d, *J* = 3 6 Hz, 1H), 6 79 (*app*

d, $J$ = 3 6 Hz, 1H), 6 01 (s, 1H), 5 63 (d, $J$ = 2 0 Hz, 1H), 3 87 (s, 3H), 2 02 (s 3H), LC/MS C-18 column, $t_r$ = 1 47 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS $m/z$ 250 (M+H) ES-HRMS $m/z$ 250 0696 (M+H calcd for $C_{12}H_{12}NO_5$ requires 250 0710)

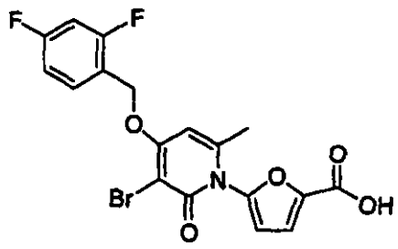
Step 2 Preparation of methyl 5-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-2-furoate



To a room temperature solution of methyl 5-(4-hydroxy-6-methyl-2-oxopyridin-1(2*H*)-yl)-2-furoate (step 1) (3 19 g, 12 8 mmol) in DMF (14 mL) was added portion-wise solid *N*-bromosuccinimide (2 29 g, 12 9 mmol) The reaction was stirred vigorously for 1 0 h, followed by the sequential addition of $K_2CO_3$ (1 88 g, 13 6 mmol), DMF (4 0 mL), and 2,4 difluorobenzyl bromide (2 00 mL, 15 55 mmol) The resulting suspension was stirred for 9 0 hours until complete formation of desired product was seen by LCMS analysis The reaction was then diluted with saturated brine (300 mL) and extracted with ethyl acetate (3 X 300 mL) The resulting organic extracts were $Na_2SO_4$ dried, filtered, and concentrated *in vacuo* to a residue that was subjected to $SiO_2$ chromatography with a gradient elution using ethyl acetate/hexanes (40 60 to 60 40) to furnish a solid (3 20 mg, 55 %) $^1$H NMR (400 MHz, $d_7$-DMF) δ 7 78 (*app* q, $J$ = 8 6 Hz, 1H), 7 48 (*app* d, $J$ = 3 6 Hz, 1H), 7 33 (*app* dt, $J$ = 10 0, 2 4 Hz, 1H), 7 21 (*app* dt, $J$ = 8 5, 1 8 Hz, 1H), 6 92 (d, $J$ = 3 6 Hz, 1H), 6 81 (s, 1H), 5 47 (s,

2H), 3 88 (s, 3H), 2 15 (s, 3H), LC/MS C-18 column, $t_r$ = 3 11 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS *m/z* 454 (M+H) ES-HRMS *m/z* 454 0117 (M+H calcd for $C_{19}H_{15}BrF_2N_2O_5$ requires 454 0096)

Step 3 5-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-2-furoic acid



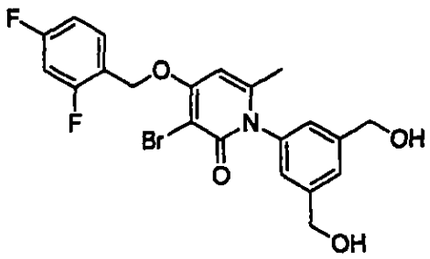
To a room temperature solution of methyl 5-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-2-furoate (step 2) (3 00 g, 6 61 mmol) in THF (20 mL) was added dropwise an aqueous solution of sodium hydroxide (3 0 M, 4 00 mL, 12 0 mmol) The reaction was then heated to 60 °C for 12 0 hours The resulting suspension was then diluted with 800 mL of ethyl acetate and neutralized with an aqueous solution of hydrochloric acid (3 0 N, 4 0 mL, 12 mmol) The resulting biphasic solution was then concentrated *in vacuo* to a volume of 90 mL At this time a white solid began to form and the resulting solid suspension was allowed to sit until precipitation appeared to stop (approximately 1 0 hour) The precipitate was collected and dried *in vacuo* (1 0 mm Hg) to furnish the solid acid as an intermediate (2 27 g, 78 %) $^1$H NMR (400 MHz, $d_7$-DMF) δ 7 79 (*app* q, *J* = 8 0 Hz, 1H), 7 32 (t, *J* = 9 2 Hz, 1H), 7 20 (*app* t, *J* = 7 4 Hz, 1H), 6 88 (*app* d, *J* = 2 5 Hz, 1H), 6 74 (s, 1H), 6 51 (d, *J* = 2 5 Hz, 1H), 5 44 (s, 2H), 2 10 (s, 3H), LC/MS C-18 column, $t_r$ = 2 77 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with

detection 254 nm, at 50°C) ES-MS *m/z* 440 (M+H) ES-HRMS *m/z* 439 9959 (M+H calcd for $C_{18}H_{13}BrF_2NO_5$ requires 439 9940)

Step 4 Preparation of the title compound

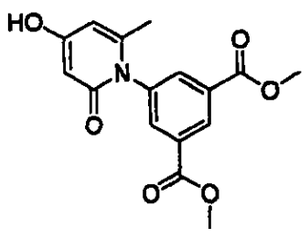
To a room temperature suspersion of 5-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-2-furoic acid (1 00 g, 2 27 mmol) in THF (8 0 mL) was added 2-chloro-4,6 dimethoxy-1,3,5 triazine (610 mg, 3 47 mmol) and N-methyl morpholine (NMM, 368 mg, 3 62 mmol) sequentially The resulting solution was matured for 2 hours and then a saturated aqueous solution of ammonium hydroxide (1 5 mL) was added The resulting suspension was allowed to continue for 1 additional hour The reaction mixture was diluted with 800 mL of brine and extracted with ethyl acetate (3 X 600 mL) The organic extracts were separated, $Na_2SO_4$ dried, and concentrated *in vacuo* and the resulting residue was subjected to $SiO_2$ chromatography with ethyl acetate/hexanes/methanol (57 38 5) to provide the title compound (710 mg, 71 %) $^1$H NMR (400 MHz, $d_7$-DMF) δ 8 07 (s, 1H), 7 79 (*app* q, *J* = 8 6 Hz, 1H), 7 50 (*br s*, 1H), 7 32 (*app* dt, *J* = 10 1, 2 2 Hz, 1H), 7 30 (*app* dd, *J* = 8 0, 3 3 Hz, 1H), 7 20 (*app* dt, *J* = 8 6, 2 0 Hz, 1H), 6 81 (s, 1H), 6 79 (d, *J* = 3 4 Hz, 1H), 5 47 (s, 2H), 2 14 (s, 3H), LC/MS C-18 column, $t_r$ = 2 60 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS *m/z* 439 (M+H) ES-HRMS *m/z* 439 0088 (M+H calcd for $C_{18}H_{14}BrF_2N_2O_4$ requires 439 0010)

Example 717



1-[3,5-bis(hydroxymethyl)phenyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one

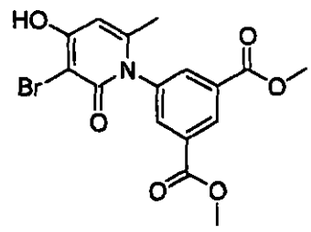
Step 1 Preparation of dimethyl 5-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)isophthalate



Dimethyl 5-aminoisophthalate (24 45 g, 117 mmol) was dissolved in 500 ml toluene and heated to reflux 5-(1-hydroxy-3-oxobutylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (40 0 g, 175 3 mmol) was added and refluxed for 15 minutes The reaction was evaporated 500 ml of acetonitrile and p-toluenesulphonic acid (22 25 g, 117 mmol) was added and refluxed for 1 hour The reaction was allowed to cool to room temperature and stand over night The resulting precipitate was filtered, washed three times with 250 ml water and 250 ml acetonitrile and dried *in vacuo* to give a tan solid (18 85 g, 51% yield) $^1$H NMR (300 MHz, DMSO-$d_6$) δ 10 70 (br s, 1H), 8 47 (t, $J$ = 1 54 Hz, 1H), 7 99 (d, $J$ = 1 47 Hz, 2H), 5 90 (d, $J$ = 1 61 Hz, 1H), 5 55 (d, $J$ = 2 42 Hz, 1H), 3 87 (s, 6H), 1 82 (s, 3H), LC/MS, $t_r$ = 1 79 minutes (5 to 95% acetonitrile/water

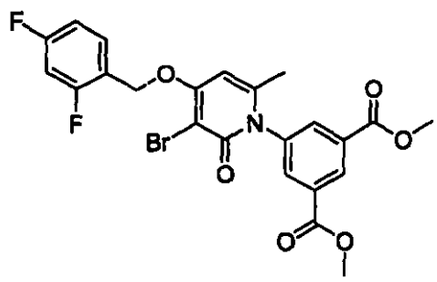
over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 318 (M+H) ES-HRMS *m/z* 318 0994 (M+H calcd for $C_{16}H_{16}NO_6$ requires 318 0972)

Step 2 Preparation of dimethyl 5-(3-bromo-4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)isophthalate



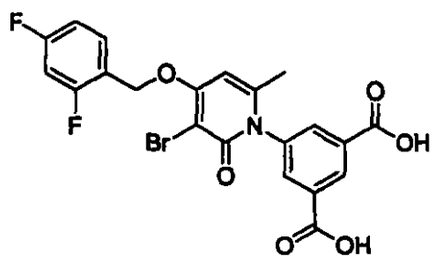
Dimethyl 5-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)isophthalate (from Step 1) (18 0 g, 56 7 mmol) was stirred at room temperature with N-Bromosuccinimide (10 6 g, 59 6 mmol) in 35 ml of *N,N*-dimethylformamide and 180 ml of methylene chloride After stirring for 1 hour, a white precipitate had formed The precipitate was filtered, washed with acetonitrile and dried *in vacuo* to give a white solid (11 55 g, 51%) $^1$H NMR (400 MHz, DMSO-$d_6$) δ 11 49 (br s, 1H), 8 49 (t, *J* = 1 24 Hz, 1H), 8 06 (d, *J* = 1 47 Hz, 2H), 6 07 (s, 1H), 3 88 (s, 6H), 1 82 (s, 3H), LC/MS, $t_r$ = 1 81 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 396 (M+H) ES-HRMS *m/z* 396 0102 (M+H calcd for $C_{16}H_{15}BrNO_6$ requires 396 0077)

Step 3 Preparation of dimethyl 5-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]isophthalate



Dimethyl 5-(3-bromo-4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)isophthalate (from Step 2) (11 3 g, 28 5 mmol) was stirred briskly with 2,4-difluorobenzylbromide (3 66 ml, 28 5 mmol) and $K_2CO_3$ (5 91 g, 42 8 mmol) in 50 ml of *N,N*-dimethylformamide at room temperature for 3 hours The reaction was then poured into 1L of cold water and the resulting precipitate was filtered, washed with water and diethyl ether, and dried *in vacuo* to yield a white solid (13 8 g, 93%) $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8 51 (t, *J* = 1 60 Hz, 1H), 8 12, (d, *J* = 1 60 Hz, 2H), 7 67 (*app* q, *J* = 7 92 Hz, 1H), 7 34 (*app* dt, *J* = 9 94, 2 19 Hz, 1H), 7 17 (dt, *J* = 8 53, 2 11 Hz, 1H), 6 68 (s, 1H), 5 33 (s, 2H), 3 88 (s, 6H), 1 93 (s, 3H), LC/MS, $t_r$ = 2 77 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 522 (M+H) ES-HR/MS *m/z* 522 0335 (M+H calcd for $C_{23}H_{19}BrF_2NO_6$ requires 522 0358)

Step 4 Preparation of 5-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]isophthalic acid



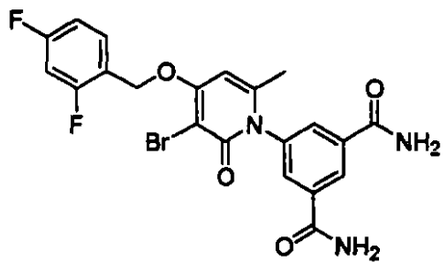

Dimethyl 5-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]isophthalate (from Step 3) (5 0 g, 9 57 mmol) was stirred at room temperature with 2 5 N NaOH (15 3 ml, 38 3 mmol) in 30 ml of 5 1 THF/water for 1 hour The reaction was then acidified with 1 N HCl and the resulting precipitate was filtered, washed with water, and dried *in vacuo* to yield a white solid (4 48 g, 95%) $^1$H NMR (400 MHz, DMSO-$d_6$) δ 13 50 (br s, 2H), 8 51 (t, *J* = 1 41 Hz, 1H), 8 02,

452
454

(d, $J$ = 1 48 Hz, 2H), 7 67 (*app* q, $J$ = 7 88 Hz, 1H), 7 32 (dt, $J$ = 9 94, 2 19 Hz, 1H), 7 16 (dt, $J$ = 8 52, 1 99 Hz, 1H), 6 68 (s, 1H), 5 32 (s, 2H), 1 94 (s, 3H), LC/MS, $t_r$ = 2 27 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 494 (M+H) ES-HRMS *m/z* 494 0054 (M+H calcd for $C_{21}H_{15}BrF_2NO_6$ requires 494 0045)

Step 5 Preparation of the title compound 5-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]isophthalic acid (from Step 4 above) (500 mg, 1 01 mmol) was added to a solution of 1M borane-dimethylsulfide complex in tetrahydrofuran (9 0 ml, 9 00 mmol) in 2 5 ml tetrahydrofuran at 0°C The reaction was allowed to warm to room temperature while stirring After stirring overnight, more 1M borane-dimethylsulfide complex in tetranydrofuran (0 60 ml, 0 60 mmol) was added and stirring at room temperature After 4 hours, ice chips were added to quench the reaction The reaction was extracted 2 times with ethyl acetate and the combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated The resulting solid was washed with acetonitrile and diethyl ether and dried *in vacuo* to give a white solid (281 mg, 60%) $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7 66 (*app* q, $J$ = 7 92 Hz, 1H), 7 35 (s, 1H), 7 33 (dt, $J$ = 9 40, 2 24 Hz, 1H), 7 16 (dt, $J$ = 8 52, 1 88 Hz, 1H), 6 99 (s, 2H), 6 62 (s, 1H), 5 31 (s, 2H), 5 27 (br s, 2H), 4 51 (s, 4H), 1 93 (s, 3H), LC/MS, $t_r$ = 2 19 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 466 (M+H) ES-HRMS *m/z* 466 0454 (M+H calcd for $C_{21}H_{19}BrF_2NO_4$ requires 466 0460)

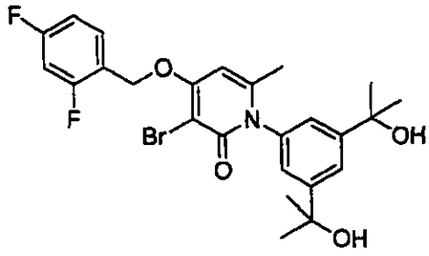
Example 718



5-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]isophthalamide

5-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]isophthalic acid (Example 717, step 4) (500 mg, 1 01 mmol) was dissolved in 4 ml of tetrahydrofuran 0 5M ammonia in 1,4-dioxane (12 12 ml, 6 06 mmol) was added, followed, in order, by EDCI (494 mg, 2 53 mmol), 1-hydroxybenzotriazole (342 mg, 2 53 mmol) and triethylamine (563 μl, 4 04 mmol) The reaction was stirred at room temperature overnight The reaction evaporated and water was used to triturate the product The resulting solid was filtered and washed with water, acetonitrile, ethyl acetate and diethyl ether, and dried *in vacuo* to give a white solid (202 mg, 41%) $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8 45 (s, 1H), 8 08 (br s, 2H), 7 86, (d, *J* = 1 34 Hz, 2H), 7 67 (*app* q, *J* = 7 92 Hz, 1H), 7 55 (br s, 2H), 7 33 (dt, *J* = 9 94, 2 18 Hz, 1H), 7 17 (dt, *J* = 8 59, 1 92 Hz, 1H), 6 70 (s, 1H), 5 34 (s, 2H), 1 96 (s, 3H), LC/MS, $t_r$ = 2 10 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 492 (M+H) ES-HRMS *m/z* 492 0381 (M+*H* calcd for $C_{21}H_{17}BrF_2N_3O_4$ requires 492 0365)

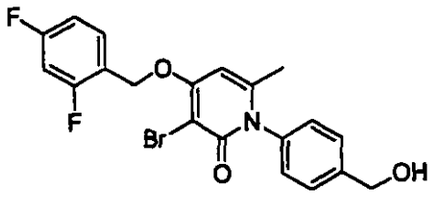
Example 719



1-[3,5-bis(1-hydroxy-1-methylethyl)phenyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one

Dimethyl 5-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]isophthalate (Example 717, step 3) (500 mg, 0 96 mmol) was added dro pwise to a solution of 3M MeMgBr in diethyl ether (1 6 ml, 4 79 mmol) in 15 ml of tetrahydrofuran at -5°C and stirred at -5°C The reaction turned red After 2 5 hours, the reaction was quenched with a saturated $NH_4Cl$ solution and extracted 2 times with ethyl acetate The combined organic layers were washed with $NaHCO_3$ solution and brine, dried over $MgSO_4$ and evaporated The resulting solid was washed with diethyl ether and dried *in vacuo* to give a white solid (329 mg, 66%) $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 7 69 - 7 63 (m, 2H), 7 33 (dt, $J$ = 9 87, 2 41 Hz, 1H), 7 16 (dt, $J$ = 8 46, 1 75 Hz, 1H), 7 07 (d, $J$ 1 48 Hz, 2H), 6 61 (s, 1H), 5 32 (s, 2H), 5 06 (s, 2H), 1 89 (s, 3H), 1 41 (s, 12H), LC/MS, $t_r$ = 2 45 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS $m/z$ 522 (M+H) ES-HRMS $m/z$ 522 1098 (M+H calcd for $C_{25}H_{27}BrF_2NO_4$ requires 522 1086)

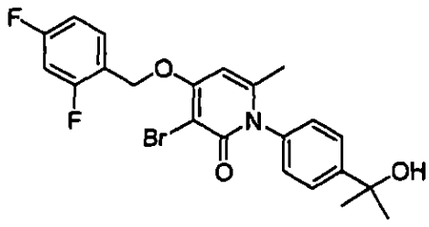
Example 720



3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[4-(hydroxymethyl)phenyl]-6-methylpyridin-2(1H)-one

4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoic acid (Example 203) (500 mg, 1 11 mmol) was added to a solution of 2M borane-dimethylsulfide complex in tetrahydrofuran (3 33 ml, 6 66 mmol) in 2 5 ml tetrahydrofuran at 0°C The reaction was allowed to warm to room temperature while stirring After 2 5 hours, ice chips were added to quench the reaction The resulting precipitate was filtered, washed with diethyl ether and dried *in vacuo* to give a white solid (160 mg, 33%) $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7 66 (*app* q, *J* = 7 88 Hz, 1H), 7 42 (d, *J* = 8 19 Hz, 2H), 7 33 (dt, *J* = 9 87, 2 06 Hz, 1H), 7 19 - 7 14 (m, 3H), 6 62 (s, 1H), 5 31 (s, 2H), 5 30 (s, 1H), 4 54 (d, *J* = 5 24, 2H), 1 92 (s, 3H), LC/MS, $t_r$ = 2 36 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 436 (M+H) ES-HRMS *m/z* 436 0374 (M+H calcd for $C_{20}H_{17}BrF_2NO_3$ requires 436 0354)

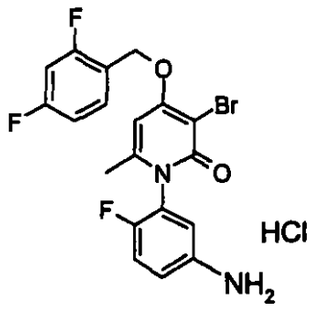
Example 721



3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[4-(1-hydroxy-1-methylethyl)phenyl]-6-methylpyridin-2(1H)-one

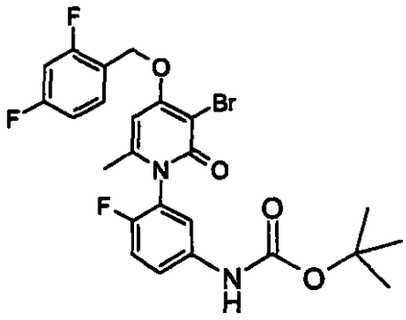
Methyl-4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoate (Example 202) (500 mg, 1 08 mmol) was added dropwise to a solution of 3M MeMgBr in diethyl ether (0 90 ml, 2 69 mmol) in 15 ml of tetrahydrofuran at -5°C and stirred at -5°C After 2 75 hours, more 3M MeMgBr in diethyl ether (0 45 ml, 1 35 mmol) was added and stirred at -5°C After 4 hours, the reaction was quenched with a saturated $NH_4Cl$ solution and extracted 2 times with ethyl acetate The combined organic layers were washed with $NaHCO_3$ solution and brine, dried over $MgSO_4$ and evaporated The resulting solid was washed with diethyl ether and dried *in vacuo* to give a white solid (268 mg 53%) $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 7 66 (*app* q, $J$ = 7 92 Hz, 1H), 7 57 (d, $J$ = 8 46 Hz, 2H), 7 33 (dt, $J$ = 9 87, 2 11 Hz, 1H), 7 16 (dt, $J$ = 8 59, 2 24 Hz, 1H), 7 14 (d, $J$ = 8 63 Hz, 2H), 6 62 (s, 1H), 5 31 (s, 2H), 5 12 (s, 1H), 1 91 (s, 3H), 1 44 (s, 6H), LC/MS, $t_r$ = 2 54 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 464 (M+H) ES-HRMS *m/z* 464 0604 (M+H calcd for $C_{22}H_{21}BrF_2NO_3$ requires 464 0667)

Example 722



1-(5-amino-2-fluorophenyl)-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one hydrochloride

Step 1 Preparation of tert-butyl 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorophenylcarbamate

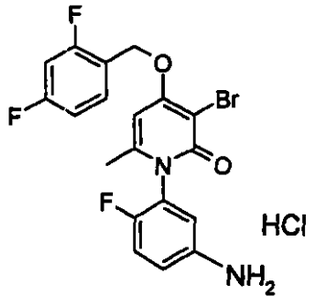


A solution of the compound of Example 519 (4 3 g, 9 2 mmol) in *tert*-butanol (50 mL) was flushed with nitrogen Diphenyl phosphoryl azide (2 mL, 9 2 mmol) and triethyl amine (1 3 mL, 9 2 mmol) were added After heating at 90 C for 20 h, the reaction mixture was concentrated *in vacuo* The residue was diluted with methylene chloride and was washed sequentially with aqueous ammonium chloride and aqueous $NaHCO_3$ The organic layer was concentrated *in vacuo*, the resulting solids were suspended in acetonitrile and filtered to give the title compound (2 9 g, 58%) $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ 7 64 (q, $J$ = 7 2 and 14 4 Hz, 1H), 7 49 (m, 1H), 7 43 (m, 1H), 7 24 (t, $J$ = 9 6 Hz, 1H), 7 04 (t, $J$ = 8 4 Hz, 2H), 6 62 (s, 1H), 5 35 (s, 2H), 2 09 (s, 3H), 1 49 (s, 9H) ppm $^{19}$ F NMR (300 MHz,

455
457

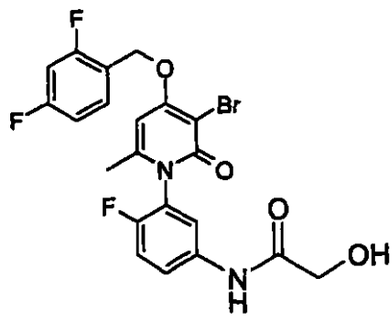
$CD_3OD$) δ -111 53 (1F), -115 93 (1 F), -132 58 ppm ES-HRMS *m/z* 540 0822 (M+H calcd for $C_{24}H_{23}BrF_3N_2O_4$ requires 540 0820)

Step 2 Preparation of 1-(5-amino-2-fluorophenyl)-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one hydrochloride



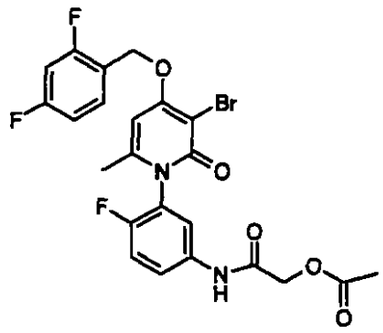

The product of Step 1, (2 9 g, 5 3 mmol) was dissolved in tetrahydrofuran (75 mL) and 6N HCl (10 mL) The reaction mixture was heated at 60 C for 18h and was concentrated in vacuo to give the final product (1 89 g, 75%) $^1H$ NMR (400 MHz, $CD_3OD$) δ 7 64 (q, *J* = 8 4 and 15 2 Hz, 1H), 7 56 (m, 2H), 7 46 (m, 1H), 7 05 (m, 2H), 6 69 (s, 1H), 5 37 (s, 2H), 2 10 (s, 3H) ppm $^{19}$ F NMR (400 MHz, $CD_3OD$) δ -111 37 (1F), -115 86 (1 F), -123 16 ppm ES-HRMS *m/z* 440 0334 (M+H calcd for $C_{19}H_{15}BrF_3N_2O_2$ requires 440 0295)

Example 723




N-{3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorophenyl}-2-hydroxyacetamide

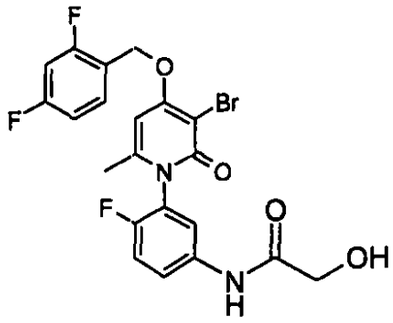
Step 1 Preparation of 2-({3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorophenyl}amino)-2-oxoethyl acetate



A solution of the compound of Example 722 (0 5 g, 1 05 mmol) in tetrahydrofuran (20 mL) was treated with triethyl amine (0 3 mL, 2 1 mmol) and acetoxy acetylchloride (0 12 mL, 1 15 mmol) After stirring at room temperature for 2h, the reaction was complete The reaction mixture was poured into saturated aqueous ammonium chloride The solids were filtered off and were washed with water and diethyl ether Title product was isolated as a white solid (0 32 g, 58%) $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 7 65 (m, 3H), 7 32 (t, $J$ = 8 4 Hz, 1H), 7 04 (t, $J$ = 8 4 Hz, 2H), 6 64 (s, 1H), 5 35 (s, 2H), 4 68 (s, 2H), 2 15 (s, 3H), 2 10 (s, 3H) ppm $^{19}$ F NMR (400 MHz, $CD_3OD$) $\delta$ -111 56 (1F), -115 99 (1 F), -129 48 (1F) ppm LC/MS, $t_r$ = 5 35 minutes (5 to 95% acetonitrile/water over 8 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS $m/z$ 540 (M+H)

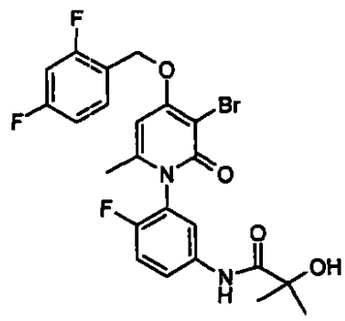
Step 2 Preparation of N-{3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorophenyl}-2-hydroxyacetamide

456
459



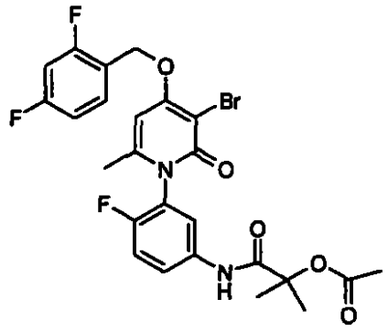
The product of Step 1, (0 1 g, 0 18 mmol) was suspended ın tetrahydrofuran (10 mL), methanol (2 mL), and 2 5 N NaOH (1 mL) After stırrıng at room temperature for 1 hour, the reactıon was complete and tıe organıcs were removed *ın vacuo* The aqueous layer was acıdıfıed to pH 1 wıth 6N HCl, the solıds were suspended ın water, fıltered, and washed wıth dıethyl ether The tıtle compound was obtaıned as a whıte powder (56 2 mg, 61%) $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 7 75 (dq, $J$ = 2 9, 4 8 and 9 2 Hz, 1H), 7 71 (dd, $J$ = 2 4 and 6 8 Hz, 1H), 7 64 (q, $J$ = 8 and 14 8 Hz, 1H), 7 32 (t, $J$ = 9 6 Hz, 1H), 7 04 (t, $J$ = 8 8 Hz, 2H), 6 64 (s, 1H), 5 36 (s, 2H), 4 10 (s, 2H), 2 10 (s 3H) ppm $^{19}$ F NMR (400 MHz, $CD_3OD$) $\delta$ -111 54 (1F), -115 99 (1 F), -129 71 (1F) ppm LC/MS, $t_r$ = 5 04 mınutes (5 to 95% acetonıtrıle/water over 8 mınutes at 1 ml/mın wıth detectıon 254 nm, at 50°C) ES-MS *m/z* 498 (M+H)

Example 724



N-{3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorophenyl}-2-hydroxy-2-methylpropanamide

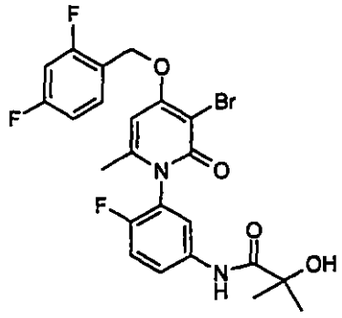
Step 1 Preparation of 2-({3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorophenyl}amino)-1,1-dimethyl-2-oxoethyl acetate



A solution of the compound of Example 722 (0 5 g, 1 05 mmol) in tetrahydrofuran (20 mL) was treated with triethyl amine (0 3 mL, 2 1 mmol) and 1-chlorocarbonyl-1-methylethyl acetate (0 16 mL, 1 15 mmol) After stirring at room temperature for 2h, the reaction was complete The reaction mixture was poured into saturated aqueous ammonium chloride The solids were filtered off and were washed with water and diethyl ether The compound of Step 1 was isolated as a white solid (0 23 g, 39%) $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 7 64 (m, 2H), 7 54 (dd, $J$ = 2 8 and 6 8 Hz, 1H), 7 30 (t, $J$ = 9 2 Hz, 1H), 7 04 (t, $J$ = 9 2 Hz, 2H), 6 64 (s, 1H), 5 35 (s, 2H), 2 11 (s, 3H), 2 08 (s, 3H), 1 61 (s, 6H) ppm $^{19}$ F NMR (400 MHz, $CD_3OD$) $\delta$ -111 57 (1F), -116 00 (1 F), -129 56 (1F) ppm LC/MS, $t_r$ = 5 65 minutes (5 to 95% acetonitrile/water over 8 minutes at 1 ml/min with detection 254 nm, at 50°C) ES-MS $m/z$ 568 (M+H)

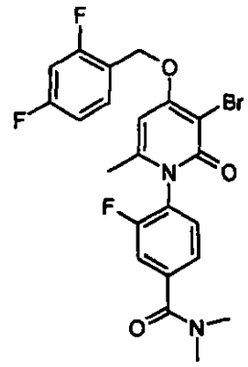
Step 2 Preparation of N-{3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorophenyl}-2-hydroxy-2-methylpropanamide

457
459



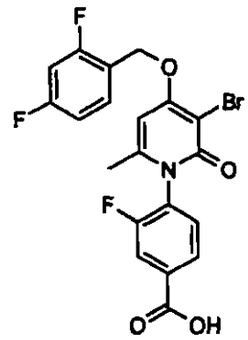
The product of Step 1 (0 1 g, 0 17mmol) was suspended ın tetrahydrofuran (10 mL), methanol (2 mL), and 2 5 N NaOH (1 mL) After stırrıng at room temperature for 1 hour, the reactıon was complete and the organıcs were removed *ın vacuo* The aqueous layer was acidıfıed to pH 1 wıth 6N HCl, the solıds were suspended ın water, fıltered, and washed wıth dıethyl ether The tıtle compound was obtaıned as a whıte powder (56 mg, 61%) $^1$H NMP (400 MHz, $CD_3OD$) δ 7 75 (dq, *J* = 2 8, 4 4 and 9 2 Hz, 1H), 7 69 (dd, *J* = 2 8 and 6 8 Hz, 1H), 7 64 (q, *J* = 8 and 14 8 Hz, 1H), 7 31 (t, *J* = 9 2 Hz, 1H), 7 04 (t, *J* = 8 4 Hz, 2H), 6 64 (s, 1H), 5 35 (s, 2H), 2 10 (s, 3H), 1 43 (s, 6H) ppm $^{19}$ F NMR (400 MHz, $CD_3OD$) δ -111 55 (1F), -115 95 (1 F), -129 80 (1F) ppm LC/MS, $t_r$ = 5 34 mınutes (5 to 95% acetonıtrıle/water over 8 mınutes at 1 ml/mın wıth detectıon 254 nm, at 50°C) ES-MS *m/z* 526 (M+H)

Example 725



4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-3-fluoro-N,N-dimethylbenzamide

Step 1 Preparation of 4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-3-fluorobenzoic acid

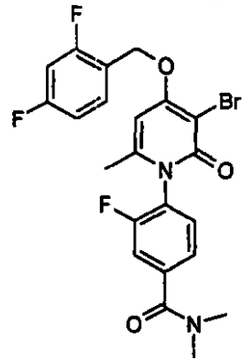


Compound of Example 604 (4 1 g, 8 5mmol) was suspended in tetrahydrofuran (30 mL), methanol (15 mL), water (15 mL) and 2 5 N NaOH (6 8 mL, 17 mmol)) After stirring at room temperature for 2 hour, the reaction was complete and the organics were removed The aqueous layer was acidified to pH 1 with 3N HCl, the solids were suspended in water, filtered, and washed with diethyl ether The title compound was obtained as a white powder and used without further purification (4 4 g) $^{1}$H NMR (400 MHz, $CD_3OD$) $\delta$ 8 00 (dd, $J$ = 1 8 and 8 8 Hz, 1H), 7 93 (dd, $J$ = 1 48 and 10 Hz, 1H), 7 64 (q, $J$ = 8 and 14 8 Hz, 1H), 7 49 (t, $J$ = 7 6 Hz, 1H), 7 05 (t, $J$ = 10 Hz, 2H), 6 66 (s, 1H), 5 36 (s, 2H), 2 08 (s, 3H) ppm $^{19}$ F NMR (400 MHz, $CD_3OD$) $\delta$ -111 48 (1F), -115 96 (1 F), -

458
460

123 35 (1F) ppm ES-HRMS *m/z* 468 9987 (M+H calcd for $C_{20}H_{14}BrF_3NO_4$ requires 469 0086)

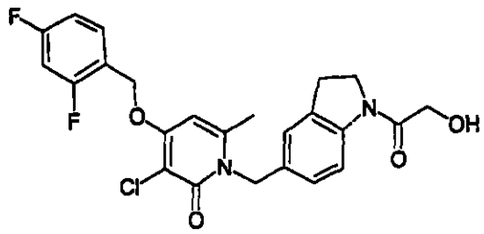
Step 2 Preparation of 4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-3-fluoro-



N,N-dimethylbenzamide

A solution of the product of Step 1 (0 5 g, 1 07 mmol) in *N,N*-dimethyl formamide was cooled to 0 C *Iso*-butyl chloroformate (0 14 mL, 1 07 mmol) and *N*-methyl morpholine (0 12 mL, 1 07 mmol) were added After 20 minutes, *N,N*-dimethylamine (2 0 M, 1 1 mL, 2 14 mmol) was added and the reaction mixture was warmed to room temperature over 18 h The reaction mixture was partitioned between ethyl acetate and saturated aqueous $NaHCO_3$ The organics were washed with brine and concentrated *in vacuo* The resulting semi-solid was treated with ethyl acetate and acetone to precipitate the title compound (90 mg, 17%) $^1$H NMR (400 MHz, dmso-$d_6$) δ 7 67 (q, *J* = 8 and 14 8 Hz, 1H), 7 52 (m, 2H), 7 35 (m, 2H), 7 18 (td, *J* = 2 8 and 8 8 Hz, 1H), 6 73 (s, 1H), 5 34 (s, 2H), 2 98 (s, 3H), 2 91 (s, 3H), 2 00 (s, 3H) ppm $^{19}$ F NMR (400 MHz, dmso-$d_6$) δ -109 50 (1F), -113 63 (1 F), -122 09 (1F) ppm ES-HRMS *m/z* 496 0570 (M+H calcd for $C_{22}H_{19}BrF_3N_2O_3$ requires 496 0558)

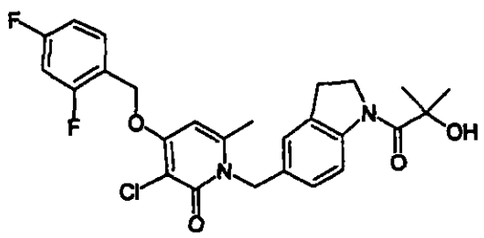
Example 726



3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[(1-glycoloyl-2,3-dihydro-1H-indol-5-yl)methyl]-6-methylpyridin-2(1H)-one

A 10 mL round bottomed flask equipped with stirbar and nitrogen inlet was charged with compound of Example 633 (180 mg, 0 43 mmol), acetoxyacetyl chloride (51 µL, 0 47 mmol), triethylamine (119 µL, 0 86 mmol) and tetrahydrofuran (3 0 mL) After stirring at 25° C for 20 min the reaction was completed by LC-MS NaOH (2 5M, 2 24 mmol, 1 0 mL) and MeOH (2 0mL) was added and stirred for 20 min to give the title compound The compound precipitated out of solution The precipitated was filtered and washed with water and diethyl ether to obtain the title compound (130 mg, 64%) as a white solid $^1$H NMR (400 MHz, (DMSO) δ 7 9 (d, *J* = 8 2, 1H), 7 6 (q, *J* = 8 5 and 6 9 Hz, 1H), 7 3 (t, *J* = 8 7 Hz, 1H), 7 1 (t, *J* = 7 9 Hz, 1H), 6 9 (s, 2H), 6 5 (s, 1H), 5 25 (s, 2H), 4 1 (d, *J* = 5 5 Hz, 2H), 3 9 (t, *J* = 8 6 Hz, 2H), 3 42 (t, *J* = 5 4 Hz, 1H), 3 35 (t, *J* = 4 8 Hz, 1H), 3 2 (t, *J* = 8 5 Hz, 2H), 2 3 (s, 3H) ppm ES-HRMS *m/z* 475 1220 (M+H calcd for $C_{24}H_{22}ClF_2N_2O_4$ requires 475 1231)

Example 727

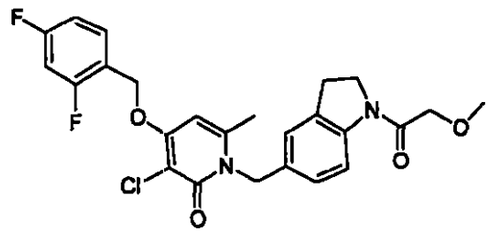


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461

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1H-indol-5-yl]methyl}-6-methylpyridin-2(1H)-one

A 10 mL round bottomed flask equipped with stirbar and nitrogen inlet was charged with compound of Example 633 (200 mg, 0 48 mmol), 1-chlorocarbonyl-1-methylethyl acetate (104 3 µL, 0 72 mmol), triethylamine (133 µL, 0 96 mmol) and tetrahydrofuran (4 0 mL) After stirring at 25° C for 20 min the reaction was completed by LC-MS NaOH (2 5M, 2 24 mmol, 1 5 mL) and MeOH (2 0mL) was added and stirred for 20 min to give the title compound The compound precipitated out of solution The precipitate was filtered and washed with water and diethyl ether to obtain a white solid (240 mg, 99%) $^1$H NMR (400 MHz, (DMSO) δ 8 0 (d, $J$ = 8 3, 1H), 7 6 (q, $J$ = 8 6 and 6 9 Hz, 1H), 7 3 (td, $J$ = 2 5 and 7 8 Hz, 1H), 7 1 (td, $J$ = 1 75 and 6 7 Hz, 1H), 6 95 (s, 1H), 6 89 (d, $J$ = 8 5 Hz, 1H), 6 58 (s, 1H), 5 25 (s, 2H), 4 3 (t, $J$ = 8 3 Hz, 2H), 3 42 (t, $J$ = 5 4 Hz, 1H), 3 35 (t, $J$ = 5 2 Hz, 1H), 3 0 (t, $J$ = 8 2 Hz, 2H), 2 3 (s, 3H), 1 3 (s, 6H) ppm ES-HRMS $m/z$ 503 1561 (M+H calcd for $C_{26}H_{26}ClF_2N_2O_4$ requires 503 1544)

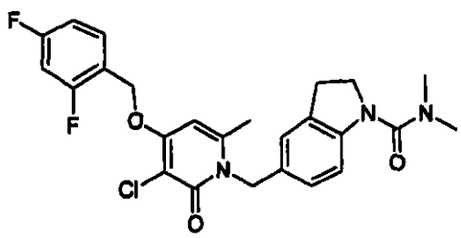
Example 728




3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(methoxyacetyl)-2,3-dihydro-1H-indol-5-yl]methyl}-6-methylpyridin-2(1H)-one

A 10 mL round bottomed flask equipped with stirbar and nitrogen inlet was charged with compound of Example 633 (200 mg, 0 48 mmol), methoxyacetyl chloride (66 µL, 0 72 mmol), triethylamine (134 µL, 0 96 mmol) and tetrahydrofuran (4 0 mL) After stirring at 25° C for 20 min the reaction was completed by LC-MS The compound precipitated out of solution The precipitate was filtered and washed with water and diethyl ether to obtain a white solid (195 mg, 83%) $^1$H NMR (400 MHz, (DMSO) δ 8 0 (d, *J* = 8 0, 1H), 7 6 (q, *J* = 8 6 and 6 7 Hz, 1H), 7 3 (td, *J* = 2 4 and 6 7 Hz, 1H), 7 1 (td, *J* = 1 88 and 6 6 Hz, 1H), 6 9 (s, 2H), 6 58 (s, 1H), 5 25 (s, 2H), 4 15 (s, 2H), 3 9 (t, *J* = 8 3 Hz, 2H), 3 45 (m, 1H), 3 4 (m, 1H), 3 32 (s, 3H), 3 0 (t, *J* = 8 5 Hz, 2H), 2 3 (s, 3H) ppm ES-HRMS *m/z* 489 1387 (M+H calcd for $C_{25}H_{24}ClF_2N_2O_4$ requires 489 1387)

Example 729



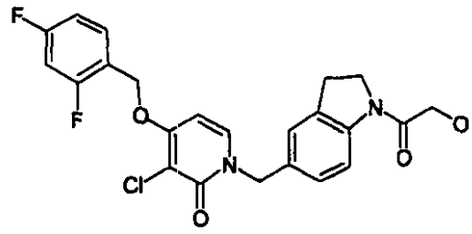
5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-N,N-dimethylindoline-1-carboxamide

A 10 mL round bottomed flask equipped with stirbar and nitrogen inlet was charged with compound of Example 633 (200 mg, 0 48 mmol), dimethylcarbamyl chloride (66 µL, 0 72 mmol), triethylamine (133 µL, 0 96 mmol) and tetrahydrofuran (4 0 mL) After stirring at 25° C for 5 min the reaction was completed by LC-MS The compound precipitated out of solution The

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490

precipitate was filtered and washed with water and diethyl ether to obtain a white solid (198 mg, 85%) $^1$H NMR (400 MHz, (DMSO) δ 7 6 (q, *J* = 7 4 Hz, 1H), 7 3 (t, *J* = 8 9 Hz, 1H), 7 1 (t, *J* = 8 5 Hz, 2H), 6 93 (s, 1H), 6 86 (s, 1H), 6 58 (s, 1H), 5 25 (s, 2H), 3 9 (t, *J* = 8 2 Hz, 2H), 3 45 (m, 1H), 3 4 (m, 1H), 2 9 (t, *J* = 8 3 Hz, 2H), 2 8 (s, 6H), 2 3 (s, 3H) ppm ES-HRMS *m/z* 488 1548 (M+H calcd for $C_{25}H_{24}ClF_2N_2O_4$ requires 488 1547)

Example 730

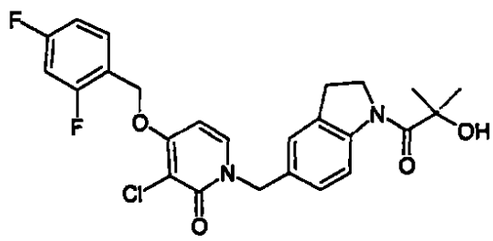


3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[(1-glycoloyl-2,3-dihydro-1H-indol-5-yl)methyl]pyridin-2(1H)-one

A 10 mL round bottomed flask equipped with stirbar and nitrogen inlet was charged with compound of Example 88 (200 mg, 0 5 mmol), acetoxyacetyl chloride (59 µL, 0 55 mmol), triethylamine (140 µL, 1 0 mmol) and tetrahydrofuran (3 0 mL) After stirring at 25° C for 20 min the reaction was completed by LC-MS NaOH (2 5M, 2 24 mmol, 1 0 mL) and MeOH (2 0mL) was added and stirred for 20 min to give the title compound The compound precipitated out of solution The precipitated was filtered and washed with water and diethyl ether to obtain the title compound (200 mg, 83%) as a white solid $^1$H NMR (400 MHz, (DMSO) δ 7 98 (d, *J* = 8 1, 1H), 7 9 (d, *J* = 7 8 Hz, 1H), 7 6 (q, *J* = 8 6 and 6 6 Hz, 1H) 7 3 (dt, *J* = 2 4 and 7 2 Hz, 1H), 7 1 (m, 2H), 6 56 (d, *J* =7 8 Hz, 1H), 5 25 (s, 2H),5 1 (s, 2H), 4 8 (t, *J* = 5 8 Hz, 1H), 4 1 (d, *J* = 5 6 Hz, 2H), 3 9 (t,

$J$ = 7 9 Hz, 2H), 3 1 (t, $J$ = 7 9 Hz, 2H) ppm ES-HRMS $m/z$ 461 1088 (M+H calcd for $C_{23}H_{20}ClF_2N_2O_4$ requires 461 1074)

Example 731

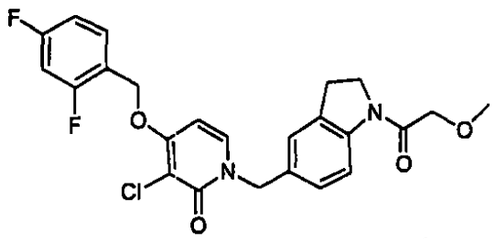


Preparation of 3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[(1-glycoloyl-2,3-dihydro-1H-indol-5-yl)methyl]pyridin-2(1H)-one

A 10 mL round bottomed flask equipped with stirbar and nitrogen inlet was charged with compound of Example 88 (200 mg, 0 50 mmol), 1-chlorocarbonyl-1-methylethyl acetate (80 µL, 0 55 mmol), triethylamine (140 µL, 1 0 mmol) and tetrahydrofuran (4 0 mL) After stirring at 25° C for 20 min the reaction was completed by LC-MS NaOH (2 5M, 2 24 mmol, 1 5 mL) and MeOH (2 0mL) was added and stirred for 20 min to give the title compound The compound precipitated out of solution The precipitated was filtered and washed with water and diethyl ether to obtain the title compound (136 mg, 55%) a white solid $^1$H NMR (400 MHz, (DMSO) δ 7 98 (d, $J$ = 8 1, 1H), 7 9 (d, $J$ = 7 8 Hz, 1H), 7 6 (q, $J$ = 8 6 and 6 6 Hz, 1H), 7 3 (m, 1H), 7 1 (m, 2H), 6 56 (d, $J$ =7 8 Hz, 1H), 5 25 (s, 2H),5 0 (s, 2H), 4 3 (t, $J$ = 7 8 Hz, 2H), 3 0 (t, $J$ = 7 9 Hz, 2H), 1 3 (s, 6H) ppm ES-HRMS $m/z$ 489 1376 (M+H calcd for $C_{25}H_{24}ClF_2N_2O_4$ requires 489 1387)

Example 732

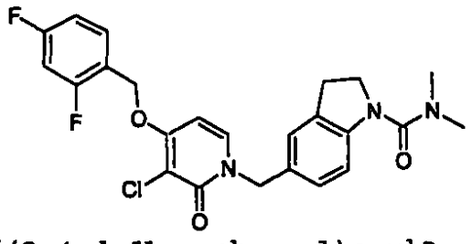
461
463



3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(methoxyacetyl)-2,3-dihydro-1H-indol-5-yl]methyl}pyridin-2(1H)-one

A 10 mL round bottomed flask equipped with stirbar and nitrogen inlet was charged with the compound of Example 88 (200 mg, 0 5 mmol), methoxyacetyl chloride (69 µL, 0 75 mmol), triethylamine (139 µL, 1 0 mmol) and tetrahydrofuran (4 0 mL) After stirring at 25° C for 20 min the reaction was completed by LC-MS The compound precipitated out of solution The precipitate was filtered and washed with water and diethyl ether to obtain a white solid (195 mg, 83%) $^1$H NMR (400 MHz, (DMSO) δ 7 98 (d, *J* = 8 2, 1H), 7 9 (d, *J* = 7 7 Hz, 1H), 7 6 (d, *J* = 8 5 Hz, 1H), 7 3 (t, *J* = 9 6 Hz, 1H), 7 1 (m, 3H), 6 56 (d, *J* =7 8 Hz, 1H), 5 25 (s, 2H),5 1 (s, 2H), 4 1 (s, 2H), 3 98 (t, *J* = 7 9 Hz, 2H), 3 33 (s, 3H), 3 0 (t, *J* = 7 9 Hz, 2H) ppm ES-HRMS *m/z* 461 1088 (M+H calcd for $C_{23}H_{20}ClF_2N_2O_4$ requires 461 1074)

Example 733



5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]2-oxopyridin-1(2H)-yl]methyl}-N, N-dimethylindoline-1-carboxamide

A 10 mL round bottomed flask equipped with stirbar and nitrogen inlet was charged with the compound of Example 88 (200 mg, 0 5 mmol), dimethylcarbamyl chloride (69 µL, 0 75 mmol), triethylamine (139 µL, 1 0 mmol) and tetrahydrofuran (4 0 mL) After stirring at 25° C for 5 min the reaction was completed by LC-MS The compound precipitated out of solution The precipitate was filtered and washed with water and diethyl ether to obtain a white solid (188 mg, 58%) $^1$H NMR (400 MHz, (DMSO) δ 7 9 (d, *J* = 8 1, 1H), 7 6 (q, *J* = 8 6 and 6 6 Hz, 1H), 7 3 (t, *J* = 9 3 Hz, 1H), 7 1 (m, 3H), 6 8 (d, *J* =8 0 Hz, 1H), 6 5 (d, *J* = 7 8 Hz, H), 5 25 (s, 2H),5 0 (s, 2H), 3 7 (t, *J* = 8 6 Hz, 2H), 2 9(t, *J* = 7 9 Hz, 2H), 2 8 (s, 6H) ppm ES-HRMS *m/z* 474 1387 (M+H calcd for $C_{24}H_{23}ClF_2N_3O_3$ requires 474 1391)

BIOLOGICAL EVALUATION

p38 Kinase Assay

Cloning of human p38a

The coding region of the human p38a cDNA was obtained by PCR-amplification from RNA isolated from the human monocyte cell line THP 1 First strand CDNA was synthesized from total RNA as follows 2 µg of RNA was annealed to 100 ng of random hexamer primers in a 10 µl reaction by heating to 70° C for 10 minutes followed by 2 minutes on ice cDNA was then synthesized by adding 1 µl of RNAsin (Promega, Madison Wis ), 2 µl of 50 mM dNTP's, 4 µl of 5X buffer, 2 µl of 100 mM DTT and 1 µl (200 U) of Superscript II™ AMV reverse transcriptase Random primer, dNTP's and Superscript II™ reagents were all purchased from Life-Technologies, Gaithersburg, Mass The reaction was incubated at 42° C for 1 hour Amplification of p38 cDNA was performed by aliquoting 5 µl of the reverse

464
462

transcriptase reaction into a 100 µl PCR reaction containing the following 80 µl dH sub 2 O, 2 µl 50 mM dNTP's, 1 µl each of forward and reverse primers (50 pmol/µl), 10 µl of 10X buffer and 1 µl Expand™ polymerase (Boehringer Mannheim) The PCR primers incorporated Bam HI sites onto the 5' and 3' end of the amplified fragment, and were purchased from Genosys The sequences of the forward and reverse primers were 5'-GATCGAGGATTCATGTCTCAGGAGAGGCCCA-3' and 5'GATCGAGGATTCTCAGGACTCCATCTCTTC-3' respectively The PCR amplification was carried out in a DNA Thermal Cycler (Perkin Elmer) by repeating 30 cycles of 94° C for 1 minute, 60° C for 1 minute and 68° C for 2 minutes After amplification, excess primers and unincorporated dNTP's were removed from the amplified fragment with a Wizard™ PCR prep (Promega) and digested with Bam HI (New England Biolabs) The Bam HI digested fragment was ligated into BamHI digested pGEX 2T plasmid DNA (PharmaciaBiotech) using T-4 DNA ligase (New England Biolabs) as described by T Maniatis, Molecular Cloning A Laboratory Manual, 2nd ed (1989) The ligation reaction was transformed into chemically competent E coli DH10B cells purchased from Life-Technologies following the manufacturer's instructions Plasmid DNA was isolated from the resulting bacterial colonies using a Promega Wizard™ miniprep kit Plasmids containing the appropriate Bam HI fragment were sequenced in a DNA Thermal Cycler (Perkin Elmer) with Prism™ (Applied Biosystems Inc ) cDNA clones were identified that coded for both human p38a isoforms (Lee et al Nature 372, 739) One of the clones that contained the cDNA for p38a-2 (CSB-2) inserted in the cloning site of PGEX 2T, 3' of the GST coding region was designated pMON 35802 The sequence obtained for this clone is an exact match of the cDNA clone reported by

Lee et al This expression plasmid allows for the production of a GST-p38a fusion protein

Expression of human p38a

GST/p38a fusion protein w as expressed from the plasmid pMON 35802 in E coli, stain DH10B (Life Technologies, Gibco-BRL) Overnight cultures were grown in Luria Broth (LB) containing 100 mg/ml ampicillin The next day, 500 ml of fresh LB was inoculated with 10 ml of overnight culture, and grown in a 2 liter flask at 37° C with constant shaking until the culture reached an absorbance of 0 8 at 600 nm Expression of the fusion protein was induced by addition of isopropyl b-D-thiogalactosidase (IPTG) to a final concentration of 0 05 mM The cultures were shaken for three hours at room temperature, and the cells were harvested by centrifugation The cell pellets were stored frozen until protein purification

Purification of P38 Kinase-alpha

All chemicals were from Sigma Chemical Co unless noted Twenty grams of E coli cell pellet collected from five 1 L shake flask fermentations was resuspended in a volume of PBS (140 mM NaCl, 2 7 mM KCl, 10 mM Na sub 2 HPO sub 4, 1 8 mM KH sub 2 PO sub 4, pH 7 3) up to 200 ml The cell suspension was adjusted to 5 mM DTT with 2 M DTT and then split equally into five 50 ml Falcon conical tubes The cells were sonnicated (Ultrasonics model W375) with a 1 cm probe for 3 times 1 minutes (pulsed) on ice Lysed cell material was removed by centrifugation (12,000 x g, 15 minutes) and the clarified supernatant applied to glutathione-sepharose resin (Pharmacia)

Glutathione-Sepharose Affinity Chromatography

Twelve ml of a 50% glutathione sepharose-PBS suspension was added to 200 ml clarified supernatant and incubated batchwise for 30 minutes at room temperature The resin was collected by centrifugation (600 times g, 5 min) and washed with 2 times 150 ml PBS/1% Triton X-100, followed by 4 times 40 ml PBS To cleave the p38 kinase from the GST-p38 fusion protein, the glutathione-sepharose resin was resuspended in 6 ml PBS containing 250 units thrombin protease (Pharmacia, specific activity >7500 units/mg) and mixed gently for 4 hours at room temperature The glutathione-sepharose resin was removed by centrifugation (600 times g, 5 min) and wasned 2 times 6 ml with PBS The PBS wash fractions and digest supernatant containing p38 kinase protein were pooled and adjusted to 0 3 mM PMSF

Mono Q Anion Exchange Chromatography

The thrombin-cleaved p38 kinase was further purified by FPLC-anion exchange chromatography Thrombin-cleaved sample was diluted 2-fold with Buffer A (25 mM HEPES, pH 7 5, 25 mM beta-glycerophosphate, 2 mM DTT, 5% glycerol) and injected onto a Mono Q HR 10/10 (Pharmacia) anion exchange column equilibrated with Buffer A The column was eluted with a 160 ml 0 1 M-0 6 M NaCl/Buffer A gradient (2 ml/minute flowrate) The p38 kinase peak eluting at 200 mM NaCl was collected and concentrated to 3-4 ml with a Filtron 10 concentrator (Filtron Corp )

Sephacryl S100 Gel Filtration Chromatography

The concentrated Mono Q- p38 kinase purified sample was purified by gel filtration chromatography (Pharmacia HiPrep 26/60 Sephacryl S100 column equilibrated with Buffer B (50 mM HEPES, pH 7 5, 50 mM NaCl, 2 mM DTT, 5% glycerol)) Protein was eluted from the column with Buffer B at a 0 5 ml/minute flowrate and protein was detected by absorbance at 280 nm

Fractions containing p38 kinase (detected by SDS-polyacrylamide gel electrophoresis) were pooled and frozen at -80° C Typical purified protein yields from 5 L E coli shake flasks fermentations were 35 mg p38 kinase

In Vitro Assay

The ability of compounds to inhibit human p38 kinase alpha was evaluated using two in vitro assay methods In the first method, activated human p38 kinase alpha phosphorylates a biotinylated substrate, PHAS-I (phosphorylated heat and acid stable protein-insulin inducible), in the presence of gamma $^{32}$P-ATP ($^{32}$P-ATP) PHAS-I was biotinylated prior to the assay and provides a means of capturing the substrate, which is phosphorylated during the assay p38 Kinase was activated by MKK6 Compounds were tested in 10 fold serial dilutions over the range of 100 μM to 0 001 μM using 1% DMSO Each concentration of inhibitor was tested in triplicate

All reactions were carried out in 96 well polypropylene plates Each reaction well contained 25 mM HEPES pH 7 5, 10 mM magnesium acetate and 50 μM unlabeled ATP Activation of p38 was required to achieve sufficient signal in the assay Biotinylated PHAS-I was used at 1-2 μg per 50 μl reaction volume, with a final concentration of 1 5 μM Activated human p38 kinase alpha was used at 1 μg per 50 μl reaction volume representing a final concentration of 0 3 μM Gamma $^{32}$P-ATP was used to follow the phosphorylation of PHAS-I $^{32}$P-ATP has a specific activity of 3000 Ci/mmol and was used at 1 2 μCi per 50 μl reaction volume The reaction proceeded either for one hour or overnight at 30° C

Following incubation, 20 μl of reaction mixture was transferred to a high capacity streptavidin coated filter plate (SAM-streptavidin-matrix, Promega) prewetted with

phosphate buffered saline The transferred reaction mix was allowed to contact the streptavidin membrane of the Promega plate for 1-2 minutes Following capture of biotinylated PHAS-I with $^{32}P$ incorporated, each well was washed to remove unincorporated $^{32}P$-ATP three times with 2M NaCl, three washes of 2M NaCl with 1% phosphoric, three washes of distilled water and finally a single wash of 95% ethanol Filter plates were air-dried and 20 µl of scintillant was added The plates were sealed and counted

A second assay format was also employed that is based on p38 kinase alpha induced phosphorylation of EGFRP (epidermal growth factor receptor peptide, a 21 mer) in the presence $^{33}P$-ATP Compounds were tested in 10 fold serial dilutions over the range of 100 µM to 0 001 µM in 1% DMSO Each concentration of inhibitor was tested in triplicate Compounds were evaluated in 50 µl reaction volumes in the presence of 25 mM Hepes pH 7 5, 10 mM magnesium acetate, 4% glycerol, 0 4% bovine serum albumin, 0 4mM DTT, 50 µM unlabeled ATP, 25 µg EGFRP (200 µM), and 0 05 µCi $^{33}P$-ATP Reactions were initiated by addition of 0 09 µg of activated, purified human GST-p38 kinase alpha Activation was carried out using GST-MKK6 (5 1,p38 MKK6) for one hour at 30° C in the presence of 50 µM ATP Following incubation for 60 minutes at room temperature, the reaction was stopped by addition of 150 µl of AG 1 times 8 resin in 900 mM sodium formate buffer, pH 3 0 (1 volume resin to 2 volumes buffer) The mixture was mixed three times with pipetting and the resin was allowed to settle A total of 50 µl of clarified solution head volume was transferred from the reaction wells to Microlite-2 plates 150 µl of Microscint 40 was then added to each well of the Microlite plate, and the plate was sealed, mixed, and counted

Representative compounds that exibit $IC_{50}$ values between 1 and 25 μM (p38 alpha kinase assay) are Example Nos 20, 22, 23, 39, 43, 44, 48, 50, 52, 53, 55, 57, 58, 62, 92, 115, 118, 136, 139, 141, 142, 149, 156, 157, 169, 174, 219, 220, 244, 245, 387, 288, 289, 291, 292, 293, 294, 295, 296, 298, 297, 300, 301, 302 304, 305, 309, 310, 311, 323, 360, 394, 403, 414, 415, 416, 418, 420, 444, 447, 449, 451, 452, 471, 485, 486, 496, 498, 499, 503, 506, 561, 569, 574, 575 and 576

Representatve compounds that exibit $IC_{50}$ values between 25 and 100 μM (p38 alpha kinase assay) are Example Nos 1, 25, 33, 35, 37, 42, 45, 47, 49, 119, 204, 308, 558, 560, 564, 565, 566, 568 and 577

Representatve compounds that exibit $IC_{50}$ values less than 1 μM (p38 alpha kinase assay) are Example Nos 6, 14, 8, 17, 10, 15, 4, 117, 161, 162, 165, 170, 171, 172, 173 176, 179, 217, 218, 219, 220, 221, 223, 225, 230, 231, 234, 235, 272, 273, 275, 276, 278, 280, 282, 286, 285, 290 312, 313, 314, 315, 316, 317, 318, 320, 321, 322, 364, 366, 400, 402, 405, 421, 422, 423, 446, 448, 450, 458, 466, 467, 468, 469, 470, 481, 482, 483, 484, 487, 489, 492, 493, 494, 495, 504, 521, 522, 523 557, 587, 589, 590, 591, 597, 609, 610, 613, 629, 642, and 643

Representatve compounds that exibit $IC_{50}$ values greater than 100 μM (p38 alpha kinase assay) are Example Nos 3, 11, 38, 56, 116, 121, 237, 236, 413, 497 and 578

TNF Cell Assays

Method of Isolation of Human Peripheral Blood Mononuclear Cells

Human whole blood was collected in Vacutainer tubes containing EDTA as an anticoagulant A blood sample (7 ml) was carefully layered over 5 ml PMN Cell Isolation Medium (Robbins

Scientific) in a 15 ml round bottom centrifuge tube The sample was centrifuged at 450-500 times g for 30-35 minutes in a swing out rotor at room temperature After centrifugation, the top band of cells were removed and washed 3 times with PBS w/o calcium or magnesium The cells were centrifuged at 400 times g for 10 minutes at room temperature The cells were resuspended in Macrophage Serum Free Medium (Gibco BRL) at a concentration of 2 million cells/ml

LPS Stimulation of Human PBMs

PBM cells (0 1 ml, 2 million/ ml) were co-incubated with 0 1 ml compound (10-0 41 μM, final concentration) for 1 hour in flat bottom 96 well microtiter plates Compounds were dissolved in DMSO initially and diluted in TCM for a final concentration of 0 1% DMSO LPS (Calbiochem, 20 ng/ml, final concentration) was then added at a volume of 0 010 ml Cultures were incubated overnight at 37° C Supernatants were then removed and tested by ELISA for TNF-a and IL1-b Viability was analyzed using MTS After 0 1 ml supernatant was collected, 0 020 ml MTS was added to remaining 0 1 ml cells The cells were incubated at 37° C for 2-4 hours, then the O D was measured at 490-650 nM

Maintenance and Differentiation of the U937 Human Histiocytic Lymphoma Cell Line

U937 cells (ATCC) were propagated in RPMI 1640 containing 10% fetal bovine serum, 100 IU/ml penicillin, 100 μg/ml streptomycin, and 2 mM glutamine (Gibco) Fifty million cells in 100 ml media were induced to terminal monocytic differentiation by 24 hour incubation with 20 ng/ml phorbol 12-myristate 13-acetate (Sigma) The cells were washed by centrifugation (200 times g for 5 min) and resuspended in 100 ml fresh medium After 24-48 hours, the cells were harvested,

centrifuged, and resuspended in culture medium at 2 million cells/ml

LPS Stimulation of TNF production by U937 Cells

U937 cells (0 1 ml, 2 million/ml) were incubated with 0 1 ml compound (0 004-50 μM, final concentration) for 1 hour in 96 well microtiter plates Compounds were prepared as 10 mM stock solutions in DMSO and diluted in culture medium to yield a final DMSO concentration of 0 1% in the cell assay LPS (E coli, 100 ng/ml final concentration) was then added at a volume of 0 02 ml After 4 hour incubation at 37° C , the amount of TNF- alpha released in the culture medium was quantitated by ELISA Inhibitory potency is expressed as IC50 (μM)

Rat Assay

The efficacy of the novel compounds in blocking the production of TNF also was evaluated using a model based on rats challenged with LPS Male Harlen Lewis rats [Sprague Dawley Co ] were used in this model Each rat weighed approximately 300 g and was fasted overnight prior to testing Compound administration was typically by oral gavage (although intraperitoneal, subcutaneous and intravenous administration were also used in a few instances) 1 to 24 hours prior to the LPS challenge Rats were administered 30 μg/kg LPS [salmonella typhosa, Sigma Co ] intravenously via the tail vein Blood was collected via heart puncture 1 hour after the LPS challenge Serum samples were stored at -20° C until quantitative analysis of TNF- alpha by Enzyme Linked-Immuno-Sorbent Assay ("ELISA") [Biosource] Additional details of the assay are set forth in Perretti, M , et al , Br J Pharmacol

(1993), 110, 868-874, which is incorporated by reference in this application

Mouse Assay

Mouse Model of LPS-Induced TNF Alpha Production

TNF alpha was induced in 10-12 week old BALB/c female mice by tail vein injection with 100 ng lipopolysaccharide (from S Typhosa) in 0 2 ml saline One hour later mice were bled from the retroorbital sinus and TNF concentrations in serum from clotted blood were quantified by ELISA Typically, peak levels of serum TNF ranged from 2-6 ng/ml one hour after LPS injection

The compounds tested were administered to fasted mice by oral gavage as a suspension in 0 2 ml of 0 5% methylcellulose and 0 025% Tween 20 in water at 1 hour or 6 hours prior to LPS injection The 1 hour protocol allowed evaluation of compound potency at Cmax plasma levels whereas the 6 hour protocol allowed estimation of compound duration of action Efficacy was determined at each time point as percent inhibition of serum TNF levels relative to LPS injected mice that received vehicle only

Induction and Assessment of Collagen-Induced Arthritis in Mice

Arthritis was induced in mice according to the procedure set forth in J M Stuart, Collagen Autoimmune Arthritis, Annual Rev Immunol 2 199 (1984), which is incorporated herein by reference Specifically, arthritis was induced in 8-12 week old DBA/1 male mice by injection of 50 μg of chick type II collagen (CII) (provided by Dr Marie Griffiths, Univ of Utah, Salt Lake City, Utah) in complete Freund's adjuvant (Sigma) on day 0 at the base of the tail Injection volume was 100 μl Animals were boosted on day 21 with 50 μg of CII in

incomplete Freund's adjuvant (100 μl volume) Animals were evaluated several times each week for signs of arthritis Any animal with paw redness or swelling was counted as arthritic Scoring of arthritic paws was conducted in accordance with the procedure set forth in Wooley et al , Genetic Control of Type II Collagen Induced Arthritis in Mice Factors Influencing Disease Suspectibility and Evidence for Multiple MHC Associated Gene Control , Trans Proc , 15 180 (1983) Scoring of severity was carried out using a score of 1-3 for each paw (maximal score of 12/mouse) Animals displaying any redness or swelling of digits or the paw were scored as 1 Gross swelling of the whole paw or deformity was scored as 2 Ankylosis of joints was scored as 3 Animals were evaluated for 8 weeks 8-10 animals per group were used

The invention and the manner and process of making and using it, are now described in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, to make and use the same It is to be understood that the foregoing describes preferred embodiments of the present invention and that modifications may be made therein without departing from the spirit or scope of the present invention as set forth in the claims To particularly point out and distinctly claim the subject matter regarded as invention, the following claims conclude this specification

468
469

What is claimed is

1 A compound of the formula



or a pharmaceutically acceptable salt thereof, wherein

$R_1$ is H, halogen, $NO_2$, alkyl, carboxaldehyde, hydroxyalkyl, dihydroxyalkyl, arylalkoxy, arylalkyl, alkenyl, alkynyl, arylalkynyl, -CN, aryl, alkanoyl, alkoxy, alkoxyalkyl, haloalkyl, haloalkoxy, carboxyl, or arylalkanoyl,

wherein the aryl portion of arylalkoxy, arylalkyl, and arylalkanoyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, nitro, CN, haloalkyl, haloalkoxy or $CO_2P$,

wherein the alkyl portion of the alkyl, hydroxyalkyl, dihydroxyalkyl, arylalkoxy, arylalkyl, alkanoyl, alkoxy, alkoxyalkyl and arylalkanoyl groups is unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkoxycarbonyl, or $C_3$-$C_7$ cycloalkyl,

$R_2$ is H, OH, halogen, $-OSO_2-(C_1-C_6)$ alkyl, $-OSO_2$-aryl, arylalkoxy, aryloxy, arylthio, arylthioalkoxy, arylalkynyl, alkoxy, aryloxy($C_1$-$C_6$)alkyl, alkyl, alkynyl, $-OC(O)NH(CH_2)_n$aryl, $-OC(O)N(alkyl)(CH_2)_n$aryl, alkoxyalkoxy, dialkylamino, alkyl, alkoxy, aryl, arylalkyl, heteroaryl, heteroarylalkyl, arylalkenyl, heterocycloalkyl, heterocycloalkylalkyl, alkoxyalkoxy, $NR_8R_9$, dialkylamino, or $CO_2R$, wherein

n is 0, 1, 2, 3, 4, 5 or 6,

each of which groups is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently

halogen, -($C_1$-$C_6$)alkyl-N(R)-$CO_2R_{30}$, haloalkyl, heteroaryl, heteroarylalkyl, -$NR_6R_7$, $R_6R_7N$-($C_1$-$C_6$ alkyl)-, -$C(O)NR_6R_7$, -($C_1$-$C_4$)alkyl-$C(O)NR_6R_7$, -($C_1$-$C_4$ alkyl)-$NRC(O)NR_{16}R_{17}$, haloalkoxy, alkyl CN, hydroxyalkyl, dihydroxyalkyl, alkoxy, alkoxycarbonyl, phenyl, -$SO_2$-phenyl wherein the phenyl and -$SO_2$-phenyl groups are optionally substituted with 1, 2, or 3 groups that are independently halogen or $NO_2$, or -$OC(O)NR_6R_7$, wherein

$R_{16}$ and $R_{17}$ are independently H or $C_1$-$C_6$ alkyl, or

$R_{16}$, $R_{17}$ and the nitrogen to which they are attached form a morpholinyl ring,

$R_6$ and $R_7$ are independently at each occurrence H, alkyl, hydroxyalkyl, dihydroxyalkyl, alkoxy, alkanoyl, arylalkyl, arylalkoxy, alkoxycarbonyl, -$SO_2$-alkyl, OH, alkoxy, alkoxyalkyl, arylalkoxycarbonyl, -($C_1$-$C_4$)alkyl-$CO_2$-alkyl, heteroarylalkyl, or arylalkanoyl, wherein each is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, OH, SH, heterocycloalkyl, heterocycloalkylalkyl, $C_3$-$C_7$ cycloalkyl, alkoxy, $NH_2$, NH(alkyl), N(alkyl)(alkyl), -O-alkanoyl, alkyl, haloalkyl, carboxaldehyde, or haloalkoxy, or

$R_6$, $R_7$, and the nitrogen to which they are attached form a morpholinyl, pyrrolidinyl, thiomorpholinyl, thiomorpholinyl S-oxide, thiomorpholinyl S,S-dioxide, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently $C_1$-$C_4$ alkyl, alkoxycarbonyl,

$C_1$-$C_4$ alkoxy, hydroxyl, hydroxyalkyl, dihydroxyalkyl, or halogen,

R at each occurrence is independently hydrogen or $C_1$-$C_6$ alkyl optionally substituted with 1 or 2 groups that are independently OH, SH, halogen, amino, monoalkylamino, dialkylamino or $C_3$-$C_6$ cycloalkyl,

$R_{30}$ is $C_1$-$C_6$ alkyl optionally substituted with 1 or 2 groups that are independently OH, SH, halogen, amino, monoalkylamino, dialkylamino or $C_3$-$C_6$ cycloalkyl,

each $R_8$ is independently hydrogen, alkyl, alkanoyl, arylalkyl and arylalkanoyl, wherein each of the above is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, alkoxy, alkoxycarbonyl, halogen, or haloalkyl,

each $R_9$ is hydrogen, alkyl, alkanoyl, arylalkyl, cycloalkyl, cycloalkylalkyl, alkenyl, heteroaryl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, arylalkanoyl, -$SO_2$-phenyl, and aryl wherein each of the above is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, alkoxy, alkoxycarbonyl, halogen, or haloalkyl,

$R_3$ is H, halogen alkoxycarbonyl, arylalkoxycarbonyl, aryloxycarbonyl, arylalkyl, -OC(O)NH$(CH_2)_n$aryl, arylalkoxy, -OC(O)N(alkyl)$(CH_2)_n$aryl, aryloxy, arylthio, thioalkoxy, arylthioalkoxy, alkenyl, -$NR_6R_7$, $NR_6R_7$-($C_1$-$C_6$)alkyl, or alkyl, wherein

the aryl portion of arylalkoxycarbonyl, aryloxycarbonyl, arylalkyl, -OC(O)NH$(CH_2)_n$aryl, arylalkoxy, -OC(O)N(alkyl)$(CH_2)_n$aryl, and arylthioalkoxy, is unsubstituted or substituted with 1, 2, 3, 4, or 5

groups that are independently, halogen, alkoxy, alkyl, haloalkyl, or haloalkoxy,

wherein n is 0, 1, 2, 3, 4, 5, or 6, or

$R_4$ is hydrogen or $R_4$ is alkyl unsubstituted or substituted with one or two groups that are independently $CO_2R$, $-CO_2-(C_1-C_6)$alkyl, $-C(O)NR_6R_7$, $-C(O)R_6$, $-N(R_{30})C(O)NR_{16}R_{17}$, $-N(R_{30})C(O)-(C_1-C_6)$alkoxy, or $-NR_6R_7$, arylalkoxy, arylalkyl, heteroaryl, heteroarylalkyl, hydroxyalkyl, dihydroxyalkyl, haloalkyl, $R_6R_7N-(C_1-C_6$ alkyl)-, $-NR_6R_7$, alkoxy, carboxaldehyde, $-C(O)NR_6R_7$, $CO_2R$, alkoxyalkyl, or alkoxyalkoxy, wherein the heteroaryl or aryl portions of is the above are unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, hydroxy, alkoxy, alkyl, $-CO_2-(C_1-C_6)$alkyl, $-CONR_6R_7$, $-NR_6R_7$, $R_6R_7N-(C_1-C_6)$alkyl-, nitro, haloalkyl, or haloalkoxy, and

$R_5$ is H, aryl, arylalkyl, arylthioalkyl, alkyl optionally substituted with 1, 2, or 3 groups that are independently arylalkoxycarbonyl, $-NR_8R_9$, halogen, $-C(O)NR_8R_9$, alkoxycarbonyl, $C_3-C_7$ cycloalkyl, or alkanoyl, alkoxy, alkoxyalkyl optionally substituted with one trimethylsilyl group, amino, alkoxycarbonyl, hydroxyalkyl, dihydroxyalkyl, alkynyl, $-SO_2$-alkyl, alkoxy optionally substituted with one trimethylsilyl group, heterocycloalkylalkyl, cycloalkyl, cycloalkylalkyl, -alkyl-S-aryl, -alkyl-$SO_2$-aryl, heteroarylalkyl, heterocycloalkyl, heteroaryl, or alkenyl optionally substituted with alkoxycarbonyl, wherein

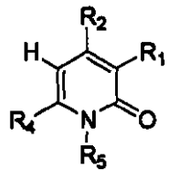
each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, halogen, alkoxy, hydroxyalkyl, dihydroxyalkyl, arylalkoxy, thioalkoxy, alkoxycarbonyl, arylalkoxycarbonyl, $CO_2R$, CN, OH, hydroxyalkyl, dihydroxyalkyl, amidinooxime, $-NR_6R_7$, $-NR_8R_9$, $R_6R_7N-$

($C_1$-$C_6$ alkyl)-, carboxaldehyde, $SO_2$alkyl, -$SO_2H$, -$SO_2NR_6R_7$, alkanoyl wherein the alkyl portion is optionally substituted with OH, halogen or alkoxy, -$C(O)NR_6R_7$, -($C_1$-$C_4$ alkyl)-$C(O)NR_6R_7$ amidino, haloalkyl, -($C_1$-$C_4$ alkyl)-$NR_{15}C(O)NR_{16}R_{17}$, -($C_1$-$C_4$ alkyl)-$NR_{15}C(O)R_{18}$, -O-$CH_2$-O, -O-$CH_2CH_2$-O-, or haloalkoxy, wherein

$R_{15}$ is H or $C_1$-$C_6$ alkyl, and

$R_{18}$ is $C_1$-$C_6$ alkyl optionally substituted with -O-($C_2$-$C_6$ alkanoyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ dihydroxyalkyl, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, amino $C_1$-$C_6$ alkyl, mono or dialkylamino $C_1$-$C_6$ alkyl

2 A compound according to claim 1, of the formula




or a pharmaceutically acceptable salt thereof, wherein

$R_1$ is H, halogen, alkyl, carboxaldehyde, hydroxyalkyl, dihydroxyalkyl, arylalkoxy, arylalkyl, alkenyl, alkynyl, arylalkynyl, CN, alkanoyl, alkoxy, alkoxyalkyl, haloalkyl, carboxyl, or arylalkanoyl,

wherein the aryl portion of arylalkoxy, arylalkyl, and arylalkanoyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, nitro, CN, haloalkyl, haloalkoxy or $CO_2R$,

wherein the alkyl portion of the alkyl, hydroxyalkyl, dihydroxyalkyl, arylalkoxy, arylalkyl, alkanoyl, alkoxy, alkoxyalkyl and arylalkanoyl groups is unsubstituted or substituted with 1, 2, or 3 groups

that are independently halogen, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkoxycarbonyl, or cyclopropyl,

$R_2$ is H, OH, halogen, $-OSO_2-(C_1-C_6)$ alkyl, $-OSO_2$-aryl, arylalkoxy, aryloxy, arylthioalkoxy, arylalkynyl, alkoxy, phenyloxy$(C_1-C_6)$alkyl, $-OC(O)NH(CH_2)_n$aryl, $-OC(O)N(alkyl)(CH_2)_n$aryl, alkyl, alkynyl, alkoxyalkoxy, dialkylamino, heteroaryl, heterocycloalkyl, aryloxyalkyl, or $CO_2R$, wherein

each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, $-NR_6R_7$, haloalkyl, haloalkoxy, alkyl, heteroaryl, heteroarylalkyl, $-(C_1-C_4)$alkyl-$C(O)NR_6R_7$, $R_6R_7N-(C_1-C_6$ alkyl)-, $-C(O)NR_6R_7$, $-(C_1-C_4$ alkyl)$-NRC(O)NR_{16}R_{17}$, CN, hydroxyalkyl, dihydroxyalkyl, $-OC(O)NR_6R_7$, or $-(C_1-C_6)$alkyl-$N(R)-CO_2R_{30}$, wherein

$R_{16}$ and $R_{17}$ are independently H or $C_1$-$C_6$ alkyl, or

$R_{16}$, $R_{17}$ and the nitrogen to which they are attached form a morpholinyl ring,

$R_6$ and $R_7$ are independently at each occurrence H, alkyl, hydroxyalkyl, dihydroxyalkyl, alkoxy, alkoxyalkyl, alkanoyl, arylalkyl, arylalkoxy, arylalkoxycarbonyl, or arylalkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, alkoxy, alkyl, OH, SH, carboxaldehyde, haloalkyl, or haloalkoxy, or

$R_6$, $R_7$, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, thiomorpholinyl S-oxide, thiomorpholinyl S,S-dioxide, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently $C_1$-$C_4$ alkyl, alkoxycarbonyl,

hydroxyl, hydroxyalkyl, dihydroxyalkyl, or halogen,

n is 0, 1, 2, 3, 4, 5 or 6,

R at each occurrence is independently H or $C_1$-$C_6$ alkyl optionally substituted with 1 or 2 groups that are independently OH, SH, halogen, amino monoalkylamino, dialkylamino or $C_3$-$C_6$ cycloalkyl,

$R_{30}$ is $C_1$-$C_6$ alkyl optionally substituted with 1 or 2 groups that are independently OH, SH, halogen, amino, monoalkylamino, dialkylamino or $C_3$-$C_6$ cycloalkyl,

$R_4$ is H, alkyl optionally substituted with one or two groups that are independently $CO_2R$, $-CO_2$alkyl, $-C(O)NR_6R_7$, $-C(O)R_6$, $-N(R_{30})C(O)NR_{16}R_{17}$, $-N(R_{30})C(O)-(C_1-C_6)$alkoxy, or $-NR_6R_7$, aryla_koxy, heteroaryl, arylalkyl, hydroxyalkyl, dihydroxyalkyl, haloalkyl, $-NR_6R_7$, $-C(O)NR_6R_7$, alkoxy, alkoxyalkyl, or alkoxyalkoxy, wherein the heteroaryl or aryl portions of the above are unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, hydroxy, alkoxy, alkyl, $-CO_2-(C_1-C_6)$alkyl, $-CONR_6R_7$ $-NR_6R_7$, $R_6R_7N-(C_1-C_6)$alkyl-, nitro, haloalkyl, or haloalkoxy, and

$R_5$ is H, arylalkyl, alkyl optionally substituted with 1, 2, or 3 groups that are independently arylalkoxycarbonyl, $-NR_8R_9$, halogen, $-C(O)NR_8R_9$, alkoxycarbonyl, or alkanoyl, alkoxyalkyl optionally substituted with one trimethylsilyl group, alkoxycarbonyl, amino, hydroxyalkyl, dihycroxyalkyl, alkenyl optionally substituted with alkoxycarbonyl, alkynyl, $-SO_2$-alkyl, aryl, alkoxy optionally substituted with one trimethylsilyl group, heterocycloalkylalkyl, heteroarylalkyl, heterocycloalkyl, or heteroaryl, wherein

each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, halogen, alkoxy, arylalkoxy, hydroxyalkyl, dihydroxyalkyl, thioalkoxy, -$SO_2$alkyl, alkoxycarbonyl, arylalkoxycarbonyl, $CO_2R$, CN, OH, amidinooxime, $NR_8R_9$, $R_6R_7N$-($C_1$-$C_6$ alkyl)-, -$C(O)NR_6R_7$, amidino, hydroxyalkyl, dihydroxyalkyl, carboxaldehyde, -$NR_6R_7$, haloalkyl, -($C_1$-$C_4$ alkyl)-$C(O)NR_6R_7$, -($C_1$-$C_4$ alkyl)-$CO_2R$, -($C_1$-$C_4$ alkyl)-$C_1$-$C_6$ alkoxycarbonyl, -($C_1$-$C_4$ alkyl)-CN, -($C_1$-$C_4$ alkyl)-$NR_{15}C(O)R_{18}$, -O-$CH_2$-O-, -O-$CH_2CH_2$-O-, phenyl or haloalkoxy,

$R_8$ is hydrogen, alkyl, alkanoyl, arylalkyl and arylalkanoyl,

$R_9$ is alkyl, alkanoyl, arylalkyl, heteroaryl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, and arylalkanoyl

3 A compound according to claim 2 wherein

$R_1$ is H, halogen, alkyl optionally substituted with $C_1$-$C_4$ alkoxycarbonyl, carboxaldehyde, hydroxyalkyl, dihydroxyalkyl, phenyl($C_1$-$C_6$)alkoxy, phenyl($C_1$-$C_6$)alkyl, CN, alkanoyl, alkoxy, $C_2$-$C_4$ alkynyl, $C_2$-$C_6$ alkenyl optionally substituted with $C_1$-$C_4$ alkoxycarbonyl, alkoxyalkyl, haloalkyl, or phenyl($C_1$-$C_6$)alkanoyl,

wherein the phenyl groups are unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, nitro, CN, $CF_3$, $OCF_3$ or $CO_2R$,

wherein the alkyl groups are unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, methoxy, or ethoxy,

$R_2$ is OH, phenyl$(C_1-C_6)$alkoxy, phenyloxy, phenyloxy$(C_1-C_6)$alkyl, phenyl $(C_1-C_4)$ thioalkoxy, $C_1-C_8$ alkoxy, alkoxyalkoxy, -O-$SO_2$phenyl, alkynyl, phenyl $(C_2-C_4)$ alkynyl, alkyl, -OC(O)NH$(CH_2)_n$phenyl, -OC(O)N(alkyl)$(CH_2)_n$phenyl, dialkylamino, pyridyl, pyrimidyl, pyridazyl, pyrazolyl, imidazolyl, pyrrolyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, tetrazolyl, pyrazinyl, benzimidazolyl, triazinyl, tetrahydrofuryl, piperidinyl, hexahydropyrimidinyl, thiazolyl, thienyl, or $CO_2R$, wherein n is 0, 1, 2, 3, 4, 5 or 6,

each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, $NR_6R_7$, haloalkyl, haloalkoxy, hydroxyalkyl, dihydroxyalkyl, alkyl, phenyl, pyridyl, piperidinyl, piperazinyl, -$(C_1-C_6)$alkyl-N(R)-$CO_2R_{30}$, $R_6R_7N$-$(C_1-C_6$ alkyl)-, -C(O)$NR_6R_7$, -$(C_1-C_4)$alkyl-C(O)$NR_6R_7$, -$(C_1-C_4$ alkyl)-NRC(O)$NR_{16}P_{17}$, or -OC(O)$NR_6R_7$, wherein

$R_6$ and $R_7$ are independently at each occurrence H, alkyl, $(C_1-C_4)$ hydroxyalkyl, $(C_1-C_4)$ dihydroxyalkyl, $(C_1-C_4)$ alkoxy, $(C_1-C_4)$ alkoxy $(C_1-C_4)$ alkyl, $(C_1-C_4)$ alkanoyl, phenyl $(C_1-C_4)$ alkyl, phenyl $(C_1-C_4)$ alkoxy, phenyl $(C_1-C_4)$ alkoxycarbonyl, or phenyl $(C_1-C_4)$ alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, OH, SH, $C_3-C_6$ cycloalkyl, $(C_1-C_4)$ alkoxy, $(C_1-C_4)$ alkyl, $CF_3$, carboxaldehyde, $NH_2$, NH$(C_1-C_6)$alkyl, N$(C_1-C_6)$alkyl $(C_1-C_6)$alkyl, $OCF_3$, or

$R_6$, $R_7$, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2

groups that are independently $C_1$-$C_4$ alkyl, hydroxy, hydroxy $C_1$-$C_4$ alkyl, $C_1$-$C_4$ dihydroxyalkyl, $C_1$-$C_4$ alkoxycarbonyl, or halogen, and

$R_4$ is H, alkyl optionally substituted with one or two groups that are independently $CO_2R$, $-CO_2$alkyl, $-C(O)NR_6R_7$, $-C(O)R_6$, $-N(R_{30})C(O)NR_{16}R_{17}$, $-N(R_{30})C(O)-(C_1-C_6)$alkoxy, or $-NR_6R_7$, $-C(O)NR_6R_7$, phenyl$(C_1-C_6)$alkoxy, phenyl$(C_1-C_6)$alkyl, hydroxyalkyl, dihydroxyalkyl, haloalkyl, alkoxy, alkoxyalkyl, or alkoxyalkoxy, wherein

the phenyl groups are unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, hydroxy, alkoxy, alkyl, nitro, $CF_3$, $OCF_3$,

$R_5$ is phenyl$(C_1-C_6)$alkyl, $(C_1-C_6)$alkyl optionally substituted with 1, 2, 3, 4, or 5 groups that are independently phenyl $C_1$-$C_4$ alkoxycarbonyl, $-NR_8R_9$, halogen, $-C(O)NR_8R_9$, alkoxycarbonyl, or alkanoyl, phenyl, alkoxy, $C_2$-$C_6$ alkynyl, $C_2$-$C_6$ alkenyl optionally substituted with alkoxycarbonyl, indolyl, quinolinyl, isoquinolinyl, isoindolyl, dihydroindolyl, pyrazolyl, imidazolyl, dihydroisoindolyl, indolon-2-yl, indazolyl, benzimidazolyl, pyridyl, imidazolidine dione, pyrazolyl$(C_1-C_6$ alkyl), imidazolyl$(C_1-C_6$ alkyl), piperidinyl$(C_1-C_6)$alkyl, pyrrolidinyl$(C_1-C_6)$alkyl, imidazolidinyl$(C_1-C_6)$alkyl, tetrahydroisoquinolinyl$(C_1-C_6)$alkyl, 1H-indazolyl$(C_1-C_6)$alkyl, dihydroindolon-2-yl$(C_1-C_6$ alkyl), indolinyl$(C_1-C_6$ alkyl), dihydrobenzimidazolyl$(C_1-C_6$ alkyl), or dihydrobenzoimidazolonyl$(C_1-C_6$ alkyl), pyridyl $(C_1-C_6)$ alkyl, pyridazinyl $(C_1-C_6)$ alkyl, pyrimidinyl $(C_1-C_6)$ alkyl, pyrazinyl $(C_1-C_6)$ alkyl, tetrahydrofuryl$(C_1-C_6)$alkyl, naphthyl$(C_1-C_6)$alkyl, morpholinyl $(C_1-C_6)$ alkyl, tetrahydrofuryl $(C_1-C_6)$ alkyl, thienyl $(C_1-C_6)$ alkyl,

piperazinyl ($C_1$-$C_6$) alkyl, indolyl ($C_1$-$C_6$) alkyl, quinolinyl($C_1$-$C_6$) alkyl, isoquirolinyl($C_1$-$C_6$) alkyl, isoindolyl($C_1$-$C_6$) alkyl, dihydroindolyl($C_1$-$C_6$) alkyl, pyrazolyl($C_1$-$C_4$) alkyl, imidazolyl($C_1$-$C_4$) alkyl, dihydroisoindolyl($C_1$-$C_6$) alkyl, indoon-2-yl($C_1$-$C_6$) alkyl, indolon-2-yl($C_1$-$C_6$) alkyl, or morpholinyl $C_1$-$C_6$ alkyl, wherein

each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently $C_1$-$C_6$ alkyl, halogen, $C_1$-$C_6$ alkoxy, phenyl $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ thioalkoxy, $C_1$-$C_6$ alkoxycarbonyl, $CO_2R$, CN, -$SO_2$($C_1$-$C_6$)alkyl, amidinooxime, $NR_8R_9$, -$NR_6R_7$, $NR_6R_7$ $C_1$-$C_6$ alkyl, -C(O)$NR_6R_7$, -($C_1$-$C_4$)alkyl-C(O)$NR_6R_7$, amidino, $C_1$-$C_4$ haloalkyl, hydroxy $C_1$-$C_6$ alkyl, $C_1$-$C_6$ dihydroxyalkyl, or $C_1$-$C_4$ haloalkoxy, wherein

$R_8$ is hydrogen, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkanoyl, phenyl $C_1$-$C_6$ alkyl and phenyl $C_1$-$C_6$ alkanoyl, and

$R_9$ is aminoalkyl mono $C_1$-$C_6$ alkylamino $C_1$-$C_6$ alkyl di $C_1$-$C_6$ alkylamino $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkanoyl, phenyl $C_1$-$C_6$ alkyl, indazolyl, and phenyl $C_1$-$C_6$ alkanoyl

4 A compound according to claim 3, wherein

$R_1$ is H, halogen, $C_1$-$C_4$ alkyl optionally substituted with $C_1$-$C_4$ alkoxycarbonyl, $C_2$-$C_4$ alkenyl optionally substituted with $C_1$-$C_4$ alkoxycarbonyl, $C_2$-$C_4$ alkynyl, or carboxaldehyde,

$R_2$ is benzyloxy, OH, phenyloxy, phenyloxy($C_1$-$C_6$)alkyl, phenyl ($C_1$-$C_4$) thioalkoxy, or pyridyl, wherein each of the above is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, -($C_1$-$C_6$)alkyl-N(R)-$CO_2R_{30}$, $NR_6R_7$, -($C_1$-$C_4$)alkyl-C(O)$NR_6R_7$, ($C_1$-$C_4$) haloalkyl, -C(O)$NR_6R_7$, -($C_1$-$C_4$ alkyl)-NRC(O)$NR_{16}R_{17}$, ($C_1$-$C_4$) haloalkoxy,

hydroxyalkyl, $C_1$-$C_6$ dihydroxyalkyl, ($C_1$-$C_6$) alkyl, pyridyl, or $R_6R_7N$-($C_1$-$C_6$ alkyl)-

A compound according to claim 4, wherein

$R_5$ is indolyl, pyridyl, pyridazinyl, pyrimidinyl, indazolyl, tetrahydroquinolyl, tetrahydroisoquinolyl, pyrazolyl, imidazolyl, furanyl, quinolinyl, isoquinolinyl, isoindolyl, dihydroindolyl, dihydroisoindolyl, indolon-2-yl, or pyrazinyl, each of which is unsubstituted or substituted with 1, 2, 3, 4 or 5 groups that are independently $C_1$-$C_4$ alkyl, halogen, $CF_3$, $OCF_3$, $-CO_2CH_3$, $C_1$-$C_4$ hydroxyalkyl, dihydroxyalkyl, $C_1$-$C_4$ alkoxy, $-CO_2(C_1$-$C_5$ alkyl), benzyloxy, $-NR_6R_7$, $-(C_1$-$C_4)$alkyl-$C(O)NR_6R_7$, $-NR_8R_9$, $NR_6R_7$-($C_1$-$C_4$ alkyl), $-C(O)NR_6R_7$, or amidinooxime, wherein

$R_6$ and $R_7$ are independently at each occurrence H, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ dihydroxyalkyl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkoxy $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkanoyl, phenyl $C_1$-$C_4$ alkyl, phenyl $C_1$-$C_4$ alkoxy, or phenyl $C_1$-$C_4$ alkanoyl, wherein each is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, OH, SH, $C_3$-$C_6$ cycloalkyl, aryl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkyl, OH, $CF_3$, or $OCF_3$, or

$R_6$, $R_7$, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently $C_1$-$C_4$ alkyl, hydroxy, hydroxy $C_1$-$C_4$ alkyl, $C_1$-$C_4$ dihydroxyalkyl, or halogen

6 A compound according to claim 5, wherein

$R_5$ is indolyl, pyridyl, pyrimidinyl, pyrazolyl, furanyl, indazolyl, dihydroindolyl, dihydroisoindolyl, indolon-2-yl, or pyrazinyl, each of which is unsubstituted or

substituted with 1, 2, 3, or 4 groups that are independently $C_1$-$C_4$ alkyl, halogen, $CF_3$, $OCF_3$, $-CO_2CH_3$, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ dihydroxyalkyl, $C_1$-$C_4$ alkoxy, $-CO_2(C_1$-$C_5$ alkyl), benzyloxy, $-C(O)NR_6R_7$, $-NR_8R_9$, $-(C_1$-$C_4)$alkyl-$C(O)NR_6R_7$, $-NR_6R_7$, $NR_6R_7$-$(C_1$-$C_4$ alkyl)-, and amidinooxime

7 A compound according to claim 6, wherein $R_5$ is indolyl, pyridyl, pyrimidinyl, dihydroindolyl, dihydroisoindolyl, pyrazolyl, or pyrazinyl, each of which is unsubstituted or substituted with 1, 2, 3, or 4 groups that are independently $C_1$-$C_4$ alkyl, halogen, $CF_3$, $OCF_3$, $-CO_2CH_3$, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ dihydroxyalkyl, $C_1$-$C_4$ alkoxy, $-CO_2(C_1$-$C_5$ alkyl), benzyloxy, $-C(O)NR_6R_7$, $NR_8R_9$, $-(C_1$-$C_4)$alkyl-$C(O)NR_6R_7$, $-NR_6R_7$, $NR_6R_7$-$(C_1$-$C_4$ alkyl)-, or amidinooxime, wherein

$R_6$ and $R_7$ are independently at each occurrence H, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ dihydroxyalkyl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkanoyl, $C_1$-$C_4$ alkoxy $C_1$-$C_4$ alkyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently halogen, OH, SH, $C_3$-$C_6$ cycloalkyl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkyl, OH, $CF_3$, or $OCF_3$

8 A compound according to claim 7, wherein $R_5$ is indolyl, pyridyl, pyrimidinyl, dihydroindolyl, dihydroisoindolyl, pyrazolyl, or pyrazinyl, each of which is unsubstituted or substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkyl, halogen, $CF_3$, $OCF_3$, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ dihydroxyalkyl, $C_1$-$C_4$ alkoxy, $-C(O)NR_6R_7$, $-(C_1$-$C_4)$alkyl-$C(O)NR_6R_7$, $NR_8R_9$, $-NR_6R_7$, or $NR_6R_7$-$(C_1$-$C_4$ alkyl)-, wherein

$R_6$ and $R_7$ are independently at each occurrence H, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ dihydroxyalkyl, $C_1$-$C_4$ alkanoyl, or $C_1$-$C_4$ alkoxy, each of which is optionally substituted with 1, 2, or 3 groups that are independently halogen, OH, SH, $C_3$-$C_6$ cycloalkyl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkyl, OH, $CF_3$, or $OCF_3$

9 A compound according to claim 4, wherein

$R_5$ is phenyl, phenyl($C_1$-$C_6$)alkyl, or ($C_1$-$C_6$)alkyl, wherein each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, halogen, alkoxy, benzyloxy, hydroxyalkyl, dihydroxyalkyl, thioalkoxy, -$CO_2$($C_1$-$C_5$ alkyl), $CO_2R$, CN, amidinooxime, -$NR_8R_9$, -$NR_6R_7$, $R_6R_7N$-($C_1$-$C_6$ alkyl)-, -C(O)$NR_6R_7$, -($C_1$-$C_4$)alkyl-C(O)$NR_6R_7$, amidino, $CF_3$, or $OCF_3$,

$R_8$ is hydrogen, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkanoyl, phenyl $C_1$-$C_6$ alkyl and phenyl $C_1$-$C_6$ alkanoyl, and

$R_9$ is aminoalkyl, mono $C_1$-$C_6$ alkylamino $C_1$-$C_6$ alkyl, di $C_1$-$C_6$ alkylamino $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkanoyl, phenyl $C_1$-$C_4$ alkyl, indazolyl, and phenyl $C_1$-$C_4$ alkanoyl

10 A compound according to claim 4, wherein

$R_5$ is phenyl, phenyl($C_1$-$C_6$)alkyl, which is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, halogen, alkoxy, benzyloxy, thioalkoxy, -$CO_2$($C_1$-$C_5$ alkyl), $CO_2R$, CN, amidinooxime, -$NR_8R_9$, -$NR_6R_7$, $R_6R_7N$-($C_1$-$C_6$ alkyl)-, -C(O)$NR_6R_7$, -($C_1$-$C_4$)-C(O)$NR_6R_7$, amidino, $CF_3$, or $OCF_3$, wherein

$R_6$ and $R_7$ are independently at each occurrence H, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ dihydroxyalkyl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkoxy $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkanoyl,

phenyl $C_1$-$C_4$ alkyl, phenyl $C_1$-$C_4$ alkoxy, or phenyl $C_1$-$C_4$ alkanoyl, wherein each is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, OH, SH, $C_3$-$C_6$ cycloalkyl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkyl, $CF_3$, or $OCF_3$, or

$R_6$, $R_7$, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently $C_1$-$C_4$ alkyl, hydroxy, hydroxy $C_1$-$C_4$ alkyl, $C_1$-$C_4$ dihydroxyalkyl, or halogen,

$R_8$ is hydrogen, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkanoyl, phenyl $C_1$-$C_6$ alkyl and phenyl $C_1$-$C_6$ alkanoyl, and

$R_9$ is aminoalkyl, mono $C_1$-$C_6$ alkylamino $C_1$-$C_6$ alkyl, di $C_1$-$C_6$ alkylamino $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkanoyl, phenyl $C_1$-$C_4$ alkyl, indazolyl, and phenyl $C_1$-$C_4$ alkanoyl

11 A compound according to claim 10, wherein

$R_5$ is phenyl, benzyl or phenethyl, wherein each is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently $C_1$-$C_6$ alkyl, $-NR_6R_7$, $-C(O)NR_6R_7$ $-(C_1$-$C_4$ alkyl)$-C(O)NR_6R_7$, $-NR_8R_9$, halogen, $C_1$-$C_6$ alkoxy, $CO_2R$, $-(C_1$-$C_4$ alkyl)$-CO_2R$, $C_1$-$C_6$ thioalkoxy, amidinooxime, $C_1$-$C_6$ alkoxycarbonyl, $-(C_1$-$C_4$ alkyl)$-C_1$-$C_6$ alkoxycarbonyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ dihydroxyalkyl, $-(C_1$-$C_4$ alkyl)$-CN$, CN, phenyl $C_1$-$C_6$ alkoxy, OH, $C_1$-$C_4$ haloalkyl, $C_1$-$C_4$ haloalkoxy, $R_6R_7N-(C_1$-$C_6$ alkyl)-, $-(C_1$-$C_4$ alkyl)$-NR_{15}C(O)R_{16}$, amidinooxime, $-SO_2(C_1$-$C_6$ alkyl), $-O-CH_2-O-$, $-O-CH_2CH_2-O-$, phenyl $C_1$-$C_4$ alkoxy, or phenyl, wherein

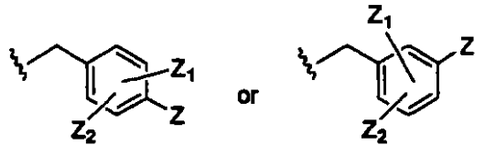
$R_6$ and $R_7$ are independently at each occurrence H, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ dihydroxyalkyl, $C_1$-$C_4$ alkanoyl, or $C_1$-$C_4$ alkoxy, each of which is optionally subst tuted with 1, 2, or 3 groups that

are independently halogen, OH, SH, $C_3$-$C_6$ cycloalkyl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkyl, OH, $CF_3$, or $OCF_3$

12 A compound according to claim 11, wherein $R_5$ is phenyl, benzyl or phenethyl, each of which is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently CN, halogen, $C_1$-$C_4$ alkoxy, $CF_3$, $OCF_3$, $C_1$-$C_4$ alkyl, $-NR_8R_9$, $-NR_6R_7$, $R_6R_7N$-($C_1$-$C_6$ alkyl)-, or $-C(O)NR_6R_7$, wherein

$R_6$ and $R_7$ are independently at each occurrence H, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ dihydroxyalkyl, $C_1$-$C_4$ alkanoyl, or $C_1$-$C_4$ alkoxy, each of which is optionally substituted with 1, 2, or 3 groups that are independently halogen, OH, SH, $C_3$-$C_6$ cycloalkyl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkyl, OH, $CF_3$, or $OCF_3$

13 A compound according to claim 4, wherein the $R_5$ group is of the formula




wherein

$Z_1$ and $Z_2$ are independently H, halogen, $C_1$-$C_4$ alkyl, or $CO_2R$, and

Z is $-C(O)NR_6R_7$ $-(C_1$-$C_4)$alkyl-$C(O)NR_6R_7$, $-(C_1$-$C_4$ alkyl)-$NR_{15}C(O)R_{18}$, $-NR_6R_7$, $R_6R_7N$-($C_1$-$C_6$ alkyl)-, $-NR_8R_9$, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ dihydroxyalkyl, $C_1$-$C_6$ alkyl, $CO_2R$, or halogen, wherein

$R_6$ and $R_7$ at each occurrence are independently H, OH, $C_1$-$C_6$ alkyl, amino $C_1$-$C_4$ alkyl, NH($C_1$-$C_6$ alkyl)alkyl, N($C_1$-$C_6$ alkyl)($C_1$-$C_6$ alkyl) $C_1$-$C_6$ alkyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ dihydroxyalkyl, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, or -

$SO_2(C_1\text{-}C_6$ alkyl) each of which is optionally substituted with 1, 2, or 3 groups that are independently halogen, OH, SH, $C_3\text{-}C_6$ cycloalkyl, $C_1\text{-}C_4$ alkoxy, $C_1\text{-}C_4$ alkyl, OH, $CF_3$, or $OCF_3$,

or

$R_6$, $R_7$, and the nitrogen to which they are attached form a piperidinyl, pyrrolidinyl, piperazinyl, or a morpholinyl, thiomorpholinyl, ring optionally substituted with 1 or 2 groups that are independently alkyl, hydroxy, hydroxy $C_1\text{-}C_4$ alkyl, $C_1\text{-}C_4$ dihydroxyalkyl, or halogen, and

$R_{18}$ is $C_1\text{-}C_6$ alkyl optionally substituted with -O-($C_2\text{-}C_6$ alkanoyl, $C_1\text{-}C_6$ hydroxyalkyl, $C_1\text{-}C_4$ dihydroxyalkyl, $C_1\text{-}C_6$ alkoxy, $C_1\text{-}C_6$ alkoxy $C_1\text{-}C_6$ alkyl, amino $C_1\text{-}C_6$ alkyl, mono or dialkylamino $C_1\text{-}C_6$ alkyl

14 A compound according to claim 4, wherein

$R_5$ is pyrazolyl($C_1\text{-}C_6$ alkyl), imidazolyl($C_1\text{-}C_6$ alkyl), thienyl($C_1\text{-}C_6$ alkyl), furanyl($C_1\text{-}C_6$ alkyl), piperidinyl($C_1\text{-}C_6$)alkyl, pyrrolidinyl($C_1\text{-}C_6$)alkyl, imidazolidinyl($C_1\text{-}C_6$)alkyl, piperazinyl($C_1\text{-}C_6$)alkyl, pyridyl($C_1\text{-}C_6$)alkyl, pyrimidyl($C_1\text{-}C_6$)alkyl, pyridazyl($C_1\text{-}C_6$)alkyl, pyrazinyl($C_1\text{-}C_6$)alkyl, isoquinolinyl($C_1\text{-}C_6$)alkyl, tetrahydroisoquinolinyl($C_1\text{-}C_6$)alkyl, indolyl($C_1\text{-}C_6$)alkyl, 1H-indazolyl($C_1\text{-}C_6$)alkyl, dihydroindolyl($C_1\text{-}C_6$ alkyl), dihydroindolon-2-yl($C_1\text{-}C_6$ alkyl), indolinyl($C_1\text{-}C_6$ alkyl), dihydroisoindolyl($C_1\text{-}C_6$ alkyl), dihydrobenzimdazolyl($C_1\text{-}C_6$ alkyl), or dihydrobenzoimidazolonyl($C_1\text{-}C_6$ alkyl), wherein each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently ($C_1\text{-}C_6$)alkyl, halogen, ($C_1\text{-}C_6$)alkoxy, ($C_1\text{-}C_6$)hydroxyalkyl, $C_1\text{-}C_6$ dihydroxyalkyl, phenyl($C_1\text{-}C_6$)alkoxy, ($C_1\text{-}C_6$)thioalkoxy, ($C_1\text{-}C_6$)alkoxycarbonyl, phenyl($C_1$-

$C_6$)alkoxycarbonyl, OH, $CO_2R$, CN, amidinooxime, $-NR_8R_9$, $-NR_6R_7$, $R_6R_7N-(C_1-C_6$ alkyl)-, $-C(O)NR_6R_7$, $-(C_1-C_4$ alkyl)$-C(O)NR_6R_7$ amidino, piperazinyl, morpholinyl, $-SO_2(C_1-C_6)$ alkyl, $-SO_2NH_2$, $-SO_2NH(C_1-C_6)$alkyl, $-SO_2N(C_1-C_6)$alkyl $(C_1-C_6)$alkyl, $(C_1-C_4)$haloalkyl, $-(C_1-C_4$ alkyl)$-NR_{15}C(O)NR_{16}R_{17}$, $-(C_1-C_4$ alkyl)$-NR_{15}C(O)R_{18}$, $-O-CH_2-O$, $-O-CH_2CH_2-O-$, or $(C_1-C_4)$haloalkoxy, wherein

$R_6$ and $R_7$ are independently at each occurrence H, $(C_1-C_6)$alkyl, $(C_1-C_6)$alkoxy, $(C_1-C_6)$alkoxy$(C_1-C_6)$alkyl, $(C_1-C_6)$alkoxycarbonyl, $(C_1-C_6)$hydroxyalkyl, $C_1-C_6$ dihydroxyalkyl, $-(C_1-C_4)$alkyl$-CO_2-(C_1-C_6)$alkyl, $(C_1-C_6)$alkanoyl, phenyl$(C_1-C_6)$alkyl, phenyl$(C_1-C_6)$alkoxy, or phenyl$(C_1-C_6)$alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, $(C_1-C_4)$alkoxy, OH, SH, $C_3-C_6$ cycloalkyl, $NH_2$, $NH(C_1-C_6$ alkyl), $N(C_1-C_6$ alkyl$)(C_1-C_6$ alkyl), $(C_1-C_4)$alkyl, $CF_3$ or $OCF_3$, or

$R_6$, $R_7$, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently $C_1-C_4$ alkyl, hydroxy, hydroxy $C_1-C_4$ alkyl, $C_1-C_4$ dihydroxyalkyl, or halogen, and

$R_{18}$ is $C_1-C_6$ alkyl optionally substituted with $-O-(C_2-C_6$ alkanoyl, $C_1-C_6$ hydroxyalkyl, $C_1-C_6$ dihydroxyalkyl, $C_1-C_6$ alkoxy, $C_1-C_6$ alkoxy $C_1-C_6$ alkyl, amino $C_1-C_6$ alkyl, mono or dialkylamino $C_1-C_6$ alkyl,

15 A compound according to claim 14, wherein

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$R_5$ is pyrazolyl($C_1$-$C_6$ alkyl), imidazolyl($C_1$-$C_6$ alkyl), benzimidazolyl($C_1$-$C_6$ alkyl), thienyl($C_1$-$C_6$ alkyl), pyrimidyl($C_1$-$C_6$)alkyl indolyl($C_1$-$C_6$ alkyl), dinydroindolyl($C_1$-$C_6$ alkyl), dihydroisoindolyl($C_1$-$C_6$ alkyl), dihydroindolon-2-yl($C_1$-$C_6$ alkyl), pyridinyl($C_1$-$C_6$ alkyl), piperazinyl($C_1$-$C_6$ alkyl), or pyrazinyl($C_1$-$C_6$ alkyl) each of which is optionally substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkyl, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ dihydroxyalkyl, halogen, -C(O)$NR_6R_7$, -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$ $C_1$-$C_6$ alkoxycarbonyl, -$NR_6R_7$, $R_6R_7N$-($C_1$-$C_6$ alkyl)-, haloalkyl, $C_1$-$C_6$ alkanoyl,

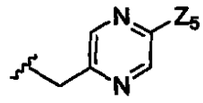
$R_6$ and $R_7$ at each occurrence are independently H, $C_1$-$C_6$ alkyl optionally substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkoxycarbonyl, halogen, $C_3$-$C_6$ cycloalkyl, OH, SH, or $C_1$-$C_4$ alkoxy,

or

$R_6$, $R_7$, and the nitrogen to which they are attached form a piperidinyl, pyrrolidinyl, piperazinyl, or a morpholinyl ring optionally substituted with 1 or 2 groups that are independently alkyl, hydroxy, hydroxy $C_1$-$C_4$ alkyl, $C_1$-$C_4$ dihydroxyalkyl, or halogen

16 A compound according to claim 15, wherein

$R_5$ is of the formula



wherein

$Z_5$ is $C_1$-$C_4$ alkyl, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ dihydroxyalkyl, halogen -C(O)$NR_6R_7$, -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$ $C_1$-$C_6$ alkoxycarbonyl, $R_6R_7N$-($C_1$-$C_6$ alkyl)-, -$NR_6R_7$, $CF_3$, or $C_1$-$C_6$ alkanoyl, wherein

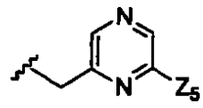
$R_6$ and $R_7$ at each occurrence are independently H, $C_1$-$C_6$ alkyl optionally substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkoxycarbonyl, halogen, $C_3$-$C_6$ cycloalkyl, OH, SH, or $C_1$-$C_4$ alkoxy,

or

$R_6$, $R_7$, and the nitrogen to which they are attached form a piperidinyl, pyrrolidinyl, piperazinyl, or a morpholinyl ring optionally substituted with 1 or 2 groups that are independently alkyl, hydroxy, hydroxy $C_1$-$C_4$ alkyl, $C_1$-$C_4$ dihydroxyalkyl, or halogen

17 A compound according to claim 15, wherein

$R_5$ is of the formula



wherein

$Z_5$ is $C_1$-$C_4$ alkyl, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ dihydroxyalkyl, halogen, $-C(O)NR_6R_7$, $-(C_1$-$C_4$ alkyl$)-C(O)NR_6R_7$ $C_1$-$C_6$ alkoxycarbonyl, $R_6R_7N-(C_1$-$C_6$ alkyl$)-$, $-NR_6R_7$, $CF_3$, or $C_1$-$C_6$ alkanoyl, wherein

$R_6$ and $R_7$ at each occurrence are independently H, $C_1$-$C_6$ alkyl optionally substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkoxycarbonyl, halogen, $C_3$-$C_6$ cycloalkyl, OH, SH, or $C_1$-$C_4$ alkoxy,

or

$R_6$, $R_7$, and the nitrogen to which they are attached form a piperidinyl, pyrrolidinyl, piperazinyl, or a morpholinyl ring optionally substituted with 1 or 2 groups that are independently alkyl, hydroxy, hydroxy $C_1$-$C_4$ alkyl, $C_1$-$C_4$ dihydroxyalkyl, or halogen

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18 A compound according to either claim 16 or 17, wherein

$Z_5$ is $C_1$-$C_4$ alkyl, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ dihydroxyalkyl, halogen, $C_1$-$C_6$ alkoxycarbonyl, $CF_3$, or $C_2$-$C_6$ alkanoyl

19 A compound according to either claim 16 or 17, wherein

$Z_5$ is $C_1$-$C_4$ alkyl, $-C(O)NR_6R_7$, $-(C_1$-$C_4$ alkyl)$-C(O)NR_6R_7$, $R_6R_7N-(C_1$-$C_6$ alkyl)-, or $-NR_6R_7$, $CF_3$, or $C_1$-$C_4$ alkanoyl, wherein

$R_6$ and $R_7$ at each occurrence are independently H, $C_1$-$C_6$ alkyl optionally substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkoxycarbonyl, halogen, $C_3$-$C_6$ cycloalkyl, OH, SH, or $C_1$-$C_4$ alkoxy,

or

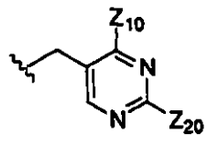
$R_6$, $R_7$, and the nitrogen to which they are attached form a piperidinyl, pyrrolidinyl, piperazinyl, or a morpholinyl ring optionally substituted with 1 or 2 groups that are independently alkyl, hydroxy, hydroxy $C_1$-$C_4$ alkyl, $C_1$-$C_4$ dihydroxyalkyl, or halogen

20 A compound according to claim 19, wherein

$Z_5$ is $-C(O)NR_6R_7$, $-(C_1$-$C_4$ alkyl$)-C(O)NR_6R_7$, $R_6R_7N-(C_1$-$C_6$ alkyl)-, or $-NR_6R_7$, wherein

$R_6$ and $R_7$ at each occurrence are independently H, $C_1$-$C_6$ alkyl optionally substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkoxycarbonyl, halogen, cyclopropyl, OH, SH, or $C_1$-$C_4$ alkoxy

21 A compound according to claim 15, wherein

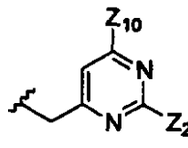
$R_5$ is of the formula  , wherein

$Z_{10}$ is H or methyl, and

$Z_{20}$ is hydroxy($C_1$-$C_4$)alkyl, $C_1$-$C_4$ dihydroxyalkyl, OH, halogen, haloalkyl, ($C_1$-$C_4$)alkyl, $OCF_3$, -$NR_6R_7$, $R_6R_7N$-($C_1$-$C_6$ alkyl)-, -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$, or -C(O)$NR_6R_7$, wherein

$R_6$ and $R_7$ at each occurrence are independently H, $C_1$-$C_6$ alkyl optionally substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkoxycarbonyl, halogen, $C_3$-$C_6$ cycloalkyl, OH, SH, or $C_1$-$C_4$ alkoxy

22 A compound according to claim 15, wherein

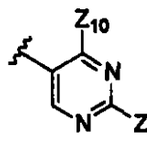
$R_5$ is of the formula  , wherein

$Z_{10}$ is H or methyl, and

$Z_{20}$ is hydroxy($C_1$-$C_4$)alkyl, $C_1$-$C_4$ dihydroxyalkyl, OH, halogen, $CF_3$, ($C_1$-$C_4$)alkyl, $OCF_3$, -$NR_6R_7$, $R_6R_7N$-($C_1$-$C_6$ alkyl)-, -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$, or -C(O)$NR_6R_7$, wherein

$R_6$ and $R_7$ at each occurrence are independently H, $C_1$-$C_6$ alkyl optionally substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkoxycarbonyl, halogen, $C_3$-$C_6$ cycloalkyl, OH, SH, or $C_1$-$C_4$ alkoxy

23 A compound according to claim 15, wherein

$R_5$ is of the formula  , wherein

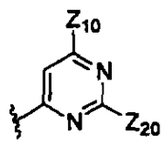
$Z_{10}$ is H or methyl, and

$Z_{20}$ is hydroxy($C_1$-$C_4$)alkyl, $C_1$-$C_4$ dihydroxyalkyl, OH, halogen, haloalkyl, ($C_1$-$C_4$)alkyl, $OCF_3$, -$NR_6R_7$, $R_6R_7N$-($C_1$-$C_6$ alkyl)-, -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$, or -C(O)$NR_6R_7$, wherein

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$R_6$ and $R_7$ at each occurrence are independently H, $C_1$-$C_6$ alkyl optionally substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkoxycarbonyl, halogen, $C_3$-$C_6$ cycloalkyl, OH, SH, or $C_1$-$C_4$ alkoxy

24 A compound according to claim 15, wherein

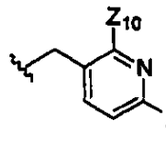
$R_5$ is of the formula  , wherein

$Z_{10}$ is H or methyl, and

$Z_{20}$ is hydroxy($C_1$-$C_4$)alkyl, $C_1$-$C_4$ dihydroxyalkyl, OH, halogen, $CF_3$, ($C_1$-$C_4$)alkyl, $OCF_3$, -$NR_6R_7$, $R_6R_7N$-($C_1$-$C_6$ alkyl)-, -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$, or -C(O)$NR_6R_7$, wherein

$R_6$ and $R_7$ at each occurrence are independently H, $C_1$-$C_6$ alkyl optionally substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkoxycarbonyl, halogen, $C_3$-$C_6$ cycloalkyl, OH, SH, or $C_1$-$C_4$ alkoxy

25 A compound according to claim 15, wherein

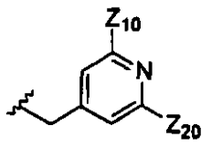
$R_5$ is of the formula  , wherein

$Z_{10}$ is H or methyl, and

$Z_{20}$ is hydroxy($C_1$-$C_4$)alkyl, $C_1$-$C_4$ dihydroxyalkyl, OH, halogen, haloalkyl, ($C_1$-$C_4$)alkyl, $OCF_3$, -$NR_6R_7$, $R_6R_7N$-($C_1$-$C_6$ alkyl)-, -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$, or -C(O)$NR_6R_7$, wherein

$R_6$ and $R_7$ at each occurrence are independently H, $C_1$-$C_6$ alkyl optionally substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkoxycarbonyl, halogen, $C_3$-$C_6$ cycloalkyl, OH, SH, or $C_1$-$C_4$ alkoxy

26 A compound according to claim 15, wherein

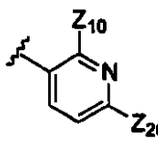
$R_5$ is of the formula  , wherein

$Z_{10}$ is H or methyl, and

$Z_{20}$ is hydroxy($C_1$-$C_4$)alkyl, $C_1$-$C_4$ dihydroxyalkyl, OH, halogen, $CF_3$, ($C_1$-$C_4$)alkyl, $OCF_3$, -$NR_6R_7$, $R_6R_7N$-($C_1$-$C_6$ alkyl)-, -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$, or -C(O)$NR_6R_7$, wherein

$R_6$ and $R_7$ at each occurrence are independently H, $C_1$-$C_6$ alkyl optionally substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkoxycarbonyl halogen, $C_3$-$C_6$ cycloalkyl, OH, SH, or $C_1$-$C_4$ alkoxy

27 A compound according to claim 15, wherein

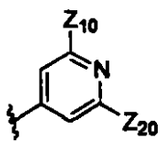
$R_5$ is of the formula  , wherein

$Z_{10}$ is H or methyl, and

$Z_{20}$ is hydroxy($C_1$-$C_4$)alkyl, $C_1$-$C_4$ dihydroxyalkyl, OH, halogen, haloalkyl, ($C_1$-$C_4$)alkyl, $OCF_3$, -$NR_6R_7$, $R_6R_7N$-($C_1$-$C_6$ alkyl)-, -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$, or -C(O)$NR_6R_7$, wherein

$R_6$ and $R_7$ at each occurrence are independently H, $C_1$-$C_6$ alkyl optionally substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkoxycarbonyl, halogen, $C_3$-$C_6$ cycloalkyl, OH, SH, or $C_1$-$C_4$ alkoxy

28 A compound according to claim 15, wherein

$R_5$ is of the formula  , wherein

$Z_{10}$ is H or methyl, and

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$Z_{20}$ is hydroxy($C_1$-$C_4$)alkyl-, $C_1$-$C_4$ dihydroxyalkyl, OH, halogen, $CF_3$, ($C_1$-$C_4$)alkyl, $OCF_3$, -$NR_6R_7$, $R_6R$-N-($C_1$-$C_6$ alkyl)-, -($C_1$-$C_4$ alkyl)-$C(O)NR_6R_7$, or -$C(O)NR_5R$-, wherein $R_6$ and $R_7$ at each occurrence are independently H, $C_1$-$C_6$ alkyl optionally substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkoxycarbonyl, halogen, $C_3$-$C_6$ cycloalkyl, OH, SH, or $C_1$-$C_4$ alkoxy

29 A compound according to claim 4, wherein $R_5$ is phenyl, which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently $C_1$-$C_4$ alkyl, -$C(O)NR_6R_7$, -($C_1$-$C_4$ alkyl)-$C(O)NR_6R_7$ -$NR_6R_7$, $NR_6R_7$($C_1$-$C_6$ alkyl), $C_1$-$C_6$ hydroxyalkyl, dihydroxyalkyl, halogen, $C_1$-$C_4$ alkoxy, $CO_2R$, OH, $C_1$-$C_6$ alkoxycarbonyl, $CF_3$, -($C_1$-$C_4$ alkyl)-$NR_{15}C(O)NR_{16}R_{17}$, -($C_1$-$C_4$ alkyl)-$NR_{15}C(O)R_{18}$, wherein

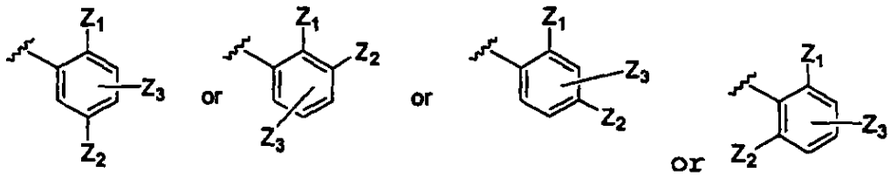
$R_{15}$ is H or $C_1$-$C_6$ alkyl

$R_{16}$ and $R_{17}$ are independently H or $C_1$-$C_6$ alkyl, or

$R_{16}$, $R_{17}$, and the nitrogen to which they are attached form a morpholinyl ring, and

$R_{18}$ is $C_1$-$C_6$ alkyl optionally substituted with -O-($C_2$-$C_6$ alkanoyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ dihydroxyalkyl, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, amino $C_1$-$C_6$ alkyl, mono or dialkylamino $C_1$-$C_6$ alkyl

30 A compound according to claim 29, wherein $R_5$ is of the formula




$Z_1$ is H, halogen, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ haloalkyl, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ dihydroxyalkyl, or $C_1$-$C_4$ alkoxy, and

$Z_2$ is $C_1$-$C_4$ alkyl, -C(O)$NR_6R_7$, -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$ -$NR_6R_7$, $NR_6R_7$($C_1$-$C_6$ alkyl), $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ dihydroxyalkyl, halogen, $C_1$-$C_4$ alkoxy, $CO_2R$, OH, $C_1$-$C_6$ alkoxycarbonyl, or $C_1$-$C_4$ haloalkyl,

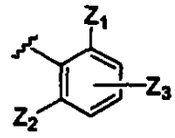
$Z_3$ is H, $C_1$-$C_4$ alkyl, -C(O)$NR_6R_7$, -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$ -$NR_6R_7$, $NR_6R_7$($C_1$-$C_6$ alkyl), $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ dihydroxyalkyl, halogen, $C_1$-$C_4$ alkoxy, $CO_2R$, OH $C_1$-$C_6$ alkoxycarbonyl, or $C_1$-$C_4$ haloalkyl,

wherein

$R_6$ and $R_7$ at each occurrence are independently H, OH, $C_1$-$C_6$ alkyl, amino $C_1$-$C_4$ alkyl, NH($C_1$-$C_6$ alkyl)alkyl, N($C_1$-$C_6$ alkyl)($C_1$-$C_6$ alkyl) $C_1$-$C_6$ alkyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ dihydroxyalkyl, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, -$SO_2$($C_1$-$C_6$ alkyl), -$SO_2NH_2$, -$SO_2$NH($C_1$-$C_6$ alkyl), -$SO_2$N($C_1$-$C_6$ alkyl)($C_1$-$C_6$ alkyl), or $C_1$-$C_6$ alkanoyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently halogen, OH, SH, $C_3$-$C_6$ cycloalkyl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkyl, OH, $CF_3$, or $OCF_3$

31 A compound according to claim 30, wherein

$R_5$ is of the formula




wherein

$Z_1$ is H, halogen, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ haloalkyl, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ dihydroxyalkyl, or $C_1$-$C_4$ alkoxy, and

$Z_2$ is $C_1$-$C_4$ alkyl, -C(O)$NR_6R_7$, -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$ -$NR_6R_7$, $NR_6R_7$($C_1$-$C_6$ alkyl), $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ dihydroxyalkyl, halogen, $C_1$-$C_4$ alkoxy, $CO_2R$, OH, $C_1$-$C_6$ alkoxycarbonyl, or $C_1$-$C_4$ haloalkyl,

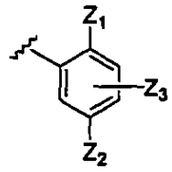
$Z_3$ is H, $C_1$-$C_4$ alkyl, -C(O)$NR_6R_7$, -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$ -$NR_6R_7$, $NR_6R_7$($C_1$-$C_6$ alkyl), $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$

dihydroxyalkyl, halogen, $C_1$-$C_4$ alkoxy, $CO_2R$, OH, $C_1$-$C_6$ alkoxycarbonyl, or $C_1$-$C_4$ haloalkyl, wherein

$R_6$ and $R_7$ at each occurrence are independently H, OH, $C_1$-$C_6$ alkyl, amino $C_1$-$C_4$ alkyl, $NH(C_1$-$C_6$ alkyl)alkyl, $N(C_1$-$C_6$ alkyl)($C_1$-$C_6$ alkyl) $C_1$-$C_6$ alkyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ dihydroxyalkyl, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl -$SO_2(C_1$-$C_6$ alkyl), -$SO_2NH_2$, -$SO_2NH(C_1$-$C_6$ alkyl), -$SO_2N(C_1$-$C_6$ alkyl)($C_1$-$C_6$ alkyl), or $C_1$-$C_6$ alkanoyl, each of which is optionally substituted with 1, 2 or 3 groups that are independently halogen, OH, SH, $C_3$-$C_6$ cycloalkyl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkyl, OH, $CF_3$, or $OCF_3$

32 A compound according to claim 30, wherein

$R_5$ is of the formula




wherein

$Z_1$ is H, halogen, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ haloalkyl, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ dihydroxyalkyl, or $C_1$-$C_4$ alkoxy, and

$Z_2$ is $C_1$-$C_4$ alkyl, -$C(O)NR_6R_7$ -($C_1$-$C_4$ alkyl)-$C(O)NR_6R_7$ -$NR_6R_7$, $NR_6R_7(C_1$-$C_6$ alkyl), $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ dihydroxyalkyl, halogen, $C_1$-$C_4$ alkoxy, $CO_2R$, OH, $C_1$-$C_6$ alkoxycarbonyl, or $C_1$-$C_4$ haloalkyl,

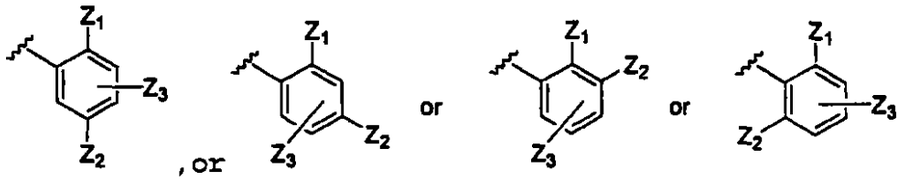
$Z_3$ is H, $C_1$-$C_4$ alkyl, -$C(O)NR_6R_7$, -($C_1$-$C_4$ alkyl)-$C(O)NR_6R_7$ -$NR_6R_7$, $NR_6R_7(C_1$-$C_6$ alkyl), $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ dihydroxyalkyl, halogen, $C_1$-$C_4$ alkoxy, $CO_2R$, OH, $C_1$-$C_6$ alkoxycarbonyl, or $C_1$-$C_4$ haloalkyl, wherein

$R_6$ and $R_7$ at each occurrence are independently H, OH, $C_1$-$C_6$ alkyl, amino $C_1$-$C_4$ alkyl, $NH(C_1$-$C_6$ alkyl)alkyl, $N(C_1$-$C_6$ alkyl)($C_1$-$C_6$ alkyl) $C_1$-$C_6$ alkyl, $C_1$-$C_6$ hydroxyalkyl,

$C_1$-$C_6$ dihydroxyalkyl, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, -$SO_2$($C_1$-$C_6$ alkyl), -$SO_2NH_2$, -$SO_2NH$($C_1$-$C_6$ alkyl), -$SO_2N$($C_1$-$C_6$ alkyl)($C_1$-$C_6$ alkyl), or $C_1$-$C_6$ alkanoyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently halogen, OH, SH, $C_3$-$C_6$ cycloalkyl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkyl, OH, $CF_3$, or $OCF_3$

33 A compound according to claim 29, wherein

$R_5$ is either



wherein

$Z_1$ is H, halogen, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ haloalkyl, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ dihydroxyalkyl, or $C_1$-$C_4$ alkoxy, and

$Z_2$ is $C_1$-$C_4$ alkyl, -$C(O)NR_6R_7$, -($C_1$-$C_4$ alkyl)-$C(O)NR_6R_7$ -$NR_6R_7$, $NR_6R_7$($C_1$-$C_6$ alkyl), $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ dihydroxyalkyl, halogen, $C_1$-$C_4$ alkoxy, $CO_2R$, $C_1$-$C_6$ alkoxycarbonyl, -($C_1$-$C_4$ alkyl)-$NR_{15}C(O)NR_{16}R_{17}$, or -($C_1$-$C_4$ alkyl)-$NR_{15}C(O)R_{18}$,

$Z_3$ is H, $C_1$-$C_4$ alkyl, -$C(O)NR_6R_7$, -($C_1$-$C_4$ alkyl)-$C(O)NR_6R_7$ -$NR_6R_7$, $NR_6R_7$($C_1$-$C_6$ alkyl), $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ dihydroxyalkyl, halogen, $C_1$-$C_4$ alkoxy, $CO_2R$, $C_1$-$C_6$ alkoxycarbonyl, -($C_1$-$C_4$ alkyl)-$NR_{15}C(O)NR_{16}R_{17}$, or -($C_1$-$C_4$ alkyl)-$NR_{15}C(O)R_{18}$,

$R_6$, $R_7$, and the nitrogen to which they are attached form a piperidinyl, pyrrolidinyl, piperazinyl, or a morpholinyl ring optionally substituted with 1 or 2 groups that are independently alkyl, hydroxy, hydroxy $C_1$-$C_4$ alkyl, $C_1$-$C_4$ dihydroxyalkyl, or halogen,

$R_{15}$ is H or $C_1$-$C_6$ alkyl,

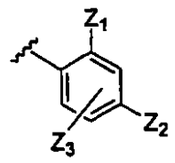
$R_{16}$ and $R_{17}$ are independently H or $C_1$-$C_6$ alkyl, or

$R_{16}$, $R_{17}$, and the nitrogen to which they are attached form a morpholinyl ring

$R_{18}$ is $C_1$-$C_6$ alkyl optionally substituted with -O-($C_2$-$C_6$ alkanoyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ dihydroxyalkyl, $C_1$-$C_6$ alkoxy, $C_2$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, amino $C_1$-$C_6$ alkyl, mono or dialkylamino $C_1$-$C_6$ alkyl

34 A compound according to claim 33, wherein

$R_5$ is of the formula



$Z_1$ is H, halogen, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ haloalkyl, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ dihydroxyalkyl, or $C_1$-$C_4$ alkoxy, and

$Z_2$ is $C_1$-$C_4$ alkyl, $-C(O)NR_6R_7$, $-(C_1$-$C_4$ alkyl)$-C(O)NR_6R_7$ $-NR_6R_7$, $NR_6R_7(C_1$-$C_6$ alkyl), $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ dihydroxyalkyl, halogen, $C_1$-$C_4$ alkoxy, $CO_2R$, $C_1$-$C_6$ alkoxycarbonyl, $-(C_1$-$C_4$ alkyl)$-NR_{15}C(O)NR_{16}R_{17}$, or $-(C_1$-$C_4$ alkyl)$-NR_{15}C(O)R_{18}$,

$Z_3$ is H, $C_1$-$C_4$ alkyl, $-C(O)NR_6R_7$, $-(C_1$-$C_4$ alkyl)$-C(O)NR_6R_7$ $-NR_6R_7$, $NR_6R_7(C_1$-$C_6$ alkyl), $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ dihydroxyalkyl, halogen, $C_1$-$C_4$ alkoxy, $CO_2R$, $C_1$-$C_6$ alkoxycarbonyl, $-(C_1$-$C_4$ alkyl)$-NR_{15}C(O)NR_{16}R_{17}$, or $-(C_1$-$C_4$ alkyl)$-NR_{15}C(O)R_{18}$,

$R_6$, $R_7$, and the nitrogen to which they are attached form a piperidinyl, pyrrolidinyl, piperazinyl, or a morpholinyl ring optionally substituted with 1 or 2 groups that are independently alkyl, hydroxy, hydroxy $C_1$-$C_4$ alkyl, $C_1$-$C_4$ dihydroxyalkyl, or halogen,

$R_{15}$ is H or $C_1$-$C_6$ alkyl,

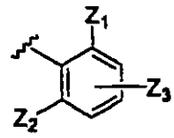
$R_{16}$ and $R_{17}$ are independently H or $C_1$-$C_6$ alkyl, or

$R_{16}$, $R_{17}$, and the nitrogen to which they are attached form a morpholinyl ring,

$R_{18}$ is $C_1$-$C_6$ alkyl optionally substituted with -O-($C_2$-$C_6$ alkanoyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ dihydroxyalkyl, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, amino $C_1$-$C_6$ alkyl, mono or dialkylamino $C_1$-$C_6$ alkyl

35 A compound according to claim 33, wherein

$R_5$ is of the formula



wherein

$Z_1$ is H, halogen, $C_1$-$C_4$ alkyl $C_1$-$C_4$ haloalkyl, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ dihydroxyalkyl, or $C_1$-$C_4$ alkoxy, and

$Z_2$ is $C_1$-$C_4$ alkyl, $-C(O)NR_6R_7$, -($C_1$-$C_4$ alkyl)-$C(O)NR_6R_7$ $-NR_6R_7$, $NR_6R_7$($C_1$-$C_6$ alkyl), $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ dihydroxyalkyl, halogen, $C_1$-$C_4$ alkoxy, $CO_2R$, $C_1$-$C_6$ alkoxycarbonyl, -($C_1$-$C_4$ alkyl)-$NR_{15}C(O)NR_{16}R_{17}$, or -($C_1$-$C_4$ alkyl)-$NR_{15}C(O)R_{18}$,

$Z_3$ is H, $C_1$-$C_4$ alkyl, $-C(O)NR_6R_7$, -($C_1$-$C_4$ alkyl)-$C(O)NR_6R_7$ $-NR_6R_7$, $NR_6R_7$($C_1$-$C_6$ alkyl), $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ dihydroxyalkyl, halogen, $C_1$-$C_4$ alkoxy, $CO_2R$, $C_1$-$C_6$ alkoxycarbonyl, -($C_1$-$C_4$ alkyl)-$NR_{15}C(O)NR_{16}R_{17}$, or -($C_1$-$C_4$ alkyl)-$NR_{15}C(O)R_{18}$,

$R_6$, $R_7$, and the nitrogen to which they are attached form a piperidinyl, pyrrolidinyl, piperazinyl, or a morpholinyl ring, each of which is optionally substituted with 1 or 2 groups that are independently alkyl, hydroxy, hydroxy $C_1$-$C_4$ alkyl, $C_1$-$C_4$ dihydroxyalkyl, or halogen,

$R_{15}$ is H or $C_1$-$C_6$ alkyl,

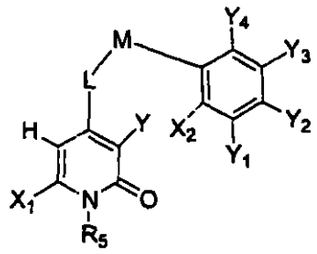
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$R_{16}$ and $R_{17}$ are independently H or $C_1$-$C_6$ alkyl, or

$R_{16}$, $R_{17}$, and the nitrogen to which they are attached form a morpholinyl ring,

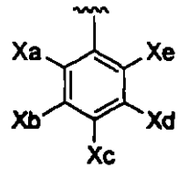
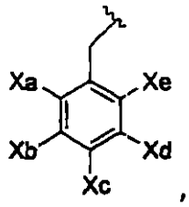
$R_{18}$ is $C_1$-$C_6$ alkyl optionally substituted with -O-($C_2$-$C_6$ alkanoyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ dihydroxyalkyl, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, amino $C_1$-$C_6$ alkyl, mono or dialkylamino $C_1$-$C_6$ alkyl

36 A compound of the formula



or a pharmaceutically acceptable salt thereof, wherein

L and M are independently selected from -O-, -$CH_2$-, -S-,-NR-, -N(R)-N(R)-, C(=O)-, -$SO_2$-,

$R_5$ is  or  , wherein

$X_1$, $X_2$, $X_a$, $X_b$, $X_c$, $X_d$, and $X_e$ at are independently selected from -C(O)$NR_6R_7$, -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$, -$NR_6R_7$, hydroxy($C_1$-$C_4$)alkyl, $C_1$-$C_4$ dihydroxyalkyl, H, OH, halogen, haloalkyl, alkyl, haloalkoxy, heteroaryl, heterocycloalkyl, $C_3$-$C_7$ cycloalkyl, $R_6R_7$N-($C_1$-$C_6$ alkyl)-, -$CO_2$-($C_1$-$C_6$)alkyl, -N(R)C(O)$NR_6R_7$, -N(R)C(O)-($C_1$-$C_6$)alkoxy, $CO_2$R-($C_1$-$C_6$ alkyl)-, or -$SO_2NR_6R_7$, wherein the heteroaryl and heterocycloalkyl groups are optionally substituted with -$NR_6R_7$, -C(O)$NR_6R_7$, $R_6R_7$N-($C_1$-$C_6$ alkyl)-, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, or halogen, or

$R_5$ is heteroaryl or heteroarylalkyl, wherein the heteroaryl and heteroaryl groups are optionally substituted with 1, 2, 3, or 4 groups that are independently $-C(O)NR_6R_7$, $-(C_1-C_4$ alkyl)$-C(O)NR_6R_7$, $-NR_6R_7$, hydroxy$(C_1-C_4)$alkyl, $C_1-C_4$ dihydroxyalkyl, H, OH, halogen, haloalkyl, alkyl, haloalkoxy, $R_6R_7N-(C_1-C_6$ alkyl$)-$, $-CO_2-(C_1-C_6)$alkyl, $-N(R)C(O)NR_6R_7$, or $-N(R)C(O)-(C_1-C_6)$alkoxy, wherein

$R_6$ and $R_7$ are independently at each occurrence H, $C_1-C_6$ alkyl, $C_1-C_6$ alkoxy, $C_1-C_6$ alkoxy $C_1-C_6$ alkyl, $C_1-C_6$ alkoxycarbonyl, OH, $C_1-C_6$ hydroxyalkyl, $C_1-C_4$ dihydroxyalkyl, $C_1-C_6$ thiohydroxyalkyl, $-(C_1-C_4)$alkyl-$CO_2$-alkyl, pyridyl $C_1-C_6$ alkyl, $C_1-C_6$ alkanoyl, benzyl, phenyl $C_1-C_6$ alkoxy, or phenyl $C_1-C_6$ alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, $C_3-C_6$ cycloalkyl, $C_1-C_6$ alkoxy, piperidinyl $C_1-C_6$ alkyl, morpholinyl $C_1-C_6$ alkyl, piperazinyl $C_1-C_6$ alkyl, OH, SH, $NH_2$, NH(alkyl), N(alkyl)(alkyl), $-O-C_1-C_4$ alkanoyl, $C_1-C_4$ alkyl, $CF_3$, or $OCF_3$, or

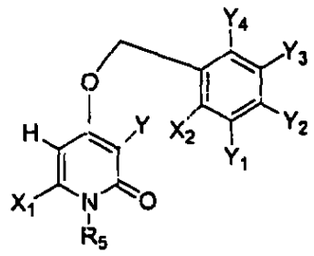
$R_6$, $R_7$, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently $C_1-C_4$ alkyl, $C_1-C_4$ alkoxy, hydroxy, hydroxy $C_1-C_4$ alkyl, $C_1-C_4$ dihydroxyalkyl, or halogen,

R at each occurrence is independently H or $C_1-C_6$ alkyl, and

Y, $Y_1$, $Y_2$, $Y_3$, and $Y_4$ are independently selected from H, halogen, alkyl, carboxaldehyde, hydroxyalkyl, dihydroxyalkyl, alkenyl, alkynyl, CN, alkanoyl, alkoxy, alkoxyalkyl, haloalkyl, and carboxyl

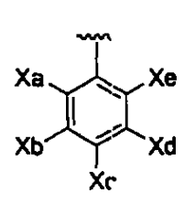
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37 A compound according to claim 36 of the formula

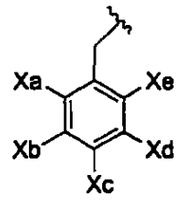


or a pharmaceutically acceptable salt thereof

38 A compound according to claim 37, wherein



$R_5$ is



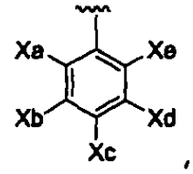
or

39 A compound according to claim 31, wherein

$Y_2$, $Y_4$ and Y are independently halogen, and

$Y_1$ and $Y_3$ are both hydrogen

40 A compound according to claim 39, wherein



$R_5$ is ,

$X_1$ and $X_2$ are independently H, methyl, $NR_6R_7$, -($C_1$-$C_4$ alkyl)-$C(O)NR_6R_7$, $R_6R_7N$-($C_1$-$C_6$ alkyl)-, $-C(O)NR_6R_7$, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ dihydroxyalkyl, or -($C_1$-$C_4$ alkyl)-morpholinyl, and

$X_a$ and $X_e$ are independently halogen, $NH_2$, NH($C_1$-$C_6$ alkyl), N($C_1$-$C_6$ alkyl)($C_1$-$C_6$ alkyl), methyl, or hydrogen

41 A compound according to claim 40, wherein

one of $X_b$ and $X_c$ is hydrogen and the other is $-NR_6R_7$, $R_6R_7N-(C_1-C_6$ alkyl)-, $-C(O)NR_6R_7$, $-SO_2NR_6R_7$, or halogen, where

$R_6$ and $R_7$ are independently at each occurrence H, $C_1-C_6$ alkyl, $C_1-C_6$ alkoxy, $C_1-C_6$ alkoxy $C_1-C_6$ alkyl, $C_1-C_6$ alkoxycarbonyl, OH, $C_1-C_6$ hydroxyalkyl, $C_1-C_6$ dihydroxyalkyl, $-(C_1-C_4)$alkyl-$CO_2$-alkyl, pyridyl $C_1-C_6$ alkyl, $C_1-C_6$ alkanoyl, benzyl, phenyl $C_1-C_6$ alkoxy, or phenyl $C_1-C_6$ alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, $C_3-C_6$ cycloalkyl, $C_1-C_6$ alkoxy, piperidinyl $C_1-C_6$ alkyl, morpholinyl $C_1-C_6$ alkyl, piperazinyl $C_1-C_6$ alkyl, OH, SH, $NH_2$, NH(alkyl), N(alkyl)(alkyl), $-O-C_1-C_4$ alkanoyl, $C_1-C_4$ alkyl, $CF_3$, or $OCF_3$, or

$R_6$, $R_7$, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently $C_1-C_4$ alkyl, $C_1-C_4$ alkoxy, hydroxy, hydroxy $C_1-C_4$ alkyl, $C_1-C_4$ dihydroxyalkyl, or halogen

42 A compound according to claim 41, wherein

$R_6$ and $R_7$ are independently at each occurrence H, $C_1-C_6$ alkyl, $C_1-C_6$ alkoxy, $C_1-C_6$ alkoxy $C_1-C_6$ alkyl, $C_1-C_6$ alkoxycarbonyl, OH, $C_1-C_6$ hydroxyalkyl, $C_1-C_6$ dihydroxyalkyl, $-(C_1-C_4)$alkyl-$CO_2$-alkyl, pyridyl $C_1-C_6$ alkyl, $C_1-C_6$ alkanoyl, benzyl, phenyl $C_1-C_6$ alkoxy, or phenyl $C_1-C_6$ alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, $C_3-C_6$ cycloalkyl, $C_1-C_6$ alkoxy, piperidinyl $C_1-C_6$ alkyl, morpholinyl $C_1-C_6$ alkyl, piperazinyl $C_1-C_6$ alkyl, OH, $NH_2$, NH(alkyl),

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N(alkyl)(alkyl), -O-($C_1$-$C_4$ alkanoyl, $C_1$-$C_4$ alkyl, $CF_3$, or $OCF_3$

43 A compound according to claim 42, wherein

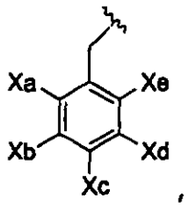
$X_a$ is hydrogen, methyl, fluorine, or chlorine,

$X_c$ and $X_d$ are both hydrogen,

$X_b$ is $-NR_6R_7$, $-(C_1$-$C_4$ alkyl$)-C(O)NR_6R_7$, $R_6R_7N-(C_1$-$C_6$ alkyl$)-$, $-C(O)NR_6R_7$, wherein

$R_6$ and $R_7$ are independently at each occurrence H, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_4$ dihydroxyalkyl, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl or $C_1$-$C_6$ alkanoyl, wherein each of the above is optionally substituted with 1, 2, or 3 groups that are independently OH, SH, halogen or $C_3$-$C_6$ cycloalkyl

44 A compound according to claim 39, wherein

$R_5$ is 

,

$X_a$ is H, fluoro, chloro, or methyl,

$X_e$ is hydrogen, halogen, or methyl, and

$X_b$ is H,

$X_d$ is H or halogen,

45 A compound according to claim 44, wherein

$X_c$ is $-SO_2NR_6R_7$, or halogen, wherein

$R_6$ and $R_7$ are independently at each occurrence H, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxycarbonyl, OH, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ dihydroxyalkyl, $-(C_1$-$C_4)$alkyl-$CO_2$-alkyl, pyridyl $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkanoyl, benzyl, phenyl $C_1$-$C_6$ alkoxy, or

phenyl $C_1$-$C_6$ alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, $C_3$-$C_6$ cycloalkyl, $C_1$-$C_6$ alkoxy, piperidinyl $C_1$-$C_6$ alkyl, morpholinyl $C_1$-$C_6$ alkyl, piperazinyl $C_1$-$C_6$ alkyl, OH, SH, $NH_2$, NH(alkyl), N(alkyl)(alkyl), -O-$C_1$-$C_4$ alkanoyl, $C_1$-$C_4$ alkyl, $CF_3$, or $OCF_3$, or

$R_6$, $R_7$, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, hydroxy, hydroxy $C_1$-$C_4$ alkyl, $C_1$-$C_4$ dihydroxyalkyl, or halogen, or

$X_c$ is fluoro, chloro, $-NH_2$, -NH($C_1$-$C_6$ alkyl), -N($C_1$-$C_6$ alkyl)($C_1$-$C_6$ alkyl), $-SO_2NH_2$, $-SO_2NH(C_1$-$C_6$ alkyl), $-SO_2N(C_1$-$C_6$ alkyl)($C_1$-$C_6$ alkyl), or piperazinyl, wherein the piperazinyl group is optionally substituted with 1 or 2 groups that are independently $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, hydroxy, hydroxy $C_1$-$C_4$ alkyl, $C_1$-$C_4$ dihydroxyalkyl, or halogen

46 A compound according to claim 44, wherein

$X_c$ is $-C(O)NR_6R_7$, -($C_1$-$C_6$ alkyl)-$C(O)NR_6R_7$, $-NR_6R_7$, or $R_6R_7N$-($C_1$-$C_6$ alkyl)-, wherein

$R_6$ and $R_7$ are independently at each occurrence H, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxycarbonyl, OH, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ dihydroxyalkyl, $C_1$-$C_6$ dihydroxyalkyl, -($C_1$-$C_4$)alkyl-$CO_2$-alkyl, pyridyl $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkanoyl, benzyl, phenyl $C_1$-$C_6$ alkoxy, or phenyl $C_1$-$C_6$ alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are

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independently, halogen, $C_3$-$C_6$ cycloalkyl, $C_1$-$C_6$ alkoxy, piperidiryl $C_1$-$C_6$ alkyl, morpholinyl $C_1$-$C_6$ alkyl, piperazinyl $C_1$-$C_6$ alkyl, OH, $-NH_2$, -NH(alkyl), -N(alkyl)(alkyl), $-O-C_1$-$C_4$ alkanoyl, $C_1$-$C_4$ alkyl, $CF_3$, or $OCF_3$, or

$R_6$, $R_7$, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, hydroxy, hydroxy $C_1$-$C_4$ alkyl, $C_1$-$C_4$ dihydroxyalkyl, or halogen

47 A compound according to claim 46, wherein

$R_6$ is hydrogen, and

$R_7$ is $C_1$-$C_6$ alkyl or $C_1$-$C_6$ alkanoyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently $NH_2$, $NH(C_1$-$C_6$ alkyl), $N(C_1$-$C_6$ alkyl)$(C_1$-$C_6$ alkyl), OH, SH, cyclopropyl, or $C_1$-$C_4$ alkoxy,

48 A compound according to claim 47, wherein

$X_c$ is $-C(O)NR_6R_7$

49 A compound according to claim 47, wherein

$X_c$ is $NR_6R_7$, or $R_6R_7N-(C_1$-$C_6$ alkyl)-

50 A compound according to claim 38, wherein

$X_a$ is hydrogen,

two of $X_b$, $X_c$, and $X_d$ are hydrogen and the other is $-C(O)NR_6R_7$ $-(C_1$-$C_6$ alkyl)$-C(O)NR_6R_7$, $-NR_6R_7$, $R_6R_7N-(C_1$-$C_6$ alkyl)- or $-CO_2-(C_1$-$C_6)$alkyl, wherein

$R_6$ and $R_7$ are independently at each occurrence H, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxycarbonyl, OH, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$

dihydroxyalkyl, -($C_1$-$C_4$)alkyl-$CO_2$-alkyl, pyridyl $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkanoyl, benzyl, phenyl $C_1$-$C_6$ alkoxy, or phenyl $C_1$-$C_6$ alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, $C_3$-$C_6$ cycloalkyl, $C_1$-$C_6$ alkoxy, piperidinyl $C_1$-$C_6$ alkyl, morpholinyl $C_1$-$C_6$ alkyl, piperazinyl $C_1$-$C_6$ alkyl, OH, $NH_2$, NH(alkyl), N(alkyl)(alkyl), -O-$C_1$-$C_4$ alkanoyl, $C_1$-$C_4$ alkyl, $CF_3$, or $OCF_3$, or

$R_6$, $R_7$, and the nitrogen to which they are attached form a morpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, hydroxy, hydroxy $C_1$-$C_4$ alkyl, $C_1$-$C_4$ dihydroxyalkyl, or halogen, and

$X_e$ is hydrogen, methyl, $C_1$-$C_2$ alkoxy, or halogen

51 A compound according to claim 50, wherein

$X_b$ is -C(O)$NR_6R_7$ -($C_1$-$C_6$ alkyl)-C(O)$NR_6R_7$, -$NR_6R_7$, or $R_6R_7N$-($C_1$-$C_6$ alkyl)- wherein

$R_6$ is hydrogen or $C_1$-$C_4$ alkyl,

$R_7$ is OH, $C_1$-$C_6$ alkyl or $C_1$-$C_6$ alkanoyl, wherein the alkyl and alkanoyl groups substituted with 1, 2, or 3 groups that are independently $NH_2$, NH($C_1$-$C_6$ alkyl), N($C_1$-$C_6$ alkyl)($C_1$-$C_6$ alkyl), $C_3$-$C_6$ cycloalkyl, OH, or $C_1$-$C_4$ alkoxy

52 A compound according to claim 38, wherein

$X_a$ is halogen or methyl,

$X_b$ is H, -$NR_6R_7$, $R_6R_7N$-($C_1$-$C_6$ alkyl)-, -C(O)$NR_6R_7$, or -$CO_2$-($C_1$-$C_6$)alkyl,

$X_c$ is -$NR_6R_7$, $R_6R_7N$-($C_1$-$C_6$ alkyl)-, -C(O)$NR_6R_7$, halogen, -$CO_2$-($C_1$-$C_6$)alkyl, $NH_2$, NH($C_1$-$C_6$ alkyl), N($C_1$-$C_6$ alkyl)($C_1$-$C_6$ alkyl), -$SO_2NH_2$, -$SO_2$NH($C_1$-$C_6$ alkyl), -$SO_2$N($C_1$-$C_6$ alkyl)($C_1$-$C_6$

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alkyl), or piperazinyl, wherein the piperazinyl group is optionally substituted with 1 or 2 groups that are independently $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, hydroxy, hydroxy $C_1$-$C_4$ alkyl, $C_1$-$C_4$ dihydroxyalkyl, or halogen,

$X_d$ is hydrogen,

$X_e$ is H, methyl, $NH_2$, $NH(C_1$-$C_6$ alkyl) or $N(C_1$-$C_6$ alkyl)($C_1$-$C_6$ alkyl)

53 A compound according to claim 38, wherein

$X_1$, $X_2$, $X_a$, $X_b$, $X_c$, $X_d$, and $X_e$ are independently selected from H, OH, halogen, $CF_3$ alkyl, $OCF_3$, pyridyl, pyridazinyl, pyrimidyl, pyrazinyl, thienyl, furyl, pyrrolyl, piperidinyl, piperazinyl, or $C_3$-$C_7$ cycloalkyl, wherein each of the above is optionally substituted with $-NR_6R_7$, $-C(O)NR_6R_7$, $-(C_1$-$C_4$ alkyl)$-C(O)NR_6R_7$, $R_6R_7N-(C_1$-$C_6$ alkyl)-, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, or halogen

54 A compound according to claim 37, wherein

$R_5$ is a heteroaryl or heteroarylalkyl group, where each heteroaryl is pyrazolyl, imidazolyl, furanyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrazolyl, imidazolyl, dihydroindolyl, dihydroisoindolyl, indolon-2-yl, quinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, dihydroisoquinolinyl or indolyl, each of which is optionally substituted with 1, 2, 3, or 4 groups that are independently $-C(O)NR_6R_7$, $-(C_1$-$C_4$ alkyl)$-C(O)NR_6R_7$, $-NR_6R_7$, hydroxy($C_1$-$C_4$)alkyl, $C_1$-$C_4$ dihydroxyalkyl, hydrogen, hydroxy, halogen, haloalkyl, alkyl, haloalkoxy, $R_6R_7N-(C_1$-$C_6$ alkyl)-, $-CO_2-(C_1$-$C_6$)alkyl, $-N(R)C(O)NR_6R_7$, or $-N(R)C(O)-(C_1$-$C_6$)alkoxy, wherein

$R_6$ and $R_7$ are independently at each occurrence H, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxycarbonyl, OH, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$

dihydroxyalkyl, $C_1$-$C_6$ thiohydroxyalkyl, -($C_1$-$C_4$)alkyl-$CO_2$-alkyl, pyridyl $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkanoyl, benzyl, phenyl $C_1$-$C_6$ alkoxy, or phenyl $C_1$-$C_6$ alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, $C_3$-$C_6$ cycloalkyl, $C_1$-$C_6$ alkoxy, piperidinyl $C_1$-$C_6$ alkyl, morpholinyl $C_1$-$C_6$ alkyl, piperazinyl $C_1$-$C_6$ alkyl, OH SH, $NH_2$, NH(alkyl), N(alkyl)(alkyl), -O-$C_1$-$C_4$ alkanoyl, $C_1$-$C_6$ alkyl, $CF_3$, or OCF

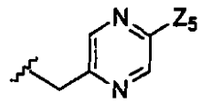
55 A compound according to claim 54, wherein
$Y_2$, $Y_4$, and Y are independently halogen, and
$Y_1$ and $Y_3$ are both hydrogen

56 A compound according to claim 55, wherein
$X_1$ and $X_2$ are independently H, methyl, -$NR_6R_7$, $R_6R_7N$-($C_1$-$C_6$ alkyl)-, -C(O)$NR_6R_7$, -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ dihydroxyalkyl, or -($C_1$-$C_4$ alkyl)-morpholinyl

57 A compound according to claim 56, wherein
$R_5$ is pyridyl $C_1$-$C_6$ alkyl, pyrimidinyl $C_1$-$C_6$ alkyl, or pyrazinyl $C_1$-$C_6$ alkyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently hydroxy($C_1$-$C_4$)alkyl, $C_1$-$C_4$ dihydroxyalkyl, OH, halogen, $CF_3$, ($C_1$-$C_4$)alkyl, $OCF_3$, -$NR_6R_7$, -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$, $R_6R_7N$-($C_1$-$C_6$ alkyl)-, or -C(O)$NR_6R_7$

58 A compound according to claim 57, wherein
$R_5$ is of the formula

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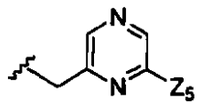
wherein

$Z_5$ is hydroxy($C_1$-$C_4$)alkyl, $C_1$-$C_4$ dihydroxyalkyl, OH, halogen, $CF_3$, ($C_1$-$C_4$)alkyl, $OCF_3$, -$NR_6R_7$, $R_6R_7N$-($C_1$-$C_6$ alkyl)-, -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$, or -C(O)$NR_6R_7$, wherein

$R_6$ and $R_7$ at each occurrence are independently H, $C_1$-$C_6$ alkyl optionally substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkoxycarbonyl, halogen, $C_3$-$C_6$ cycloalkyl, OH, SH, or $C_1$-$C_4$ alkoxy

59 A compound according to claim 57, wherein

$R_5$ is of the formula

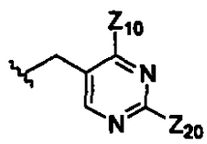


wherein

$Z_5$ is hydroxy($C_1$-$C_4$)alkyl, $C_1$-$C_4$ dihydroxyalkyl, OH, halogen, $CF_3$, ($C_1$-$C_4$)alkyl, $OCF_3$, -$NR_6R_7$, $R_6R_7N$-($C_1$-$C_6$ alkyl)-, -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$, or -C(O)$NR_6R_7$, wherein

$R_6$ and $R_7$ at each occurrence are independently H, $C_1$-$C_6$ alkyl optionally substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkoxycarbonyl, halogen, $C_3$-$C_6$ cycloalkyl, OH, SH, or $C_1$-$C_4$ alkoxy

60 A compound according to claim 57, wherein

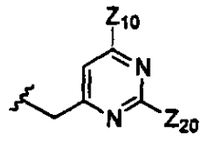
$R_5$ is of the formula  , wherein

$Z_{10}$ is H or methyl, and

$Z_{20}$ is -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$, hydroxy($C_1$-$C_4$)alkyl, $C_1$-$C_4$ dihydroxyalkyl, OH, halogen, $CF_3$, ($C_1$-$C_4$)alkyl, $OCF_3$, -$NR_6R_7$, $R_6R_7N$-($C_1$-$C_6$ alkyl)-, or -C(O)$NR_6R_7$, wherein

$R_6$ and $R_7$ at each occurrence are independently H, $C_1$-$C_6$ alkyl optionally substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkoxycarbonyl, halogen, $C_3$-$C_6$ cycloalkyl, OH, SH, or $C_1$-$C_4$ alkoxy

61 A compound according to claim 57, wherein

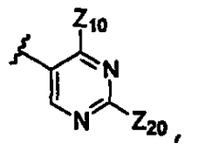
$R_5$ is of the formula  , wherein

$Z_{10}$ is H or methyl, and

$Z_{20}$ is -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$, hydroxy($C_1$-$C_4$)alkyl, $C_1$-$C_4$ dihydroxyalkyl, OH, halogen, $CF_3$, ($C_1$-$C_4$)alkyl, $OCF_3$, -$NR_6R_7$, $R_6R_7N$-($C_1$-$C_6$ alkyl)-, or -C(O)$NR_6R_7$, wherein

$R_6$ and $R_7$ at each occurrence are independently H, $C_1$-$C_6$ alkyl optionally substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkoxycarbonyl, halogen, $C_3$-$C_6$ cycloalkyl, OH, SH, or $C_1$-$C_4$ alkoxy

62 A compound according to claim 57, wherein

$R_5$ is of the formula  , wherein

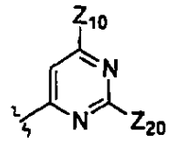
$Z_{10}$ is H or methyl, and

$Z_{20}$ is -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$, hydroxy($C_1$-$C_4$)alkyl, $C_1$-$C_4$ dihydroxyalkyl, OH, halogen, $CF_3$, ($C_1$-$C_4$)alkyl, $OCF_3$, -$NR_6R_7$, $R_6R_7N$-($C_1$-$C_6$ alkyl)-, or -C(O)$NR_6R_7$, wherein

$R_6$ and $R_7$ at each occurrence are independently H, $C_1$-$C_6$ alkyl optionally substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkoxycarbonyl, halogen, $C_3$-$C_6$ cycloalkyl, OH, SH, or $C_1$-$C_4$ alkoxy

63 A compound according to claim 57, wherein

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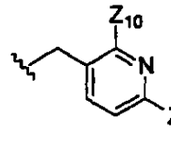
$R_5$ is of the formula  , wherein

$Z_{10}$ is H or methyl, and

$Z_{20}$ is $-(C_1-C_4$ alkyl)$-C(O)NR_6R_7$, hydroxy$(C_1-C_4)$alkyl, $C_1-C_4$ dihydroxyalkyl, OH, halogen, $CF_3$, $(C_1-C_4)$alkyl, $OCF_3$, $-NR_6R_7$, $R_6R_7N-(C_1-C_6$ alkyl$)-$, or $-C(O)NR_6R_7$, wherein

$R_6$ and $R_7$ at each occurrence are independently H, $C_1-C_6$ alkyl optionally substituted with 1, 2, or 3 groups that are independently $C_1-C_4$ alkoxycarbonyl, halogen, $C_3-C_6$ cycloalkyl, OH, SH, or $C_1-C_4$ alkoxy

64 A compound according to claim 57, wherein

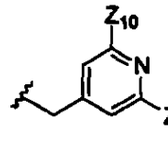
$R_5$ is of the formula  , wherein

$Z_{10}$ is H or methyl, and

$Z_{20}$ is $-(C_1-C_4$ alkyl$)-C(O)NR_6R_7$, hydroxy$(C_1-C_4)$alkyl, $C_1-C_4$ dihydroxyalkyl, OH, halogen, $CF_3$, $(C_1-C_4)$alkyl, $OCF_3$ $-NR_6R_7$, $R_6R_7N-(C_1-C_6$ alkyl$)-$, or $-C(O)NR_6R_7$, wherein

$R_6$ and $R_7$ at each occurrence are independently H, $C_1-C_6$ alkyl optionally substituted with 1, 2, or 3 groups that are independently $C_1-C_4$ alkoxycarbonyl, halogen, $C_3-C_6$ cycloalkyl, OH, SH, or $C_1-C_4$ alkoxy

65 A compound according to claim 57, wherein

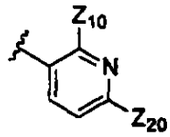
$R_5$ is of the formula  , wherein

$Z_{10}$ is H or methyl, and

$Z_{20}$ is -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$, hydroxy($C_1$-$C_4$)alkyl, $C_1$-$C_4$ dihydroxyalkyl, OH, halogen, $CF_3$, ($C_1$-$C_4$)alkyl, $OCF_3$, -$NR_6R_7$, $R_6R_7N$-($C_1$-$C_6$ alkyl)-, or -C(O)$NR_6R$- wherein

$R_6$ and $R_7$ at each occurrence are independently H, $C_1$-$C_6$ alkyl optionally substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkoxycarbonyl, halogen, $C_3$-$C_6$ cycloalkyl, OH, SH, or $C_1$-$C_4$ alkoxy

66 A compound according to claim 57, wherein

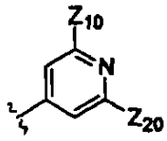
$R_5$ is of the formula  , wherein

$Z_{10}$ is H or methyl, and

$Z_{20}$ is -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$, hydroxy($C_1$-$C_4$)alkyl, $C_1$-$C_4$ dihydroxyalkyl, OH, halogen, $CF_3$, ($C_1$-$C_4$)alkyl, $OCF_3$, -$NR_6R_7$, $R_6R_7N$-($C_1$-$C_6$ alkyl)-, or -C(O)$NR_6R_7$, wherein

$R_6$ and $R_7$ at each occurrence are independently H, $C_1$-$C_6$ alkyl optionally substituted with 1, 2, or 3 groups that are independently $C_1$-$C_4$ alkoxycarbonyl, halogen, $C_3$-$C_6$ cycloalkyl, OH, SH, or $C_1$-$C_4$ alkoxy

67 A compound according to claim 57, wherein

$R_5$ is of the formula  , wherein

$Z_{10}$ is H or methyl, and

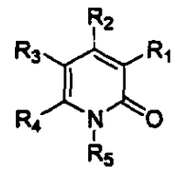
$Z_{20}$ is -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$, hydroxy($C_1$-$C_4$)alkyl, $C_1$-$C_4$ dihydroxyalkyl, OH, halogen, $CF_3$, ($C_1$-$C_4$)alkyl, $OCF_3$, -$NR_6R_7$, $R_6R_7N$-($C_1$-$C_6$ alkyl)-, or -C(O)$NR_6R_7$, wherein

$R_6$ and $R_7$ at each occurrence are independently H, $C_1$-$C_6$ alkyl optionally substituted with 1, 2, or 3 groups

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that are independently $C_1$-$C_4$ alkoxycarbonyl halogen, $C_3$-$C_6$ cycloalkyl, OH, SH, or $C_1$-$C_4$ alkoxy

68 A method of treating a TNF mediated disorder, a p38 kinase mediated disorder, inflammation and/or arthritis in a subject, the method comprising treating a subject having or susceptible to such disorder or condition with a compound of the formula



or a pharmaceutically acceptable salt thereof, wherein

$R_1$ is H, halogen, $NO_2$, alkyl carboxaldehyde, hydroxyalkyl, dihydroxyalkyl, arylalkoxy, arylalkyl, alkenyl, alkynyl, arylalkynyl, -CN, aryl, alkanoyl, alkoxy, alkoxyalkyl, haloalkyl, haloalkoxy, carboxyl, or arylalkanoyl,

wherein the aryl portion of arylalkoxy, arylalkyl and arylalkanoyl is unsubstituted or substituted with 1, 2 3, 4, or 5 groups that are independently halogen, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, nitro, CN, haloalkyl, haloalkoxy or $CO_2R$,

wherein the alkyl portion of the alkyl, hydroxyalkyl, dihydroxyalkyl, arylalkoxy, arylalkyl, alkanoyl, alkoxy, alkoxyalkyl and arylalkanoyl groups is unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkoxycarbonyl, or $C_3$-$C_7$ cycloalkyl,

$R_2$ is H, OH, halogen, $-OSO_2-(C_1-C_6)$ alkyl, $-OSO_2$-aryl, arylalkoxy, aryloxy, arylthio, arylthioalkoxy, arylalkynyl, alkoxy, aryloxy($C_1$-$C_6$)alkyl, alkyl, alkynyl, $-OC(O)NH(CH_2)_n$aryl, $-OC(O)N(alkyl)(CH_2)_n$aryl, alkoxyalkoxy, dialkylamino, alkyl, alkoxy, aryl, arylalkyl, heteroaryl,

heteroarylalkyl, arylalkenyl, heterocycloalkyl, heterocycloalkylalkyl, alkoxyalkoxy, $NR_8R_9$, dialkylamino, or $CO_2R$, wherein

n is 0, 1, 2, 3, 4, 5 or 6,

each of which groups is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, $-(C_1-C_6)$alkyl-$N(R)-CO_2R_{10}$, haloalkyl, heteroaryl, heteroarylalkyl, $-NR_6R_7$, $R_6R-N-(C_1-C_6$ alkyl)-, $-C(O)NR_6R_7$, $-(C_1-C_4$ alkyl)$-C(O)NR_6R_7$, $-(C_1-C_4$ alkyl)$-NRC(O)NR_{16}R_{17}$, haloalkoxy, alkyl, CN, alkoxy, alkoxycarbonyl, phenyl, $-SO_2$-phenyl wherein the phenyl and $-SO_2$-phenyl groups are optionally substituted with 1, 2, or 3 groups that are independently halogen or $NO_2$, or $-OC(O)NR_6R_7$, wherein

$R_{16}$ and $R_{17}$ are independently H or $C_1-C_6$ alkyl, or

$R_{16}$, $R_{17}$ and the nitrogen to which they are attached form a morpholinyl ring,

$R_6$ and $R_7$ are independently at each occurrence H, alkyl, hydroxyalkyl, dihydroxyalkyl, alkoxy, alkanoyl, arylalkyl, arylalkoxy, alkoxycarbonyl, $-SO_2$-alkyl, OH, alkoxy, alkoxyalkyl, arylalkoxycarbonyl, $-(C_1-C_4)$alkyl-$CO_2$-alkyl, heteroarylalkyl, or arylalkanoyl, wherein each is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, OH, SH, heterocycloalkyl, heterocycloalkylalkyl, $C_3-C_7$ cycloalkyl, alkoxy, $NH_2$, NH(alkyl), N(alkyl)(alkyl), -O-alkanoyl, alkyl, haloalkyl, carboxaldehyde, or haloalkoxy, or

$R_6$, $R_7$, and the nitrogen to which they are attached form a morpholinyl, pyrrolidinyl, thiomorpholinyl, thiomorpholinyl S-oxide,

thiomorpholinyl S,S-dioxide, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently $C_1$-$C_4$ alkyl, alkoxycarbonyl, $C_1$-$C_4$ alkoxy, hydroxyl, hydroxyalkyl, dihydroxyalkyl, or halogen,

R at each occurrence is independently hydrogen or $C_1$-$C_6$ alkyl optionally substituted with optionally substituted with 1 or 2 groups that are independently OH, SH, nalogen, amino, monoalkylamino, dialkylamino or $C_3$-$C_6$ cycloalkyl,

$R_{30}$ is $C_1$-$C_6$ alkyl optionally substituted with 1 or 2 groups that are independently OH, SH, halogen, amino, monoalkylamino, dialkylamino or $C_3$-$C_6$ cycloalkyl,

each $R_8$ is independently hydrogen, alkyl, alkanoyl, arylalkyl and arylalkanoyl, wherein each of the above is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, alkoxy, alkoxycarbonyl, halogen, or haloalkyl,

each $R_9$ is hydrogen, alkyl, alkanoyl, arylalkyl, cycloalkyl, cycloalkylalkyl, alkenyl, heteroaryl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, arylalkanoyl, -$SO_2$-phenyl, and aryl wherein each of the above is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, alkoxy, alkoxycarbonyl, halogen, or haloalkyl,

$R_3$ is H, halogen, alkoxycarbonyl, arylalkoxycarbonyl, aryloxycarbonyl, arylalkyl, -OC(O)NH$(CH_2)_n$aryl, arylalkoxy, -OC(O)N(alkyl)$(CH_2)_n$aryl, aryloxy, arylthio,

thioalkoxy, arylthioalkoxy, alkenyl, $-NR_6R_7$, $NR_6R_7-(C_1-C_6)$alkyl, or alkyl, wherein

the aryl portion of arylalkoxycarbonyl, aryloxycarbonyl, arylalkyl, $-OC(O)NH(CH_2)_n$aryl, arylalkoxy, $-OC(O)N(alkyl)(CH_2)_n$aryl, and arylthioalkoxy, is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, alkoxy, alkyl, haloalkyl, or haloalkoxy,

wherein n is 0, 1, 2, 3, 4, 5, or 6, or

$R_4$ is hydrogen or $R_4$ is alkyl unsubstituted or substituted with one or two groups that are independently $CO_2R$, $-CO_2-(C_1-C_6)$alkyl, $-C(O)NR_6R_7$, $-(C_1-C_4$ alkyl$)-C(O)NR_6R_7$, $-N(R_{30})C(O)NR_{16}R_{17}$, $-N(R_{30})C(O)-(C_1-C_6)$alkoxy, or $-NR_6R_7$, arylalkoxy, arylalkyl, heteroaryl, hydroxyalkyl, dihydroxyalkyl, haloalkyl, $R_6R_7N-(C_1-C_6$ alkyl$)-$, $-NR_6R_7$, alkoxy, carboxaldehyde, $CO_2R$, alkoxyalkyl, or alkoxyalkoxy, wherein the aryl portion of arylalkoxy and arylalkyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, hydroxy, alkoxy, alkyl, $-CO_2-(C_1-C_6)$alkyl, $-CONR_6R_7$, $-NR_6R_7$, $R_6R_7N-(C_1-C_6)$alkyl-, nitro, haloalkyl, or haloalkoxy, and

$R_5$ is H, aryl, arylalkyl, arylthioalkyl, alkyl optionally substituted with 1, 2, or 3 groups that are independently arylalkoxycarbonyl, $-NR_8R_9$, halogen, $-C(O)NR_8R_9$, alkoxycarbonyl, $C_3-C_7$ cycloalkyl, or alkanoyl, alkoxy, alkoxyalkyl optionally substituted with one trimethylsilyl group, amino, alkoxycarbonyl, hydroxyalkyl, dihydroxyalkyl, alkynyl, $-SO_2-$alkyl, alkoxy optionally substituted with one trimethylsilyl group, heterocycloalkylalkyl, cycloalkyl, cycloalkylalkyl, -alkyl-S-aryl, -alkyl-$SO_2$-aryl, heteroarylalkyl, heterocycloalkyl, heteroaryl, or alkenyl optionally substituted with alkoxycarbonyl, wherein

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each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, halogen, alkoxy, hydroxyalkyl, dihydroxyalkyl, arylalkoxy, thioalkoxy, alkoxycarbonyl, arylalkoxycarbonyl, $CO_2R$, CN, OH, hydroxyalkyl, dihydroxyalkyl, amidinooxime, $-NR_6R_7$, $-NR_8R_9$, $R_6R_7N-(C_1-C_6$ alkyl)-, carboxaldehyde, $SO_2$alkyl, $-SO_2H$, $-SO_2NR_6R_7$, alkanoyl wherein the alkyl portion is optionally substituted with OH, halogen or alkoxy, $-C(O)NR_6R_7$, $-(C_1-C_4$ alkyl)$-C(O)NR_6R_7$ amidino, haloalkyl, $-(C_1-C_4$ alkyl)$-NR_{15}C(O)NR_{16}R_{17}$, $-(C_1-C_4$ alkyl)$-NR_{15}C(O)R_{18}$, $-O-CH_2-O$, $-O-CH_2CH_2-O-$, or haloalkoxy, wherein

$R_{15}$ is H or $C_1-C_6$ alkyl,

$R_{18}$ is $C_1-C_6$ alkyl optionally substituted with $-O-(C_2-C_6$ alkanoyl, $C_1-C_6$ hydroxyalkyl, $C_1-C_6$ dihydroxyalkyl, $C_1-C_6$ alkoxy, $C_1-C_6$ alkoxy $C_1-C_6$ alkyl, amino $C_1-C_6$ alkyl, mono or dialkylamino $C_1-C_6$ alkyl

69 A method according to claim 68 for treating or preventing inflammation, arthritis, rheumatoid arthritis, spondylarthropathies, gouty arthritis, osteoarthritis, systemic lupus erthematosus, juvenile arthritis, neuroinflammation, pain, neuropathic pain, fever, pulmonary disorders, lung inflammation, adult respiratory distress syndrome, pulmonary sarcoisosis, asthma, silicosis, chronic pulmonary inflammatory disease, cardiovascular disease, arteriosclerosis, myocardial infarction, thrombosis, congestive heart failure, cardiac reperfusion injury, cardiomyopathy, reperfusion injury, renal reperfusion injury, ischemia including stroke and brain ischemia, brain trauma, brain edema, liver disease and nephritis, gastrointestinal conditions, inflammatory bowel disease, Crohn's disease,

gastritis, irritable bowel syndrome, ulcerative colitis, ulceratiuve diseases, gastric ulcers, ophthalmic diseases, retinitis, retinopathies, uveitis, ocular photopnobia, acute injury to the eye tissue, ophthalmological conditions, corneal graft rejection, ocular neovascularization, retinal neovascularization, neovascularization following injury or infection, diabetic retinopathy, retrolental fibroplasias, neovascular glaucoma, diabetes, diabetic nephropatny, skin-related conditions, psoriasis, eczema, burns, dermatitis, keloid formation, scar tissue formation, argiogenic disorders, viral and bacterial infections, sepsis, septic shock, gram negative sepsis, malaria, meningitis, opportunistic infections, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDS related complex), pneumonia, herpes virus, myalgias due to infection, influenza, endotoxic shock, toxic shock syndrome, autoimmune disease, graft vs host reaction and allograft rejections, treatment of bone resorption diseases, osteoporosis, multiple sclerosis, disorders of the female reproductive system, endometriosis, hemaginomas, infantile hemagionmas, angiofibroma of the nasopharynx, avascular necrosis of bone, benign and malignant tumors/neoplasia, cancer, colorectal cancer, brain cancer, bone cancer, epithelial call-derived neoplasia (epithelial carcinoma), basal cell carcinoma, adenocarcinoma, gastrointestinal cancer, lip cancer, mouth cancer, esophageal cancer, small bowel cancer, stomach cancer, colon cancer, liver cancer, bladder cancer, pancreas cancer, ovarian cancer, cervical cancer, lung cancer, breast cancer, skin cancer, squamus cell and/or basal cell cancers, prostate cancer, renal cell carcinoma, and other known cancers that affect epithelial cells throughout the body, leukemia, lymphoma, systemic lupus erthrematosis (SLE), angiogenesis including neoplasia,

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metastasis, central nervous system disorders, central nervous system disorders having an inflammatory or apoptotic component, Alzheimer's disease, Parkinson's disease, Huntington s disease, amyotrophic lateral sclerosis, spinal cord injury, canine B-cell lymphoma, and peripheral neuropathy

70 A compound according to claim 1, which is

1-benzyl-4-(benzyloxy)-3-bromopyridin-2(1*H*)-one,

3-bromo-1-(4-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-dimethylphenyl)-6-methylpyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-(4-fluorobenzyl)pyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(3-fluorobenzyl)pyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1*H*)-one,

4-bromo-2-(2,6-dichlorophenyl)-5-[(2,4-difluorobenzyl)oxy]pyridazin-3(2*H*)-one,

3-bromo-1-(2,6-dichlorophenyl)-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-bromo-1-(3-fluorobenzyl)-4-[(3-methylbenzyl)oxy]pyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(pyridin-4-ylmethyl)pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo 1-(3-fluorobenzyl)pyridin-2(1*H*)-one,

1-benzyl-4-(benzyloxy)-3-bromo-6-methylpyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2-methoxy-6-methylphenyl)-6-methylpyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2-fluorobenzyl)pyridin-2(1*H*)-one,

3-bromo-4-[(4-fluorobenzyl)oxy]-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1*H*)-one,

3-bromo-1-(2,6-dichlorophenyl)-4-[(4-fluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-(4-methylbenzyl)pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-(4-chlorobenzyl)pyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(3-methoxybenzyl)pyridin-2(1*H*)-one,

4-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]methyl}benzoic acid,

4-(benzyloxy)-3-bromo-1-(2-fluorobenzyl)pyridin-2(1*H*)-one,

3-bromo-1-(2,6-dimethylphenyl)-4-[(4-fluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-[4-(methylthio)benzyl]pyridin-2(1*H*)-one,

1-benzyl-4-(benzyloxy)-3-chloropyridin-2(1*H*)-one,

4-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]methyl}-*N*'-hydroxybenzenecarboximidamide,

methyl 4-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]methyl}benzoate,

3-bromo-4-[(3-chlorobenzyl)oxy]-1-(3-fluorobenzyl)pyridin-2(1*H*)-one,

3-bromo-1-(3-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one,

4-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]methyl}benzonitrile,

4-(benzyloxy)-3-bromo-1-(2,6-dichlorophenyl)-6-methylpyridin-2(1*H*)-one,

3-bromo-4-[(4-fluorobenzyl)oxy]-1-(pyridin-4-ylmethyl)pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-(4-bromobenzyl)pyridin-2(1*H*)-one,

4-{[3-bromo-4-[(4-fluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}benzonitrile,

1-(3-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]-3-iodopyridin-2(1*H*)-one,

4-bromo-2-(2,6-dichlorophenyl)-5-{[2-(hydroxymethyl)benzyl]oxy}pyridazin-3(2*H*)-one,

3-bromo-4-[(4-fluorobenzyl)oxy]-1-(pyridin-3-ylmethyl)pyridin-2(1*H*)-one,

3-bromo-1-(2,4-difluorobenzyl)-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-bromo-4-[(4-fluorobenzyl)oxy]-6-methyl-1-(pyridin-2-ylmethyl)pyridin-2(1*H*)-one, or a pharmaceutically acceptable salt thereof

71 A compound according to claim 1, which is

3-bromo-4-[(4-chlorobenzyl)oxy]-1-(4-fluorobenzyl)pyridin-2(1*H*)-one,

1-benzyl-3-bromo-4-[(4-chlorobenzyl)oxy]pyridin-2(1*H*)-one,

3-bromo-1-(4-chlorobenzyl)-4-[(4-chlorobenzyl)oxy]pyridin-2(1*H*)-one,

3-bromo-4-[(4-chlorobenzyl)oxy]-1-[2-(phenylthio)ethyl]pyridin-2(1*H*)-one,

3-bromo-4-[(4-chlorobenzyl)oxy]-1-(2-phenylethyl)pyridin-2(1*H*)-one,

3-bromo-4-hydroxy-1-(4-hydroxybenzyl)pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-(piperidin-3-ylmethyl)pyridin-2(1*H*)-one hydrochloride,

3-bromo-1-(4-methoxybenzyl)-4-phenoxypyridin-2(1*H*)-one,

1-benzyl-2-oxo-4-phenoxy-1,2-dihydropyridine-3-carbaldehyde,

3-bromo-4-[(4-chlorobenzyl)oxy]-1-(4-methoxybenzyl)pyridin-2(1*H*)-one,

3-bromo-4-[(4-fluorobenzyl)oxy]-1-(3-phenylpropyl)pyridin-2(1*H*)-one,

4-(benzyloxy)-1-[4-(benzyloxy)benzyl]-3-bromopyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-[2-(trifluoromethyl)benzyl]pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-[3-(trifluoromethyl)benzyl]pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-(piperidin-4-ylmethyl)pyridin-2(1*H*)-one hydrochloride,

1-benzyl-4-(benzylthio)-3-bromopyridin-2(1*H*)-one,

1-benzyl-3-bromo-4-{[2-(trifluoromethyl)benzyl]oxy}pyridin-2(1*H*)-one,

1-benzyl-4-[(2,6-dichlorobenzyl)oxy]pyridin-2(1*H*)-one,

1-benzyl-4-(benzyloxy)-3-(hydroxymethyl)pyridin-2(1*H*)-one,

1-benzyl-3-bromo-4-[(2,6-dichlorobenzyl)oxy]pyridin-2(1*H*)-one,

1-benzyl-4-[(3-chlorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

1-benzyl-3-bromo-4-[(3-chlorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

1-benzyl-3-bromo-4-[(2-chlorobenzyl)oxy]pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-ethylpyridin-2(1*H*)-one,

4-(benzyloxy)-1-(4-bromobenzyl)pyridin-2(1*H*)-one,

3-bromo-1-(4-methylbenzyl)-4-[(4-methylbenzyl)oxy]pyridin-2(1*H*)-one,

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methyl 4-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]methyl}benzoate,

4-(benzyloxy)-3-bromo 1-(2-thien-3-ylethyl)pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo 1-(2-thien-2-ylethyl)pyridin-2(1*H*)-one,

1-benzyl-4-[(3-chlorobenzyl)oxy]pyridin-2(1*H*)-one,

3-bromo-1-(4-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one,

4-(benzyloxy)-1-(3-fluorobenzyl)pyridin-2(1*H*)-one,

4-(benzyloxy)-1-(2-fluorobenzyl)pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-methylpyridin-2(1*H*)-one hydrobromide,

4-(benzyloxy)-3-bromo-1-methylpyridin-2(1*H*)-one,

3-bromo-1-(3-chlorobenzyl)-4-[(4-chlorobenzyl)oxy]pyridin-2(1*H*)-one,

3-bromo-1-(3-chlorobenzyl)-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one,

4-(benzyloxy)-1-(4-chlorobenzyl)pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-[4-(trifluoromethoxy)benzyl]pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-(4-tert-butylbenzyl)pyridin-2(1*H*)-one,

1-benzyl-4-(benzyloxy)-6-methylpyridin-2(1*H*)-one,

1-benzyl-4-(benzyloxy)-3,5-dibromo-6-methylpyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-[4-(trifluoromethyl)benzyl]pyridin-2(1*H*)-one,

1-benzyl-4-[(2-chlorobenzyl)oxy]pyridin-2(1*H*)-one,

1-(2-bromobenzyl)-3-[(2-bromobenzyl)oxy]pyridin-2(1*H*)-one,

methyl 5-chloro-1-(4-chlorobenzyl)-6-oxo-1,6-dihydropyridine-3-carboxylate,

3-benzyl-4-hydroxy-1-(2-phenylethyl)pyridin-2(1*H*)-one,

5-bromo-1-(2-chloro-6-fluorobenzyl)-3-methylpyridin-2(1*H*)-one,

1-(2-bromobenzyl)-3-[(2-bromobenzyl)oxy]pyridin-2(1*H*)-one,

1-benzyl-4-(benzyloxy)pyridin-2(1*H*)-one,

1-benzyl-4-(benzyloxy)-3-bromopyridin-2(1*H*)-one,

1-benzyl-4-(benzyloxy)-2-oxo-1,2-dihydropyridine-3-carbaldehyde,

1-benzyl-4-chloro-2-oxo-1,2-dihydropyridine-3-carbaldehyde,

1-benzyl-4-hydroxy-2-oxo-1,2-dihydropyridine-3-carbaldehyde,

1-benzyl-4-(benzyloxy)-3-methylpyridin-2(1*H*)-one,

4-(benzyloxy)-1-(4-fluorobenzyl)pyridin-2(1*H*)-one,

1-benzyl-4-(benzyloxy)-3,5-dibromopyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-[4-(methylthio)benzyl]pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-(4-fluorobenzyl)pyridin-2(1*H*)-one,

1-benzyl-4-(benzyloxy)-3-chloropyridin-2(1*H*)-one,

3-bromo-1-(4-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one,

1-benzyl-3-bromo-2-oxo-1,2-dihydropyridin-4-yl methyl(phenyl)carbamate,

1-benzyl-3-bromo-4-(2-phenylethyl)pyridin-2(1*H*)-one,

1-benzyl-3-bromo-4-(3-phenylpropyl)pyridin-2(1*H*)-one,

1-benzyl-3-methyl-4-(2-phenylethyl)pyridin-2(1*H*)-one,

1-benzyl-3-methyl-4-(3-phenylpropyl)pyridin-2(1*H*)-one,

1-benzyl-4-(benzylthio)-3-methylpyridin-2(1*H*)-one,

1-benzyl-4-(benzylthio)-3-bromopyridin-2(1*H*)-one,

(product) 1-benzyl-2-oxo-1,2-dihydropyridin-4-yl methanesulfonate,

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3-acetyl-4-hydroxy-6-methyl-1-[choro]phenylpyridin-2(1*H*)-one,

6-(benzyloxy)-1-methyl 2-oxo-1,2-dihydropyridine-3-carbonitrile,

3-benzoyl-6-(benzyloxy)-1-methylpyridin-2(1*H*)-one,

3-benzyl-6-(benzyloxy) 1-methylpyridin-2(1*H*)-one,

1-benzyl-4-hydroxypyridin-2(1*H*)-one,

1-benzyl-2-oxo-1,2-dihydropyridin-4-yl methanesulfonate,

1-benzyl-4-(benzylthio)pyridin-2(1*H*)-one

1-benzyl-4-(benzylthio)-3-bromopyridin-2(1*H*)-one,

4-amino-1-benzylpyridin-2(1*H*)-one,

1-benzyl-4-(benzyloxy)pyridin-2(1*H*)-one,

1-benzyl-4-hydroxypyridin-2(1*H*)-one,

1-benzyl-2-oxo-1,2-dihydropyridin-4-yl methyl(phenyl)carbamate,

or a pharmaceutically acceptable thereof

72 A compound according to claim 1, which is

4-(benzyloxy)-1-(4-methylbenzyl)pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromopyridin-2(1*H*)-one,

methyl 4-{[4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl]methyl} benzoate,

methyl-4-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]methyl} benzoate,

4-{[4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl]methyl} benzonitrile,

4-(benzyloxy)-1-(4-*tert*-butylbenzyl)pyridin-2(1*H*)-one,

4-(benzyloxy)-1-[4-(trifluoromethyl)benzyl]pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-[4-(trifluoromethyl) benzyl]pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-[3-(trifluoromethyl) benzyl]pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-[2-(trifluoromethyl) benzyl]pyridin-2(1*H*)-one,

4-(benzyloxy)-1-[4-(trifluoromethoxy)benzyl]pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-[4-(trifluoromethoxy) benzyl]pyridin-2(1*H*)-one,

1-benzyl-4-hydroxy-6-methylpyridin-2(1H)-one,

1-benzyl-6-methyl-2-oxo-1,2-dihydropyridin-4-yl 4-bromobenzenesulfonate,

1-benzyl-3-bromo-4-[(3-chlorobenzyl)oxy]-6-methylpyridin-2(1h)-one,

1-benzyl-6-methyl-2-oxo-1,2-dihydropyridin-4-yl 4-bromobenzenesulfonate,

1-benzyl-3-bromo-4-[(3-chlorobenzyl)oxy]-6-methylpyridin-2(1H)-one,

1-Benzyl-4-[2,6-(dichlorobenzyl]oxy]pyridin-2(1H)-one,

4-[(2,6-dichlororbenzyl)oxy]pyridine-1-oxide,

4-[(2,6-dichlorobenzyl)oxy]pyridine 1-oxide,

1-Benzyl-3-bromo-4-[2,6-(dichlorobenzyl)oxy]pyridin-2(1H)-one,

1-Benzyl-3-bromo-4-[(4-methylbenzyl)oxy]pyridin-2(1H)-one,

1-Benzyl-4-[benzylthio]-3-bromopyridin-2(1H)-one,

1-benzyl-4-(benzyloxy)-3-iodopyridin-2(1H)-one,

1-benzyl-4-(benzyloxy)-3-vinylpyridin-2(1H)-one,

1-benzyl-4-(benzyloxy)-3-ethylpyridin-2(1H)-one,

3-acetyl-4-(benzyloxy)-1-(2-chlorophenyl)-6-methylpyridin-2(1H)-one,

3-acetyl-1-(2-chlorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one,

1-benzyl-3-bromo-4-hydroxypyridin-2(1H)-one,

1-benzyl-3-bromo-2-oxo-1,2-dihydropyridin-4-yl trifluoromethanesulfonate,

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1-benzyl-3-bromo-4-(phenylethynyl)pyridin-2(1H)-one,

3-bromo-1-(3-fluorobenzyl)-6-methyl-4-(2-phenylethyl)pyridin-2(1H)-one,

1-(3-fluorobenzyl)-4-hydroxy-6-methylpyridin-2(1H)-one,

3-bromo-1-(3-fluorobenzyl)-4-hydroxy-6-methylpyridin-2(1H)-one,

3-bromo-1-(3-fluorobenzyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl trifluoromethanesulfonate,

3-bromo-1-(3-fluorobenzyl)-6-methyl-4-(phenylethynyl)pyridin-2(1H)-one,

3-acetyl-1-(2,6-dichlorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one,

1-(2,6-dichlorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one,

4-(benzyloxy)-1-(2,6-dichlorophenyl)-6-methylpyridin-2(1h)-one,

3-bromo-1-(3-fluorobenzyl)-4-(2-phenylethyl)pyridin-2(1h)-one,

3-bromo-1-(3-fluorobenzyl)-4-hydroxypyridin-2(1H)-one,

3-bromo-1-(3-fluorobenzyl)-2-oxo-1,2-dihydropyridin-4-yl trifluoromethanesulfonate,

3-bromo-1-(3-fluorobenzyl)-4-(phenylethynyl)pyridin-2(1H)-one,

4-(benzyloxy)-3-ethynyl-1-(3-fluorobenzyl)pyridin-2(1H)-one,

4-(benzyloxy)-1-(3-fluorobenzyl)-3-iodopyridin-2(1H)-one,

4-(benzyloxy)-1-(3-fluorobenzyl)-3-[(trimethylsilyl)ethynyl]pyridin-2(1H)-one,

4-(benzylamino)-3-bromo-1-(3-fluorobenzyl)pyridin-2(1H)-one,

1-(3-fluorobenzyl)-4-hydroxypyridin-2(1H)-one,

4-(benzylamino)-1-(3-fluorobenzyl)pyridin-2(1H)-one,

or a pharmaceutically acceptable salt thereof

73 A compound according to claim 1, which is

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2-fluorobenzyl)pyridin-2(1*H*)-one,

3-bromo-4-[(4-fluorobenzyl)oxy]-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1*H*)-one,

3-bromo-4-[(4-fluorobenzyl)oxy]-6-methyl-1-(pyridin-4-ylmethyl)pyridin-2(1*H*)-one,

3-bromo-1-(2,6-dichlorophenyl)-4-[(4-fluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(3-methoxybenzyl)pyridin-2(1*H*)-one,

3-bromo-1-(2,6-dimethylphenyl)-4-[(4-fluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-bromo-4-[(3-chlorobenzyl)oxy]-1-(3-fluorobenzyl)pyridin-2(1*H*)-one,

3-bromo-4-[(4-fluorobenzyl)oxy]-1-(pyridin-4-ylmethyl)pyridin-2(1*H*)-one,

3-bromo-1-(3-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one,

4-{[3-bromo-4-[(4-fluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}benzonitrile,

1-(3-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]-3-iodopyridin-2(1*H*)-one,

3-bromo-4-[(4-fluorobenzyl)oxy]-1-(pyridin-3-ylmethyl)pyridin-2(1*H*)-one,

3-bromo-1-(2,4-difluorobenzyl)-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-bromo-4-[(4-fluorobenzyl)oxy]-6-methyl-1-(pyridin-2-ylmethyl)pyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(3-fluorobenzyl)pyridin-2(1*H*)-one,

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3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(pyridin-3-ylmetryl)pyridin-2(1*H*)-one,

3-bromo-1-(2,6-dichlorophenyl)-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-bromo-1-(3-fluorobenzyl)-4-[(3-methylbenzyl)oxy]piperidin-2-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(pyridin-4-ylmethyl)pyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2-methoxy-6-methylphenyl)-6-methylpyridin-2(1*H*)-one,

or a pharmaceutically acceptable salt thereof

74 A compound according to claim 1, which is

1-(1-acetyl-2,3-dihydro-1*H*-indol-5-yl)-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(1-glycoloyl-2,3-dihydro-1*H*-indol-5-yl)-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-indol-5-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[1-(*N*-methylglycyl)-2,3-dihydro-1*H*-indol-5-yl]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-indol-5-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1*H*-indol-5-yl]-6-methylpyridin-2(1*H*)-one,

5-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]indoline-1-carboxamide,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[1-(methylsulfonyl)-2,3-dihydro-1*H*-indol-5-yl]pyridin-2(1*H*)-one,

1-(1-acetyl-1*H*-indol-5-yl)-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(1-glycoloyl-1*H*-indol-5-yl)-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(2-hydroxy-2-methylpropanoyl)-1*H*-indol-5-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[1-(*N*-methylglycyl)-1*H*-indol-5-yl]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(3-hydroxypropanoyl)-1*H*-indol-5-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(3-hydroxy-3-methylbutanoyl)-1*H*-indol-5-yl]-6-methylpyridin-2(1*H*)-one,

5-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-1*H*-indole-1-carboxamide,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[1-(methylsulfonyl)-1*H*-indol-5-yl]pyridin-2(1*H*)-one,

1-(2-acetyl-2,3-dihydro-1*H*-isoindol-5-yl)-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(2-glycoloyl-2,3-dihydro-1*H*-isoindol-5-yl)-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[2-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-isoindol-5-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[2-(*N*-methylglycyl)-2,3-dihydro-1*H*-isoindol-5-yl]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[2-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-isoindol-5-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[2-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1*H*-isoindol-5-yl]-6-methylpyridin-2(1*H*)-one,

5-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-

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oxopyridin-1(2*H*)-yl]-1,3-dihydro-2*H*-isoindole-2-carboxamide,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[2-(methylsulfonyl)-2,3-dihydro-1*H*-isoindol-5-yl]pyridin-2(1*H*)-one,

1-(2-acetyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(2-glycoloyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-6-methylpyridin-2(1*H*)-one

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[2-(2-hydroxy-2-methylpropanoyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[2-(*N*-methylglycyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[2-(3-hydroxypropanoyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[2-(3-hydroxy-3-methylbutanoyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-6-methylpyridin-2(1*H*)-one,

6-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-3,4-dihydroisoquinoline-2(1*H*)-carboxamide,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[2-(methylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]pyridin-2(1*H*)-one,

1-(2-acetyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(2-glycoloyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[2-(2-hydroxy-2-methylpropanoyl)-1,2,3,4-tetrahydroisoquinolin-7-yl]-6-

methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[2-(*N*-methylglycyl)-1,2,3,4-tetrahydroisoquinolin-7-yl]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[2-(3-hydroxypropanoyl)-1,2,3,4-tetrahydroisoquinolin-7-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[2-(3-hydroxy-3-methylbutanoyl)-1,2,3,4-tetrahydroisoquinolin-7-yl]-6-methylpyridin-2(1*H*)-one,

7-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-3,4-dihydroisoquinoline-2(1*H*)-carboxamide,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[2-(methylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-7-yl]pyridin-2(1*H*)-one,

1-(1-acetyl-1*H*-benzimidazol-5-yl)-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(1-glycoloyl-1*H*-benzimidazol-5-yl)-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(2-hydroxy-2-methylpropanoyl)-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[1-(*N*-methylglycyl)-1*H*-benzimidazol-5-yl]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(3-hydroxypropanoyl)-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(3-hydroxy-3-methylbutanoyl)-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

5-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-

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500

oxopyridin-1(2*H*)-yl]-1*H*-benzimidazole-1-carboxamide,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[1-(methylsulfonyl)-1*H*-benzimidazol-5-yl]pyridin-2(1*H*)-one,

3-chloro-1-(1,3-diacetyl-2,3-dihydro-1*H*-benzimidazol-5-yl)-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

1-(3-acetyl-1-glycoloyl-2,3-dihydro-1*H*-benzimidazol-5-yl)-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

1-[3-acetyl-1-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

1-[3-acetyl-1-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

1-[3-acetyl-1-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

1-[3-acetyl-1-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-acetyl-5-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

1-(1-acetyl-3-glycoloyl-2,3-dihydro-1*H*-benzimidazol-5-yl)-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2 4-difluorobenzyl)oxy]-1-(1,3-diglycoloyl-2,3-dihydro-1*H*-benzimidazol-5-yl)-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[3-glycoloyl-1-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[3-glycoloyl-1-(*N*-

methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[3-glycoloyl-1-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

5-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-3-glycoloyl-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[3-glycoloyl-1-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[3-glycoloyl-1-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

1-[1-acetyl-3-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-glycoloyl-3-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

1-[1,3-bis(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[3-(2-hydroxy-2-methylpropanoyl)-1-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[3-(2-hydroxy-2-methylpropanoyl)-1-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(3-hydroxy-3-methylbutanoyl)-3-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

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501

5-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-3-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[3-(2-hydroxy-2-methylpropanoyl)-1-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

1-[1-acetyl-3-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-glycoloyl-3-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(2-hydroxy-2-methylpropanoyl)-3-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

1-[1,3-bis(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(3-hydroxypropanoyl)-3-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(3-hydroxy-3-methylbutanoyl)-3-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

5-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-3-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[3-(*N*-methylglycyl)-1-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]pyridin-2(1*H*)-one,

1-[1-acetyl-3-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-

methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluoroberzyl)oxy]-1-[1-glycoloyl-3-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(2-hydroxy-2-methylpropanoyl)-3-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[3-(3-hydroxypropanoyl)-1-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

1-[1,3-bis(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(3-hydroxy-3-methylbutanoyl)-3-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

5-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-3-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[3-(3-hydroxypropanoyl)-1-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

1-[1-acetyl-3-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-glycoloyl-3-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[3-(3-hydroxy-3-methylbutanoyl)-1-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[3-(3-hydroxy-3-

methylbutanoyl)-1-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[3-(3-hydroxy-3-methylbutanoyl)-1-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

1-[1,3-bis(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

5-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-3-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[3-(3-hydroxy-3-methylbutanoyl)-1-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

3-acetyl-6-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

6-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-3-glycoloyl-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

6-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-3-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

6-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-3-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

6-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-3-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

6-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-3-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

5-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-1*H*-benzimidazole-1,3(2*H*)-dicarboxamide,

6-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-3-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

1-[1-acetyl-3-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-glycoloyl-3-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(2-hydroxy-2-methylpropanoyl)-3-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[1-(*N*-methylglycyl)-3-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(3-hydroxypropanoyl)-3-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(3-hydroxy-3-methylbutanoyl)-3-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-6-methylpyridin-2(1*H*)-one,

5-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-3-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

1-[1,3-bis(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

1-[3-acetyl-1-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

1-(1-acetyl-1*H*-pyrrol-3-yl)-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(1-glycoloyl-1*H*-pyrrol-3-yl)-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(2-hydroxy-2-methylpropanoyl)-1*H*-pyrrol-3-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[1-(*N*-methylglycyl)-1*H*-pyrrol-3-yl]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(3-hydroxypropanoyl)-1*H*-pyrrol-3-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(3-hydroxy-3-methylbutanoyl)-1*H*-pyrrol-3-yl]-6-methylpyridin-2(1*H*)-one,

3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-1*H*-pyrrole-1-carboxamide,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[1-(methylsulfonyl)-1*H*-pyrrol-3-yl]pyridin-2(1*H*)-one,

1-(1-acetyl-1*H*-imidazol-4-yl)-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(1-glycoloyl-1*H*-imidazol-4-yl)-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(2-hydroxy-2-methylpropanoyl)-1*H*-imidazol-4-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[1-(*N*-methylglycyl)-1*H*-imidazol-4-yl]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(3-hydroxypropanoyl)-1*H*-imidazol-4-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(3-hydroxy-3-methylbutanoyl)-1*H*-imidazol-4-yl]-6-methylpyridin-2(1*H*)-one,

4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-1*H*-imidazole-1-carboxamide,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[1-(methylsulfonyl)-1*H*-imidazol-4-yl]pyridin-2(1*H*)-one,

1-(1-acetyl-1*H*-pyrazol-4-yl)-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(1-glycoloyl-1*H*-pyrazol-4-yl)-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(2-hydroxy-2-methylpropanoyl)-1*H*-pyrazol-4-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[1-(*N*-methylglycyl)-1*H*-pyrazol-4-yl]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(3-hydroxypropanoyl)-1*H*-pyrazol-4-yl]-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[1-(3-hydroxy-3-methylbutanoyl)-1*H*-pyrazol-4-yl]-6-methylpyridin-2(1*H*)-one,

4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-1*H*-pyrazole-1-carboxamide,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[1-(methylsulfonyl)-1*H*-pyrazol-4-yl]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-isoquinolin-7-yl-6-methylpyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(isoquinolin-6-ylmethyl)pyridin-2(1*H*)-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1,3-dihydro-2*H*-indol-2-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(2,3-dihydro-1*H*-indol-5-ylmethyl)pyridin-2(1*H*)-one,

1-[(1-acetyl-2,3-dihydro-1*H*-indol-5-yl)methyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[(1-glycoloyl-2,3-dihydro-1*H*-indol-5-yl)methyl]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-indol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(*N*-

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methylglycyl)-2,3-dihydro-1*H*-indol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-indol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1*H*-indol-5-yl]methyl}pyridin-2(1*H*)-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}indoline-1-carboxamide,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(methylsulfonyl)-2,3-dihydro-1*H*-indol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(2,3-dihydro-1*H*-isoindol-5-ylmethyl)pyridin-2(1*H*)-one,

1-[(2-acetyl-2,3-dihydro-1*H*-isoindol-5-yl)methyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[(2-glycoloyl-2,3-dihydro-1*H*-isoindol-5-yl)methyl]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[2-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-isoindol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[2-(*N*-methylglycyl)-2,3-dihydro-1*H*-isoindol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[2-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-isoindol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[2-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1*H*-isoindol-5-yl]methyl}pyridin-2(1*H*)-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-

1(2*H*)-yl]methyl}-1,3-dihydro-2*H*-isoindole-2-carboxamide,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[2-(methylsulfonyl)-2,3-dihydro-1*H*-isoindol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(1,2,3,4-tetrahydroisoquinolin-6-ylmethyl)pyridin-2(1*H*)-one,

1-[(2-acetyl-1,2,3,4-tetrahydroisoquinolin-6-yl)methyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[(2-glycoloyl-1,2,3,4-tetrahydroisoquinolin-6-yl)methyl]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[2-(2-hydroxy-2-methylpropanoyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[2-(*N*-methylglycyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[2-(3-hydroxypropanoyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[2-(3-hydroxy-3-methylbutanoyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]methyl}pyridin-2(1*H*)-one,

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3,4-dihydroisoquinoline-2(1*H*)-carboxamide,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[2-(methylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(1,2,3,4-tetrahydroisoquinolin-5-ylmethyl)pyridin-2(1*H*)-one,

1-[(2-acetyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[(2-glycoloyl-

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1,2,3,4-tetrahydroisoquinolin-5-yl)methyl]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[2-(2-hydroxy-2-methylpropanoyl)-1,2,3,4-tetrahydroisoquinolin-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[2-(*N*-methylglycyl)-1,2,3,4-tetrahydroisoquinolin-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[2-(3-hydroxypropanoyl)-1,2,3,4-tetrahydroisoquinolin-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[2-(3-hydroxy-3-methylbutanoyl)-1,2,3,4-tetrahydroisoquinolin-5-yl]methyl}pyridin-2(1*H*)-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3,4-dihydroisoquinoline-2(1*H*)-carboxamide,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[2-(methylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(2,3-dihydro-1*H*-benzimidazol-5-ylmethyl)pyridin-2(1*H*)-one,

1-[(1-acetyl-2,3-dihydro-1*H*-benzimidazol-5-yl)methyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[(1-glycoloyl-2,3-dihydro-1*H*-benzimidazol-5-yl)methyl]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-

yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

1-[(3-acetyl-2,3-dihydro-1*H*-benzimidazol-5-yl)methyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-chloro-1-[(1,3-diacetyl-2,3-dihydro-1*H*-benzimidazol-5-yl)methyl]-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one,

1-[(3-acetyl-1-glycoloyl-2,3-dihydro-1*H*-benzimidazol-5-yl)methyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one,

1-{[3-acetyl-1-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one,

1-{[3-acetyl-1-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one,

1-{[3-acetyl-1-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one,

1-{[3-acetyl-1-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-acetyl-5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

1-{[3-acetyl-1-(methylsulfonyl)-2,3-dihydro-1*H*-

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benzimidazol-5-yl]methyl}-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[(3-glycoloyl-2,3-dihydro-1*H*-benzimidazol-5-yl)methyl]pyridin-2(1*H*)-one,

1-[(1-acetyl-3-glycoloyl-2,3-dihydro-1*H*-benzimidazol-5-yl)methyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[(1,3-diglycoloyl-2,3-dihydro-1*H*-benzimidazol-5-yl)methyl]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-glycoloyl-1-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-glycoloyl-1-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-glycoloyl-1-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-glycoloyl-1-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-glycoloyl-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-glycoloyl-1-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

1-{[1-acetyl-3-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}-3-chloro-4-[(2,4-

difluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-glycoloyl-3-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

1-{[1,3-bis(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-(2-hydroxy-2-methylpropanoyl)-1-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-(2-hydroxy-2-methylpropanoyl)-1-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(3-hydroxy-3-methylbutanoyl)-3-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-(2-hydroxy-2-methylpropanoyl)-1-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

1-{[1-acetyl-3-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-glycoloyl-3-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(2-hydroxy-2-

methylpropanoyl)-3-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

1-{[1,3-bis(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(3-hydroxypropanoyl)-3-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(3-hydroxy-3-methylbutanoyl)-3-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-(*N*-methylglycyl)-1-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

1-{[1-acetyl-3-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-glycoloyl-3-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(2-hydroxy-2-methylpropanoyl)-3-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-(3-hydroxypropanoyl)-1-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

1-{[1,3-bis(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(3-hydroxy-3-methylbutanoyl)-3-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(3-hydroxypropanoyl)-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-(3-hydroxypropanoyl)-1-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

1-{[1-acetyl-3-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-glycoloyl-3-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-(3-hydroxy-3-methylbutanoyl)-1-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-(3-hydroxy-3-methylbutanoyl)-1-(*N*-methylglycyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-(3-hydroxy-3-methylbutanoyl)-1-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-

1H-benzimidazole-1-carboxamide,

1-{[1,3-bis(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1H)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-(3-hydroxy-3-methylbutanoyl)-1-(3-hydroxypropanoyl)-2,3-dihydro- H-benzimidazol-5-yl]methyl}pyridin-2(1H)-one,

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]methyl}-2,3-dihydro-1H-benzimidazole-1-carboxamide,

3-acetyl-6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]methyl}-2,3-dihydro-1H-benzimidazole-1-carboxamide

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]methyl}-3-glycoloyl-2,3-dihydro-1H-benzimidazole-1-carboxamide,

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]methyl}-3-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1H-benzimidazole-1-carboxamide,

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]methyl}-3-(N-methylglycyl)-2,3-dihydro-1H-benzimidazole-1-carboxamide,

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]methyl}-3-(3-hydroxypropanoyl)-2,3-dihydro-1H-benzimidazole-1-carboxamide,

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]methyl}-3-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1H-benzimidazole-1-carboxamide,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]methyl}-1H-benzimidazole-1,3(2H)-dicarboxamide,

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]methyl}-3-(methylsulfonyl)-2,3-dihydro-1H-benzimidazole-1-carboxamide,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[3-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

1-{[1-acetyl-3-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-glycoloyl-3-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(2-hydroxy-2-methylpropanoyl)-3-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(*N*-methylglycyl)-3-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(3-hydroxypropanoyl)-3-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[1-(3-hydroxy-3-methylbutanoyl)-3-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}pyridin-2(1*H*)-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

1-{[1,3-bis(methylsulfonyl)-2,3-dihydro-1*H*-benzimidazol-5-yl]methyl}-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1,3-dihydro-2*H*-benzimidazol-2-one,

1-acetyl-5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-

1(2*H*)-yl]methyl}-1-glycoloyl-1,3-dinydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(2-hydroxy-2-metnylpropanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(*N*-methylglycyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4 difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(3-hydroxypropanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4 difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(3-hydroxy-3-methylbutanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(methylsulfonyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

1-acetyl-6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1,3-dihydro-2*H*-benzimidazol-2-one,

1,3-diacetyl-5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1,3-dihydro-2*H*-benzimidazol-2-one,

3-acetyl-5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-glycoloyl-1,3-dihydro-2*H*-benzimidazol-2-one,

3-acetyl-5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(2-hydroxy-2-methylpropanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

3-acetyl-5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(*N*-methylglycyl)-1,3-dihydro-2*H*-

benzimidazol-2-one,

3-acetyl-5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(3-hydroxypropanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

3-acetyl-5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(3-hydroxy-3-methylbutanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

3-acetyl-5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

3-acetyl-5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(methylsulfonyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-glycoloyl-1,3-dihydro-2*H*-benzimidazol-2-one,

1-acetyl-5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-glycoloyl-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1,3-diglycoloyl-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-glycoloyl-1-(2-hydroxy-2-methylpropanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-glycoloyl-1-(*N*-methylglycyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-glycoloyl-1-(3-hydroxypropanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-

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1(2*H*)-yl]methyl}-3-glycoloyl-1-(3-hydroxy-3-methylbutanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-glycoloyl-2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-glycoloyl-1-(methylsulfonyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

6-{[3-chloro-4-[(2,4 difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(2-hydroxy-2-methylpropanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

1-acetyl-5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(2-hydroxy-2-methylpropanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-glycoloyl-3-(2-hydroxy-2-methylpropanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1,3-bis(2-hydroxy-2-methylpropanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(2-hydroxy-2-methylpropanoyl)-1-(*N*-methylglycyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(2-hydroxy-2-methylpropanoyl)-1-(3-hydroxypropanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(3-hydroxy-3-methylbutanoyl)-3-(2-hydroxy-2-methylpropanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(2-hydroxy-2-methylpropanoyl)-2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(2-hydroxy-2-methylpropanoyl)-1-(methylsulfonyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(*N*-methylglycyl)-1,3-dinydro-2*H*-benzimidazol-2-one,

1-acetyl-5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(*N*-methylglycyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-glycoloyl-3-(*N*-methylglycyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(2-hydroxy-2-methylpropanoyl)-3-(*N*-methylglycyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1,3-bis(*N*-methylglycyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(3-hydroxypropanoyl)-3-(*N*-methylglycyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(3-hydroxy-3-methylbutanoyl)-3-(*N*-methylglycyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(*N*-methylglycyl)-2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(*N*-methylglycyl)-1-(methylsulfonyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(3-hydroxypropanoyl)-1,3-dihydro-2*H*-

benzimidazol-2-one,

1-acetyl-5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(3-hydroxypropanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-glycoloyl-3-(3-hydroxypropanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(2-hydroxy-2-methylpropanoyl)-3-(3-hydroxypropanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(3-hydroxypropanoyl)-1-(*N*-methylglycyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1,3-bis(3-hydroxypropanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(3-hydroxy-3-methylbutanoyl)-3-(3-hydroxypropanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(3-hydroxypropanoyl)-2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(3-hydroxypropanoyl)-1-(methylsulfonyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(3-hydroxy-3-methylbutanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

1-acetyl-5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(3-hydroxy-3-methylbutanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-

1(2*H*)-yl]methyl}-1-glycoloyl-3-(3-hydroxy-3-methylbutanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(3-hydroxy-3-methylbutanoyl)-1-(2-hydroxy-2-methylpropanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(3-hydroxy-3-methylbutanoyl)-1-(*N*-methylglycyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(3-hydroxy-3-methylbutanoyl)-1-(3-hydroxypropanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1,3-bis(3-hydroxy-3-methylbutanoyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(3-hydroxy-3-methylbutanoyl)-2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(3-hydroxy-3-methylbutanoyl)-1-(methylsulfonyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

3-acetyl-6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-glycoloyl-2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(2-hydroxy-2-methylpropanoyl)-2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

6-{[3-chloro-4-[(2,4 difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(*N*-methylglycyl)-2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(3-hydroxypropanoyl)-2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(3-hydroxy-3-methylbutanoyl)-2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-2-oxo-1*H* benzimidazole-1,3(2*H*)-dicarboxamide,

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(methylsulfonyl)-2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

6-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(methylsulfonyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

1-acetyl-5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(methylsulfonyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-glycoloyl-3-(methylsulfonyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4 difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(2-hydroxy-2-methylpropanoyl)-3-(methylsulfonyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(*N*-methylglycyl)-3-(methylsulfonyl)-1,3-dihydro-2*H*-benzimidazol-2 one,

5-{[3-chloro-4-[(2,4 difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(3-hydroxypropanoyl)-3-(methylsulfonyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1-(3-hydroxy-3-methylbutanoyl)-3-(methylsulfonyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-3-(methylsulfonyl)-2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}-1,3-bis(methylsulfonyl)-1,3-dihydro-2*H*-benzimidazol-2-one,

3-benzyl-4-hydroxy-1-(2-phenylethyl)pyridin-2(1*H*)-one,

1-benzyl-4-hydroxy-2-oxo-1,2-dihydropyridine-3-carbaldehyde,

1-benzyl-4-chloro-2-oxo-1,2-dihydropyridine-3-carbaldehyde,

methyl 5-chloro-1-(4-chlorobenzyl)-6-oxo-1,6-dihydropyridine-3-carboxylate,

5-bromo-1-(2-chloro-6-fluorobenzyl)-3-methylpyridin-2(1*H*)-one,

3-bromo-1-(2,6-dichlorophenyl)-4-[(4-fluorophenyl)ethynyl]-6-methylpyridin-2(1*H*)-one,

3-bromo-1-(2,6-dichlorophenyl)-4-[(4-fluorophenyl)ethynyl]-6-methylpyridin-2(1*H*)-one,

methyl 3-chloro-4-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzoate,

4-[(2,4-difluorobenzyl)oxy]-1-(3-fluorobenzyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile,

4-[(2,4-difluorobenzyl)oxy]-6-(hydroxymethyl)-1-(2,4,6-trifluorophenyl)pyridin-2(1*H*)-one,

4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[2-(trifluoromethyl)phenyl]pyridin-2(1*H*)-one,

3-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzaldehyde,

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4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluoro-4-morpholin-4-ylphenyl)-6-methylpyridin-2(1*H*)-one,

4-[(2,4-difluorobenzyl)oxy]-1-[2,6-difluoro-4-(4-methylpiperazin-1-yl)phenyl]-6-methylpyridin-2(1*H*)-one,

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzoic acid,

4-[(2,4-difluorobenzyl)oxy]-1-[4-(dimethylamino)-2,6-difluorophenyl]-6-methylpyridin-2(1*H*)-one,

4-[(2,4-difluorobenzyl)oxy]-1-{2,6-difluoro-4-[(2-hydroxyethyl)(methyl)amino]phenyl}-6-methylpyridin-2(1*H*)-one,

methyl 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzoate,

3-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-4-methylbenzoic acid,

4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-(hydroxymethyl)pyridin-2(1*H*)-one,

3-bromo-1-{[5-(chloromethyl)pyrazin-2-yl]methyl}-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

1-[2-chloro-5-(hydroxymethyl)phenyl]-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluoro-4-hydroxyphenyl)-6-methylpyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[4-(hydroxymethyl)-2-methoxyphenyl]-6-methylpyridin-2(1*H*)-one,

methyl 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-4-methylbenzoate,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-{3-[(4-methylpiperazin-1-yl)carbonyl]phenyl}pyridin-2(1*H*)-one,

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*-[2- dimethylamino)ethyl]benzamide,

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*-(2-methoxyethyl)benzamide,

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*-[2-(dimethylamino)ethyl]-*N*-methylbenzamide,

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*-(2-hydroxyethyl)-*N*-methylbenzamide,

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*-(2-methoxyethyl)-*N*-methylbenzamide,

4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzamide,

methyl 3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-4-fluorobenzoate,

4-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-3-methylbenzoic acid,

1-(4-bromo-2-methylphenyl)-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

1-[(1-acetyl-1*H*-indol-5-yl)methyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[(5-methylpyrazin-2-yl)methyl]pyridin-2(1*H*)-one,

methyl 2-({[3-bromo-1-(2,6-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl]oxy}methyl)-3,5-difluorobenzylcarbamate,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-{[5-(hydroxymethyl)pyrazin-2-yl]methyl}-6-methylpyridin-2(1*H*)-one,

4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}-*N*,*N*-dimethylbenzamide,

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*-(2-hydroxyethyl)-4-methylbenzamide,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-{4-[(4-methylpiperazin-1-yl)carbonyl]benzyl}pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(1*H*-indol-5-ylmethyl)pyridin-2(1*H*)-one,

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*-methylbenzamide,

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzamide,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[5-(hydroxymethyl)pyrazin-2-yl]methyl}-6-methylpyridin-2(1*H*)-one,

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*-(2-methoxyethyl)-4-methylbenzamide,

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*,4-dimethylbenzamide,

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*,*N*,4 trimethylbenzamide,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[2-methyl-5-(morpholin-4-ylcarbonyl)phenyl]pyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[5-(1-hydroxy-1-methylethyl)-2-methylphenyl]-6-methylpyridin-2(1*H*)-one,

1-(2-bromobenzyl)-3-[(2-bromobenzyl)oxy]pyridin-2(1*H*)-one,

1-(2-bromobenzyl)-3-[(2-bromobenzyl)oxy]pyridin-2(1*H*)-one,

3-bromo-1-(4-methoxybenzyl)-4-phenoxypyridin-2(1*H*)-one,

1-benzyl-2-oxo-4-phenoxy-1,2-dihydropyridine-3-carbaldehyde,

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-(3-dimethylaminomethyl-benzyl)-6-methyl-1H-pyridin-2-one,

N-{3-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-benzyl}-2-hydroxy-acetamide,

3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1-[4-(piperidine-1-carbonyl)-benzyl]-1H-pyridin-2-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-[(ethoxyamino)methyl]pyridin-2(1*H*)-one,

4-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-

pyridin-1-ylmethyl]-N-isopropyl-benzamide,

*N*-(3-aminopropyl)-4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}benzamide hydrochloride,

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*,4-dimethylbenzamide,

4-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-N,N-bis-(2-hydroxy-ethyl)-benzamide,

3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1-[4-(pyrrolidine-1-carbonyl)-benzyl]-1H-pyridin-2-one,

4-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-N-hydroxy-benzamide,

4-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-N-methyl-benzamide,

4-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-N-(2-dimethylamino-ethyl)-benzamide,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(1*H*-indazol-5-ylmethyl)pyridin-2(1*H*)-one,

3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1-[4-(4-methyl-piperazine-1-carbonyl)-benzyl]-1H-pyridin-2-one,

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-4-methylbenzaldehyde,

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-(4-dimethylaminomethyl-benzyl)-6-methyl-1H-pyridin-2-one,

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*-(2-methoxyethyl)-4-methylbenzamide,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[2-(dimethylamino)-4,6-difluorophenyl]-6-methylpyridin-2(1*H*)-one hydrochloride,

*N*-(2-aminoethyl)-4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}benzamide hydrochloride,

4-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-N-(2-hydroxy-ethyl)-benzamide,

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-(4-hydroxymethyl-benzyl)-6-methyl-1H-pyridin-2-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[2,6-difluoro-4-(4-methylpiperazin-1-yl)phenyl]-6-methylpyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[2-(dimethylamino)-4,6-difluorophenyl]-6-methylpyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[2,6-difluoro-4-(4-methylpiperazin-1-yl)phenyl]-6-methylpyridin-2(1*H*)-one,

4-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-N-(2-methoxy-ethyl)-benzamide,

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-{4-[(2-hydroxy-ethylamino)-methyl]-benzyl}-6-methyl-1H-pyridin-2-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-[(dimethylamino)methyl]pyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[2-methyl-5-(morpholin-4-ylcarbonyl)phenyl]pyridin-2(1*H*)-one,

3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1-(4-methylaminomethyl-benzyl)-1H-pyridin-2-one,

3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1-[4-(morpholine-4-carbonyl)-benzyl]-1H-pyridin-2-one,

*N*-(2-aminoethyl)-3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzamide,

*N*-(3-aminopropyl)-3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzamide hydrochloride,

4-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-N-(2-methoxy-ethyl)-N-methyl-benzamide,

1-(4-Aminomethyl-benzyl)-3-bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1H-pyridin-2-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[4-(piperazin-1-ylcarbonyl)benzyl]pyridin-2(1*H*)-one hydrochloride,

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-[4-(isopropylamino-

methyl)-benzyl]-6-methyl-1H-pyridin-2-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-dimethylphenyl)-6-methylpyridin-2(1*H*)-one,

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-{3-[(2-hydroxy-ethylamino)-methyl]-benzyl}-6-methyl-1H-pyridin-2-one

1-(3-Aminomethyl-benzyl)-3-bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1H-pyridin-2-one,

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-(4-hydroxy-benzyl)-6-methyl-1H-pyridin-2-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-[(dimethylamino)methyl]pyridin-2(1*H*)-one,

N-{3-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-benzyl}-acetamide,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-{2,6-difluoro-4-[(2-hydroxyethyl)(methyl)amino]phenyl}-6-methylpyridin-2(1*H*)-one,

ethyl 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzoate,

1-[3-(aminomethyl)benzyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one trifluoroacetate,

1-(3-{[Bis-(2-hydroxy-ethyl)-amino]-methyl}-benzyl)-3-bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1H-pyridin-2-one,

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-[3-(isopropylamino-methyl)-benzyl]-6-methyl-1H-pyridin-2-one,

{3-[3-Bromo-4-(2,4-difluoro-benzyloxy)-2-oxo-2H-pyridin-1-ylmethyl]-benzyl}-carbamic acid tert-butyl ester,

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzamide,

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-[4-(1-hydroxy-1-methyl-ethyl)-benzyl]-6-methyl-1H-pyridin-2-one,

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-(3-dimethylaminomethyl-benzyl)-1H-pyridin-2-one,

3-Bromo-4-(2,4-difluoro-berzyloxy)-6-methyl-1-(3-piperidin-1-ylmethyl-benzyl)-1H-pyridin-2-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-{[(2-methoxyethyl)amino]methyl}pyridin-2(1*H*)-one,

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*-methylbenzamide,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-{2,4-difluoro-6-[(2-hydroxyethyl)(methyl)amino]phenyl}-6-methylpyridin-2(1*H*)-one,

3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1-(3-morpholin-4-ylmethyl-benzyl)-1H-pyridin-2-one,

3-bromo-1-(2,6-dimethylphenyl)-6-methyl-4-[(2,4,6-trifluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-bromo-1-(2,6-dimethylphenyl)-6-methyl-4-[(2,4,6-trifluorobenzyl)oxy]pyridin-2(1*H*)-one,

1-(4-{[Bis-(2-hydroxy-ethyl)-amino]-methyl}-benzyl)-3-bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1H-pyridin-2-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluoro-4-morpholin-4-ylphenyl)-6-methylpyridin-2(1*H*)-one,

4-Benzyloxy-3-bromo-1-(4-fluoro-benzyl)-1H-pyridin-2-one,

4-[3-Chloro-4-(2,4-difluoro-benzyloxy)-2-oxo-2H-pyridin-1-ylmethyl]-benzamide,

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*,*N*,4-trimethylbenzamide,

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*-isopropylbenzamide,

4-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-benzamide,

3-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-benzonitrile,

3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1-(3-

piperazin-1-ylmethyl-benzyl)-1H-pyridin-2-one,

4-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-N-(2-hydroxy-ethyl)-N-methyl-benzamide,

methyl 4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-3-chlorobenzoate,

3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1-[3-(morpholine-4-carbonyl)-benzyl]-1H-pyridin-2-one,

3-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-N,N-bis-(2-hydroxy-ethyl)-benzamide,

4-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-benzoic acid methyl ester,

3-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-N-hydroxy-benzamide,

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-(3-hydroxymethyl-benzyl)-6-methyl-1H-pyridin-2-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(3-fluorobenzyl)pyridin-2(1*H*)-one,

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-(3-fluoro-benzyl)-1H-pyridin-2-one,

N-{3-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-benzyl}-methanesulfonamide,

3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1-[3-(pyrrolidine-1-carbonyl)-benzyl]-1H-pyridin-2-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1*H*)-one,

*N*-(3-aminopropyl)-3-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}benzamide hydrochloride,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1*H*)-one,

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-(3-methylaminomethyl-benzyl)-1H-pyridin-2-one,

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4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-3,5-dichlorobenzenesulfonamide,

3-bromo-4-[(2 4-difluorobenzyl)oxy]-1-[4-(dimethylamino)-2,6-difluorophenyl]-6-methylpyridin-2(1*H*)-one,

3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1-(4-piperidin-1-ylmethyl-benzyl)-1H-pyridin-2-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(pyridin-4-ylmethyl)pyridin-2(1*H*)-one

*N*-(2-aminoethyl)-3-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}benzamide hydrochloride

3-bromo-1-[2-chloro-5 (hydroxymethyl)phenyl]-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-methylpyridin-2(1*H*)-one,

3-chloro-1-[2-chloro-5-(hydroxymethyl)phenyl]-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*-(2-hydroxyethyl)-4-methylbenzamide,

2-{3-[3-Bromo-4-(2,4-difluoro-benzyloxy)-2-oxo-2H-pyridin-1-ylmethyl]-phenyl}-acetamide,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[3-(piperazin-1-ylcarbonyl)benzyl]pyridin-2(1*H*)-one hydrochloride,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-methylpyridin-2(1*H*)-one,

4-[3-Bromo-4-(2,4-difluoro-benzyloxy)-2-oxo-2H-pyridin-1-ylmethyl]-benzoic acid methyl ester,

1-(3-Aminomethyl-2-fluoro-benzyl)-3-bromo-4-(2,4-difluoro-benzyloxy)-1H-pyridin-2-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-(morpholin-4-ylmethyl)pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-(4-fluorobenzyl)pyridin-2(1*H*)-

one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(1*H*-indol-5-ylmethyl)pyridin-2(1*H*)-one,

1-[3-(aminomethyl)benzyl]-3-bromo-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one trifluoroacetate,

1-[3-(2-aminoethyl)benzyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one trifluoroacetate,

1-[3-(aminomethyl)benzyl]-3-bromo-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-bromo-1-(2,6-dichlorophenyl)-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*-(2-hydroxyethyl)benzamide,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(pyridin-4-ylmethyl)pyridin-2(1*H*)-one,

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-(4-methoxy-benzyl)-6-methyl-1H-pyridin-2-one,

4-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-N,N-dimethyl-benzamide,

3-bromo-6-methyl-1-(pyridin-4-ylmethyl)-4-[(2,4,6-trifluorobenzyl)oxy]pyridin-2(1*H*)-one,

4-[3-Bromo-4-(2,4-difluoro-benzyloxy)-2-oxo-2H-pyridin-1-ylmethyl]-benzamide,

3-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-N-methyl-benzamide,

{3-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-benzyl}-carbamic acid methyl ester,

3-bromo-4-[(2,6-difluorobenzyl)oxy]-1-(2,6-dimethylphenyl)-6-methylpyridin-2(1*H*)-one,

4-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-benzonitrile,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(pyridin-

4-ylmethyl)pyridin-2(1*H*)-one,

1-benzyl-4-(benzyloxy)-3-bromo-6-methylpyridin-2(1*H*)-one,

1-Benzyl-4-benzyloxy-3-bromo-6-methyl-1H-pyridin-2-one,

1-benzyl-4-(benzyloxy)-3-bromo-6-methylpyridin-2(1*H*)-one,

1-Benzyl-3-bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1H-pyridin-2-one,

{3-[3-Bromo-4-(2,4-difluoro-benzyloxy)-2-oxo-2H-pyridin-1-ylmethyl]-phenyl}-acetonitrile,

3-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-N-(2-hydroxy-ethyl)-benzamide,

3-Chloro-4-(2,4-difluoro-benzyloxy)-1-(3-fluoro-benzyl)-1H-pyridin-2-one,

1-Allyl-3-chloro-4-(2,4-difluoro-benzyloxy)-6-methyl-1H-pyridin-2-one,

3-Chloro-4-(2,4-difluoro-benzyloxy)-1-[4-(isopropylamino-methyl)-benzyl]-1H-pyridin-2-one,

methyl 3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-4-methylbenzoate,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-(hydroxymethyl)-1-(2,4,6-trifluorophenyl)pyridin-2(1*H*)-one,

3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1-(4-piperazin-1-ylmethyl-benzyl)-1H-pyridin-2-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-(hydroxymethyl)pyridin-2(1*H*)-one,

3-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-N,N-dimethyl-benzamide,

3-bromo-1-(3-fluorobenzyl)-4-[(3-methylbenzyl)oxy]pyridin-2(1*H*)-one,

3-Bromo-1-(3-fluoro-benzyl)-4-(3-methyl-benzyloxy)-1H-pyridin-2-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(1,2,3,4-tetrahydroisoquinolin-5-ylmethyl)pyridin-2(1*H*)-one,

3-bromo-1-(3-fluorobenzyl)-4-[(3-methylbenzyl)oxy]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(isoquinolin-5-ylmethyl)pyridin-2(1*H*)-one trifluoroacetate,

3-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-benzamide,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-({5-[(4-methylpiperazin-1-yl)carbonyl]pyrazin-2-yl}methyl)pyridin-2(1*H*)-one trifluoroacetate,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[5-(hydroxymethyl)-2-methylphenyl]-6-methylpyridin-2(1*H*)-one,

1-allyl-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(pyridin-3-ylmethyl)pyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2-methoxy-6-methylphenyl)-6-methylpyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2-methoxy-6-methylphenyl)-6-methylpyridin-2(1*H*)-one,

3-[3-Bromo-4-(2,4-difluoro-benzyloxy)-2-oxo-2H-pyridin-1-ylmethyl]-benzamide,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-(hydroxymethyl)-1-(2 4,6-trifluorophenyl)pyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[2-(trifluoromethyl)phenyl]pyridin-2(1*H*)-one,

4-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-benzoic acid,

3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1-(4-morpholin-4-ylmethyl-benzyl)-1H-pyridin-2-one,

4-(2,4-Difluoro-benzyloxy)-1-(3-fluoro-benzyl)-3-iodo-1H-pyridin-2-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(2,4,6-

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trifluorophenyl)pyridin-2(1*H*)-one,

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*-hydroxybenzamide

3-bromo-1-(2,6-dichlorophenyl)-4-[(2,6-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-(4-Benzyloxy-3-bromo-2-oxo-2H-pyridin-1-ylmethyl)-benzonitrile,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[3-(pyrrolidin-1-ylcarbonyl)phenyl]pyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2-fluorobenzyl)pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-(4-methylbenzyl)pyridin-2(1*H*)-one,

3-{[3-chloro-4-[(2,4-difluorobenzyl)amino]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}benzonitrile,

3-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-N-isopropyl-benzamide,

3-bromo-1-(4-bromo-2,6-difluorophenyl)-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-bromo-4-[(4-fluorobenzyl)oxy]-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1*H*)-one,

3-bromo-4-[(4-fluorobenzyl)oxy]-6-methyl-1-(pyridin-4-ylmethyl)pyridin-2(1*H*)-one,

3-bromo-4-[(4-fluorobenzyl)oxy]-6-methyl-1-(pyridin-4-ylmethyl)pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-(4-chlorobenzyl)pyridin-2(1*H*)-one,

4-Benzyloxy-3-bromo-1-(4-chloro-benzyl)-1H-pyridin-2-one,

3-bromo-1-(4-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-bromo-1-(2,6-dichlorophenyl)-4-[(4-fluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-Bromo-1-(4-fluoro-benzyl)-4-(4-fluoro-benzyloxy)-1H-pyridin-2-one,

methyl 4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzoate,

4-(4-Benzyloxy-3-bromo-2-oxo-2H-pyridin-1-ylmethyl)-benzoic acid,

4-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]methyl}benzoic acid,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(2,4,6-trifluorophenyl)pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-(2-fluorobenzyl)pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-(hydroxymethyl)pyridin-2(1*H*)-one,

*N*-(2-aminoethyl)-4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzamide hydrochloride,

4-Benzyloxy-3-bromo-1-(4-methylsulfanyl-benzyl)-1H-pyridin-2-one,

1-Benzyl-4-benzyloxy-3-chloro-1H-pyridin-2-one,

4-(benzyloxy)-3-bromo-1-[4-(methylthio)benzyl]pyridin-2(1*H*)-one,

1-benzyl-4-(benzyloxy)-3-chloropyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-{[5-(hydroxymethyl)pyrazin-2-yl]methyl}-6-methylpyridin-2(1*H*)-one,

3-bromo-1-(2,6-dimethylphenyl)-4-[(4-fluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-bromo-1-(2,6-dimethylphenyl)-4-[(4-fluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-[3-(isopropylamino-methyl)-benzyl]-1H-pyridin-2-one,

3-[3-Chloro-4-(2,4-difluoro-benzyloxy)-2-oxo-2H-pyridin-1-ylmethyl]-2-fluoro-benzamide,

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5-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}-*N*-(2,3-dihydroxypropyl)pyrazine-2-carboxamide,

{3-[3-Bromo-4-(2,4-difluoro-benzyloxy)-2-oxo-2H-pyridin-1-ylmethyl]-phenyl}-acetic acid ethyl ester,

4-(4-Benzyloxy-3-bromo-2-oxo-2H-pyridin-1-ylmethyl)-N-hydroxy-benzamidine,

4-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]methyl}-*N*'-hydroxybenzenecarboximidamide,

ethyl 5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}pyrazine-2-carboxylate,

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-(3-methoxy-benzyl)-1H-pyridin-2-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[(5-methylpyrazin-2-yl)methyl]pyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(3-methoxybenzyl)pyridin-2(1*H*)-one,

4-(4-Benzyloxy-3-bromo-2-oxo-2H-pyridin-1-ylmethyl)-benzoic acid methyl ester,

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-(4-dimethylaminomethyl-benzyl)-1H-pyridin-2-one,

3-Chloro-4-(2,4-difluoro-benzyloxy)-1-(3-methanesulfonyl-benzyl)-1H-pyridin-2-one,

4-(4-Benzyloxy-3-bromo-2-oxo-2H-pyridin-1-ylmethyl)-benzoic acid methyl ester,

methyl 4-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]methyl}benzoate,

ethyl 5-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}pyrazine-2-carboxylate,

4-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]methyl}benzonitrile,

4-(4-Benzyloxy-3-bromo-2-oxo-2H-pyridin-1-ylmethyl)-

benzonitrile,

{3-[3-Bromo-4-(4-fluoro-benzyloxy)-2-oxo-2H-pyridin-1-ylmethyl]-benzyl}-carbamic acid tert-butylester,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[5-(1-hydroxy-1-methylethyl)-2-methylphenyl]-6-methylpyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-(2,6-dichlorophenyl)-6-methylpyridin-2(1*H*)-one,

1-(3-Aminomethyl-benzyl)-4-benzyloxy-3-bromo-1H-pyridin-2-one,

3-bromo-4-[(4-fluorobenzyl)oxy]-1-(pyridin-4-ylmethyl)pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-(4-bromobenzyl)pyridin-2(1*H*)-one,

4-Benzyloxy-3-bromo-1-(4-bromo-benzyl)-1H-pyridin-2-one,

5-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-oxo-1,6-dihydropyridine-2-carbaldehyde,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{[5-(hydroxymethyl)pyrazin-2-yl]methyl}-6-methylpyridin-2(1*H*)-one,

4-(4-Benzyloxy-3-bromo-2-oxo-2H-pyridin-1-ylmethyl)-benzamide,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[3-(piperazin-1-ylcarbonyl)phenyl]pyridin-2(1*H*)-one hydrochloride,

3-bromo-4-[(2,4-difluorobenzyl)amino]-1-(3-fluorobenzyl)pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[(5-methylpyrazin-2-yl)methyl]pyridin-2(1*H*)-one,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[5-(hydroxymethyl)-2-methylphenyl]-6-methylpyridin-2(1*H*)-one,

3-bromo-1-(3-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-Bromo-1-(3-fluoro-benzyl)-4-(4-fluoro-benzyloxy)-1H-pyridin-2-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[3-(morpholin-4-ylcarbonyl)phenyl]pyridin-2(1*H*)-one,

3-(4-Benzyloxy-3-bromo-2-oxo-2H-pyridin-1-ylmethyl)-benzoic acid methyl ester,

3-bromo-1-(3-fluorobenzyl)-4-{[2-(hydroxymethyl)benzyl]oxy}pyridin-2(1*H*)-one,

3-Bromo-1-(3-fluoro-benzyl)-4-(2-hydroxymethyl-benzyloxy)-1H-pyridin-2-one,

1-Benzo[1,3]dioxol-5-ylmethyl-3-bromo-4-(2,4-difluoro-benzyloxy)-1H-pyridin-2-one,

3-bromo-4-[(2,6-difluorobenzyl)oxy]-6-methyl-1-(pyridin-4-ylmethyl)pyridin-2(1*H*)-one,

3-bromo-4-[(3-chlorobenzyl)oxy]-1-(3-fluorobenzyl)pyridin-2(1*H*)-one,

3-bromo-4-[(3-chlorobenzyl)oxy]-1-(3-fluorobenzyl)pyridin-2(1*H*)-one,

3-Bromo-4-(3-chloro-benzyloxy)-1-(3-fluoro-benzyl)-1H-pyridin-2-one,

4-(benzyloxy)-3-bromo-1-(3-fluorobenzyl)pyridin-2(1*H*)-one,

4-Benzyloxy-3-bromo-1-(3-fluoro-benzyl)-1H-pyridin-2-one,

3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1-[3-(piperidine-1-carbonyl)-benzyl]-1H-pyridin-2-one,

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*,*N*-dimethylbenzamide,

3-[3-Chloro-4-(2,4-difluoro-benzyloxy)-2-oxo-2H-pyridin-1-ylmethyl]-2-fluoro-benzoic acid methyl ester,

1-(3-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]-3-iodopyridin-2(1*H*)-one,

1-(3-Fluoro-benzyl)-4-(4-fluoro-benzyloxy)-3-iodo-1H-pyridin-2-one,

*N*-(3-aminopropyl)-4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-

6-methyl-2-oxopyridin-1(2*H*)-yl]benzamide hydrochloride,

4-{[3-bromo-4-[(4-fluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}benzonitrile,

4-[3-Bromo-4-(4-fluoro-benzyloxy)-2-oxo-2H-pyridin-1-ylmethyl]-benzonitrile,

3-Bromo-1-(3-fluoro-benzyl)-4-(2,3,4-trifluoro-benzyloxy)-1H-pyridin-2-one,

1-benzyl-4-(benzyloxy)-3-bromopyridin-2(1*H*)-one,

5-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}-*N*-(2-hydroxyethyl)-*N*-methylpyrazine-2-carboxamide,

4-(4-Benzyloxy-3-bromo-2-oxo-2H-pyridin-1-ylmethyl)-benzonitrile,

3-bromo-1-(2,4-difluorobenzyl)-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-Bromo-1-(2,4-difluoro-benzyl)-4-(2,4-difluoro-benzyloxy)-1H-pyridin-2-one,

4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*-(2-hydroxyethyl)benzamide,

3-bromo-4-[(4-fluorobenzyl)oxy]-1-(pyridin-3-ylmethyl)pyridin-2(1*H*)-one,

1-Benzyl-4-benzyloxy-3-bromo-1H-pyridin-2-one,

3-bromo-1-(cyclopropylmethyl)-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

1-(4-Aminomethyl-benzyl)-4-benzyloxy-3-bromo-1H-pyridin-2-one,

3-bromo-1-(4-fluorobenzyl)-4-[(4-fluorobenzyl)amino]-6-methylpyridin-2(1*H*)-one,

3-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-benzoic acid methyl ester,

5-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}-*N*,*N*-dimethylpyrazine-2-

carboxamide,

3-bromo-4-[(4-fluorobenzyl)oxy]-6-methyl-1-(pyridin-2-ylmethyl)pyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-dimethylphenyl)-6-methylpyridin-2(1*H*)-one,

3-bromo-1-(2,6-dichlorophenyl)-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

4-(benzyloxy)-1-(4-bromobenzyl)pyridin-2(1*H*)-one,

3-bromo-4-hydroxy-1-(4-hydroxybenzyl)pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-[2-(trifluoromethyl)benzyl]pyridin-2(1*H*)-one,

1-benzyl-4-[(3-chlorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo 1-(piperidin-3-ylmethyl)pyridin-2(1*H*)-one hydrochloride,

1-benzyl-3-bromo-2-oxo-1,2-dihydropyridin-4-yl methyl(phenyl)carbamate,

4-(benzylamino)-1-(3-fluorobenzyl)-6-methyl-3-nitropyridin-2(1*H*)-one,

tert-butyl 4-[3-bromo-1-(3-fluorobenzyl)-2-oxo-1,2-dihydropyridin-4-yl]piperazine-1-carboxylate,

ethyl [4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]acetate,

*N*-[3-bromo-1-(3-fluorobenzyl)-2-oxo-1,2-dihydropyridin-4-yl]benzenesulfonamide,

3-bromo-4-[(4-tert-butylbenzyl)oxy]-1-(3-fluorobenzyl)pyridin-2(1*H*)-one,

*N*-[3-bromo-1-(3-fluorobenzyl)-2-oxo-1,2-dihydropyridin-4-yl]-1-phenylmethanesulfonamide,

1-(biphenyl-2-ylmethyl)-3-bromo-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one,

4-(biphenyl-2-ylmethoxy)-3-bromo-1-(3-

fluorobenzyl)pyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorophenyl)amino]-1-(3-fluorobenzyl)pyridin-2(1*H*)-one,

4-anilino-3-bromo-1-(3-fluorobenzyl)pyridin-2(1*H*)-one,

methyl 4-{[3-bromo-1-(3-fluorobenzyl)-2-oxo-1,2-dihydropyridin-4-yl]amino}benzoate,

3-bromo-1-(3-fluorobenzyl)-4-[(3,4,5-trimethoxyphenyl)amino]pyridin-2(1*H*)-one,

3-bromo-1-(3-fluorobenzyl)-4-[4-(4-fluorophenyl)piperazin-1-yl]pyridin-2(1*H*)-one,

3-bromo-1-(3-fluorobenzyl)-4-(4-methylpiperazin-1-yl)pyridin-2(1*H*)-one trifluoroacetate,

*N*-[3-bromo-1-(3-fluorobenzyl)-2-oxo-1,2-dihydropyridin-4-yl]-2,5-difluorobenzamide,

*N*-[3-bromo-1-(3-fluorobenzyl)-2-oxo-1,2-dihydropyridin-4-yl]-2,4-difluorobenzamide,

3-bromo-1-(cyclohexylmethyl)-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]propanoic acid,

*N*-[3-bromo-1-(3-fluorobenzyl)-2-oxo-1,2-dihydropyridin-4-yl]-*N'*-(2,4-difluorophenyl)urea,

3-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]propanamide,

4-(benzyloxy)-3-bromo-1-(3-morpholin-4-yl-3-oxopropyl)pyridin-2(1*H*)-one,

*N*-(3-aminopropyl)-3-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]propanamide hydrochloride,

4-(benzyloxy)-3-bromo-1-(3-oxo-3-piperazin-1-ylpropyl)pyridin-2(1*H*)-one hydrochloride,

4-(benzyloxy)-3-bromo-1-(2-morpholin-4-ylethyl)pyridin-2(1*H*)-one,

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3-bromo-1-(3-fluorobenzyl)-4-{[4-fluoro-2-(trifluoromethyl)benzyl]amino}pyridin-2(1*H*)-one,

*N*-(2-aminoethyl)-3-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]propanamide hydrochloride,

[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]acetic acid,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(tetrahydrofuran-2-ylmethyl)pyridin-2(1*H*)-one,

4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(tetrahydrofuran-2-ylmethyl)pyridin-2(1*H*)-one,

methyl 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridine-1(2*H*)-carboxylate,

1-allyl-3-(2,4-difluorobenzyl)-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

4-(benzyloxy)-1-(2,2-diethoxyethyl)pyridin-2(1*H*)-one,

methyl *N*-acetyl-3-[4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl]alaninate,

benzyl *N*-acetyl-3-[4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl]alaninate,

benzyl *N*-[(benzyloxy)carbonyl]-3-[4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl]alaninate,

4-(benzyloxy)-1-(2-oxopropyl)pyridin-2(1*H*)-one,

5-{[4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl]methyl}-5-methylimidazolidine-2,4-dione,

ethyl [4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl]acetate,

2-[4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl]acetamide,

1-benzyl-4-(benzyloxy)-3,5-dibromopyridin-2(1*H*)-one,

4-(benzyloxy)-1-ethylpyridin-2(1*H*)-one,

4-(benzyloxy)-1-(4-tert-butylbenzyl)pyridin-2(1*H*)-one,

4-{[4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl]methyl}benzonitrile,

tert-butyl 3-{[4-(benzyloxy)-2-oxopyridin-1(2*H*)-

yl]methyl}piperidine-1-carboxylate,

1,3-dibenzyl-4-hydroxy-6-methylpyridin-2(1*H*)-one,

1-benzyl-6-methyl-2-oxo-1,2-dihydropyridin-4-yl methanesulfonate,

4-(benzyloxy)-1-(4-bromobenzyl)pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromopyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-[2-(trifluoromethyl)benzyl]pyridin-2(1*H*)-one,

1-benzyl-4-(1-naphthylmethoxy)pyridin-2(1*H*)-one,

1-benzyl-4-(benzylthio)-3,5-dibromopyridin-2(1*H*)-one,

1-benzyl-4-[(2,6-dichlorobenzyl)oxy]pyridin-2(1*H*)-one,

1-benzyl-3-[(benzylamino)methyl]-4-(benzyloxy)pyridin-2(1*H*)-one,

1-benzyl-4-(benzyloxy)-3-{[(2-cyclohexylethyl)amino]methyl}pyridin-2(1*H*)-one,

1-benzyl-4-(benzylthio)-5-methylpyridin-2(1*H*)-one,

1-benzyl-3-bromo-6-methyl-2-oxo-1,2-dihydropyridin-4-yl methanesulfonate,

1-benzyl-3-bromo-6-methyl-4-{[2-(trifluoromethyl)benzyl]oxy}pyridin-2(1*H*)-one,

1-benzyl-6-methyl-2-oxo-1,2-dihydropyridin-4-yl 4-bromobenzenesulfonate,

1-benzyl-4-[(3-chlorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

1-benzyl-3-bromo-6-methyl-2-oxo-1,2-dihydropyridin-4-yl 4-bromobenzenesulfonate,

4-phenoxy-1-{[2-(trimethylsilyl)ethoxy]methyl}pyridin-2(1*H*)-one,

1-benzyl-4-phenoxypyridin-2(1*H*)-one,

1-(4-methoxybenzyl)-4-phenoxypyridin-2(1*H*)-one,

3-bromo-4-hydroxy-1-(4-hydroxybenzyl)pyridin-2(1*H*)-one hydrochloride,

4-(benzyloxy)-3-bromo-1-(piperidin-3-ylmethyl)pyridin-2(1*H*)-one,

1-benzyl-4-[(2,6-dichlorobenzyl)oxy]pyridin-2(1*H*)-one,

1-benzyl-4-(benzyloxy)-3,5-dibromopyridin-2(1*H*)-one

3-bromo-1-(3-fluorobenzyl)-4-[(*E*)-2-(4-fluorophenyl)vinyl]pyridin-2(1*H*)-one,

1-benzyl-4-(benzyloxy)-2-oxo-1,2-dihydropyridine-3-carbaldehyde,

1-benzyl-4-(benzyloxy)pyridin-2(1*H*)-one,

1-benzyl-4-(benzyloxy)pyridin-2(1*H*)-one,

1-benzyl-4-(benzylthio)pyridin-2(1*H*)-one,

methyl 4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]benzoate,

benzyl (5-nitro-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl)acetate,

ethyl 3-bromo-4-[(2,4 difluorobenzyl)oxy]-6-methyl-2-oxo-2*H*-1,2'-bipyridine-5'-carboxylate,

4-(benzyloxy)-1-(4-methylbenzyl)pyridin-2(1*H*)-one,

[5-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-2-methyl-6-oxo-1,6-dihydropyridin-3-yl]methyl carbamate,

4-(benzyloxy)-1-(4-chlorobenzyl)pyridin-2(1*H*)-one,

methyl (2*E*)-4-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]but-2-enoate,

4-(benzyloxy)-1-(2-fluorobenzyl)pyridin-2(1*H*)-one,

*tert*-butyl 4-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]methyl}piperidine-1-carboxylate,

4-(benzyloxy)-1-(3-fluorobenzyl)pyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-5-(1,2-dihydroxyethyl)-6-methylpyridin-2(1*H*)-one,

1-benzyl-4-hydroxy-6-methylpyridin-2(1*H*)-one,

4-({[3-bromo-1-(3-fluorobenzyl)-2-oxo-1,2-dihydropyridin-4-yl]oxy}methyl)benzonitrile,

1-benzyl-4-(benzyloxy)-6-methylpyridin-2(1*H*)-one,

5-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-2-methyl-6-oxo-1,6-dihydropyridine-3-carbaldehyde oxime,

1-benzyl-4-(benzylthio)-3-methylpyridin-2(1*H*)-one,

1-benzyl-4-[(4-methylbenzyl)oxy]pyridin-2(1*H*)-one,

1-benzyl-4-(benzyloxy)-3,5-dibromo-6-methylpyridin-2(1*H*)-one,

1-benzyl-4-(benzyloxy)-3,5-dibromo-6-methylpyridin-2(1*H*)-one,

3-bromo-1-(3-fluorobenzyl)-4-(1-phenylethoxy)pyridin-2(1*H*)-one,

4-(benzyloxy)-1-[4-(trifluoromethyl)benzyl]pyridin-2(1*H*)-one,

2-({[3-bromo-2-oxo-1-(pyridin-3-ylmethyl)-1,2-dihydropyridin-4-yl]oxy}methyl)-5-fluorobenzonitrile,

5-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-2-methyl-6-oxo-1,6-dihydropyridine-3-carbonitrile,

4-(benzyloxy)-1-(3-fluorobenzyl)-3-(trifluoromethyl)pyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-methyl-5-oxiran-2-ylpyridin-2(1*H*)-one,

1-benzyl-4-[(3-chlorobenzyl)oxy]pyridin-2(1*H*)-one,

1-benzyl-4-[(3-chlorobenzyl)oxy]pyridin-2(1*H*)-one,

5-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-2-methyl-6-oxo-1,6-dihydropyridine-3-carbaldehyde,

*tert*-butyl 3-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]methyl}piperidine-1-carboxylate,

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3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-methyl-5-vinylpyridin-2(1*H*)-one,

4-(benzyloxy)-1-[4-(trifluoromethoxy)benzyl]pyridin-2(1*H*)-one,

3-bromo-4-[(4-chlorobenzyl)oxy]-1-[2-(phenylthio)ethyl]pyridin-2(1*H*)-one,

3-Bromo-4-(4-chloro-benzyloxy)-1-(2-phenylsulfanyl-ethyl)-1H-pyridin-2-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(2-morpholin-4-ylethyl)pyridin-2(1*H*)-one,

4-[(2,4-difluorobenzyl)oxy]-6-(hydroxymethyl)-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one,

4-{[2-(Aminomethyl)-4-fluorobenzyl]oxy}-3-bromo-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one trifluoroacetate,

4-(benzyloxy)-1-(4-fluorobenzyl)pyridin-2(1*H*)-one,

4-(benzyloxy)-1-(4-fluorobenzyl)pyridin-2(1*H*)-one,

4-Benzyloxy-3-bromo-1-methanesulfonyl-1H-pyridin-2-one,

*tert*-butyl 4-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]piperidine-1-carboxylate,

1-benzyl-4-(benzyloxy)-3-vinylpyridin-2(1*H*)-one,

4-(benzyloxy)-1-[4-(methylthio)benzyl]pyridin-2(1*H*)-one,

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-(2-methyl-4-methylamino-pyrimidin-5-ylmethyl)-1H-pyridin-2-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

1-benzyl-3-bromo-4-{[2-(trifluoromethyl)benzyl]oxy}pyridin-2(1*H*)-one,

1-benzyl-3-bromo-4-{[2-(trifluoromethyl)benzyl]oxy}pyridin-2(1*H*)-one,

4-[(2,4-difluorobenzyl)oxy]-1-[5-(hydroxymethyl)-2-methylphenyl]-6-methylpyridin-2(1*H*)-one,

4-(benzyloxy)-1-[4-(methylsulfonyl)benzyl]pyridin-2(1*H*)-

one,

4-Phenoxy-1H-pyridin-2-one,

1-benzyl-4-[(2-chlorobenzyl)oxy]pyridin-2(1*H*)-one,

1-benzyl-4-[(2-chlorobenzyl)oxy]pyridin-2(1*H*)-one,

methyl 4-{[4-(benzyloxy)-2-oxopyridin-1(2*H*)-yl]methyl}benzoate,

4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-methylpyridin-2(1*H*)-one,

1-(3-fluorobenzyl)-4-(phenylethynyl)pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-(piperidin-4-ylmethyl)pyridin-2(1*H*)-one hydrochloride,

4-(benzyloxy)-3-bromo-1-(piperidin-4-ylmethyl)pyridin-2(1*H*)-one hydrochloride,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[2-(methylthio)pyrimidin-4-yl]pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-piperidin-4-ylpyridin-2(1*H*)-one hydrochloride,

4-Benzyloxy-1-difluoromethyl-1H-pyridin-2-one,

4-Benzyloxy-3-bromo-1-(2-chloro-phenyl)-6-methyl-1H-pyridin-2-one,

3-Bromo-6-methyl-1-pyridin-3-ylmethyl-4-[(pyridin-3-ylmethyl)-amino]-1H-pyridin-2-one,

1-(3,4-Dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (2,4-difluoro-phenyl)-amide,

1-(2,6-Dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (2,4-difluoro-phenyl)-amide,

5-Chloro-1-(2,6-dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (2,4-difluoro-phenyl)-amide,

5-Chloro-1-(2,6-dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid methyl-phenyl-amide,

1-(2,6-Dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid benzylamide,

1-(2,6-Dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (3-dimethylamino-propyl)-amide,

1-(2,6-Dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (2-morpholin-4-yl-ethyl)-amide,

N-[5-Acetyl-1-(4-chloro-benzyl)-6-methyl-2-oxo-1,2-dihydro-pyridin-3-yl]-4-chloro-benzamide,

1-(2,6-Dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid N'-(3-chloro-5-trifluoromethyl-pyridin-2-yl)-hydrazide,

*N*-allyl-2-[(1-benzyl-6-oxo-1,6-dihydropyridin-3-yl)carbonyl]hydrazinecarbothioamide,

*1-Benzyl-5-[5-(3,4-dichloro-benzylsulfanyl)-[1,3,4]oxadiazol-2-yl]-1H-pyridin-2-one,*

*N'*-{[(1-benzyl-6-oxo-1,6-dihydropyridin-3-yl)carbonyl]oxy}pyridine-4-carboximidamide,

1-(2,6-Dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid 3-trifluorometnyl-benzylamide,

1-Benzyl-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (2-morpholin-4-yl-ethyl)-amide,

5-[4-(3-Chloro-phenyl)-piperazine-1-carbonyl]-1-(3,4-dichloro-benzyl)-1H-pyridin-2-one,

5-Chloro-1-(2,6-dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid benzylamide,

1-(4-Chloro-benzyl)-5-[3-(4-chloro-phenyl)-[1,2,4]oxadiazol-5-yl]-1H-pyridin-2-one,

1-(4-Chloro-benzyl)-5-[3-(4-chloro-phenyl)-[1,2,4]oxadiazol-5-yl]-1H-pyridin-2-one,

2-Chloro-N-[1-(2,6-dichloro-benzyl)-6-oxo-5-trifluoromethyl-1,6-dihydro-pyridin-3-yl]-4-fluoro-benzamide,

N-[1-(2,6-Dichloro-benzyl)-6-oxo-5-trifluoromethyl-1,6-dihydro-pyridin-3-yl]-4-isopropoxy-benzamidE,

1-(2,6-Dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-

carboxylic acid (4-trifluoromethoxy-phenyl)-amide,

1-(2,6-Dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (3-trifluoromethyl-phenyl)-amide,

5-Chloro-1-(2,6-dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (3-trifluoromethyl-phenyl)-amide,

1-(2,6-Dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (4-chloro-phenyl)-amide,

1-(2,6-Dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (2-dimethylamino-ethyl)-amide,

5-Methyl-1-phenyl-1H-pyridin-2-one,

3-Bromo-1-(3-fluoro-benzyl)-4-(3-methoxy-phenyl)-1H-pyridin-2-one,

3-Bromo-1-(3-fluoro-benzyl)-4-(3-isopropyl-phenyl)-1H-pyridin-2-one,

3'-Bromo-1'-(3-fluoro-benzyl)-6-methoxy-1'H-[3,4']bipyridinyl-2'-one,

4-Benzo[1,3]dioxol-5-yl-3-bromo-1-(3-fluoro-benzyl)-1H-pyridin-2-one,

3-Bromo-1-(3-fluoro-benzyl)-4-thiophen-3-yl-1H-pyridin-2-one,

3-Bromo-1-(3-fluoro-benzyl)-4-(3-trifluoromethyl-phenyl)-1H-pyridin-2-one,

3-Bromo-1-(3-fluoro-benzyl)-4-naphthalen-2-yl-1H-pyridin-2-one,

3-Bromo-1-(3-fluoro-benzyl)-4-(4-fluoro-phenyl)-1H-pyridin-2-one,

1-Benzenesulfonyl-4-benzyloxy-3-bromo-1H-pyridin-2-one,

4-[3-Amino-1-(2,4-difluoro-phenyl)-propoxy]-3-bromo-6-methyl-1-pyridin-3-ylmethyl-1H-pyridin-2-one,

1-(4-Bromo-2,6-difluoro-phenyl)-4-(2,4-difluoro-benzyloxy)-6-methyl-1H-pyridin-2-one,

2-[1-(4-Amino-2-methyl-pyrimidin-5-ylmethyl)-3-bromo-6-

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methyl-2-oxo-1,2-dihydro-pyridin-4-yloxymethyl]-5-fluoro-benzonitrile,

4-(2,4-Difluoro-benzyloxy)-6-methyl-1-(2,4,6-trifluoro-phenyl)-1H-pyridin-2-one,

1-(2-Chloro-4-hydroxy-phenyl)-4-(2,4-difluoro-benzyloxy)-6-methyl-1H-pyridin-2-one,

3-[4-(2,4-Difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-yl]-benzoic acid methyl ester,

3-Bromo-1-(2,6-difluoro-phenyl)-4-methoxy-6-methyl-5-vinyl-1H-pyridin-2-one

3-Bromo-1-(2,6-difluoro-phenyl)-4-methoxy-6-methyl-5-styryl-1H-pyridin-2-one,

1-(2,6-Difluoro-phenyl)-4-methoxy-6-methyl-5-phenethyl-1H-pyridin-2-one,

3-Bromo-1-(2,6-difluoro-phenyl)-4-methoxy-6-methyl-5-phenethyl-1H-pyridin-2-one,

1-(1*H*-indazol-5-yl)-4-(1*H*-indazol-5-ylamino)-6-methylpyridin-2(1*H*)-one,

5-Bromo-4-(2,4-difluoro-benzyloxy)-1-(2,6-difluoro-phenyl)-2-[2-(2,4-difluoro-phenyl)-ethyl]-6-oxo-1,6-dihydro-pyridine-3-carbaldehyde,

4-[3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-yl]-pyrimidine-2-carbonitrile,

3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-[1,2']bipyridinyl-5'-carboxylic acid,

3-Bromo-4-(5-carboxy-pyridin-2-yloxy)-6-methyl-2-oxo-2H-[1,2']bipyridinyl-5'-carboxylic acid,

3-Bromo-4-(2,4-difluoro-benzyloxy)-6,6'-dimethyl-2-oxo-2H-[1,2']bipyridinyl-3'-carbonitrile,

3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-[1,2']bipyridinyl-5'-carboxylic acid methylamide,

3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-

[1,2']bipyridinyl-5'-carboxylic acid (2-hydroxy-ethyl)-amide,

3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-[1,2']bipyridinyl-5'-carboxylic acid (2-methoxy-ethyl)-amide,

3-Bromo-1-(2,6-difluoro-phenyl)-4-methoxy-6-metnyl-5-(4-methyl-benzyl)-1H-pyridin-2-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-5-(1,2-dinydroxy-2-phenylethyl)-6-methylpyridin-2(1H)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-5'-(1-hydroxy-1-methylethyl)-6-methyl-2H-1,2'-bipyridin-2-one,

4-Benzyloxy-1H-pyridin-2-one,

4-Benzyloxy-3-methyl-1H-pyridin-2-one,

2-Oxo-6-phenethyl-1,2-dihydro-pyridine-3-carbonitrile,

2-Oxo-6-phenyl-1,2-dihydro-pyridine-3-carbonitrile,

6-Oxo-1,6-dihydro-[2,3']bipyridinyl-5-carbonitrile,

6-Oxo-1,6-dihydro-[2,3']bipyridinyl-5-carboxylic acid,

3-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]methyl}benzamide,

3-bromo-4-[(4-fluorobenzyl)oxy]-1-(4-methoxybenzyl)pyridin-2(1*H*)-one,

3-bromo-4-[(4-fluorobenzyl)oxy]-1-(4-methoxybenzyl)pyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[2-fluoro-5-(hydroxymethyl)phenyl]-6-methylpyridin-2(1*H*)-one,

3-chloro-1-(4-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-chloro-1-(4-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-bromo-1-(3-chlorobenzyl)-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-bromo-4-[(3,4-difluorobenzyl)oxy]-1-(3-fluorobenzyl)pyridin-2(1*H*)-one,

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3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-4-methylbenzoic acid,

3-bromo-1-(3-chlorobenzyl)-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-bromo-1-(3-chlorobenzyl)-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one,

4-{[3-chloro-4-[(2,4-difluorobenzyl)amino]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}benzonitrile trifluoroacetate,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-{[5-(1-hydroxy-1-methylethyl)pyrazin-2-yl]methyl}-6-methylpyridin-2(1*H*)-one,

4-(benzylamino)-3-bromo-1-(3-fluorobenzyl)pyridin-2(1*H*)-one,

4-(benzylamino)-3-bromo-1-(3-fluorobenzyl)pyridin-2(1*H*)-one,

2-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}benzonitrile,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[2-fluoro-6-(4-methylpiperazin-1-yl)phenyl]-6-methylpyridin-2(1*H*)-one trifluoroacetate,

4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*-methylbenzamide,

1-[2-(aminomethyl)benzyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-bromo-1-(4-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one,

1-[2-(aminomethyl)benzyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[3-(piperidin-1-ylcarbonyl)phenyl]pyridin-2(1*H*)-one,

1-benzyl-3-bromo-4-[(4-chlorobenzyl)oxy]pyridin-2(1*H*)-one,

4-[(2,4-difluorobenzyl)oxy]-1-(3-fluorobenzyl)-3-

methylpyridin-2(1*H*)-one,

4-(benzyloxy)-1-[4-(benzyloxy)benzyl]-3-bromopyridin-2(1*H*)-one,

4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*-hydroxybenzamide,

4-(benzyloxy)-1-[4-(benzyloxy)benzyl]-3-bromopyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-[4-(trifluoromethyl)benzyl]pyridin-2(1*H*)-one,

3-bromo-1-(cyclopropylmethyl)-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one,

3-bromo-1-(cyclopropylmethyl)-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one,

1-benzyl-3-bromo-4-[(3-chlorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

1-benzyl-3-bromo-4-[(3-chlorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

1-benzyl-3-bromo-4-[(3-chlorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

2-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}benzonitrile,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-({5-[(methylamino)methyl]pyrazin-2-yl}methyl)pyridin-2(1*H*)-one trifluoroacetate,

3-bromo-1-(3-fluorobenzyl)-4-[(2-methylbenzyl)oxy]pyridin-2(1*H*)-one,

3-bromo-1-(3-fluorobenzyl)-4-[(2-methylbenzyl)oxy]pyridin-2(1*H*)-one,

methyl 3-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}benzoate,

3-bromo-1-(3-fluorobenzyl)-6-methyl-4-(2-phenylethyl)pyridin-2(1*H*)-one,

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3-bromo-1-(3-fluorobenzyl)-6-methyl-4-(2-pherylethyl)pyr_din-2(1*H*) one,

1-benzyl-3-bromo-4-[(4-metnylbenzyl)oxy]pyridin-2(1*H*)-one,

1-benzyl-3-bromo-4-[(4-methylbenzyl)oxy]pyridin-2(1*H*)-one,

1-benzyl-3-bromo-4-[(4-metnylbenzyl)oxy]pyridin-2(1*H*)-one,

4-(benzyloxy)-1-(3-fluorobenzyl)-3-iodopyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[3-(hydroxymethyl)phenyl]-6-methylpyridin-2(1*H*)-one,

4-(benzyloxy)-1-(3-fluorobenzyl)-3-iodopyridin-2(1*H*)-one,

3-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}benzoic acid,

3-bromo-4-[(4-fluorobenzyl)oxy]-1-[2-(hydroxymethyl)benzyl]pyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[(5-{[(2-hydroxyethyl)(methyl)amino]metnyl}pyrazin-2-yl)methyl]-6-methylpyridin-2(1*H*)-one trifluoroacetate (salt),

4-(benzyloxy)-3-bromo-1-[(6-fluoropyridin-3-yl)methyl]pyridin-2(1*H*)-one,

3-bromo-4-[(4-chlorobenzyl)oxy]-1-(4-fluorobenzyl)pyridin-2(1*H*)-one,

3-bromo-4-[(4-chloro-2-fluorobenzyl)amino]-1-(3-fluorobenzyl)pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-ethylpyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-ethylpyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-ethylpyridin-2(1*H*)-one,

2-(2-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}phenyl)acetamide,

1-benzyl-3-bromo-4-[(2-chlorobenzyl)oxy]pyridin-2(1*H*)-one,

1-benzyl-3-bromo-4-[(2-chlorobenzyl)oxy]pyridin-2(1*H*)-one,

methyl 2-{[3-bromo-4-[(4-fluorobenzyl)oxy]-2-oxopyridin-1(2*H*)-yl]methyl}benzoate,

3-bromo-1-(2,6-dichlorophenyl)-4-[2-(4-fluorophenyl)ethyl]-6-methylpyridin-2(1*H*)-one,

3-bromo-1-(2,6-dichlorophenyl)-4-[2-(4-fluorophenyl)ethyl]-6-methylpyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-{5-[(isopropylamino)methyl]-2-methylphenyl}-6-methylpyridin-2(1*H*)-one hydrochloride,

3-bromo-1-(3-fluorobenzyl)-4-(2-phenylethyl)pyridin-2(1*H*)-one,

*N*-{3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzyl}-*N'*-methylurea,

3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[3-(hydroxymethyl)phenyl]-6-methylpyridin-2(1*H*)-one,

3-bromo-1-(3-fluorobenzyl)-4-[(3-fluorobenzyl)oxy]pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-[2-(2-thienyl)ethyl]pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-[2-(2-thienyl)ethyl]pyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)amino]-1-(2,6-difluorophenyl)-6-methylpyridin-2(1*H*)-one trifluoroacetate,

3-bromo-4-[(2,4-difluorobenzyl)amino]-1-(2,6-difluorophenyl)-6-methylpyridin-2(1*H*)-one trifluoroacetate,

3-bromo-4-[(4-chlorobenzyl)oxy]-1-(4-methoxybenzyl)pyridin-2(1*H*)-one,

3-bromo-4-[(4-chlorobenzyl)oxy]-1-(4-methoxybenzyl)pyridin-2(1*H*)-one,

3-bromo-1-(4-chlorobenzyl)-4-[(4-

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chlorobenzyl)oxy]pyridin-2(1*H*)-one,

3-bromo-1-(3-fluorobenzyl)-4-[(4-methoxybenzyl)oxy]pyridin-2(1*H*)-one,

3-bromo-1-(3,5-dibromo-2,6-difluoro-4-hydroxyphenyl)-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-[4-(trifluoromethoxy)benzyl]pyridin-2(1*H*)-one

4-(benzyloxy)-3-bromo-1-[4-(trifluoromethoxy)benzyl]pyridin-2(1*H*)-one,

*N*'-{3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzyl}-*N*,*N*-dimethylurea,

3-bromo-4-[(4-fluorobenzyl)oxy]-1-[4-(trifluoromethyl)benzyl]pyridin-2(1*H*)-one,

2-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}benzamide,

*N*-{3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzyl}morpholine-4-carboxamide,

*N*-{3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzyl}methanesulfonamide,

4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*-isopropylbenzamide,

4-(allylamino)-3-bromo-1-(2,6-difluorophenyl)-5-iodo-6-methylpyridin-2(1*H*)-one,

4-(allylamino)-3-bromo-1-(2,6-difluorophenyl)-5-iodo-6-methylpyridin-2(1*H*)-one,

(4-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]methyl}phenyl)acetic acid,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[4-(pyrrolidin-1-ylcarbonyl)phenyl]pyridin-2(1*H*)-one,

1-benzyl-4-(benzyloxy)-3-iodopyridin-2(1*H*)-one,

1-(biphenyl-4-ylmethyl)-3-bromo-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one,

4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzoic acid,

4-(benzyloxy)-3-bromo-1-[2-(3-thienyl)ethyl]pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-[2-(3-thienyl)ethyl]pyridin-2(1*H*)-one,

3-bromo-4-[(4-fluorobenzyl)oxy]-1-[3-(trifluoromethyl)benzyl]pyridin-2(1*H*)-one,

*N*-[3-bromo-1-(3-fluorobenzyl)-2-oxo-1,2-dihydropyridin-4-yl]-4-fluorobenzamide,

methyl 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzylcarbamate,

1-benzyl-4-(benzylthio)-3-bromopyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-(4-tert-butylbenzyl)pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-(4-tert-butylbenzyl)pyridin-2(1*H*)-one,

*N*-{3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzyl}-2-methoxyacetamide,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-({5-[(dimethylamino)methyl]pyrazin-2-yl}methyl)-6-methylpyridin-2(1*H*)-one trifluoroacetate,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[4-(piperazin-1-ylcarbonyl)phenyl]pyridin-2(1*H*)-one hydrochloride,

4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*,*N*-bis(2-hydroxyethyl)benzamide,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-{5-[(dimethylamino)methyl]-2-methylphenyl}-6-methylpyridin-2(1*H*)-one hydrochloride,

1-benzyl-3-bromo-4-(2-phenylethyl)pyridin-2(1*H*)-one,

1-(3-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]-3-

methylpyridin-2(1*H*)-one,

4-(benzyloxy)-1-(piperidin-3-ylmethyl)pyridin-2(1*H*)-one trifluoroacetate,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[4-(morpholin-4-ylcarbonyl)phenyl]pyridin-2(1*H*)-one,

4-(benzyloxy)-1-(3-fluorobenzyl)-3-methylpyridin-2(1*H*)-one,

*N*-{3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzyl}glycinamide hydrochloride,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-5-iodo-6-methylpyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[4-(piperidin-1-ylcarbonyl)phenyl]pyridin-2(1*H*)-one,

*N*-[3-bromo-1-(3-fluorobenzyl)-2-oxo-1,2-dihydropyridin-4-yl]-2,6-difluorobenzamide,

2-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]methyl}benzonitrile,

5-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}-*N*-methylpyrazine-2-carboxamide,

3-chloro-4-[(2,4-difluorobenzyl)amino]-1-(2,6-difluorophenyl)-6-methylpyridin-2(1*H*)-one,

3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzoic acid,

3-bromo-1-(3-fluorobenzyl)-4-[(3-fluorobenzyl)amino]pyridin-2(1*H*)-one,

3-bromo-1-(3-fluorobenzyl)-4-[(3-methoxybenzyl)oxy]pyridin-2(1*H*)-one,

3-bromo-1-(4-tert-butylbenzyl)-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1*H*)-one,

*N*-{3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzyl}acetamide,

2-({3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-

oxopyridin-1(2*H*)-yl]benzyl}amino)-2-oxoethyl acetate,

1-benzyl-4-(benzyloxy)-3-methylpyridin-2(1*H*)-one

*N*-{3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzyl}urea,

1-benzyl-4-(benzyloxy)-3-ethylpyridin-2(1*H*)-one,

*N*-{3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]benzyl}-2-hydroxyacetamide,

3-bromo-4-[(4-chlorobenzyl)oxy]-1-(2-phenylethyl)pyridin-2(1*H*)-one,

3-bromo-1-(3-chlorobenzyl)-4-[(4-chlorobenzyl)oxy]pyridin-2(1*H*)-one,

1-[3-(aminomethyl)phenyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1*H*)-one,

2-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]methyl}benzamide,

1-(4-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one,

1-[2-(aminomethyl)benzyl]-4-(benzyloxy)-3-bromopyridin-2(1*H*)-one,

methyl 3-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]propanoate,

1-benzyl-4-(benzyloxy)-3-methylpyridin-2(1*H*)-one,

4-(allylamino)-1-(2,6-difluorophenyl)-5-iodo-6-methylpyridin-2(1*H*)-one,

4-(allylamino)-1-(2,6-difluorophenyl)-5-iodo-6-methylpyridin-2(1*H*)-one,

3-bromo-1-(3-fluorobenzyl)-4-(phenylethynyl)pyridin-2(1*H*)-one,

4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-*N*,*N*-dimethylbenzamide,

{4-[({4-(benzyloxy)-3-bromo-1-[4-(carboxymethyl)benzyl]-1,2-dihydropyridin-2-yl}oxy)methyl]phenyl}acetic acid,

4-(benzyloxy)-3-bromo 1-[3-(trifluoromethyl)benzyl]pyridin-2(1*H*)-one,

4-(benzyloxy)-3-ethynyl-1-(3-fluorobenzyl)pyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-{3-[(dimethylamino)methyl]phenyl}-6-methylpyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-methylpyridin-2(1*H*)-one,

1-benzyl-3-bromo-4-(phenylethynyl)pyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-methylpyridin-2(1*H*)-one,

3-bromo-1-(3-fluorobenzyl)-4-{[4-(trifluoromethyl)benzyl]oxy}pyridin-2(1*H*)-one,

4-(benzylamino)-3-bromo-1-(2,6-difluorophenyl)-5-iodo-6-methylpyridin-2(1*H*)-one,

4-[(2,4-difluorobenzyl)oxy]-1-(4-methoxybenzyl)-6-methylpyridin-2(1*H*)-one,

4-(benzyloxy)-3-bromo-1-methylpyridin-2(1*H*)-one hydrobromide,

4-(benzyloxy)-3-bromo-1-[4-(morpholin-4-ylcarbonyl)phenyl]pyridin-2(1*H*)-one,

5-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-oxo-1,6-dihydropyridine-2-carboxylic acid,

1-benzyl-3-bromo-4-[(2,6-dichlorobenzyl)oxy]pyridin-2(1*H*)-one,

3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]-2-methylbenzoic acid,

4-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]benzoic acid,

ethyl *N*-(5-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2*H*)-yl]methyl}-2-methylpyrimidin-4-yl)glycinate trifluoroacetate,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-methyl-5-[(*E*)-2-phenylvinyl]pyridin-2(1*H*)-

one,

3-bromo-1-(3-fluorobenzyl)-4-{[3-(trifluoromethyl)benzyl]amino}pyridin-2(1*H*)-one,

3-bromo-4-[(4-fluorobenzyl)oxy]-1-(3-phenylpropyl)pyridin-2(1*H*)-one,

3-bromo-1-(4-*tert*-butylbenzyl)-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one,

4-(allylamino)-3-bromo-1-(2,6-difluorophenyl)-6-methylpyridin-2(1*H*)-one,

1-cyclohexyl-4-[(2,4-difluorobenzyl)oxy]-3,6-dimethylpyridin-2(1*H*)-one,

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-5-(hydroxymethyl)-6-methylpyridin-2(1*H*)-one,

1-benzyl-4-(benzyloxy)-2-oxo-1,2-dihydropyridine-3-carbaldehyde,

4-[(2,4-difluorobenzyl)oxy]-6-methyl-1 prop-2-yn-1-ylpyridin-2(1*H*)-one,

ethyl 3-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2*H*)-yl]propanoate,

1-benzyl-4-(benzyloxy)-3-(hydroxymethyl)pyridin-2(1*H*)-one,

3-Chloro-4-(2,4-difluoro-benzyloxy)-6-methyl-1-(5-methyl-pyrazin-2-ylmethyl)-1H-pyridin-2-one

3-Chloro-4-(2,4-difluoro-benzyloxy)-1-(5-hydroxymethyl-pyrazin-2-ylmethyl)-6-methyl-1H-pyridin-2-one

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-(2,3-dihydro-1H-indol-5-ylmethyl)-1H-pyridin-2-one

3-Bromo-4-(2,4-difluoro-benzyloxy)-1-[1-(2-hydroxy-acetyl)-2,3-dihydro-1H-indol-5-ylmethyl]-6-methyl-1H-pyridin-2-one

3-Bromo-4-(2,4-difluoro-benzyloxy)-6-methyl-1-(1H-pyrazol-3-ylmethyl)-1H-pyridin-2-one

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3-[3-Chloro-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-yl]-4,N-dimethy -benzamide

3-[3-Chloro-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-yl]-4-methyl-benzamide

3-[3-Chloro-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-yl]-4-fluoro-N-methyl-benzamide

4-Chloro-3-[3-chloro-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-yl]-N-methyl-benzamide

3-[3-Chloro-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-yl]-4-fluoro-benzamide

4-[3-Chloro-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-yl]-3,N-dimethyl-benzamide

3-Chloro-4-(2,4-difluoro-benzyloxy)-1-[4-(1,2-dihydroxy-ethyl)-2-methyl-phenyl]-6-methyl-1H-pyridin-2-one

N-{4-[3-Chloro-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-phenyl}-2-hydroxy-acetamide

1-Hydroxy-cyclopropanecarboxylic acid 4-[3-chloro-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-benzylamide

N-{4-[3-Chloro-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-benzyl}-2-hydroxy-acetamide

N-{4-[3-Chloro-4-(2,4-difluoro-benzyloxy)-6-methyl-2-oxo-2H-pyridin-1-ylmethyl]-phenyl}-acetamide

{2-[3-Bromo-1-(2,6-difluoro-phenyl)-6-methyl-2-oxo-1,2-dihydro-pyridin-4-yloxymethyl]-5-fluoro-benzyl}-carbamic acid ethyl ester, or a pharmaceutically acceptable salt thereof

Piridinonas sustituidas

Referencia cruzada con las solicitudes relacionadas

La presente solicitud reivindica la prioridad de la Solicitud provisional estadounidense con numero de serie 60/357 029, presentada el 14 de febrero de 2002, y de la Solicitud provisional estadounidense con numero de serie 60/436 915, presentada el 30 de diciembre de 2002, cuyas descripciones se incorporan a la presente por referencia en su totalidad

Antecedentes de la invención

Campo de la invención

La presente invencion se refiere a piridinonas sustituidas utiles para tratar enfermedades y afecciones causadas o exacerbadas por la actividad de p38 MAP quinasa desregulada Tambien se describen composiciones farmacéuticas que contienen los compuestos de piridinona, metodos para preparar los compuestos de piridona y métodos de tratamiento que utilizan los compuestos

Descripción de la tecnica relacionada

Numerosos receptores de superficie celular utilizan una o mas de las cascadas de proteina quinasa (MAP quinasa) activadas por mitogenos durante la transduccion de señal Las MAP quinasas son una familia de quinasas de serina/treonina dirigidas a proteinas, activadas por fosforilacion dual Un subgrupo de las MAP quinasas es la p38 MAP quinasa, que esta activada por una variedad de señales, incluyendo citocinas proinflamatorias tales como factor de necrosis tumoral (FNT) e interleucina-1 (IL-1), como tambien lipopolisacaridos bacterianos y estrés ambiental, como choque osmótico y radiación ultravioleta (Ono, K y J Han, Cell Signal 12 1, 2000) Dentro de la familia de la p38 quinasa, existen cuatro isozimas diferentes p38 alfa, p38 beta, p38 gama y p38 delta La

familia de la p38 quinasa funciona en dirección 3 de un estímulo activador, fosforilando y activando factores de transcripción (p ej , ATF2, CHOP y MEF2C) como también otras quinasas (p ej , MAPKAP-2 y MAPKAP-3) (Trends in Cell biology 7, 353-361, 1997,Mol Cell Biology 19, 21-30, 1999, EMBO J 20, 466-479, 2001) Al momento de la activacion, la cascada de p38 quinasa conduce a la inducción de expresion génica de varios factores involucrados en inflamación e inmunidad, incluyendo FNT, interleucina-6, factor estimulante granulocito-macrofago (GM-CSF) y repetición larga de VIH (Paul et al , Cell Signal 9 403-410, 1997) Los productos de fosforilación de la p38 estimulan la produccion de citocinas inflamatorias y otras proteinas, incluyendo FNT y IL-1 y ciclo-oxigenasa-2, y posiblemente tambien modulan los efectos de estas citocinas en sus células diana, estimulando asi los procesos de inflamación (Lee, J C et al, Nature, 372 376, 1994)

También se ha demostrado que las p38 MAP quinasas promueven la apoptosis durante la isquemia en miocitos cardiacos, lo que sugiere que los inhibidores de p38 MAP quinasa se pueden utilizar para tratar enfermedades coronarias isquemicas (J Biol Chem 274, 6272, 1999) Tambien se requieren para la replicación de VIH-1 en celulas T y pueden ser utiles para la terapia de sida Los inhibidores de la via de P38 se han utilizado para aumentar la sensibilidad del cáncer a la terapia de esta enfermedad y tambien son utiles para el tratamiento de asma (JPET 293, 281, 2000)

El FNT es una citocina y un potente mediador proinflamatorio implicado en afecciones tales como artritis, asma, choque septico, diabetes mellitus insulino-dependiente, esclerosis multiple, asma y enfermedad

intestinal inflamatoria Por lo tanto, los inhibidores de p38 MAP quinasas (requeridos para la produccion de FNT) pueden ser utiles para el tratamiento de enfermedades inflamatorias resultantes de la producción excesiva de citocina, como artritis (Boehm, J C and J L Adams, Exp Opin Ther Patentes 10 25, 2000 y referencias citadas en la presente) El FNT tambien ha estado implicado en infecciones virales, tales como VIH, virus de la gripe, virus herpes, incluyendo herpes simple del tipo 1 (HSV-1), herpes simple del tipo 2 (HSV-2), citomegalovirus (CMV), virus de varicela-zoster (VZV), virus de Epstein-Barr, virus herpes humano 6 (HHV-6), virus herpes humano 7 (HHV-7), virus herpes humano 8 (HHV-8), seudorrabia y rinotraqueitis, entre otras

También se ha demostrado que la producción excesiva o desregulada de FNT produce niveles elevados de IL-1 La inhibicion de FNT, en consecuencia, debe reducir los niveles de IL-1 (European Cytokine Netw 6, 225, 1995) y aliviar los estados de enfermedad causados por la sintesis desregulada de IL-1 Dichos estados de enfermedad incluyen artritis reumatoidea, espondilitis reumatoidea, osteoartritis, artritis gotosa, sepsis, choque séptico, choque endotóxico, sepsis por gram negativo, sindrome de choque tóxico, sindrome de distrés respiratorio del adulto, paludismo cerebral, enfermedad inflamatoria pulmonar crónica, silicosis, sarcosis pulmonar, enfermedades de resorcion ósea, lesion por reperfusión, reaccion injerto contra hospedante, rechazo de aloinjertos, fiebre y mialgias debidas a infeccion, caquexia secundaria a infección o malignidad, caquexia secundaria a sindrome de inmunodeficiencia adquirida (sida), complejo relacionado con sida (CRS), formación de queloides, formacion de tejido cicatricial, enfermedad de Crohn, colitis ulcerosa y

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También se ha demostrado que la IL-1 media una variedad de actividades biológicas tales como la activacion de celulas T helper, la induccion de fiebre, la estimulacion de prostaglandina o la produccion de colagenasa, la quimiotaxis de neutrófilos y la supresion de niveles de hierro en plasma (*Rev Infect Disease*, 6, 51 (1984)) Los niveles elevados de IL-1 tambien han estado implicados en la mediación o exacerbación de una cantidad de estados de enfermedad, incluyendo artritis reumatoidea, osteoartritis, espondilitis reumatoidea, artritis gotosa, enfermedad intestinal inflamatoria, sindrome de distres respiratorio del adulto (SDRA), soriasis, enfermedad de Crohn, colitis ulcerosa, anafilaxis, degeneracion muscular, caquexia, sindrome de Reiter, diabetes del tipo I y del tipo II, enfermedades de resorción osea, lesion por reperfusion isquémica, arteriosclerosis, trauma cerebral, esclerosis multiple, sepsis, choque séptico y sindrome de choque tóxico Los virus sensibles a la inhibicion de FNT, tales como VIH-1, VIH-2, VIH-3, tambien están afectados por la producción de IL-1 En artritis reumatoidea, tanto la IL-1 como el FNT inducen la sintesis de colagenasa y finalmente conducen a destruccion del tejido dentro de las articulaciones artriticas (*Lymphokine Cytokine Res* (11) 253-256, (1992) y *Clin Exp Immunol* 989 244-250, (1992))

La IL-6 es otra citocina proinflamatoria asociada con muchas afecciones, incluyendo inflamación En consecuencia, el FNT, la IL-1 y la IL-6 afectan a una amplia variedad de celulas y tejidos y son mediadores inflamatorios importantes de una amplia variedad de estados de enfermedad y afecciones La inhibicion de estas citocinas por inhibición o modulacion de p38 quinasa beneficia el control, la reducción y el alivio de muchos de estos

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estados de enfermedad y afecciones Por lo tanto, la presente invencion se refiere al hallazgo de inhibidores o moduladores de pequenas moleculas de p 38 quinasa y de la via de p38 quinasa

Resumen de la invencion

En un aspecto general, la invención provee compuestos de la Fórmula I (Realización I)



(I)

y sus sales farmaceuticamente aceptables, en la que

$R_1$ es H, halógeno, $NO_2$, alquilo, carboxaldehido, hidroxialquilo, dihidroxialquilo, arilalcoxi, arilalquilo, alquenilo, alquinilo, arilalquinilo, -CN, arilo, alcanoilo, alcoxi, alcoxialquilo, haloalquilo, haloalcoxi, carboxilo o arilalcanoilo,

en la que la porción arilo del arilalcoxi, arilalquilo y arilalcanoilo no se sustituye o se sustituye con 1, 2, 3, 4 o 5 grupos que son independientemente halogeno, alquilo $C_1$-$C_4$, alcoxi $C_1$-$C_4$, nitro, CN, haloalquilo, haloalcoxi o $CO_2R$,

en la que la porción alquilo de los grupos alquilo, hidroxialquilo, dihidroxialquilo, arilalcoxi, arilalquilo, alcanoilo, alcoxi, alcoxialquilo y arilalcanoilo no esta sustituida o esta sustituida con 1, 2 ó 3 grupos que son independientemente halogeno, alcoxi $C_1$-$C_4$ , alcoxi $C_1$-$C_4$ carbonilo o cicloalquilo $C_3$-$C_7$,

$R_2$ es H, OH, halógeno, -$OSO_2$-alquilo ($C_1$-$C_6$), -$OSO_2$-arilo, arilalcoxi, ariloxi, ariltio, ariltioalcoxi, arilalquinilo, alccxi, ariloxialquil($C_1$-$C_6$), alquilo, alquinilo, -OC(O)NH$(CH_2)_n$arilo, -OC(O)N(alquil)$(CH_2)_n$arilo,

alcoxialcoxi, dialquilamino, alquilo, alcoxi, arilo, arilalquilo, heteroarilo, heteroarilalquilo, arilalquenilo, heterocicloalquilo, heterocicloalquilalquilo, alcoxialcoxi, $NR_8R_9$, dialquilamino o $CO_2R$, en la que

n es 0, 1, 2, 3, 4, 5 ó 6,

cuyos grupos no se sustituyen o se sustituyen con 1, 2, 3, 4 ó 5 grupos que son independientemente halogeno, -alquil($C_1$-$C_6$)-N(R)-$CO_2R_{30}$, haloalquilo, heteroarilo, heteroarilalquilo, $-NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, $-C(O)NR_6R_7$, -alquil($C_1$-$C_4$)-$C(O)NR_6R_7$, -(alquilo $C_1$-$C_4$)-$NRC(O)NR_{16}R_{17}$, haloalcoxi, alquilo, CN, hidroxialquilo, dihidroxialquilo, alcoxi, alcoxicarbonilo, fenilo, $-SO_2$-fenilo en los que los grupos fenilo y $-SO_2$-fenilo están opcionalmente sustituidos con 1, 2 ó 3 grupos que son independientemente halogeno o $NO_2$ o $-OC(O)NR_6R_7$, en la que

$R_{16}$ y $R_{17}$ son independientemente H o alquilo $C_1$-$C_6$, o

$R_{16}$, $R_{17}$ y el nitrógeno al que estan acoplados forman un anillo morfolinilo,

$R_6$ y $R_7$ son independientemente en cada aparicion H, alquilo, hidroxialquilo, dihidroxialquilo, alcoxi, alcanoilo, arilalquilo, arilalcoxi, alcoxicarbonilo, $-SO_2$-alquilo, OH, alcoxi, alcoxialquilo, arilalcoxicarbonilo, -alquil($C_1$-$C_4$)-$CO_2$-alquilo, heteroarilalquilo o arilalcanoilo, en los que cada uno no esta sustituido o esta sustituido con 1, 2 ó 3 grupos que son independientemente halogeno, OH, SH, heterocicloalquilo, heterocicloalquilalquilo, cicloalquilo $C_3$-$C_7$, alcoxi, $NH_2$, NH(alquilo), N(alquil)(alquilo), -O-alcanoilo, alquilo, haloalquilo, carboxaldehido o haloalcoxi, o

$R_6$, $R_7$ y el nitrógeno al cual se acoplan forman un anillo morfolinilo, pirrolidinilo, tiomorfolinilo, tiomorfolinilo S-oxido, tiomorfolinilo S,S-dioxido, piperidinilo, pirrolidinilo o piperazinilo que

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opcionalmente se sustituye con 1 o 2 grupos que son independientemente alquilo $C_1$-$C_4$, alcoxicarbonilo, alcoxi $C_1$-$C_4$, hidroxilo, hidroxialquilo, dihidroxialquilo o halogeno,

R, en cada aparición, es independientemente hidrógeno o alquilo $C_1$-$C_6$ opcionalmente sustituido con 1 ó 2 grupos que son independientemente OH, SH, halogeno, amino, monoalquilamino, dialquilamino o cicloalquilo $C_3$-$C_6$,

$R_{30}$ es alquilo $C_1$-$C_6$ opcionalmente sustituido con 1 o 2 grupos que son independientemente OH, SH, halogeno, amino, monoalquilamino, dialquilamino o cicloalquilo $C_3$-$C_6$,

cada $R_8$ es independientemente hidrógeno, alquilo, alcanoilo, arilalquilo y arilalcanoilo, en el que cada uno de los anteriormente mencionados se sustituye opcionalmente con 1, 2, 3, 4 o 5 grupos que son independientemente alquilo, alcoxi, alcoxicarbonilo, halogeno o haloalquilo,

cada $R_9$ es hidrógeno, alquilo, alcanoilo, arilalquilo, cicloalquilo, cicloalquilalquilo, alquenilo, heteroarilo, aminoalquilo, monoalquilaminoalquilo, dialquilaminoalquilo, arilalcanoilo, -$SO_2$-fenilo y arilo, en el que cada uno de los anteriormente mencionados se sustituye opcionalmente con 1, 2, 3, 4 ó 5 grupos que son independientemente alquilo, alcoxi, alcoxicarbonilo, halógeno o haloalquilo,

$R_3$ es H, halogeno, alcoxicarbonilo, arilalcoxicarbonilo, ariloxicarbonilo, arilalquilo, -OC(O)NH$(CH_2)_n$arilo, arilalcoxi, -OC(O)N(alquil)$(CH_2)_n$arilo, ariloxi, ariltio, tioalcoxi, ariltioalcoxi, alquenilo, -$NR_6R_7$, $NR_6R_7$-alquil($C_1$-$C_6$) o alquilo, en el que

la porción arilo del arilalcoxicarbonilo, ariloxicarbonilo, arilalquilo, -OC(O)NH$(CH_2)_n$arilo, arilalcoxi, -OC(O)N(alquil)$(CH_2)_n$arilo y ariltioalcoxi no está sustituida o esta sustituida con 1, 2, 3, 4 ó 5 grupos que son independientemente halógeno, alcoxi, alquilo,

haloalquilo o haloalcoxi,

en la que n es 0, 1, 2, 3, 4, 5 o 6, o

$R_4$ es hidrogeno o $R_4$ es alquilo no sustituido o sustituido con uno o dos grupos que son independientemente $CO_2R$, $-CO_2$-alquil($C_1$-$C_6$), $-C(O)NR_6R_7$, $-C(O)R_6$, $-N(R_{30})C(O)NR_{16}R_{17}$, $-N(R_{30})C(O)$-alcoxi($C_1$-$C_6$) o $-NR_6R_7$, arilalcoxi, arilalquilo, heteroarilo, heteroarilalquilo, hidroxialquilo, dihidroxialquilo, haloalquilo, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, $-NR_bR_7$, alcoxi, carboxaldehido, $-C(O)NR_6R_7$, $CO_2R$, alcoxialquilo o alcoxialcoxi, en los que las porciones heteroarilo o arilo de los anteriormente mencionados no se sustituyen o se sustituyen con 1, 2, 3, 4 ó 5 grupos que son independientemente halogeno, hidroxi, alcoxi, alquilo, $-CO_2$-alquil($C_1$-$C_6$), $-CONR_6R_7$, $NR_6R_7$, $R_6R_7N$-alquil($C_1$-$C_6$)-, nitro, haloalquilo o haloalcoxi, y

$R_5$ es H, arilo, arilalquilo, ariltioalquilo, alquilo opcionalmente sustituido con 1, 2 o 3 grupos que son independientemente arilalcoxicarbonilo, $-NR_8R_9$, halogeno, $-C(O)NR_8R_9$, alcoxicarbonilo, cicloalquilo $C_3$-$C_7$ o alcanoilo, alcoxi, alcoxialquilo opcionalmente sustituido con un grupo trimetilsililo, amino, alcoxicarbonilo, hidroxialquilo, dihidroxialquilo, alquinilo, $-SO_2$-alquilo, alcoxi opcionalmente sustituido con un grupo trimetilsililo, heterocicloalquilalquilo, cicloalquilo, cicloalquilalquilo, -alquil-S-arilo, -alquil-$SO_2$-arilo, heteroarilalquilo, heterocicloalquilo, heteroarilo o alquenilo opcionalmente sustituido con alcoxicarbonilo, en los que

cada uno de los anteriormente mencionados no esta sustituido o esta sustituido con 1, 2, 3, 4 o 5 grupos que son independientemente alquilo, halógeno, alcoxi, hidroxialquilo, dihidroxialquilo, arilalcoxi, tioalcoxi, alcoxicarbonilo, arilalcoxicarbonilo, $CO_2R$, CN, OH, hidroxialquilo, dihidroxialquilo, amidino-oxima, $-NR_6R_7$, -

$NR_8R_9$, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, carboxaldehido, $SO_2$alquilo, -$SO_2H$, -$SO_2NR_6R_7$, alcanoilo en el que la porcion alquilo está opcionalmente sustituida con OH, halogeno o alcoxi, -$C(O)NR_6R_7$, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$ amidino, haloalquilo, -(alquilo $C_1$-$C_4$)-$NR_{15}C(O)NR_{16}R_{17}$, -(alquilo $C_1$-$C_4$)-$NR_{15}C(O)R_{18}$, -O-$CH_2$-O, -O-$CH_2CH_2$-O- o haloalcoxi, en la que

$R_{15}$ es H o alquilo $C_1$-$C_6$, y

$R_{18}$ es alquilo $C_1$-$C_6$ opcionalmente sustituido con -O-(alcanoilo $C_2$-$C_6$, hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-$C_6$ alquilo, alcoxi C -$C_6$, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, aminoalquilo $C_1$-$C_6$, mono o dialquilaminoalquilo $C_1$-$C_6$

La invencion tambien incluye los intermedios que son utiles en la elaboracion de los compuestos de la invención

Estos compuestos se unen y/o interactuan con p38 quinasa y/o FNT Preferentemente, inhiben la actividad de p38 quinasa y/o FNT Por lo tanto, se utilizan para tratar trastornos mediados por p38 map quinasa o FNT Preferentemente, se utilizan para tratar trastornos mediados por p38 alfa o FNT

La presente invención incluye también composiciones farmaceuticas que comprenden al menos un compuesto de formula I y al menos un vehiculo, disolvente, adyuvante o excipiente farmaceuticamente aceptable

La presente invencion tambien incluye metodos para tratar un trastorno mediado por FNT, un trastorno mediado por p38 quinasa, inflamación y/o artritis en un sujeto, comprendiendo el metcdo tratar a un sujeto que padece o es susceptible a dicho trastorno o afeccion con una cantidad terapeuticamente eficaz de un compuesto de Formula I

Descripcion detallada de la invencion

En un aspecto preferido, la invención provee compuestos de formula I, en la que

cuando $R_2$ es benciloxi, $R_3$ es H, $R_4$ es H y $R_5$ es bencilo o metilo, $R_1$ no es hidrógeno,

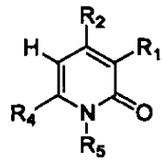
no más de dos de $R_1$, $R_2$, $R_4$ y $R_5$ son simultáneamente hidrogeno,

$R_6$ y $R_7$ no son simultáneamente OH,

cuando $R_2$ es OH, $R_4$ es metilo y $R_5$ es fenilo, $R_1$ no es acetilo, y

$R_4$ y $R_5$ no son simultáneamente hidrogeno

Realizacion 2 Compuestos de la formula




y sus sales farmaceuticamente aceptables, en la que

$R_1$ es H, halogeno, alquilo, carboxaldehido, hidroxialquilo, dihidroxialquilo, arilalcoxi, arilalquilo, alquenilo, alquinilo, arilalquinilo, CN, alcanoilo, alcoxi, alcoxialquilo, haloalquilo, carboxilo o arilalcanoilo,

en la que la porción arilo del arilalcoxi, arilalquilo y arilalcanoilo no está sustituida o esta sustituida con 1, 2, 3, 4 o 5 grupos que son independientemente halogeno, alquilo $C_1$-$C_4$, nitro, CN, haloalquilo, haloalcoxi o $CO_2R$,

en la que la porción alquilo de los grupos alquilo, hidroxialquilo, dihidroxialquilo, arilalcoxi, arilalquilo, alcanoilo, alcoxi, alcoxialquilo y arilalcanoilo no se sustituye o se sustituye con 1, 2 o 3 grupos que son independientemente halógeno, alcoxi $C_1$-$C_4$ , alcoxi $C_1$-$C_4$ carbonilo o ciclopropilo,

$R_2$ es H, OH, halógeno, $-OSO_2$-alquilo ($C_1$-$C_6$), $-OSO_2$-arilo, arilalcoxi, ariloxi, ariltioalcoxi, arilalquinilo,

alcoxi, feniloxialquil($C_1$-$C_6$), -OC(O)NH($CH_2$)$_n$arilo, -OC(O)N(alquil)($CH_2$)$_n$arilo, alquilo, alquinilo, alcoxialcoxi, dialquilamino, heteroarilo, heterocicloalquilo, ariloxialquilo o $CO_2R$, en el que

cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2, 3, 4 ó 5 grupos que son independientemente halogeno, $-NR_6R_7$, haloalquilo, haloalcoxi, alquilo, heteroarilo, heteroarilalquilo, -alquil($C_1$-$C_4$)-C(O)$NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, -C(O)$NR_6R_7$, -(alquilo $C_1$-$C_4$)-NRC(O)$NR_{16}R_{17}$, CN, hidroxialquilo, dihidroxialquilo, -OC(O)$NR_6R_7$ o -alquil($C_1$-$C_6$)-N(R)-$CO_2R_{30}$, en los que

$R_{16}$ y $R_{17}$ son independientemente H o alquilo $C_1$-$C_6$, o

$R_{16}$, $R_{17}$ y el nitrogeno al que estan acoplados forman un anillo morfolinilo,

$R_6$ y $R_7$ son independientemente, en cada aparicion, H, alquilo, hidroxialquilo, dihidroxialquilo, alcoxi, alcoxialquilo, alcanoilo, arilalquilo, arilalcoxi, arilalcoxicarbonilo o arilalcanoilo, en los que cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2 o 3 grupos que son independientemente halogeno, alcoxi, alquilo, OH, SH, carboxaldehido, haloalquilo o haloalcoxi, o

$R_6$, $R_7$ y el nitrogeno al cual se acoplan forman un anillo morfolinilo, tiomorfolinilo, tiomorfolinilo S-óxido, tiomorfolinilo S,S-dióxido, piperidinilo, pirrolidinilo o piperazinilo opcionalmente sustituido con 1 o 2 grupos que son independientemente alquilo $C_1$-$C_4$, alcoxicarbonilo, hidroxilo, hidroxialquilo, dihidroxialquilo o halogeno,

n es 0, 1, 2, 3, 4, 5 o 6,

R, en cada aparicion, es independientemente H o alquilo $C_1$-$C_6$ opcionalmente sustituido con 1 ó 2 grupos que son independientemente OH, SH, halogeno, amino,

monoalquilamino, dialquilamino o cicloalquilo $C_3$-$C_6$,

$R_{30}$ es alquilo $C_1$-$C_6$ opcionalmente sustituido con 1 ó 2 grupos que son independientemente OH, SH, halogeno, amino, monoalquilamino, dialquilamino o cicloalquilo $C_3$-$C_6$,

$R_4$ es H, alquilo opcionalmente sustituido con uno o dos grupos que son independientemente $CO_2R$, $-CO_2$alquilo, $-C(O)NR_6R_7$, $-C(O)R_6$, $-N(R_{30})C(O)NR_{16}R_{17}$, $-N(R_{30})C(O)$-alcoxi($C_1$-$C_6$) o $-NR_6R_7$, arilalcoxi, heteroarilo, arilalquilo, hidroxialquilo, dihidroxialquilo, haloalquilo, $-NR_6R_7$, $-C(O)NR_6R_7$, alcoxi, alcoxialquilo o alcoxialcoxi, en los que

las porciones heteroarilo o arilo de los anteriormente mencionados no se sustituyen o se sustituyen con 1, 2, 3, 4 ó 5 grupos que son independientemente halogeno, hidroxi, alcoxi, alquilo, $-CO_2$-alquil($C_1$-$C_6$), $-CONR_6R_7$, $-NR_6R_7$, $R_6R_7N$-alquil($C_1$-$C_6$)-, nitro, haloalquilo o haloalcoxi, y

$R_5$ es H, arilalquilo, alquilo opcionalmente sustituido con 1, 2 ó 3 grupos que son independientemente arilalcoxicarbonilo, $-NR_8R_9$, halogeno, $-C(O)NR_8R_9$, alcoxicarbonilo o alcanoilo, alcoxialquilo opcionalmente sustituido con un grupo trimetilsililo, alcoxicarbonilo, amino, hidroxialquilo, dihidroxialquilo, alquenilo opcionalmente sustituido con alcoxicarbonilo, alquinilo, $-SO_2$-alquilo, arilo, alcoxi opcionalmente sustituido con un grupo trimetilsililo, heterocicloalquilalquilo, heteroarilalquilo, heterocicloalquilo o heteroarilo, en el que

cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2, 3, 4 ó 5 grupos que son independientemente alquilo, halogeno, alcoxi, arilalcoxi, hidroxialquilo, dihidroxialquilo, tioalcoxi, $-SO_2$alquilo, alcoxicarbonilo, arilalcoxicarbonilo, $CO_2R$, CN, OH, amidino-oxima $NR_8R_9$, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, $-C(O)NR_6R_7$, amidino, hidroxialquilo, dihidroxialquilo, carboxaldehido,

$-NR_6R_7$, haloalquilo, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$, -(alquilo $C_1$-$C_4$)-$CO_2R$, -(alquilo $C_1$-$C_4$)-alcoxi $C_1$-$C_6$ carbonilo, -(alquilo $C_1$-$C_4$)-CN, -(alquilo $C_1$-$C_4$)-$NR_{15}C(O)R_{18}$, $-O-CH_2-O-$, $-O-CH_2CH_2-O-$, fenilo o haloalcoxi,

$R_8$ es hidrogeno, alquilo, alcanoilo, arilalquilo y arilalcanoilo,

$R_9$ es alquilo, alcanoilo, arilalquilo, heteroarilo, aminoalquilo, monoalquilaminoalquilo, dialquilaminoalquilo y arilalcanoilo

Realizacion 3 Compuestos de acuerdo con la realizacion 2, en la que

$R_1$ es H, halógeno, alquilo opcionalmente sustituido con alcoxi $C_1$-$C_4$ carbonilo, carboxaldehido, hidroxialquilo, dihidroxialquilo, fenilalcoxi($C_1$-$C_6$), fenilalquil($C_1$-$C_6$), CN, alcanoilo, alcoxi, alquinilo $C_2$-$C_4$, alquenilo $C_2$-$C_6$ opcionalmente sustituido con alcoxi $C_1$-$C_4$ carbonilo, alcoxialquilo, haloalquilo o fenilalcanoil($C_1$-$C_6$),

en la que los grupos fenilo no se sustituyen o se sustituyen con 1, 2, 3, 4 ó 5 grupos que son independientemente halogeno, alquilo $C_1$-$C_4$, alcoxi $C_1$-$C_4$, nitro, CN, $CF_3$, $OCF_3$ o $CO_2R$,

en la que los grupos alquilo no se sustituyen o se sustituyen con 1, 2 o 3 grupos que son independientemente halogeno, metoxi o etoxi,

$R_2$ es OH, fenilalcoxi($C_1$-$C_6$), feniloxi, feniloxialquil($C_1$-$C_6$), feniltioalcoxi ($C_1$-$C_4$), alcoxi $C_1$-$C_8$, alcoxialcoxi, $-O-SO_2$fenilo, alquinilo, fenilalquinilo ($C_2$-$C_4$), alquilo, $-OC(O)NH(CH_2)_n$fenilo, $-OC(O)N$(alquil)$(CH_2)_n$fenilo, dialquilamino, piridilo, pirimidilo, piridazilo, pirazolilo, imidazolilo, pirrolilo, tetrahidroquinolinilo, tetrahidroisoquinolinilo, tetrazolilo, pirazinilo, bencimidazolilo, triazinilo, tetrahidrofurilo, piperidinilo, hexahidropirimidinilo,

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tiazolilo, tienilo o $CO_2R$, en el que

n es 0, 1, 2, 3, 4, 5 o 6,

cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2, 3, 4 o 5 grupos que son independientemente halogeno, $NR_6R_7$, haloalquilo, haloalcoxi, hidroxialquilo, dihidroxialquilo, alquilo, fenilo, piridilo, piperidinilo, piperazinilo, -alquil($C_1$-$C_6$)-N(R)-$CO_2R_{30}$, $R_6R$-N-(alquilo $C_1$-$C_6$)-, -C(O)$NR_6R_7$, -alquil($C_1$-$C_4$)-C(O)$NR_6R_7$, -(alquilo $C_1$-$C_4$)-NRC(O)$NR_{16}R_{17}$, o -OC(O)$NR_6R_7$, en los que

$R_6$ y $R_7$ son independientemente, en cada aparición, H, alquilo, hidroxi ($C_1$-$C_4$) alquilo, dihidroxi ($C_1$-$C_4$) alquilo, alcoxi ($C_1$-$C_4$), alcoxi ($C_1$-$C_4$) alquilo ($C_1$-$C_4$), alcanoilo ($C_1$-$C_4$), fenilalquilo ($C_1$-$C_4$), fenilalcoxi ($C_1$-$C_4$), fenilalcoxi ($C_1$-$C_4$) carbonilo o fenilalcanoilo ($C_1$-$C_4$), en los que cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2 o 3 grupos que son independientemente halógeno, OH, SH, cicloalquilo $C_3$-$C_6$, alcoxi ($C_1$-$C_4$), alquilo ($C_1$-$C_4$), $CF_3$, carboxaldehido, $NH_2$, NHalquil($C_1$-$C_6$), Nalquil($C_1$-$C_6$) alquil($C_1$-$C_6$), $OCF_3$, o

$R_6$, $R_7$ y el nitrógeno al cual se acoplan forman un anillo morfolinilo, tiomorfolinilo, piperidinilo, pirrolidinilo o piperazinilo opcionalmente sustituido con 1 o 2 grupos que son independientemente alquilo $C_1$-$C_4$, hidroxi, hidroxialquilo $C_1$-$C_4$, dihidroxi $C_1$-$C_4$ alquilo, alcoxi $C_1$-$C_4$ carbonilo o halogeno, y

$R_4$ es H, alquilo opcionalmente sustituido con uno o dos grupos que son independientemente $CO_2R$, -$CO_2$alquilo, -C(O)$NR_6R_7$, -C(O)$R_6$, -N($R_{30}$)C(O)$NR_{16}R_{17}$, -N($R_{30}$)C(O)-alcoxi($C_1$-$C_6$), o -$NR_6R_7$, -C(O)$NR_6R_7$ fenilalcoxi($C_1$-$C_6$), fenilalquil($C_1$-$C_6$) hidroxialquilo, dihidroxialquilo, haloalquilo, alcoxi, alcoxialquilo o alcoxialcoxi, en los que

los grupos fenilo no se sustituyen o se sustituyen con 1, 2, 3, 4 o 5 grupos que son independientemente halogeno, hidroxi, alcoxi, alquilo, nitro, $CF_3$, $OCF_3$,

$R_5$ es fenilalquil($C_1$-$C_6$), alquil($C_1$-$C_6$)opcionalmente sustituido con 1, 2, 3, 4 ó 5 grupos que son independientemente fenilalcoxi $C_1$-$C_4$ carbonilo, $-NR_8R_9$, halógeno, $-C(O)NR_8R_9$, alcoxicarbonilo o alcanoilo, fenilo, alcoxi, alquinilo $C_2$-$C_6$, alquenilo $C_2$-$C_6$ opcionalmente sustituido con alcoxicarbonilo, indolilo, quinolinilo, isoquinolinilo, isoindolilo, dihidroindolilo, pirazolilo, imidazolilo, dihidroisoindolilo, indolon-2-ilo, indazolilo, bencimidazolilo, piridilo, imidazolidina diona, pirazolil(alquilo $C_1$-$C_6$), imidazolil(alquilo $C_1$-$C_6$), piperidinilalquil($C_1$-$C_6$), pirrolidinilalquil($C_1$-$C_6$), imidazolidinilalquil($C_1$-$C_6$), tetrahidroisoquinolinilalquil($C_1$-$C_6$), 1H-indazolilalquil($C_1$-$C_6$), dihidroindolon-2-il(alquilo $C_1$-$C_6$), indolinil(alquilo $C_1$-$C_6$), dihidrobenimidazolil(alquilo $C_1$-$C_6$) o dihidrobenzoimidazolonil(alquilo $C_1$-$C_6$), piridilalquilo ($C_1$-$C_6$), piridazinilalquilo ($C_1$-$C_6$), pirimidinilalquilo ($C_1$-$C_6$), pirazinilalquilo ($C_1$-$C_6$), tetrahidrofurilalquil($C_1$-$C_6$), naftilalquil($C_1$-$C_6$), morfolinilalquilo ($C_1$-$C_6$), tetrahidrofurilalquilo ($C_1$-$C_6$), tienilalquilo ($C_1$-$C_6$), piperazinilalquilo ($C_1$-$C_6$), indolilalquilo ($C_1$-$C_6$), quinolinilalquilo ($C_1$-$C_6$), isoquinolinilalquilo ($C_1$-$C_6$), isoindolilalquilo ($C_1$-$C_6$), dihidroindolilalquilo ($C_1$-$C_6$), pirazolilalquilo ($C_1$-$C_4$), imidazolilalquilo ($C_1$-$C_4$), dihidroisoindolilalquilo ($C_1$-$C_6$), indolon-2-ilalquilo ($C_1$-$C_6$), indolon-2-ilalquilo ($C_1$-$C_6$) o morfolinilalquilo $C_1$-$C_6$, en los que

cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2, 3, 4 o 5 grupos que son independientemente alquilo $C_1$-$C_6$, halogeno, alcoxi $C_1$-$C_6$,

fenilalcoxi $C_1$-$C_6$, tioalcoxi $C_1$-$C_6$, alcoxi $C_1$-$C_6$ carbonilo, $CO_2R$, CN, -$SO_2$alquil($C_1$-$C_6$), amidino-oxima, $NR_8R_9$, -$NR_6R_7$, $NR_6R_7$ alquilo $C_1$-$C_6$, -C(O)$NR_6R_7$, -alquil($C_1$-$C_4$)-C(O)$NR_6R_7$, amidino, haloalquilo $C_1$-$C_4$, hidroxialquilo $C_1$-$C_6$, dihidroxi $C_1$-$C_6$ alquilo o haloalcoxi $C_1$-$C_4$, en los que

$R_8$ es hidrogeno, alquilo $C_1$-$C_6$, alcanoilo $C_1$-$C_6$, fenilalquilo $C_1$-$C_6$ y fenilalcanoilo $C_1$-$C_6$, y

$R_9$ es aminoalquilo, monoalquilo $C_1$-$C_6$ aminoalquilo $C_1$-$C_6$, dialquilo $C_1$-$C_6$ aminoalquilo $C_1$-$C_6$, alquilo $C_1$-$C_6$, alcanoilo $C_1$-$C_6$, fenilalquilo $C_1$-$C_6$, indazolilo y fenilalcanoilo $C_1$-$C_6$

Realizacion 4 Compuestos de acuerdo con la realizacion 3, en la que

$R_1$ es H, halogeno, alquilo $C_1$-$C_4$ opcionalmente sustituido con alcoxi $C_1$-$C_4$ carbonilo, alquenilo $C_2$-$C_4$ opcionalmente sustituido con alcoxi $C_1$-$C_4$ carbonilo, alquinilo $C_2$-$C_4$ o carboxaldehido,

$R_2$ es benciloxi, OH, feniloxi, feniloxialquil($C_1$-$C_6$), feniltioalcoxi ($C_1$-$C_4$) o piridilo, en el que cada uno de los anteriormente mencionados se sustituye opcionalmente con 1, 2, 3, 4 o 5 grupos que son independientemente halogeno, -alquil($C_1$-$C_6$)-N(R)-$CO_2R_{30}$, $NR_6R_7$, -alquil($C_1$-$C_4$)-C(O)$NR_6R_7$, haloalquilo ($C_1$-$C_4$), -C(O)$NR_6R_7$, -(alquilo $C_1$-$C_4$)-NRC(O)$NR_{16}R_{17}$, haloalcoxi ($C_1$-$C_4$), hidroxialquilo, dihidroxi $C_1$-$C_6$ alquilo, alquilo ($C_1$-$C_6$), piridilo o $R_6R_7N$-(alquilo $C_1$-$C_6$)-

Realización 4a Compuestos de acuerdo con la realizacion 4, en la que $R_1$ es H

Realizacion 4b Compuestos de acuerdo con la realizacion 4, en la que $R_1$ es halogeno

Realización 4c Compuestos de acuerdo con la realizacion 4, en la que $R_1$ es alquilo $C_1$-$C_4$ opcionalmente sustituido con alcoxi $C_1$-$C_4$ carbonilo

Realizacion 5 Compuestos de acuerdo con la realizacion 4, en la que

$R_5$ es indolilo, piridilo, piridazinilo, pirimidinilo, indazolilo, tetrahidroquinolilo, tetrahidroisoquinolilo, pirazolilo, imidazolilo, furanilo, quinolinilo, isoquinolinilo, isoindolilo, dihidroindolilo, dihidroisoindolilo, indolon-2-ilo o pirazinilo, cada uno de los cuales no se sustituye o se sustituye con 1, 2, 3, 4 o 5 grupos que son independientemente alquilo $C_1$-$C_4$, halogeno, $CF_3$, $OCF_3$, $-CO_2CH_3$, hidroxi $C_1$-$C_4$ alquilo, dihidroxialquilo, alcoxi $C_1$-$C_4$, $-CO_2$(alquilo $C_1$-$C_5$), benciloxi, $-NR_6R_7$, -alquil($C_1$-$C_4$)-$C(O)NR_6R_7$, $-NR_8R_9$, $NR_6R_7$-(alquilo $C_1$-$C_4$), $-C(O)NR_6R_7$, o amidino-oxima, en los que

$R_6$ y $R_7$ son independientemente, en cada aparición, H, alquilo $C_1$-$C_4$, hidroxi $C_1$-$C_4$ alquilo, dihidroxi $C_1$-$C_4$ alquilo, alcoxi $C_1$-$C_4$ alcoxi $C_1$-$C_4$ alquilo $C_1$-$C_4$, alcanoilo $C_1$-$C_4$, fenilalquilo $C_1$-$C_4$, fenilalcoxi $C_1$-$C_4$ o fenilalcanoilo $C_1$-$C_4$, en los que cada uno no se sustituye o se sustituye con 1, 2 o 3 grupos que son independientemente halogeno, OH, SH, cicloalquilo $C_3$-$C_6$, arilo, alcoxi $C_1$-$C_4$, alquilo $C_1$-$C_4$, OH, $CF_3$ u $OCF_3$, o

$R_6$, $R_7$ y el nitrógeno al cual se acoplan forman un anillo morfolinilo, tiomorfolinilo, pirrolidinilo o piperazinilo opcionalmente sustituido con 1 ó 2 grupos que son independientemente alquilo $C_1$-$C_4$, hidroxi, hidroxialquilo $C_1$-$C_4$, dihidroxi $C_1$-$C_4$ alquilo o halógeno

Realización 6 Compuestos de acuerdo con la realizacion 5, en la que

$R_5$ es indolilo, piridilo, pirimidinilo, pirazolilo, furanilo, indazolilo, dihidroindolilo, dihidroisoindolilo, indolon-2-il o pirazinilo, cada uno de los cuales no se sustituye o se sustituye con 1, 2, 3 o 4 grupos que son independientemente alquilo $C_1$-$C_4$, halogeno, $CF_3$, $OCF_3$,

$-CO_2CH_3$, hidroxi $C_1$-$C_4$ alquilo, dihidroxi $C_1$-$C_4$ alquilo, alcoxi $C_1$-$C_4$, $-CO_2$(alquilo $C_1$-$C_5$), benciloxi, $-C(O)NR_6R_7$, $-NR_8R_9$, -alquil($C_1$-$C_4$)-$C(O)NR_6R_7$, $-NR_6R_7$, $NR_6R_7$-(alquilo $C_1$-$C_4$)- y amidino-oxima

Realización 7 Compuestos de acuerdo con la realizacion 6, en la que

$R_5$ es indolilo, piridilo, pirimidinilo, dihidroindolilo, dihidroisoindolilo, pirazolilo o pirazinilo, cada unc de los cuales no se sustituye o se sustituye con 1, 2, 3 ó 4 grupos que son independientemente alquilo $C_1$-$C_4$, halogeno, $CF_3$, $OCF_3$, $-CO_2CH_3$, hidroxi $C_1$-$C_4$ alquilo, dihidroxi $C_1$-$C_4$ alquilo, alcoxi $C_1$-$C_4$, $-CO_2$(alquilo $C_1$-$C_5$), benciloxi, $-C(O)NR_6R_7$, $-NR_8R_9$, -alquil($C_1$-$C_4$)-$C(O)NR_6R_7$, $-NR_6R_7$, $NR_6R_7$-(alquilo $C_1$-$C_4$)- o amidino-oxima, en los que

$R_6$ y $R_7$ son independientemente, en cada aparición, H, alquilo $C_1$-$C_4$, hidroxi $C_1$-$C_4$ alquilo, dihidroxi $C_1$-$C_4$ alquilo, alcoxi $C_1$-$C_4$ alcanoilo $C_1$-$C_4$, alcoxi $C_1$-$C_4$ alquilo $C_1$-$C_4$ cada uno de los cuales se sustituye opcionalmente con 1, 2 ó 3 grupos que son independientemente halogeno, OH, SH, cicloalquilo $C_3$-$C_6$, alcoxi $C_1$-$C_4$, alquilo $C_1$-$C_4$, OH, $CF_3$ u $OCF_3$

Realización 8 Compuestos de acuerdo con la realización 7, en la que

$R_5$ es incolilo, piridilo, pirimidinilo, dihidroindolilo, dihidroisoindolilo, pirazolilo o pirazinilo, cada uno de los cuales no se sustituye o se sustituye con 1, 2 o 3 grupos que son independientemente alquilo $C_1$-$C_4$, halogeno, $CF_3$, $OCF_3$, hidroxi $C_1$-$C_4$ alquilo, dihidroxi $C_1$-$C_4$ alquilo, alcoxi $C_1$-$C_4$, $-C(O)NR_6R_7$, -alquil($C_1$-$C_4$)-$C(O)NR_6R_7$, $NR_8R_9$, $-NR_6R_7$ o $NR_6R_7$-(alquilo $C_1$-$C_4$), en los que

$R_6$ y $R_7$ son indevendientemente, en cada aparición, H,

alquilo $C_1$-$C_4$, hidroxi $C_1$-$C_4$ alquilo, dihidroxi $C_1$-$C_4$ alquilo, alcanoilo $C_1$-$C_4$ o alcoxi $C_1$-$C_4$ cada uno de los cuales se sustituye opcionalmente con 1, 2 ó 3 grupos que son independientemente halogeno, OH, SH, cicloalquilo $C_3$-$C_6$, alcoxi $C_1$-$C_4$, alquilo $C_1$-$C_4$, OH, $CF_3$ u $OCF_3$

Realización 9 Compuestos de acuerdo con la realización 4, en la que

$R_5$ es fenilo, fenilalquil($C_1$-$C_6$) o alquil($C_1$-$C_6$), en el que

cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2, 3, 4 o 5 grupos que son independientemente alquilo, halogeno, alcoxi, benciloxi, hidroxialquilo, dihidroxialquilo, tioalcoxi, $-CO_2$(alquilo $C_1$-$C_5$), $CO_2R$, CN, amidino-oxima, $-NR_8R_9$, $-NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, $-C(O)NR_6R_7$, -alquil($C_1$-$C_4$)-$C(O)NR_6R_7$, amidino, $CF_3$ u $OCF_3$,

$R_8$ es hidrógeno, alquilo $C_1$-$C_6$, alcanoilo $C_1$-$C_6$, fenilalquilo $C_1$-$C_6$ y fenilalcanoilo $C_1$-$C_6$, y

$R_9$ es aminoalquilo, monoalquilo $C_1$-$C_6$ aminoalquilo $C_1$-$C_6$, dialquilo $C_1$-$C_6$ aminoalquilo $C_1$-$C_6$, alquilo $C_1$-$C_6$, alcanoilo $C_1$-$C_6$, fenilalquilo $C_1$-$C_4$, indazolilo y fenilalcanoilo $C_1$-$C_4$

Realizacion 10 Compuestos de acuerdo con la realizacion 4, en la que

$R_5$ es fenilo, fenilalquil($C_1$-$C_6$), que no se sustituye o se sustituye con 1, 2, 3, 4 o 5 grupos que son independientemente alquilo, halogeno, alcoxi, benciloxi, tioalcoxi, $-CO_2$(alquilo $C_1$-$C_5$), $CO_2R$, CN, amidino-oxima, $-NR_8R_9$, $-NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, $R_6R_7NC(O)$-(alquilo $C_1$-$C_4$)-, $R_6R_7NC(O)$-(alquilo $C_5$-$C_6$)-, $-C(O)NR_6R_7$, amidino, $CF_3$ u $OCF_3$, en los que

$R_6$ y $R_7$ son independientemente, en cada aparicion, H, alquilo $C_1$-$C_4$, hidroxi $C_1$-$C_4$ alquilo, dihidroxi $C_1$-$C_4$

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alquilo, alcoxi $C_1$-$C_4$, alcoxi $C_1$-$C_4$ alquilo $C_1$-$C_4$, alcanoilo $C_1$-$C_4$, fenilalquilo $C_1$-$C_4$, fenilalcoxi $C_1$-$C_4$ o fenilalcanoilo $C_1$-$C_4$, en el que cada uno no está sustituido o está sustituido con 1, 2 o 3 grupos que son independientemente halogeno, OH, SH, cicloalquilo $C_3$-$C_6$, alcoxi $C_1$-$C_4$, alquilo $C_1$-$C_4$, $CF_3$ u $OCF_3$ o

$R_6$, $R_7$ y el nitrogeno al cual se acoplan forman un anillo morfolinilo, tiomorfolinilo o piperazinilo opcionalmente sustituido con 1 o 2 grupos que son independientemente alquilo $C_1$-$C_4$, hidroxi, hidroxialquilo $C_1$-$C_4$, dihidroxi $C_1$-$C_4$ alquilo o halogeno,

$R_8$ es hidrógeno, alquilo $C_1$-$C_6$, alcanoilo $C_1$-$C_6$, fenilalquilo $C_1$-$C_6$ y fenilalcanoilo $C_1$-$C_6$, y

$R_9$ es aminoalquilo, monoalquilo $C_1$-$C_6$ aminoalquilo $C_1$-$C_6$, dialquilo $C_1$-$C_6$ aminoalquilo $C_1$-$C_6$, alcanoilo $C_1$-$C_6$, fenilalquilo $C_1$-$C_4$, indazolilo y fenilalcanoilo $C_1$-$C_4$

Realización 11 Compuestos de acuerdo con la realización 10, en la que

$R_5$ es fenilo, bencilo o fenetilo, en el que cada uno se sustituye opcionalmente con 1, 2, 3, 4 o 5 grupos que son independientemente alquilo $C_1$-$C_6$, $-NR_6R_7$, $-C(O)NR_6R_7$ -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$, $-NR_8R_9$, halogeno, alcoxi $C_1$-$C_6$, $CO_2R$, -(alquilo $C_1$-$C_4$)-$CO_2R$, tioalcoxi $C_1$-$C_6$, amidino-oxima, alcoxi $C_1$-$C_6$ carbonilo, -(alquilo $C_1$-$C_4$)-alcoxi $C_1$-$C_6$ carbonilo, hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-$C_6$ alquilo, -(alquilo $C_1$-$C_4$)-CN, CN, fenilalcoxi $C_1$-$C_6$, OH, haloalquilo $C_1$-$C_4$, haloalcoxi $C_1$-$C_4$, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, -(alquilo $C_1$-$C_4$)-$NR_{15}C(O)R_{18}$, amidino-oxima, $-SO_2$(alquilo $C_1$-$C_6$), $-O-CH_2-O-$, $-O-CH_2CH_2-O-$, fenilalcoxi $C_1$-$C_4$ o fenilo, en los que

$R_6$ y $R_7$ son independientemente, en cada aparición, H, alquilo $C_1$-$C_4$, hidroxi $C_1$-$C_4$ alquilo, dihidroxi $C_1$-$C_4$ alquilo, alcanoilo $C_1$-$C_4$ o alcoxi $C_1$-$C_4$ cada uno de los cuales se sustituye opcionalmente con 1, 2 ó 3 grupos que

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son independientemente halogeno, OH, SH, cicloalquilo $C_3$-$C_6$, alcoxi $C_1$-$C_4$, alquilo $C_1$-$C_4$, OH, $CF_3$ u $OCF_3$

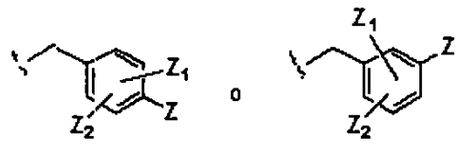
Realización 12 Compuestos de acuerdo con la realizacion 11, en la que

$R_5$ es fenilo, bencilo o fenetilo, cada uno de los cuales no se sustituye o se sustituye con 1, 2, 3, 4 ó 5 grupos que son independientemente CN, halógeno, alcoxi $C_1$-$C_4$, $CF_3$, $OCF_3$, alquilo $C_1$-$C_4$, $-NR_8R_9$, $-NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)- o $-C(O)NR_6R_7$, en los que

$R_6$ y $R_7$ son independientemente, en cada aparicion, H, alquilo $C_1$-$C_4$, hidroxi $C_1$-$C_4$ alquilo, dihidroxi $C_1$-$C_4$ alquilo, alcanoilo $C_1$-$C_4$ o alcoxi $C_1$-$C_4$ cada uno de los cuales se sustituye opcionalmente con 1, 2 o 3 grupos que son independientemente halogeno, OH, SH, cicloalquilo $C_3$-$C_6$, alcoxi $C_1$-$C_4$, alquilo $C_1$-$C_4$, OH, $CF_3$ u $OCF_3$

Realizacion 13 Compuestos de acuerdo con la realizacion 4, en la que

el grupo $R_5$ es de la formula



en la que

$Z_1$ y $Z_2$ son independientemente H, halogeno, alquilo $C_1$-$C_4$ o $CO_2R$, y

Z es $-C(O)NR_6R_7$ $-alquil(C_1-C_4)-C(O)NR_6R_7$, $-$(alquilo $C_1$-$C_4$)$-NR_{15}C(O)R_{18}$, $-NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, $-NR_8R_9$, hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-$C_6$ alquilo, alquilo $C_1$-$C_6$, $CO_2R$ o halogeno, en el que

$R_6$ y $R_7$ en cada aparicion, son independientemente H, OH, alquilo $C_1$-$C_6$, aminoalquilo $C_1$-$C_4$, NH(alquilo $C_1$-$C_6$)alquilo, N(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$) alquilo $C_1$-$C_6$,

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hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-$C_6$ alquilo, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$ o -$SO_2$(alquilo $C_1$-$C_6$), cada uno de los cuales se sustituye opcionalmente con 1, 2 o 3 grupos que son independientemente halogeno, OH, SH, cicloalquilo $C_3$-$C_6$, alcoxi $C_1$-$C_4$, alquilo $C_1$-$C_4$, OH, $CF_3$ u $OCF_3$,

o

$R_6$, $R_7$ y el nitrogeno al cual se acoplan forman un anillo piperidinilo, pirrolidinilo, piperazinilo, morfolinilo, tiomorfolinilo opcionalmente sustituido con 1 ó 2 grupos que son independientemente alquilo, hidroxi, hidroxialquilo $C_1$-$C_4$, dihidroxi $C_1$-$C_4$ alquilo o halogeno, y

$R_{18}$ es alquilo $C_1$-$C_6$ opcionalmente sustituido con -O-(alcanoilo $C_2$-$C_6$, hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-$C_4$ alquilo, alcoxi $C_1$-$C_6$, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, aminoalquilo $C_1$-$C_6$, mono o dialquilaminoalquilo $C_1$-$C_6$

Realización 14 Compuestos de acuerdo con la realización 4, en la que

$R_5$ es pirazolil(alquilo $C_1$-$C_6$), imidazolil(alquilo $C_1$-$C_6$), tienil(alquilo $C_1$-$C_6$), furanil(alquilo $C_1$-$C_6$), piperidinilalquil($C_1$-$C_6$), pirrolidinialquilil($C_1$-$C_6$), imidazolidinilalquil($C_1$-$C_6$), piperazinilalquil($C_1$-$C_6$), piridilalquil($C_1$-$C_6$), pirimidilalquil($C_1$-$C_6$), piridazilalquil($C_1$-$C_6$), pirazinilalquil($C_1$-$C_6$), isoquinolinilalquil($C_1$-$C_6$), tetrahidroisoquinolirilalquil($C_1$-$C_6$), indolilalquil($C_1$-$C_6$), 1H-indazolilalquil($C_1$-$C_6$), dihidroindolil(alquilo $C_1$-$C_6$), dihidroindolon-2-il(alquilo $C_1$-$C_6$), indolinil(alquilo $C_1$-$C_6$), dihidroisoindolil(alquilo $C_1$-$C_6$), dihidrobencimdazolil(alquilo $C_1$-$C_6$) o dihidrobenzoimidazolcnil(alquilo $C_1$-$C_6$), en el que

cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2, 3, 4 ó 5 grupos que son independientemente alquil($C_1$-$C_6$), halógeno, alcoxi($C_1$-$C_6$),

hidroxi($C_1$-$C_6$)alquilo, dihidroxi $C_1$-$C_6$ alquilo, fenilalcoxi($C_1$-$C_6$), tioalcoxi($C_1$-$C_6$), alcoxi($C_1$-$C_6$)carbonilo, fenilalcoxi($C_1$-$C_6$)carbonilo, OH, $CO_2R$, CN, amidino-oxima, -$NR_8R_9$, -$NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, -C(O)$NR_6R_7$, -(alquilo $C_1$-$C_4$)-C(O)$NR_6R_7$ amidino, piperazinilo, morfolinilo, -$SO_2$ alquilo ($C_1$-$C_6$), -$SO_2NH_2$, -$SO_2$NHalquil($C_1$-$C_6$), -$SO_2$Nalquil($C_1$-$C_6$) alquil($C_1$-$C_6$), haloalquil($C_1$-$C_4$), -(alquilo $C_1$-$C_4$)-$NR_{15}$C(O)$NR_{16}R_{17}$, -(alquilo $C_1$-$C_4$)-$NR_{15}$C(O)$R_{18}$, -O-$CH_2$-O, -O-$CH_2CH_2$-O-, o haloalcoxi($C_1$-$C_4$), en los que

$R_6$ y $R_7$ son independientemente, en cada aparición, H, alquil($C_1$-$C_6$), alcoxi($C_1$-$C_6$), alcoxi($C_1$-$C_6$)alquil($C_1$-$C_6$), alcoxi($C_1$-$C_6$)carbonilo, hidroxi($C_1$-$C_6$)alquilo, dihidroxi $C_1$-$C_6$ alquilo, -alquil($C_1$-$C_4$)-$CO_2$-alquil($C_1$-$C_6$), alcanoil($C_1$-$C_6$), fenilalquil($C_1$-$C_6$), fenilalcoxi($C_1$-$C_6$) o fenilalcanoil($C_1$-$C_6$), en los que cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2 o 3 grupos que son independientemente halogeno, alcoxi($C_1$-$C_4$), OH, SH, cicloalquilo $C_3$-$C_6$, $NH_2$, NH(alquilo $C_1$-$C_6$), N(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$), alquil($C_1$-$C_4$), $CF_3$ u $OCF_3$, o

$R_6$, $R_7$ y el nitrógeno al cual se acoplan forman un anillo morfolinilo, tiomorfolinilo, piperidinilo, pirrolidinilo o piperazinilo opcionalmente sustituido con 1 ó 2 grupos que son independientemente alquilo $C_1$-$C_4$, hidroxi, hidroxialquilo $C_1$-$C_4$, dihidroxi $C_1$-$C_4$ alquilo o halogeno, y

$R_{18}$ es alquilo $C_1$-$C_6$ opcionalmente sustituido con -O-(alcanoilo $C_2$-$C_6$, hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-$C_6$ alquilo, alcoxi $C_1$-$C_6$, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, aminoalquilo $C_1$-$C_6$, mono o dialquilaminoalquilo $C_1$-$C_6$

En esta realizacion, se prefiere que $R_6$ y $R_7$ no sean simultaneamente OH, y

$R_6$ y $R_7$ no sean simultáneamente -$SO_2$(alquilo $C_1$-$C_6$)

Realizacion 15 Compuestos de acuerdo con la realizacion 14, en la que

$R_5$ es pirazolil(alquilo $C_1$-$C_6$), imidazolil(alquilo $C_1$-$C_6$), bencimidazolil(alquilo $C_1$-$C_6$), tienil(alquilo $C_1$-$C_6$), pirimidilalquil($C_1$-$C_6$), indolil(alquilo $C_1$-$C_6$), dihidroindolil(alquilo $C_1$-$C_6$), dihidroisoindolil(alquilo $C_1$-$C_6$), dihidroindolon-3-il(alquilo $C_1$-$C_6$), piridinil(alquilo $C_1$-$C_6$), piperazinil(alquilo $C_1$-$C_6$), o pirazinil(alquilo $C_1$-$C_6$) cada uno de los cuales se sustituye opcionalmente con 1, 2 o 3 grupos que son independientemente alquilo $C_1$-$C_4$, hidroxi $C_1$-$C_4$ alquilo, dihidroxi $C_1$-$C_4$ alquilo, halogeno, $-C(O)NR_6R_7$, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$ alcoxi $C_1$-$C_6$ carbonilo, $-NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, haloalquilo, alcanoilo $C_1$-$C_6$,

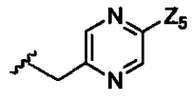
$R_6$ y $R_7$, en cada aparición, son independientemente H, alquilo $C_1$-$C_6$ opcionalmente sustituido con 1, 2 o 3 grupos que son independientemente alcoxi $C_1$-$C_4$ carbonilo, halógeno, cicloalquilo $C_3$-$C_6$, OH, SH o alcoxi $C_1$-$C_4$,

o

$R_6$, $R_7$ y el nitrogeno al cual se acoplan forman un anillo piperidinilo, pirrolidinilo, piperazinilo o morfolinilo opcionalmente sustituido con 1 ó 2 grupos que son independientemente alquilo, hidroxi, hidroxialquilo $C_1$-$C_4$, dihidroxi $C_1$-$C_4$ alquilo o halogeno

Realización 16 Compuestos de acuerdo con la realizacion 15, en la que

$R_5$ es de la formula




en la que

$Z_5$ es alquilo $C_1$-$C_4$, hidroxi $C_1$-$C_4$ alquilo, dihidroxi $C_1$-$C_4$ alquilo, halógeno, $-C(O)NR_6R_7$, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$ alcoxi $C_1$-$C_6$ carbonilo, $R_6R_7N$-(alquilo $C_1$-$C_6$)-,

$-NR_6R_7$, $CF_3$ o alcanoilo $C_1$-$C_6$, en el que

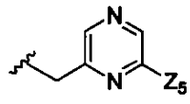
$R_6$ y $R_7$, en cada aparicion, son independientemente H, alquilo $C_1$-$C_6$ opcionalmente sustituido con 1, 2 o 3 grupos que son independientemente alcoxi $C_1$-$C_4$ carbonilo, halógeno, cicloalquilo $C_3$-$C_6$, OH, SH o alcoxi $C_1$-$C_4$,

o

$R_6$, $R_7$ y el nitrogeno al cual se acoplan forman un anillo piperidinilo, pirrolidinilo, piperazinilo o morfolinilo opcionalmente sustituido con 1 o 2 grupos que son independientemente alquilo, hidroxi, hidroxialquilo $C_1$-$C_4$, dihidroxi $C_1$-$C_4$ alquilo o halógeno

Realización 17 Compuestos de acuerdo con la realizacion 15, en la que

$R_5$ es de la fórmula



en la que

$Z_5$ es alquilo ($_1$-$C_4$, hidroxi $C_1$-$C_4$ alquilo, dihidroxi $C_1$-$C_4$ alquilo, halógeno, $-C(O)NR_6R_7$, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$ alcoxi $C_1$-$C_6$ carbonilo, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, $-NR_6R_7$, $CF_3$ o alcanoilo $C_1$-$C_6$, en el que

$R_6$ y $R_7$, en cada aparición, son independientemente H, alquilo $C_1$-$C_6$ opcionalmente sustituido con 1, 2 o 3 grupos que son independientemente alcoxi $C_1$-$C_4$ carbonilo, halogeno, cicloalquilo $C_3$-$C_6$, OH, SH o alcoxi $C_1$-$C_4$,

o

$R_6$, $R_7$ y el nitrogeno al cual se acoplan forman un anillo piperidinilo, pirrolidinilo, piperazinilo o morfolinilo opcionalmente sustituido con 1 o 2 grupos que son independientemente alquilo, hidroxi, hidroxialquilo $C_1$-$C_4$, dihidroxi $C_1$-$C_4$ alquilo o halogeno

Realizacion 18 Compuestos de acuerdo con

cualquiera de las realizaciones 16 ó 17, en las que

$Z_5$ es alquilo $C_1$-$C_4$, hidroxi $C_1$-$C_4$ alquilo, dihidroxi $C_1$-$C_4$ alquilo, halogeno, alcoxi $C_1$-$C_6$ carbonilo, $CF_3$ o alcanoilo $C_1$-$C_6$

Realización 19 Compuestos de acuerdo con cualquiera de las realizaciones 16 ó 17, en las que

$Z_5$ es alquilo $C_1$-$C_4$, $-C(O)NR_6R_7$, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)- o $-NR_6R_7$, $CF_3$ o alcanoilo $C_1$-$C_4$, en el que

$R_6$ y $R_7$, en cada aparicion, son independientemente H, alquilo $C_1$-$C_6$ opcionalmente sustituido con 1, 2 o 3 grupos que son independientemente alcoxi $C_1$-$C_4$ carbonilo, halogeno, cicloalquilo $C_3$-$C_6$, OH, SH o alcoxi $C_1$-$C_4$,

o

$R_6$, $R_7$ y el nitrogeno al cual se acoplan forman un anillo piperidinilo, pirrolidinilo, piperazinilo o morfolinilo opcionalmente sustituido con 1 o 2 grupos que son independientemente alquilo, hidroxi, hidroxialquilo $C_1$-$C_4$, dihidroxi $C_1$-$C_4$ alquilo o halógeno

Realizacion 20 Compuestos de acuerdo con la realizacion 19, en la que

$Z_5$ es $-C(O)NR_6R_7$, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)- o $-NR_6R_7$, en el que

$R_6$ y $R_7$, en cada aparicion, son independientemente H, alquilo $C_1$-$C_6$ opcionalmente sustituido con 1, 2 ó 3 grupos que son independientemente alcoxi $C_1$-$C_4$ carbonilo, halogeno, ciclopropilo, OH, SH o alcoxi $C_1$-$C_4$

Realizacion 21 Compuestos de acuerdo con la realizacion 15, en la que

$R_5$ es de la formula  , en la que

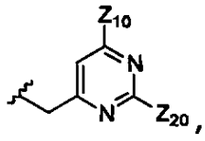
$Z_{10}$ es H o metilo, y

560
561

$Z_{20}$ es hidroxialquil($C_1$-$C_4$), dihidroxi $C_1$-$C_4$ alquilo, OH, halogeno, haloalquilo, alquil($C_1$-$C_4$), $OCF_3$, $-NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$ o -$C(O)NR_6R_7$, en el que

$R_6$ y $R_7$, en cada aparicion, son independientemente H, alquilo $C_1$-$C_6$ opcionalmente sustituido con 1, 2 o 3 grupos que son independientemente alcoxi $C_1$-$C_4$ carbonilo, halógeno, cicloalquilo $C_3$-$C_6$, OH, SH o alcoxi $C_1$-$C_4$

Realización 22 Compuestos de acuerdo con la realizacion 15, en la que

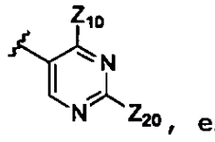
$R_5$ es de la fórmula  , en la que

$Z_{10}$ es H o metilo, y

$Z_{20}$ es hidroxialquil($C_1$-$C_4$), dihidroxi $C_1$-$C_4$ alquilo, OH, halogeno, $CF_3$ alquil($C_1$-$C_4$), $OCF_3$, $-NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$ o -$C(O)NR_6R_7$, en el que

$R_6$ y $R_7$, en cada aparicion, son independientemente H, alquilo $C_1$-$C_6$ opcionalmente sustituido con 1, 2 ó 3 grupos que son independientemente alcoxi $C_1$-$C_4$ carbonilo, halogeno, cicloalquilo $C_3$-$C_6$, OH, SH o alcoxi $C_1$-$C_4$

Realizacion 23 Compuestos de acuerdo con la realizacion 15, en la que

$R_5$ es de la formula  , en la que

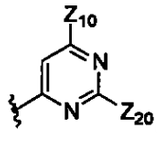
$Z_{10}$ es H o metilo, y

$Z_{20}$ es hidroxialquil($C_1$-$C_4$), dihidroxi $C_1$-$C_4$ alquilo, OH, halogeno, haloalquilo, alquil($C_1$-$C_4$), $OCF_3$, $-NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$ o -$C(O)NR_6R_7$, en el que

$R_6$ y $R_7$, en cada aparición, son independientemente H,

alquilo $C_1$-$C_6$ opcionalmente sustituido con 1, 2 ó 3 grupos que son independientemente alcoxi $C_1$-$C_4$ carbonilo, halogeno, cicloalquilo $C_3$-$C_6$, OH, SH o alcoxi $C_1$-$C_4$

Realizacion 24 Compuestos de acuerdo con la realización 15, en la que

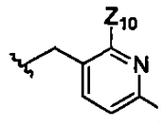
$R_5$ es de la fórmula  en la que

$Z_{10}$ es H o metilo, y

$Z_{20}$ es hidroxialquil($C_1$-$C_4$), dihidroxi $C_1$-$C_4$ alquilo, OH, halógeno, $CF_3$ alquil($C_1$-$C_4$), $OCF_3$, $-NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$ o $-C(O)NR_6R_7$, en el que

$R_6$ y $R_7$, en cada aparición, son independientemente H, alquilo $C_1$-$C_6$ opcionalmente sustituido con 1, 2 ó 3 grupos que son independientemente alcoxi $C_1$-$C_4$ carbonilo, halogeno, cicloalquilo $C_3$-$C_6$, OH, SH o alcoxi $C_1$-$C_4$

Realizacion 25 Compuestos de acuerdo con la realizacion 15, en la que

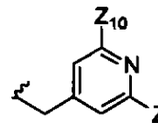
$R_5$ es de la fórmula  en la que

$Z_{10}$ es H o metilo, y

$Z_{20}$ es hidroxialquil($C_1$-$C_4$), dihidroxi $C_1$-$C_4$ alquilo, OH, halogeno, haloalquilo, alquil($C_1$-$C_4$), $OCF_3$, $-NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$ o $-C(O)NR_6R_7$, en el que

$R_6$ y $R_7$, en cada aparición, son independientemente H, alquilo $C_1$-$C_6$ opcionalmente sustituido con 1, 2 o 3 grupos que son independientemente alcoxi $C_1$-$C_4$ carbonilo, halogeno, cicloalquilo $C_3$-$C_6$, OH, SH o alcoxi $C_1$-$C_4$

Realización 26 Compuestos de acuerdo con la realizacion 15, en la que

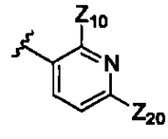
$R_5$ es de la fórmula  en la que

$Z_{10}$ es H o metilo, y

$Z_{20}$ es hidroxialquil($C_1$-$C_4$), dihidroxi $C_1$-$C_4$ alquilo, OH, halogeno, $CF_3$ alquil($C_1$-$C_4$), $OCF_3$, $-NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$ o $-C(O)NR_6R_7$, en el que

$R_6$ y $R_7$, en cada aparición, son independientemente H, alquilo $C_1$-$C_6$ opcionalmente sustituido con 1, 2 o 3 grupos que son independientemente alcoxi $C_1$-$C_4$ carbonilo, halogeno, cicloalquilo $C_3$-$C_6$, OH, SH o alcoxi $C_1$-$C_4$

Realizacion 27 Compuestos de acuerdo con la realización 15, en la que

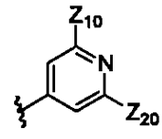
$R_5$ es de la formula  en la que

$Z_{10}$ es H o metilo, y

$Z_{20}$ es hidroxialquil($C_1$-$C_4$), dihidroxi $C_1$-$C_4$ alquilo, OH, halogeno, haloalquilo, alquil($C_1$-$C_4$), $OCF_3$, $-NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$ o $-C(O)NR_6R_7$, en el que

$R_6$ y $R_7$, en cada aparición, son independientemente H, alquilo $C_1$-$C_6$ opcionalmente sustituido con 1, 2 o 3 grupos que son independientemente alcoxi $C_1$-$C_4$ carbonilo, halogeno, cicloalquilo $C_3$-$C_6$, OH, SH o alcoxi $C_1$-$C_4$

Realizacion 28 Compuestos de acuerdo con la realizacion 15, en la que

$R_5$ es de la fórmula  , en la que

$Z_{10}$ es H o metilo, y

563
564

$Z_{20}$ es hidroxialquil($C_1$-$C_4$), dihidroxi $C_1$-$C_4$ alquilo, OH, halogeno, $CF_3$ alquil($C_1$-$C_4$), $OCF_3$, $-NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$ o $-C(O)NR_6R_7$, en el que $R_6$ y $R_7$, en cada aparición, son independientemente H, alquilo $C_1$-$C_6$ opcionalmente sustituido con 1, 2 o 3 grupos que son independientemente alcoxi $C_1$-$C_4$ carbonilo, halogeno, cicloalquilo $C_3$-$C_6$, OH, SH o alcoxi $C_1$-$C_4$

Realización 29 Compuestos de acuerdo con la realización 4, en la que

$R_5$ es fenilo, opcionalmente sustituido con 1, 2, 3, 4 o 5 grupos que son independientemente alquilo $C_1$-$C_4$, -$C(O)NR_6R_7$, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$ $-NR_6R_7$, $NR_6R_7$(alquilo $C_1$-$C_6$), hidroxi $C_1$-$C_6$ alquilo, dihidroxialquilo, halógeno, alcoxi $C_1$-$C_4$, $CO_2R$, OH, alcoxi $C_1$-$C_6$ carbonilo, $CF_3$, -(alquilo $C_1$-$C_4$)-$NR_{15}C(O)NR_{16}R_{17}$, -(alquilo $C_1$-$C_4$)-$NR_{15}C(O)R_{18}$, en los que

$R_{15}$ es H o alquilo $C_1$-$C_6$,

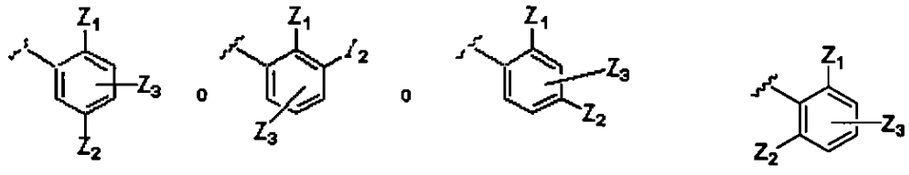
$R_{16}$ y $R_{17}$ son independientemente H o alquilo $C_1$-$C_6$, o

$R_{16}$, $R_{17}$ y el nitrógeno al que estan acoplados forman un anillo morfolinilo, y

$R_{18}$ es alquilo $C_1$-$C_6$ opcionalmente sustituido con -O-(alcanoilo $C_2$-$C_6$, hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-$C_6$ alquilo, alcoxi $C_1$-$C_6$, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, aminoalquilo $C_1$-$C_6$, mono o dialquilaminoalquilo $C_1$-$C_6$

Realizacion 30 Compuestos de acuerdo con la realización 29, en la que

$R_5$ es de la fórmula




o

$Z_1$ es H, halogeno, alquilo $C_1$-$C_4$, haloalquilo $C_1$-$C_4$, hidroxi $C_1$-$C_4$ alquilo dihidroxi $C_1$-$C_4$ alquilo o alcoxi $C_1$-$C_4$, y

$Z_2$ es alquilo $C_1$-$C_4$, $-C(O)NR_6R_7$, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$ $-NR_6R_7$, $NR_6R$-(alquilo $C_1$-$C_6$), hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-$C_6$ alquilo, halogeno, alcoxi $C_1$-$C_4$, $CO_2R$, OH, alcoxi $C_1$-$C_6$ carbonilc o haloalquilo $C_1$-$C_4$,

$Z_3$ es H, alquilo $C_1$-$C_4$, $-C(O)NR_6R_7$, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$ $-NR_6R_7$, $NR_6R$ (alquilo $C_1$-$C_6$), hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-$C_6$ alquilo, halogeno, alcoxi $C_1$-$C_4$, $CO_2R$, OH, alcoxi $C_1$-$C_6$ carbonilc o haloalquilo $C_1$-$C_4$,

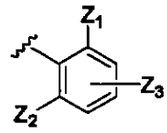
y en el que

$R_6$ y $R_7$, en cada aparicion, son independientemente H, OH, alquilo $C_1$-$C_6$, aminoalquilo $C_1$-$C_4$, NH(alquilo $C_1$-$C_6$)alquilo, N(alquilc $C_1$-$C_6$)(alquilo $C_1$-$C_6$) alquilo $C_1$-$C_6$, hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-$C_6$ alquilo, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, $-SO_2$(alquilo $C_1$-$C_6$), $-SO_2NH_2$, $-SO_2NH$(alquilo $C_1$-$C_6$), $-SO_2N$(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$) o alcanoilo $C_1$-$C_6$, cada uno de los cuales se sustituye opcionalmente con 1, 2 o 3 grupos que son independientemente halogeno, OH, SH, cicloalquilo $C_3$-$C_6$, alcoxi $C_1$-$C_4$, alquilo $C_1$-$C_4$, OH, $CF_3$ u $OCF_3$

En esta realizacion, se prefiere que al menos uno de $Z_1$, $Z_2$ y $Z_3$ no sea hidrogeno

Realizacion 31 Compuestos de acuerdo con la realizacion 30, en la que

$R_5$ es de la fórmula




en la que

$Z_1$ es H, halogeno, alquilo $C_1$-$C_4$, haloalquilo $C_1$-$C_4$, hidroxi $C_1$-$C_4$ alquilo, dihidroxi $C_1$-$C_4$ alquilo o alcoxi $C_1$-

565
566

$C_4$, y

$Z_2$ es alquilo $C_1$-$C_4$, -C(O)$NR_6R_7$, -(alquilo $C_1$-$C_4$)-C(O)$NR_6R_7$ -$NR_6R_7$, $NR_6R_7$(alquilo $C_1$-$C_6$), hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-$C_6$ alquilo, halógeno, alcoxi $C_1$-$C_4$, $CO_2R$, OH, alcoxi $C_1$-$C_6$ carbonilo o haloalquilo $C_1$-$C_4$,

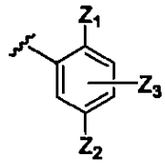
$Z_3$ es H, alquilo $C_1$-$C_4$, -C(O)$NR_6R_7$, -(alquilo $C_1$-$C_4$)-C(O)$NR_6R_7$ -$NR_6R_7$, $NR_6R_7$(alquilo $C_1$-$C_6$), hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-$C_6$ alquilo, halógeno, alcoxi $C_1$-$C_4$, $CO_2R$, OH, alcoxi $C_1$-$C_6$ carbonilc o haloalquilo $C_1$-$C_4$ y en el que

$R_6$ y $R_7$, en cada aparicion, son independientemente H, OH, alquilo $C_1$-$C_6$, aminoalquilo $C_1$-$C_4$, NH(alquilo $C_1$-$C_6$)alquilo, N(alquilc $C_1$-$C_6$)(alquilo $C_1$-$C_6$) alquilo $C_1$-$C_6$, hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-$C_6$ alquilo, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, -$SO_2$(alquilo $C_1$-$C_6$), -$SO_2NH_2$, -$SO_2$NH(alquilo $C_1$-$C_6$), -$SO_2$N(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$) o alcanoilo $C_1$-$C_6$, cada uno de los cuales se sustituye opcionalmente con 1, 2 ó 3 grupos que son independientemente halogeno, OH, SH, cicloalquilo $C_3$-$C_6$, alcoxi $C_1$-$C_4$, alquilo $C_1$-$C_4$, OH, $CF_3$ u $OCF_3$

En esta realizacion, se prefiere que al menos uno de $Z_1$, $Z_2$ y $Z_3$ no sea hidrogeno

Realización 32 Compuestos de acuerdo con la realización 30, en la que

$R_5$ es de la formula




en la que

$Z_1$ es H, halógeno, alquilo $C_1$-$C_4$, haloalquilo $C_1$-$C_4$, hidroxi $C_1$-$C_4$ alquilo, dihidroxi $C_1$-$C_4$ alquilo o alcoxi $C_1$-$C_4$, y

$Z_2$ es alquilo $C_1$-$C_4$, -C(O)$NR_6R_7$, -(alquilo $C_1$-$C_4$)-

$C(O)NR_6R_7$ $-NR_6R_7$, $NR_6R_7$(alquilo $C_1$-$C_6$), hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-$C_6$ alquilo, halógeno, alcoxi $C_1$-$C_4$, $CO_2R$, OH, alcoxi $C_1$-$C_6$ carbonilc o haloalquilo $C_1$-$C_4$,

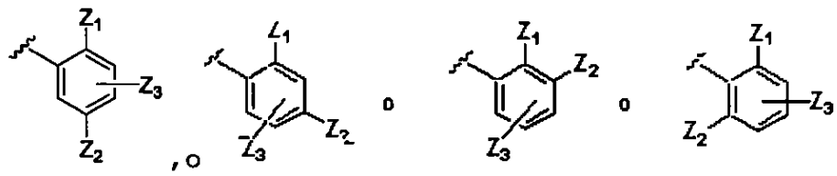
$Z_3$ es H, alquilo $C_1$-$C_4$, $-C(O)NR_6R_7$, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$ $-NR_6R_7$, $NR_6R_7$(alquilo $C_1$-$C_6$), hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-$C_6$ alquilo, halogeno, alcoxi $C_1$-$C_4$, $CO_2R$, OH, alcoxi $C_1$-$C_6$ carbonilc o haloalquilo $C_1$-$C_4$, y en el que

$R_6$ y $R_7$, en cada aparicion, son independientemente H, OH, alquilo $C_1$-$C_6$, aminoalquilo $C_1$-$C_4$, NH(alquilo $C_1$-$C_6$)alquilo, N(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$) alquilo $C_1$-$C_6$, hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-$C_6$ alquilo, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, $-SO_2$(alquilo $C_1$-$C_6$), $-SO_2NH_2$, $-SO_2NH$(alquilo $C_1$-$C_6$), $-SO_2N$(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$) o alcanoilo $C_1$-$C_6$, cada uno de los cuales se sustituye opcionalmente con 1, 2 ó 3 grupos que son independientemente halogeno, OH, SH, cicloalquilo $C_3$-$C_6$, alcoxi $C_1$-$C_4$, alquilo $C_1$-$C_4$, OH, $CF_3$ u $OCF_3$

En esta realización, se prefiere que al menos uno de $Z_1$, $Z_2$ y $Z_3$ no sea hidrogeno

Realizacion 33 Compuestos de acuerdo con la realizacion 29, en la que

$R_5$ es ya sea



en la que

$Z_1$ es H, halogeno, alquilo $C_1$-$C_4$, haloalquilo $C_1$-$C_4$, hidroxi $C_1$-$C_4$ alquilo, dihidroxi $C_1$-$C_4$ alquilo o alcoxi $C_1$-$C_4$, y

$Z_2$ es alquilo $C_1$-$C_4$, $-C(O)NR_6R_7$, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$ $-NR_6R_7$, $NR_6R_7$(alquilo $C_1$-$C_6$), hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-$C_6$ alquilo, halógeno, alcoxi $C_1$-$C_4$, $CO_2R$,

alcoxi $C_1$-$C_6$ carbonilo, -(alquilo $C_1$-$C_4$)-$NR_{15}C(O)NR_{16}R_{17}$ o -(alquilo $C_1$-$C_4$)-$NR_{15}C(O)R_{18}$,

$Z_3$ es H, alquilo $C_1$-$C_4$, $-C(O)NR_6R_7$, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$ $-NR_6R_7$, $NR_6R_7$(alquilo $C_1$-$C_6$), hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-$C_6$ alquilo, halógeno, alcoxi $C_1$-$C_4$, $CO_2R$, alcoxi $C_1$-$C_6$ carbonilo, -(alquilo $C_1$-$C_4$)-$NR_{15}C(O)NR_{16}R_{17}$ o -(alquilo $C_1$-$C_4$)-$NR_{15}C(O)R_{18}$,

$R_6$, $R_7$ y el nitrogeno al cual se acoplan forman un anillo piperidinilo, pirrolidinilo, piperazinilo o morfolinilo opcionalmente sustituido con 1 ó 2 grupos que son independientemente alquilo, hidroxi, hidroxialquilo $C_1$-$C_4$, dihidroxi $C_1$-$C_4$ alquilo o halogeno,

$R_{15}$ es H o alquilo $C_1$-$C_6$,

$R_{16}$ y $R_{17}$ son independientemente H o alquilo $C_1$-$C_6$ o

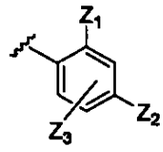
$R_{16}$, $R_{17}$ y el nitrógeno al que estan acoplados forman un anillo morfolinilc, y

$R_{18}$ es alquilo $C_1$-$C_6$ opcionalmente sustituido con -O-(alcanoilo $C_2$-$C_6$, hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-$C_6$ alquilo, alcoxi $C_1$-$C_6$, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, aminoalquilo $C_1$-$C_6$, mono o dialquilaminoalquilo $C_1$-$C_6$

En esta realización, se prefiere que al menos uno de $Z_1$, $Z_2$ y $Z_3$ no sea hicrogeno

Realización 34 Compuestos de acuerdo con la realizacion 33, en la que

$R_5$ es de la fórmula




$Z_1$ es H, halógeno, alquilo $C_1$-$C_4$, haloalquilo $C_1$-$C_4$, hidroxi $C_1$-$C_4$ alquilo, dihidroxi $C_1$-$C_4$ alquilo o alcoxi $C_1$-$C_4$, y

$Z_2$ es alquilo $C_1$-$C_4$, $-C(O)NR_6R_7$, -(alquilo $C_1$-$C_4$)-

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$C(O)NR_6R_7$ $-NR_6R_7$, $NR_6R_7$(alquilo $C_1$-$C_6$), hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-$C_6$ alquilo, halogeno, alcoxi $C_1$-$C_4$, $CO_2R$, alcoxi $C_1$-$C_6$ carbonilo, -(alquilo $C_1$-$C_4$)-$NR_{15}C(O)NR_{16}R_{17}$ o -(alquilo $C_1$-$C_4$)-$NR_{15}C(O)R_{18}$,

$Z_3$ es H, alquilo $C_1$-$C_4$, $-C(O)NR_6R_7$, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$ $-NR_6R_7$, $NR_6R_7$(alquilo $C_1$-$C_6$), hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-$C_6$ alquilo, halógeno, alcoxi $C_1$-$C_4$, $CO_2R$, alcoxi $C_1$-$C_6$ carbonilo, -(alquilo $C_1$-$C_4$)-$NR_{15}C(O)NR_{16}R_{17}$ o -(alquilo $C_1$-$C_4$)-$NR_{15}C(O)R_{18}$,

$R_6$, $R_7$ y el nitrogeno al cual se acoplan forman un anillo piperidinilo, pirrolidinilo, piperazinilo o morfolinilo opcionalmente sustituido con 1 o 2 grupos que son independientemente alquilo, hidroxi, hidroxialquilo $C_1$-$C_4$, dihidroxi $C_1$-$C_4$ alquilo o halogeno,

$R_{15}$ es H o alqui_o $C_1$-$C_6$,

$R_{16}$ y $R_{17}$ son independientemente H o alquilo $C_1$-$C_6$, o

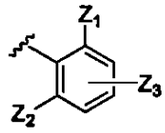
$R_{16}$, $R_{17}$ y el nitrógeno al que estan acoplados forman un anillo morfolinilo, y

$R_{18}$ es alquilo $C_1$-$C_6$ opcionalmente sustituido con -O-(alcanoilo $C_2$-$C_6$, hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-$C_6$ alquilo, alcoxi $C_1$-$C_6$, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, aminoalquilo $C_1$-$C_6$, mono o dialquilaminoalquilo $C_1$-$C_6$

En esta realizacion, se prefiere que al menos uno de $Z_1$, $Z_2$ y $Z_3$ no sea hidrógeno

Realización 35 Compuestos de acuerdo con la realizacion 33, en la que

$R_5$ es de la formula




en la que

$Z_1$ es H, halógeno, alquilo $C_1$-$C_4$ haloalquilo $C_1$-$C_4$, hidroxi $C_1$-$C_4$ alquilo, dihidroxi $C_1$-$C_4$ alquilo o alcoxi $C_1$-

$C_4$, y

$Z_2$ es alquilo $C_1$-$C_4$, -C(O)$NR_6R_7$, -(alquilo $C_1$-$C_4$)-C(O)$NR_6R_7$ -$NR_6R_7$, $NR_6R_7$(alquilo $C_1$-$C_6$), hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-$C_6$ alquilo, halógeno, alcoxi $C_1$-$C_4$, $CO_2R$, alcoxi $C_1$-$C_6$ carbonilo, -(alquilo $C_1$-$C_4$)-$NR_{15}$C(O)$NR_{16}R_{17}$ o -(alquilo $C_1$-$C_4$)-$NR_{15}$C(O)$R_{18}$,

$Z_3$ es H, alquilo $C_1$-$C_4$, -C(O)$NR_6R_7$, -(alquilo $C_1$-$C_4$)-C(O)$NR_6R_7$ -$NR_6R_7$, $NR_6R_7$(alquilo $C_1$-$C_6$), hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-$C_6$ alquilo, halogeno, alcoxi $C_1$-$C_4$, $CO_2R$, alcoxi $C_1$-$C_6$ carbonilo, -(alquilo $C_1$-$C_4$)-$NR_{15}$C(O)$NR_{16}R_{17}$ o -(alquilo $C_1$-$C_4$)-$NR_{15}$C(O)$R_{18}$,

$R_6$, $R_7$ y el nitrógeno al que están acoplados forman un anillo piperidinilo, pirrolidinilo, piperazinilo o morfolinilo, cada uno de los cuales se sustituye opcionalmente con 1 ó 2 grupos que son independientemente alquilo, hidroxi, hidroxialquilo $C_1$-$C_4$, dihidroxi $C_1$-$C_4$ alquilo o halogeno

$R_{15}$ es H o alquilo $C_1$-$C_6$,

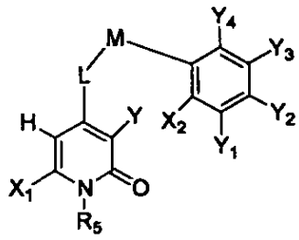
$R_{16}$ y $R_{17}$ son independientemente H o alquilo $C_1$-$C_6$, o

$R_{16}$, $R_{17}$ y el nitrogeno al que están acoplados forman un anillo morfolinilc, y

$R_{18}$ es alquilo $C_1$-$C_6$ opcionalmente sustituido con -O-(alcanoilo $C_2$-$C_6$, hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-$C_6$ alquilo, alcoxi $C_1$-$C_6$, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, aminoalquilo $C_1$-$C_6$, mono o dialquilaminoalquilo $C_1$-$C_6$

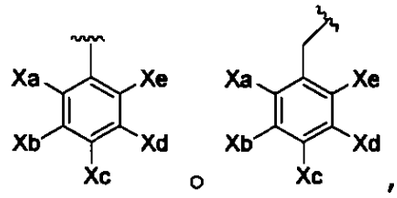
En esta realización, se prefiere que al menos uno de $Z_1$, $Z_2$ y $Z_3$ no sea hidrogeno

Realizacion 36 Un compuesto de la formula



o una sal farmaceuticamente aceptable del mismo, en la que

L y M se seleccionan independientemente entre -O-, -$CH_2$, -S-,-NR-, -N(R)-N(R)-, C(=O)-, -$SO_2$-,



$R_5$ es o , en la que

$X_1$, $X_2$, $X_a$, $X_b$, $X_c$, $X_d$, y $X_e$ se seleccionan independientemente entre -C(O)$NR_6R_7$, -(alquilo $C_1$-$C_4$)-C(O)$NR_6R_7$, -$NR_6R_7$, hidroxialquil($C_1$-$C_4$), dihidroxi $C_1$-$C_4$ alquilo, H, OH, halogeno, haloalquilo, alquilo, haloalcoxi, heteroarilo, heterocicloalquilo, cicloalquilo $C_3$-$C_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, -$CO_2$-alquil($C_1$-$C_6$), -N(R)C(O)$NR_6R_7$, -N(R)C(O)-alcoxi($C_1$-$C_6$), $CO_2$R-(alquilo $C_1$-$C_6$)- o -$SO_2NR_6R_7$, en los que los grupos heteroarilo y heterocicloalquilo se sustituyen opcionalmente con -$NR_6R_7$, -C(O)$NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$ o halogeno, o

$R_5$ es heteroarilo o heteroarilalquilo, en el que el heteroarilo y los grupos heteroarilo se sustituyen opcionalmente con 1, 2, 3 ó 4 grupos que son independientemente -C(O)$NR_6R_7$, -(alquilo $C_1$-$C_4$)-C(O)$NR_6R_7$, -$NR_6R_7$, hidroxialquil($C_1$-$C_4$), dihidroxi $C_1$-$C_4$ alquilo, H, OH, halogeno, haloalquilo, alquilo, haloalcoxi, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, -$CO_2$-alquil($C_1$-$C_6$), -N(R)C(O)$NR_6R_7$ o -N(R)C(O)-alcoxi($C_1$-$C_6$), en los que

$R_6$ y $R_7$ son independientemente, en cada aparición, H,

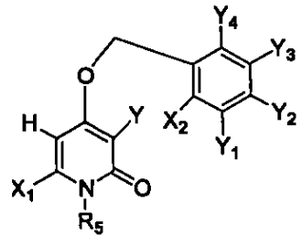
alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$ carbonilo, OH, hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-$C_4$ alquilo, tiohidroxi $C_1$-$C_6$ alquilo, -alquil($C_1$-$C_4$)-$CO_2$-alquilo, piridilalquilo $C_1$-$C_6$, alcanoilo $C_1$-$C_6$, bencilo, fenilalcoxi $C_1$-$C_6$ o fenilalcanoilo $C_1$-$C_6$, en los que cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2 o 3 grupos que son independientemente halógeno, cicloalquilo $C_3$-$C_6$, alcoxi $C_1$-$C_6$, piperidinilalquilo $C_1$-$C_6$, morfolinilalquilo $C_1$-$C_6$, piperazinilalquilo $C_1$-$C_6$, OH, SH, $NH_2$, NH(alquilo), N(alquil)(alquilo), -O-alcanoilo $C_1$-$C_4$, alquilo $C_1$-$C_4$, $CF_3$ u $OCF_3$, o

$R_6$, $R_7$ y el nitrógeno al cual se acoplan forman un anillo morfolinilo, tiomorfolinilo, piperidinilo, pirrolidinilo o piperazinilo opcionalmente sustituido con 1 ó 2 grupos que son independientemente alquilo $C_1$-$C_4$, alcoxi $C_1$-$C_4$ hidroxi, hidroxialquilo $C_1$-$C_4$, dihidroxi $C_1$-$C_4$ alquilo o halogeno,

R, en cada aparición, es independientemente H o alquilo $C_1$-$C_6$, y

Y, $Y_1$, $Y_2$, $Y_3$, y $Y_4$ se seleccionan independientemente entre H, halógeno, alquilo, carboxaldehido, hidroxialquilo, dihidroxialquilo, alquenilo, alquinilo, CN, alcanolilo, alcoxi, alcoxialquilo, haloalquilo y carboxilo

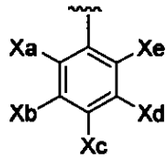
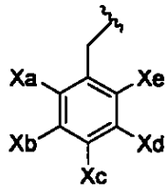
Realizacion 37 Compuestos de acuerdo con la realización 36 de la formula




o una sal farmaceuticamente aceptable de los mismos

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Realizacion 38 Compuestos de acuerdo con la realización 37, en la que

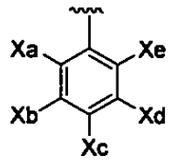
$R_5$ es  o 

Realizacion 39 Compuestos de acuerdo con la realización 31, en la que

$Y_2$, $Y_4$, y Y son independientemente halogeno, y

$Y_1$ y $Y_3$ son ambos hidrógeno

Realizacion 40 Compuestos de acuerdo con la realización 39, en la que

$R_5$ es 

$X_1$ y $X_2$ son independientemente H, metilo, $NR_6R_7$, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, $-C(O)NR_6R_7$, hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-$C_6$ alquilo o -(alquilo $C_1$-$C_4$)-morfolinilo, y

$X_a$ y $X_e$ son independientemente halogeno, $NH_2$, NH(alquilo $C_1$-$C_6$), N(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$), metilo o hidrogeno

En esta realización, se prefiere que uno de $X_a$ y $X_e$ no sea hidrogeno

Realizacion 41 Compuestos de acuerdo con la realizacion 40, en la que

uno de $X_b$ y $X_c$ es hidrogeno y el otro es $-NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, $-C(O)NR_6R_7$, $-SO_2NR_6R_7$ o halógeno, en el que

$R_6$ y $R_7$ son independientemente, en cada aparicion, H, alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$ carbonilo, OH, hidroxi $C_1$-$C_6$ alquilo, dihidroxi

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$C_1$-$C_6$ alquilo, -alquil($C_1$-$C_4$)-$CO_2$-alquilo, piridilalquilo $C_1$-$C_6$, alcanoilo $C_1$-$C_6$, bencilo, fenilalcoxi $C_1$-$C_6$ o fenilalcanoilo $C_1$-$C_6$, en los que cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2 o 3 grupos que son independientemente halogeno, cicloalquilo $C_3$-$C_6$, alcoxi $C_1$-$C_6$, piperidinilalquilo $C_1$-$C_6$, morfolinilalquilo $C_1$ $C_6$, piperazinilalquilo $C_1$-$C_6$, OH, SH, $NH_2$, NH(alquilo), N(alquil)(alquilo), -O-alcanoilo $C_1$-$C_4$, alquilo $C_1$-$C_4$, $CF_3$, u $OCF_3$, o

$R_6$, $R_7$ y el nitrogeno al cual se acoplan forman un anillo morfolinilo, tiomorfolinilo, piperidinilo, pirrolidinilo o piperazinilo opcionalmente sustituido con 1 ó 2 grupos que son independientemente alquilo $C_1$-$C_4$, alcoxi $C_1$-$C_4$ hidroxi, hidroxialquilo $C_1$-$C_4$, dihidroxi $C_1$-$C_4$ alquilo o halogeno

Realizacion 42 Compuestos de acuerdo con la realizacion 41, en la que

$R_6$ y $R_7$ son independientemente, en cada aparición, H, alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$ carbonilo, OH, hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-$C_6$ alquilo, -alquil($C_1$-$C_4$)-$CO_2$-alquilo, piridilalquilo $C_1$-$C_6$, alcanoilo $C_1$-$C_6$, bencilo, fenilalcoxi $C_1$-$C_6$, o fenilalcanoilo $C_1$-$C_6$, en los que cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2 ó 3 grupos que son independientemente halógeno, cicloalquilo $C_3$-$C_6$, alcoxi $C_1$-$C_6$, piperidinilalquilo $C_1$-$C_6$, morfolinilalquilo $C_1$-$C_6$, piperazinilalquilo $C_1$-$C_6$, OH, $NH_2$, NH(alquilo), N(alquil)(alquilo), -O-alcanoilo $C_1$-$C_4$, alquilo $C_1$-$C_4$, $CF_3$ u $OCF_3$

Realizacion 43 Compuestos de acuerdo con la realización 42, en la que

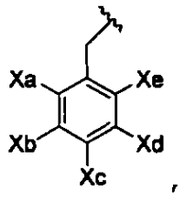
$X_a$ es hidrogeno, metilo, fluor o cloro,

$X_c$ y $X_d$ son ambos hidrogeno,

$X_b$ es $-NR_6R_7$, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, $-C(O)NR_6R_7$, en el que

$R_6$ y $R_7$ son independientemente, en cada aparicion, H, alquilo $C_1$-$C_6$, hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-$C_4$ alquilo, alcoxi $C_1$-$C_6$, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$ o alcanoilo $C_1$-$C_6$, en los que cada uno de los anteriormente mencionados se sustituye opcionalmente con 1, 2 o 3 grupos que son independientemente OH, SH, halógeno o cicloalquilo $C_3$-$C_6$

Realizacion 44 Compuestos de acuerdo con la realizacion 39, en la que

$R_5$ es 

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$X_a$ es H, fluoro, cloro o metilo,

$X_e$ es hidrogeno, halogeno o metilo, y

$X_b$ es H,

$X_d$ es H o halogeno,

Realizacion 45 Compuestos de acuerdo con la realizacion 44, en la que

$X_c$ es $-SO_2NR_6R_7$ o halógeno, en el que

$R_6$ y $R_7$ son independientemente, en cada aparicion, H, alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$ carbonilo, OH, hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-$C_6$ alquilo, -alquil($C_1$-$C_4$)-$CO_2$-alquilo, piridilalquilo $C_1$-$C_6$, alcanoilo $C_1$-$C_6$, bencilo, fenilalcoxi $C_1$-$C_6$ o fenilalcanoilo $C_1$-$C_6$, en los que cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2 ó 3 grupos que son independientemente halógeno, cicloalquilo $C_3$-$C_6$, alcoxi $C_1$-$C_6$, piperidinilalquilo $C_1$-$C_6$, morfolinilalquilo $C_1$ $C_6$, piperazinilalquilo $C_1$-$C_6$, OH, SH, $NH_2$, NH(alquilo), N(alquil)(alquilo), -O-alcanoilo $C_1$-$C_4$,

alquilo $C_1$-$C_4$, $CF_3$, u $OCF_3$, o

$R_6$, $R_7$ y el átomo de nitrógeno al que se acoplan forman un anillo morfolinilo, tiomorfolinilo, piperidinilo, pirrolidinilo o piperazinilo que opcionalmente se sustituye con 1 o 2 grupos que son independientemente alquilo $C_1$-$C_4$, alcoxi $C_1$-$C_4$, hidroxi, hidroxialquilo $C_1$-$C_4$, dihidroxi $C_1$-$C_4$ alquilo o halogeno, o

$X_c$ es fluoro, cloro, $-NH_2$, -NH(alquilo $C_1$-$C_6$), -N(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$), $-SO_2NH_2$, $-SO_2$NH(alquilo $C_1$-$C_6$), $-SO_2$N(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$) o piperazinilo, en el que el grupo piperazinilo se sustituye opcionalmente con 1 o 2 grupos que son independientemente alquilo $C_1$-$C_4$, alcoxi $C_1$-$C_4$, hidroxi, hidroxialquilo $C_1$-$C_4$, dihidroxi $C_1$-$C_4$ alquilo o halogeno

Realizacion 46 Compuestos de acuerdo con la realización 44, en la que

$X_c$ es $-C(O)NR_6R$-, -(alquilo $C_1$-$C_6$)-$C(O)NR_6R_7$, $-NR_6R_7$ o $R_6R_7$N-(alquilo $C_1$-$C_6$)-, en el que

$R_6$ y $R_7$ son independientemente, en cada aparición, H, alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$ carbonilo, OH, hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-$C_6$ alquilo, dihid-oxi $C_1$-$C_6$ alquilo, -alquil($C_1$-$C_4$)-$CO_2$-alquilo, piridilalquilo $C_1$-$C_6$, alcanoilo $C_1$-$C_6$, bencilo, fenilalcoxi $C_1$-$C_6$ o fenilalcanoilo $C_1$-$C_6$, en los que cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2 ó 3 grupos que son independientemente halógeno, cicloalquilo $C_3$-$C_6$, alcoxi $C_1$-$C_6$, piperidinilalquilo $C_1$-$C_6$, morfolinilalquilo $C_1$-$C_6$, piperazinilalquilo $C_1$-$C_6$, OH, $-NH_2$, -NH(alquilo), -N(alquil)(alquilo), O-alcanoilo $C_1$-$C_4$, alquilo $C_1$-$C_4$, $CF_3$ u $OCF_3$, o

$R_6$, $R_7$ y el nitrogeno al cual se acoplan forman un anillo morfolinilo, tiomorfolinilo, ' piperidinilo,

pirrolidinilo o piperazinilo opcionalmente sustituido con 1 o 2 grupos que son independientemente alquilo $C_1$-$C_4$, alcoxi $C_1$-$C_4$ hidroxi, hidroxialquilo $C_1$-$C_4$, dihidroxi $C_1$-$C_4$ alquilo o halogeno

Realizacion 47 Compuestos de acuerdo con la realizacion 46, en la que

$R_6$ es hidrógeno, y

$R_7$ es alquilo $C_1$-$C_6$ o alcanoilo $C_1$-$C_6$, cada uno de los cuales se sustituye opcionalmente con 1, 2 ó 3 grupos que son independientemente $NH_2$, NH(alquilo $C_1$-$C_6$), N(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$), OH, SH, ciclopropilo o alcoxi $C_1$-$C_4$,

Realizacion 48 Compuestos de acuerdo con la realizacion 47, en la que

$X_c$ es $-C(O)NR_6R_7$

Realización 49 Compuestos de acuerdo con la realizacion 47, en la que

$X_c$ es $NR_6R_7$ o $R_6R_7N$-(alquilo $C_1$-$C_6$)-

Realizacion 50 Compuestos de acuerdo con la realizacion 38, en la que

$X_a$ es hidrogeno,

dos de $X_b$, $X_c$, y $X_d$ son hidrógeno y el otro es $-C(O)NR_6R_7$ -(alquilo $C_1$-$C_6$)-$C(O)NR_6R_7$, $-NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)- o $-CO_2$-alquil($C_1$-$C_6$), en los que

$R_6$ y $R_7$ son independientemente, en cada aparicion, H, alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$ carbonilo, OH, hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-$C_6$ alquilo, -alquil($C_1$-$C_4$)-$CO_2$-alquilo, piridilalquilo $C_1$-$C_6$, alcanoilo $C_1$-$C_6$, bencilo, fenilalcoxi $C_1$-$C_6$ o fenilalcanoilo $C_1$-$C_6$, en los que cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2 o 3 grupos que son independientemente halogeno, cicloalquilo $C_3$-$C_6$, alcoxi $C_1$-$C_6$, piperidinilalquilo $C_1$-$C_6$, morfolinilalquilo $C_1$-$C_6$, piperazinilalquilo $C_1$-$C_6$, OH, $NH_2$,

NH(alquilo), N(alquil)(alquilo), -O-alcanoilo $C_1$-$C_4$, alquilo $C_1$-$C_4$, $CF_3$ u $OCF_3$, o

$R_6$, $R_7$ y el nitrogeno al que se acoplan forman un anillo morfolinilo, piperidinilo, pirrolidinilo o piperazinilo que opcionalmente se sustituye con 1 ó 2 grupos que son independientemente alquilo $C_1$-$C_4$, alcoxi $C_1$-$C_4$, hidroxi, hidroxialquilo $C_1$-$C_4$, dihidroxi $C_1$-$C_4$ alquilo o halogeno, y

$X_e$ es hidrogeno, metilo, alcoxi $C_1$-$C_2$ o halogeno

Realizacion 51 Compuestos de acuerdo con la realizacion 50, en la que

$X_b$ es $-C(O)NR_6R_7$, -(alquilo $C_1$-$C_6$)-$C(O)NR_6R_7$, $-NR_6R_7$ o $R_6R_7N$-(alquilo $C_1$-$C_6$)-, en el que

$R_6$ es hidrogeno o alquilo $C_1$-$C_4$,

$R_7$ es OH, alquilo $C_1$-$C_6$ o alcanoilo $C_1$-$C_6$, en el que los grupos alquilo y alcanoilo se sustituyen con 1, 2 o 3 grupos que son independientemente $NH_2$, NH(alquilo $C_1$-$C_6$), N(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$), cicloalquilo $C_3$-$C_6$, OH o alcoxi $C_1$-$C_4$

Realizacion 52 Compuestos de acuerdo con la realización 38, en la que

$X_a$ es halógeno o metilo,

$X_b$ es H, $-NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, $-C(O)NR_6R_7$ o $-CO_2$-alquil($C_1$-$C_6$),

$X_c$ es $-NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, $-C(O)NR_6R_7$, halógeno, $-CO_2$-alquil($C_1$-$C_6$), $NH_2$, NH(alquilo $C_1$-$C_6$), N(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$), $-SO_2NH_2$, $-SO_2$NH(alquilo $C_1$-$C_6$), $-SO_2$N(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$) o piperazinilo, en el que el grupo piperazinilo se sustituye opcionalmente con 1 o 2 grupos que son independientemente alquilo $C_1$-$C_4$, alcoxi $C_1$-$C_4$, hidroxi, hidroxialquilo $C_1$-$C_4$, dihidroxi $C_1$-$C_4$ alquilo o halogeno,

$X_d$ es hidrogeno,

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$X_e$ es H, metilo, $NH_2$, NH(alquilo $C_1$-$C_6$) o N(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$)

Realización 53 Compuestos de acuerdo con la realizacion 38, en la que

$X_1$, $X_2$, $X_a$, $X_b$, $X_c$, $X_d$ y $X_e$ se seleccionan independientemente entre H, OH, halogeno, $CF_3$, alquilo, $OCF_3$, piridilo, piridazinilo, pirimidilo, pirazinilo, tienilo, furilo, pirrolilo, piperidinilo, piperazinilo o cicloalquilo $C_3$-$C_7$, en los que cada uno de los anteriormente mencionados se sustituye con $-NR_6R_7$, $-C(O)NR_6R_7$, -(alquilc $C_1$-$C_4$)-$C(O)NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$ o halógeno

Realizacion 54 Compuestos de acuerdo con la realizacion 37, en la que

$R_5$ es un grupo heteroarilo o heteroarilalquilo, en el que cada heteroarilc es pirazolilo, imidazolilo, furanilo, piridilo, piridazinilo, pirimidinilo, pirazinilo, pirazolilo, imidazolilo, dihidroindolilo, dihidroisoindolilo, indolon-2-ilo, quinolinilo, isoquinolinilo, tetrahidroisoquinolinilo, dihidroisoquinolinilo o indolilo, cada uno de los cuales se sustituye opcionalmente con 1, 2, 3 ó 4 grupos que son independientemente $-C(O)NR_6R_7$, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$, $-NR_6R_7$, hidroxialquil($C_1$-$C_4$), dihidroxi $C_1$-$C_4$ alquilo, hidrogeno, hidroxi, halogeno, haloalquilo, alquilo, haloalcoxi, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, $-CO_2$-alquil($C_1$-$C_6$), $-N(R)C(O)NR_6R_7$ o $-N(P)C(O)$-alcoxi($C_1$-$C_6$), en los que

$R_6$ y $R_7$ son incependientemente, en cada aparicion, H, alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$ carbonilo, OH, hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-$C_6$ alquilo, tiohidroxi $C_1$-$C_6$ alquilo, -alquil($C_1$-$C_4$)-$CO_2$-alquilo, piridilalquilo $C_1$-$C_6$, alcanoilo $C_1$-$C_6$, bencilo, fenilalcoxi $C_1$-$C_6$ o fenilalcanoilo $C_1$-$C_6$, en los que cada

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uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2 o 3 grupos que son independientemente halógeno, cicloalquilo $C_3$-$C_6$, alcoxi $C_1$-$C_6$, piperidinilalquilo $C_1$-$C_6$, morfolinilalquilo $C_1$-$C_6$, piperazinilalquilo $C_1$-$C_6$, OH, SH, $NH_2$, NH(alquilo), N(alquil)(alquilo), -O-alcanoilo $C_1$-$C_4$, alquilo $C_1$-$C_4$, $CF_3$ u OCF

Realizacion 55 Compuestos de acuerdo con la realización 54, en la que

$Y_2$, $Y_4$, y Y son independientemente halogeno, y

$Y_1$ y $Y_3$ son ambos hidrógeno

Realizacion 56 Compuestos de acuerdo con la realizacion 55, en la que

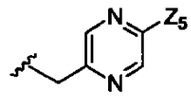
$X_1$ y $X_2$ son independientemente H, metilo, $-NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, $-C(O)NR_6R_7$, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$, hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-$C_6$ alquilo o -(alquilo $C_1$-$C_4$)-morfolinilo

Realización 57 Compuestos de acuerdo con la realizacion 56, en la que

$R_5$ es piridilalquilo $C_1$-$C_6$, pirimidinilalquilo $C_1$-$C_6$ o pirazinilalquilo $C_1$-$C_6$, cada uno de los cuales se sustituye opcionalmente con 1, 2 o 3 grupos que son independientemente hidroxialquil($C_1$-$C_4$), dihidroxi $C_1$-$C_4$ alquilo, OH, halogeno, $CF_3$, alquil($C_1$-$C_4$), $OCF_3$, $-NR_6R_7$, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)- o -$C(O)NR_6R_7$

Realización 58 Compuestos de acuerdo con la realización 57, en la que

$R_5$ es de la formula




en la que

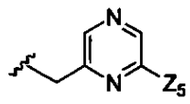
$Z_5$ es hidroxialquil($C_1$-$C_4$), dihidroxi $C_1$-$C_4$ alquilo,

OH, halogeno, $CF_3$ alquil($C_1$-$C_4$), $OCF_3$, $-NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$ o $-C(O)NR_6R_7$, en el que

$R_6$ y $R_7$, en cada aparicion, son independientemente H, alquilo $C_1$-$C_6$ opcionalmente sustituido con 1, 2 ó 3 grupos que son independientemente alcoxi $C_1$-$C_4$ carbonilo, halogeno, cicloalquilo $C_3$-$C_6$, OH, SH o alcoxi $C_1$-$C_4$

Realización 59 Compuestos de acuerdo con la realizacion 57, en la que

$R_5$ es de la formula

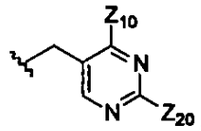


en la que

$Z_5$ es hidroxialquil($C_1$-$C_4$), dihidroxi $C_1$-$C_4$ alquilo, OH, halogeno, $CF_3$, alquil($C_1$-$C_4$), $OCF_3$, $-NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$ o $-C(O)NR_6R_7$, en el que

$R_6$ y $R_7$, en cada aparicion, son independientemente H, alquilo $C_1$-$C_6$ opcionalmente sustituido con 1, 2 ó 3 grupos que son independientemente alcoxi $C_1$-$C_4$ carbonilo, halogeno, cicloalquilo $C_3$-$C_6$, OH, SH o alcoxi $C_1$-$C_4$

Realización 60 Compuestos de acuerdo con la realización 57, en la que

$R_5$ es de la formula  , en la que

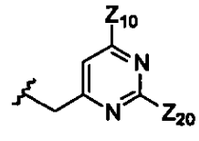
$Z_{10}$ es H o metilo, y

$Z_{20}$ es -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$, hidroxialquil($C_1$-$C_4$), dihidroxi $C_1$-$C_4$ alquilo, OH, halogeno, $CF_3$, alquil($C_1$-$C_4$), $OCF_3$, $-NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)- o $-C(O)NR_6R_7$, en el que

$R_6$ y $R_7$, en cada aparicion, son independientemente H, alquilo $C_1$-$C_6$ opcionalmente sustituido con 1, 2 o 3 grupos que son independientemente alcoxi $C_1$-$C_4$ carbonilo,

halogeno, cicloalquilo $C_3$-$C_6$, OH, SH o alcoxi $C_1$-$C_4$

Realizacion 61 Compuestos de acuerdo con la realizacion 57, en la que

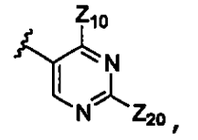
$R_5$ es de la fórmula  , en la que

$Z_{10}$ es H o metilo, y

$Z_{20}$ es -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$, hidroxialquil($C_1$-$C_4$), dihidroxi $C_1$-$C_4$ alquilo, OH, halógeno, $CF_3$, alquil($C_1$-$C_4$), $OCF_3$, $-NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)- o $-C(O)NR_6R_7$, en el que

$R_6$ y $R_7$, en cada aparición, son independientemente H, alquilo $C_1$-$C_6$ opcionalmente sustituido con 1, 2 o 3 grupos que son independientemente alcoxi $C_1$-$C_4$ carbonilo, halógeno, cicloalquilo $C_3$-$C_6$, OH, SH o alcoxi $C_1$-$C_4$

Realizacion 62 Compuestos de acuerdo con la realizacion 57, en la que

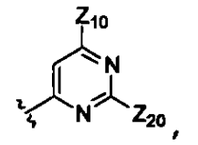
$R_5$ es de la formula  , en la que

$Z_{10}$ es H o metilo, y

$Z_{20}$ es -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$, hidroxialquil($C_1$-$C_4$), dihidroxi $C_1$-$C_4$ alqu lo, OH, halogeno, $CF_3$, alquil($C_1$-$C_4$), $OCF_3$, $-NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)- o $-C(O)NR_6R_7$, en el que

$R_6$ y $R_7$, en cada aparición, son independientemente H, alquilo $C_1$-$C_6$ opcionalmente sustituido con 1, 2 o 3 grupos que son independientemente alcoxi $C_1$-$C_4$ carbonilo, halógeno, cicloalquilo $C_3$-$C_6$, OH, SH o alcoxi $C_1$-$C_4$

Realización 63 Compuestos de acuerdo con la realización 57, en la que

$R_5$ es de la formula  , en la que

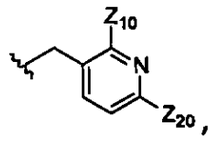
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$Z_{10}$ es H o metilo, y

$Z_{20}$ es -(alquilo $C_1$-$C_4$)-C(O)$NR_6R_7$, hidroxialquil($C_1$-$C_4$), dihidroxi $C_1$-$C_4$ alquilo, OH, halógeno, $CF_3$, alquil($C_1$-$C_4$), $OCF_3$, -$NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)- o -C(O)$NR_6R_7$, en el que

$R_6$ y $R_7$, en cada aparición, son independientemente H, alquilo $C_1$-$C_6$ opcionalmente sustituido con 1, 2 o 3 grupos que son independientemente alcoxi $C_1$-$C_4$ carbonilo, halogeno, cicloalquilo $C_3$-$C_6$, OH, SH o alcoxi $C_1$-$C_4$

Realizacion 64 Compuestos de acuerdo con la realizacion 57, en la que

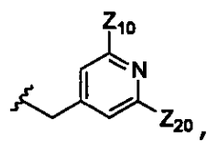
$R_5$ es de la fórmula  , en la que

$Z_{10}$ es H o metilo, y

$Z_{20}$ es -(alquilo $C_1$-$C_4$)-C(O)$NR_6R_7$, hidroxialquil($C_1$-$C_4$), dihidroxi $C_1$-$C_4$ alquilo, OH, halógeno, $CF_3$, alquil($C_1$-$C_4$), $OCF_3$, -$NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)- o -C(O)$NR_6R_7$, en el que

$R_6$ y $R_7$, en cada aparicion, son independientemente H, alquilo $C_1$-$C_6$ opcionalmente sustituido con 1, 2 o 3 grupos que son independientemente alcoxi $C_1$-$C_4$ carbonilo, halogeno, cicloalquilo $C_3$-$C_6$, OH, SH o alcoxi $C_1$-$C_4$

Realizacion 65 Compuestos de acuerdo con la realización 57, en la que

$R_5$ es de la formula  , en la que

$Z_{10}$ es H o metilo, y

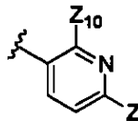
$Z_{20}$ es -(alquilo $C_1$-$C_4$)-C(O)$NR_6R_7$, hidroxialquil($C_1$-$C_4$), dihidroxi $C_1$-$C_4$ alquilo, OH, halogeno, $CF_3$, alquil($C_1$-$C_4$), $OCF_3$, -$NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)- o -C(O)$NR_6R_7$, en el que

$R_6$ y $R_7$, en cada aparicion, son independientemente H, alquilo $C_1$-$C_6$ opcionalmente sustituido con 1, 2 o 3 grupos

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que son independientemente alcoxi $C_1$-$C_4$ carbonilo, halogeno, cicloalquilo $C_3$-$C_6$, OH, SH o alcoxi $C_1$-$C_4$

Realizacion 66 Compuestos de acuerdo con la realizacion 57, en la que

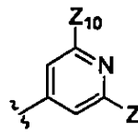
$R_5$ es de la fórmula  , en la que

$Z_{10}$ es H o metilo, y

$Z_{20}$ es -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$, hidroxialquil($C_1$-$C_4$), dihidroxi $C_1$-$C_4$ alquilo, OH, halogeno, $CF_3$, alquil($C_1$-$C_4$), $OCF_3$, $-NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)- o $-C(O)NR_6R_7$, en el que

$R_6$ y $R_7$, en cada aparicion, son independientemente H, alquilo $C_1$-$C_6$ opcionalmente sustituido con 1, 2 o 3 grupos que son independientemente alcoxi $C_1$-$C_4$ carbonilo, halógeno, cicloalquilo $C_3$-$C_6$, OH, SH o alcoxi $C_1$-$C_4$

Realización 67 Compuestos de acuerdo con la realizacion 57, en la que

$R_5$ es de la fórmula  , en la que

$Z_{10}$ es H o metilo, y

$Z_{20}$ es -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$, hidroxialquil($C_1$-$C_4$), dihidroxi $C_1$-$C_4$ alquilo, OH, halógeno, $CF_3$, alquil($C_1$-$C_4$), $OCF_3$, $-NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)- o $-C(O)NR_6R_7$, en el que

$R_6$ y $R_7$, en cada aparicion, son independientemente H, alquilo $C_1$-$C_6$ opcionalmente sustituido con 1, 2 o 3 grupos que son independientemente alcoxi $C_1$-$C_4$ carbonilo, halógeno, cicloalquilo $C_3$-$C_6$, OH, SH o alcoxi $C_1$-$C_4$

Realizacion A7 Compuestos de acuerdo con la realización 1, en la que

$R_1$ es H, halogeno, alquilo opcionalmente sustituido con alcoxi $C_1$-$C_4$ carbonilo, alquenilo $C_2$-$C_6$ opcionalmente sustituido con alcoxi $C_1$-$C_4$ carbonilo, alquinilo $C_2$-$C_4$, haloalquilo $C_1$-$C_4$, carboxaldehido, hidroxi $C_1$-$C_4$ alquilo, fenilalcoxi($C_1$-$C_6$), bencilo, fenetilo, fenpropilo, CN o fenilalcanoil($C_1$-$C_6$),

en el que los grupos fenilo no se sustituyen o se sustituyen con 1, 2 o 3 grupos que son independientemente halogeno, alquilo $C_1$-$C_4$, alcoxi $C_1$-$C_4$, nitro, CN, $CF_3$, $OCF_3$ o $CO_2H$,

$R_2$ es OH, benciloxi, feniloxi, feniloxialquil($C_1$-$C_6$), feniltioalcoxi ($C_1$-$C_4$), $-OC(O)NH(CH_2)_n$fenilo, $-OC(O)N$(alquil)$(CH_2)_n$fenilo, dialquilo($C_1$-$C_6$)amino, alquinilo $C_2$-$C_6$, piridilo, pirimidilo, piridazilo, pirazolilo, imidazolilo, pirrolilo, tetrahidroquinolinilo, tetrahidroisoquinolinilo, tetrazolilo, pirazinilo, bencimidazolilo, triazinilo, tetrahidrofurilo, piperidinilo, hexahidropirimidinilo, tiazolilo, tienilo o $CO_2H$, en el que

n es 0, 1, 2, 3, 4, 5 o 6,

cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2, 3, 4 ó 5 grupos que son independientemente halógeno, $NR_6R_7$, haloalquilo ($C_1$-$C_4$), haloalcoxi ($C_1$-$C_4$) , alquilo ($C_1$-$C_6$), piridilo, -alquil($C_1$-$C_6$)-N(R)-$CO_2R_{30}$ o $NR_6R_7$-(alquilo $C_1$-$C_6$)-,

$R_4$ es H, alquilo opcionalmente sustituido con uno o dos grupos que son independientemente $CO_2H$, $-CO_2$alquilo, $-C(O)NRR$, $-N(R_{30})C(O)NRR$, $-N(R_{30})C(O)$-alcoxi($C_1$-$C_6$) o $-NR_6R_7$, fenilalcoxi($C_1$-$C_6$), fenilalquil($C_1$-$C_6$), hidroxialquilo, en el que los grupos fenilo no se sustituyen o se sustituyen con 1, 2, 3, 4 o 5 grupos que son independientemente halógeno, hidroxi, alcoxi, alquilo, nitro, $CF_3$ u $OCF_3$, y

$R_5$ es fenialquil($C_1$-$C_6$), alquil($C_1$-$C_6$), fenilo,

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piperidinilalquilo ($C_1$-$C_6$), tienilalquilo ($C_1$-$C_6$), indolilo, quinolinilo, isoquinolinilo, isoindolilo, indol-2-onilo, indazolilo, indolilalquilo ($C_1$-$C_6$), quinolinilalquilo ($C_1$-$C_6$), isoquinolinilalquilo ($C_1$-$C_6$) , isoindolilalquilo ($C_1$-$C_6$), indol-2-onila_quilo ($C_1$-$C_6$), naftilalquil($C_1$-$C_6$), piridilalquil($C_1$-$C_6$), pirimidilalquil($C_1$-$C_6$), pirazinilalquil($C_1$-$C_6$) o en el que

cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2, 3, 4 ó 5 grupos que son independientemente alquilo, halógeno, alcoxi, benciloxi, tioalcoxi, -$CO_2$(alquilo $C_1$-$C_5$), $CO_2H$, CN, amidino-oxima, -$NR_8R_9$, -$NR_6R_7$, (alquilo $C_1$-$C_6$)-, -$C(O)NR_6R_7$, amidino, $CF_3$ u $OCF_3$,

$R_8$ es hidrógeno, alquilo $C_1$-$C_6$, alcanoilo $C_1$-$C_6$, fenilalquilo $C_1$-$C_6$ y fenilalcanoilo $C_1$-$C_6$, y

$R_9$ es aminoalquilo, monoalquilo $C_1$-$C_6$ aminoalquilo $C_1$-$C_6$, dialquilo $C_1$-$C_6$ aminoalquilo $C_1$-$C_6$, alcanoilo $C_1$-$C_6$, fenilalquilo $C_1$-$C_4$, indazolilo y fenilalcanoilo $C_1$-$C_4$

En esta realización, se prefiere que cuando $R_2$ es benciloxi, $R_4$ es H y $R_5$ es bencilo o metilo, $R_1$ no sea hidrogeno, y

no más de dos de $R_1$, $R_2$, $R_4$ y $R_5$ sean simultáneamente hidrógeno

Realización A8 Compuestos de acuerdo con la realizacion A7 en la que

$R_1$ es H, halogeno, alquilo $C_1$-$C_4$ opcionalmente sustituido con alcoxi $C_1$-$C_4$ carbonilo, alquenilo $C_2$-$C_4$ opcionalmente sustituido con alcoxi $C_1$-$C_4$ carbonilo, alquinilo $C_2$-$C_4$ o carboxaldehido,

$R_2$ es benciloxi, OH, feniloxi, feniloxialquil($C_1$-$C_6$), feniltioalcoxi ($C_1$-$C_4$) o piridilo, en el que cada uno de los anteriormente mencionados se sustituye opcionalmente con 1, 2, 3, 4 o 5 grupos que son independientemente

halógeno, -alquil($C_1$-$C_6$)-N(R)-$CO_2R_{30}$, $NR_6R_7$, -haloalquilo ($C_1$-$C_4$), haloalcoxi ($C_1$-$C_4$), alquilo ($C_1$-$C_6$), piridilo o $NR_6R_7$-(alquilo $C_1$-$C_6$)

Realización A9 Compuestos de acuerdo con la realización A7, en la que

$R_4$ es H, alquil($C_1$-$C_6$) opcionalmente sustituido con uno o dos grupos que son independientemente $CO_2H$, -$CO_2$alquilo, -C(O)NRR, -N($R_{30}$)C(O)NRR, -N($R_{30}$)C(O)-alcoxi($C_1$-$C_6$) o -$NR_6R_7$, fenilalcoxi($C_1$-$C_6$) o hidroxialquil($C_1$-$C_6$), en los que

los grupos fenilo no se sustituyen o se sustituyen con 1, 2 ó 3 grupos que son independientemente halógeno, hidroxi, alcoxi $C_1$-$C_4$, alquilo $C_1$-$C_4$, nitro, $CF_3$, $OCF_3$, y

$R_5$ es bencilo, fenetilo, fenpropilo, fenbutilo, alquil($C_1$-$C_6$), fenilo, piridilo, pirimidilo, indolilo, indazolilo, indolilalquilo ($C_1$-$C_6$), naftilalquil($C_1$-$C_6$), tienilalquil($C_1$-$C_6$), piridilalquil($C_1$-$C_6$), pirimidilalquil($C_1$-$C_6$) o pirazinilalquil($C_1$-$C_6$), y en los que

cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2 o 3 grupos que son independientemente alquilo, halogeno, alcoxi, benciloxi, tioalcoxi, -$CO_2$(alquilo $C_1$-$C_5$), $CF_3$, $OCF_3$, $CO_2H$, CN, amidino-oxima

En esta realización, se prefiere que cuando $R_2$ es benciloxi, $R_4$ es H y $R_5$ es bencilo o metilo, $R_1$ no sea hidrogeno, y

no mas de dos de $R_1$, $R_2$, $R_4$ y $R_5$ sean simultáneamente hidrógeno

Realizacion A10 Compuestos de acuerdo con la realización A7 en la que

$R_4$ es H, alquilo ($C_1$-$C_4$) opcionalmente sustituido con uno o dos grupos que son independientemente $CO_2H$, -$CO_2$alquilo, -C(O)NRF, -N($R_{30}$)C(O)NRR, -N($R_{30}$)C(O)-alcoxi($C_1$-

$C_6$) o $-NR_6R_7$, fenilalcoxi($C_1$-$C_6$), bencilo, fenetilo, fenpropilo o hidroxialquil($C_1$-$C_6$), en los que

los grupos fenilo no se sustituyen o se sustituyen con 1, 2 o 3 grupos que son independientemente halogeno, hidroxi, alcoxi $C_1$-$C_4$, alquilo $C_1$-$C_4$, nitro, $CF_3$, $OCF_3$, y

$R_5$ es indolilo, quinolinilo, isoquinolinilo, isoindolilo, indol-2-onilo, indolilalquilo ($C_1$-$C_6$), quinolininilalquilo ($C_1$-$C_6$), isoquinolinilalquilo ($C_1$-$C_6$), isoindolilalquilo ($C_1$-$C_6$), indol-2-onilalquilo ($C_1$-$C_6$), cada uno de los cuales no se sustituye o se sustituye con 1, 2 ó 3 grupos que sor independientemente alquilo $C_1$-$C_4$, halógeno, $CF_3$, $OCF_3$, $-CO_2CH_3$, hidroxi $C_1$-$C_4$ alquilo, alcoxi $C_1$-$C_4$, $-CO_2$(alquilo $C_1$-$C_5$), benciloxi, $-NR_8R_9$, $NR_6R_7$-(alquilo $C_1$-$C_6$)-, $-C(O)NR_6R_7$ o amidino-oxima, en los que

$R_6$ y $R_7$ son independientemente, en cada aparicion, H, alquilo, hidroxialquilo, alcoxi, alcoxialquilo, alcanoilo, fenilalquilo, fenilalcoxi o fenilalcanoilo, en los que cada uno no se sustituye o se sustituye con 1, 2 ó 3 grupos que son independientemente halógeno, hidroxi, alcoxi $C_1$-$C_4$, OH, SH, cicloalquilo $C_3$-$C_6$, alquilo $C_1$-$C_4$, $CF_3$ u $OCF_3$, o

$R_6$, $R_7$ y el nitrógeno al cual se acoplan forman un anillo morfolinilo, tiomorfolinilo o piperazinilo opcionalmente sustituido con 1 o 2 grupos que son independientemente alquilo $C_1$-$C_4$, hidroxi, hidroxialquilo $C_1$-$C_4$ o halogeno

Realizacion A11 Compuestos de acuerdo con la realización A7, en la que

$R_1$ es cloro, bromo, yodo o H, y

$R_5$ es bencilo, fenetilo, fenpropilo, fenilo, quinolinilo, indolilo, isoquinolinilo, isoindolilo, indol-2-onilo, indolilalquilo ($C_1$-$C_6$), quinolinilalquilo ($C_1$-$C_6$), isoquinolinilalquilo ($C_1$-$C_6$), isoindolilalquilo ($C_1$-$C_6$), indol-2-onilalquilo ($C_1$-$C_6$), piperidinilalquilo $C_1$-$C_4$,

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tienilalquilo $C_1$-$C_4$, -$CH_2$-piridilo o piridilo, cada uno de los cuales no se sustituye o se sustituye con 1, 2 ó 3 grupos que son independientemente alquilo $C_1$-$C_4$, halogeno, $CF_3$, $OCF_3$, hidroxi $C_1$-$C_4$ alquilo, alcoxi $C_1$-$C_4$, -$CO_2$(alquilo $C_1$-$C_5$), benciloxi, $NR_8R_9$, $NR_6R_7$ alquilo $C_1$-$C_4$, -$C(O)NR_6R_7$ y amidino-oxima, en los que

$R_6$ y $R_7$ son independientemente, en cada aparicion, H, alquilo, hidroxialquilo, alcoxi, alcoxialquilo, alcanoilo, fenilalquilo, fenilalcoxi o fenilalcanoilo, en los que cada uno no se sustituye o se sustituye con 1, 2 o 3 grupos que son independientemente halógeno, hidroxi, alcoxi $C_1$-$C_4$, OH, SH, cicloalquilo $C_3$-$C_6$, alquilo $C_1$-$C_4$, $CF_3$ u $OCF_3$, o

$R_6$, $R_7$ y el nitrogeno al cual se acoplan forman un anillo morfolinilo, tiomorfolinilo o piperazinilo opcionalmente sustituido con 1 o 2 grupos que son independientemente alquilo $C_1$-$C_4$, hidroxi, hidroxialquilo $C_1$-$C_4$ o halogeno

Realización A12 Compuestos de acuerdo con la realizacion A11, en la que

$R_5$ es bencilo, fenetilo, fenpropilo o fenilo, cada uno de los cuales no se sustituye o se sustituye con 1, 2 o 3 grupos que son independientemente alquilo $C_1$-$C_4$, halogeno, $CF_3$, $OCF_3$, -$CO_2CH_3$, hidroxi $C_1$-$C_4$ alquilo, alcoxi $C_1$-$C_4$, -$CO_2$(alquilo $C_1$-$C_5$), benciloxi, $NR_8R_9$, $NR_6R_7$ alquilo $C_1$-$C_4$, -$C(O)NR_6R_7$ y amidino-oxima

Realización A13 Compuestos de acuerdo con la realizacion A11, en la que

$R_5$ es quinolinilo, indolilo, isoquinolinilo, isoindolilo, indol-2-onilo, indolilalquilo ($C_1$-$C_6$), quinolinilalquilo ($C_1$-$C_6$), isoquinolinilalquilo ($C_1$-$C_6$), isoindolilalquilo ($C_1$-$C_6$), indol-2-onilalquilo ($C_1$-$C_6$), piperidinilalquilo $C_1$-$C_4$, tienilalquilo $C_1$-$C_4$, -$CH_2$-piridilo o piridilo, cada uno de los cuales no se sustituye o se

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sustituye con 1, 2 ó 3 grupos que son independientemente alquilo $C_1$-$C_4$, halogeno, $CF_3$, $OCF_3$, $-CO_2CH_3$, hidroxi $C_1$-$C_4$ alquilo, alcoxi $C_1$-$C_4$, $-CO_2$(alquilo $C_1$-$C_5$), benciloxi, $NR_8R_9$, $NR_6R_7$ alquilo $C_1$-$C_4$, $C(O)NR_6R_7$ y amidino-oxima

Realizacion A14 Compuestos de acuerdo con una cualquiera de las realizaciones A11, A12 o A13 en la que

$R_2$ es benciloxi o feneti1oxi,

cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2 ó 3, grupos que son independientemente -alquil($C_1$-$C_6$)-N(R)-$CO_2R_{30}$, fluoro, cloro, bromo, $CF_3$ o alquil($C_1$-$C_4$)

Realizacion A15 Compuestos de acuerdo con una cualquiera de las realizaciones A11, A12 o A13 en las que

$R_2$ es feniloxialquil($C_1$-$C_6$), en el que el grupo fenilo no se sustituye o se sustituye con 1, 2 o 3 grupos que son independientemente -alquil($C_1$-$C_6$)-N(R)-$CO_2R_{30}$, fluoro, cloro, bromo, $CF_3$ o alquil($C_1$-$C_4$)

Realizacion A16 Compuestos de acuerdo con la realizacion A1, en la que

$R_1$ es H, halogeno, alquilo $C_1$-$C_4$ opcionalmente sustituido con alcoxi $C_1$-$C_4$ carbonilo, alquenilo $C_2$-$C_4$ opcionalmente sustituido con alcoxi $C_1$-$C_4$ carbonilo, alquinilo $C_2$-$C_4$ o carboxaldehido

Realizacion A17 Compuestos de acuerdo con la realizacion A16, en la que

$R_2$ es benciloxi, OH, feniloxi, feniloxialquil($C_1$-$C_6$) o feniltioalcoxi ($C_1$-$C_4$), en el que cada uno de los anteriormente mencionados se sustituye opcionalmente con 1, 2, 3, 4 o 5 grupos que son independientemente halogeno, -alquil($C_1$-$C_6$)-N(R)-$CO_2R_{30}$, $NR_6R_7$, haloalquilo ($C_1$-$C_4$), haloalcoxi ($C_1$-$C_4$), alquilo ($C_1$-$C_6$), piridilo o $NR_6R_7$-(alquilo $C_1$-$C_6$)-

Realizacion A18 Compuestos de acuerdo con la

realizacion A17, en la que

$R_4$ es H o alquilo ($C_1$-$C_4$) opcionalmente sustituido con uno o dos grupos que son independientemente $CO_2H$, -$CO_2$alquilo, -C(O)NRR, -N($R_{30}$)C(O)NRR, -N($R_{30}$)C(O)-alcoxi($C_1$-$C_6$), OH o -$NR_6R_7$

Realizacion A19 Compuestos de acuerdo con la realizacion A18, en la que

$R_5$ es fenilo, naftilo, indolilo, piridilo, quinolinilo, isoquinolinilo, isoindolilo, indol-2-onilo, indolilalquilo ($C_1$-$C_6$), quinolinilalquilo ($C_1$-$C_6$), isoquinolinilalquilo ($C_1$-$C_6$), isoindolilalquilo ($C_1$-$C_6$), indol-2-onilalquilo ($C_1$-$C_6$), piridazinilo, pirimidinilo o pirazinilo, piridazinilalquilo ($C_1$-$C_6$), pirimidinilalquilo ($C_1$-$C_6$) o pirazinilalquilo ($C_1$-$C_6$), cada uno de los cuales no se sustituye o se sustituye con 1, 2, 3, 4 o 5 grupos que son independientemente alquilo $C_1$-$C_4$, halogeno, $CF_3$, $OCF_3$, -$CO_2CH_3$, hidroxi $C_1$-$C_4$ alquilo, alcoxi $C_1$-$C_4$, -$CO_2$(alquilo $C_1$-$C_5$), benciloxi, -$NR_8R_9$, -C(O)$NR_6R_7$, $NR_6R_7$ alquilo $C_1$-$C_4$ y amidino-oxima, en los que

$R_6$ y $R_7$ son independientemente, en cada aparicion, H, alquilo $C_1$-$C_4$, hidroxi $C_1$-$C_4$ alquilo, alcoxi $C_1$-$C_4$, alcoxi $C_1$-$C_4$ alquilo $C_1$-$C_4$, alcanoilo $C_1$-$C_4$, fenilalquilo $C_1$-$C_4$, fenilalcoxi $C_1$-$C_4$ o fenilalcanoilo $C_1$-$C_4$, en el que cada uno no esta sustituido o esta sustituido con 1, 2 o 3 grupos que son independientemente halógeno, hidroxi, alcoxi $C_1$-$C_4$, alquilo $C_1$-$C_4$, OH, SH, cicloalquilo $C_3$-$C_6$ $CF_3$ u $OCF_3$ o

$R_6$, $R_7$ y el nitrogeno al cual se acoplan forman un anillo morfolinilo, tiomorfolinilo o piperazinilo opcionalmente sustituido con 1 ó 2 grupos que son independientemente alquilo $C_1$-$C_4$, hidroxi, hidroxialquilo $C_1$-$C_4$ o halógeno

Realizacion A20 Compuestos de acuerdo con la realizacion A19, en la que

$R_1$ es H, halógeno, metilo, etilo, alquenilo $C_2$-$C_4$ alquinilo $C_2$-$C_4$ o carboxaldehido,

$R_2$ es benciloxi, OH, feniloxi, feniloxialquil($C_1$-$C_6$) o feniltioalcoxi ($C_1$-$C_4$), en el que cada uno de los anteriormente mencionados se sustituye opcionalmente con 1, 2, 3 o 4 grupos que son independientemente halógeno, -alquil($C_1$-$C_6$)-N(R)-CO$_2$$R_{30}$, $NR_6R_7$, $NR_6R_7$ alquilo $C_1$-$C_4$, haloalquilo ($C_1$-$C_4$), haloalcoxi ($C_1$-$C_4$), alquilo ($C_1$-$C_6$) o piridilo y

$R_4$ es H o alquilo ($C_1$-$C_4$) opcionalmente sustituido con uno o dos grupos que son independientemente $CO_2H$, -$CO_2$alquilo, -C(O)NRR, -N($R_{30}$)C(O)NRR, -N($R_{30}$)C(O)-alcoxi($C_1$-$C_6$), OH o -$NR_6R_7$

Realizacion A21 Compuestos de acuerdo con la realización A20, en la que

$R_5$ es fenilo opcionalmente sustituido con 1, 2, 3, 4 o 5 grupos que son independientemente halógeno, alquilo $C_1$-$C_6$, -$NR_{10}R_{11}$, alcoxi $C_1$-$C_4$, -C(O)$NR_{10}R_{11}$, -$CO_2H$, $NR_{10}R_{11}$ alquilo $C_1$-$C_4$, alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$ carbonilo, alcoxi $C_1$-$C_6$, CHO, -$SO_2NH_2$, haloalquilo $C_1$-$C_4$, hidroxi $C_1$-$C_6$ alquilo, -alquilo $C_1$-$C_4$-$NR_{12}$C(O)$NR_{13}R_{14}$, -alquilo $C_1$-$C_4$-$NR_{12}$C(O)-(alquilo $C_1$-$C_4$)-$NR_{13}R_{14}$, -alquilo $C_1$-$C_4$-$NR_{12}$C(O)$OR_{15}$ o -alquilo $C_1$-$C_4$-$NR_{12}$C(O)-(alquilo $C_1$-$C_4$)-$R_{15}$, en los que

$R_{10}$ y $R_{11}$, en cada aparicion, son independientemente H, alquilo $C_1$-$C_6$, aminoalquilo $C_1$-$C_4$, NH(alquilo $C_1$-$C_6$)alquilo, N(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$) alquilo $C_1$-$C_6$, hidroxi $C_1$-$C_6$ alquilo, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, OH, -$SO_2$ (alquilo $C_1$-$C_6$) o alcanoilo $C_1$-$C_6$, o

$R_{10}$, $R_{11}$ y el nitrogeno al cual se acoplan forman un anillo piperidinilo, pirrolidinilo, piperazinilo o morfolinilo opcionalmente sustituido con 1 ó 2 grupos que son independientemente alquilo o halogeno,

$R_{12}$ es H o alquilo $C_1$-$C_6$,

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$R_{13}$ y $R_{14}$ son independientemente H o alquilo $C_1$-$C_6$, o

$R_{13}$ y $R_{14}$ y el nitrogeno al que estan acoplados forman un anillo morfolinilo, y

$R_{15}$ es alcoxi $C_1$-$C_6$, -OC(O)alquilo $C_1$-$C_6$, OH

Realización A22 Compuestos de acuerdo con la realización A21, en la que

$R_5$ es fenilo opcionalmente sustituido con 1, 2, 3, 4 o 5 grupos que son independientemente halógeno, alquilo $C_1$-$C_6$, -$NR_{10}R_{11}$, $NR_{10}R_{11}$ alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_4$ o -$C(O)NR_{10}R_{11}$, -$CO_2H$, -alquilo $C_1$-$C_4$-$NR_{10}R_{11}$, alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$ carbonilo, alcoxi $C_1$-$C_6$, CHO, -$SO_2NH_2$, haloalquilo $C_1$-$C_4$, hidroxi $C_1$-$C_6$ alquilo, -alquilo $C_1$-$C_4$-$NR_{12}C(O)NR_{13}R_{14}$, -alcuilo $C_1$-$C_4$-$NR_{12}C(O)$-(alquilo $C_1$-$C_4$)-$NR_{13}R_{14}$, -alquilo $C_1$-$C_4$-$NR_{12}C(O)OR_{15}$ o -alquilo $C_1$-$C_4$-$NR_{12}C(O)$-(alquilo $C_1$-$C_4$)-$R_{15}$ en los que

$R_{10}$ y $R_{11}$, en cada aparicion, son independientemente H, alquilo $C_1$-$C_6$, aminoalquilo $C_1$-$C_4$, NH(alquilo $C_1$-$C_6$)alquilo, N(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$) alquilo $C_1$-$C_6$, hidroxi $C_1$-$C_6$ alquilo, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, OH, -$SO_2$ (alquilo $C_1$-$C_6$) o alcanoilo $C_1$-$C_6$,

$R_{12}$ es H o alquilo $C_1$-$C_6$,

$R_{13}$ y $R_{14}$ son independientemente H o alquilo $C_1$-$C_6$, o

$R_{13}$, $R_{14}$ y el nitrogeno al que están acoplados forman un anillo morfolinilo, y

$R_{15}$ es alcoxi $C_1$-$C_6$, -OC(O)alquilo $C_1$-$C_6$, OH

Realización A23 Compuestos de acuerdo con la realización A22, en la que

$R_5$ es fenilo opcionalmente sustituido con 1, 2, 3, 4 ó 5 grupos que son independientemente halógeno, alquilo $C_1$-$C_6$, -$NR_{10}R_{11}$, $NR_{10}R_{11}$ alquilo $C_1$-$C_4$, alcoxi $C_1$-$C_4$, -$C(O)NR_{10}R_{11}$, en los que

$R_{10}$ y $R_{11}$, en cada aparicion, son independientemente H, alquilo $C_1$-$C_6$, aminoalquilo $C_1$-$C_4$, NH(alquilo $C_1$-$C_6$)alquilo,

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N(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$) alquilo $C_1$-$C_6$, hidroxi $C_1$-$C_6$ alquilo, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, OH, $-SO_2$ (alquilo $C_1$-$C_6$), alcanoilo $C_1$-$C_6$

Realizacion A24 Compuestos de acuerdo con la realización A23, en la que

$R_5$ es fenilo opcionalmente sustituido con 1, 2, 3, 4 o 5 grupos que son independientemente halógeno, alquilo $C_1$-$C_6$, $-NR_{10}R_{11}$ o alcoxi $C_1$-$C_4$

Realizacion A25 Compuestos de acuerdo con la realización A23, en la que

$R_5$ se sustituye con al menos un $-C(O)NR_{10}R_{11}$

Realizacion A26 Compuestos de acuerdo con la realizacion A25, en la que

$R_{10}$ y $R_{11}$ en cada aparicion, son independientemente H, alquilo $C_1$-$C_6$, aminoalquilo $C_1$-$C_4$, NH(alquilo $C_1$-$C_6$)alquilo, N(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$) alquilo $C_1$-$C_6$, hidroxi $C_1$-$C_6$ alquilo, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$

Realizacion 27 Compuestos de acuerdo con la realizacion A26, en la que

$R_{10}$ es H

Realizacion A28 Compuestos de acuerdo con la realizacion A25, en la que

$R_{10}$ y $R_{11}$ en cada aparición, son independientemente H, alquilo $C_1$-$C_6$, OH, $-SO_2$ (alquilo $C_1$-$C_6$), alcanoilo $C_1$-$C_6$

Realizacion A29 Compuestos de acuerdo con la realización A20, en la que

$R_5$ es fenilo opcionalmente sustituido con 1, 2, 3, 4 o 5 grupos que son independientemente halogeno, alquilo $C_1$-$C_6$, $NH_2$, NH(alquilo $C_1$-$C_6$), N(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$), alcoxi $C_1$-$C_4$, $-C(O)NR_{10}R_{11}$, en los que cada uno de los grupos alquilo anteriormente mencionados está opcionalmente sustituido con 1 o 2 grupos que son independientemente OH o metoxi, en los que

$R_{10}$, $R_{11}$ y el nitrógeno al cual se acoplan forman un anillo piperidinilo, pirrolidinilo, piperazinilo o morfolinilo opcionalmente sustituido con 1 o 2 grupos que son independientemente alquilo o halógeno

Realizacion A30 Compuestos de acuerdo con la realización A20, en la que

$R_5$ es fenilo opcionalmente sustituido con 1, 2, 3, 4 ó 5 grupos que son independientemente halogeno, alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_4$, $-CO_2H$, -alquilo $C_1$-$C_4$-$NR_{10}R_{11}$, alcoxi $C_1$-$C_6$ carbonilo, alcoxi $C_1$-$C_6$, CHO, $-SO_2NH_2$, haloalquilo $C_1$-$C_4$, hidroxi $C_1$-$C_6$ alquilo, -alquilo $C_1$-$C_4$-$NR_{12}C(O)NR_{13}R_{14}$, -alquilo $C_1$-$C_4$-$NR_{12}C(O)$-(alquilo $C_1$-$C_4$)-$NR_{13}R_{14}$, -alquilo $C_1$-$C_4$-$NR_{12}C(O)OR_{15}$ o -alquilo $C_1$-$C_4$-$NR_{12}C(O)$-(alquilo $C_1$-$C_4$)-$R_{15}$, -$OC(O)$alquilo $C_1$-$C_6$ u OH en los que

$R_{12}$ es H o alquilo $C_1$-$C_6$,

$R_{13}$ y $R_{14}$ son independientemente H o alquilo $C_1$-$C_6$, o

$R_{13}$ y $R_{14}$ y el nitrogeno al que estan acoplados forman un anillo morfolinilo,

$R_{15}$ es alcoxi $C_1$-$C_6$

Realizacion A31 Compuestos de acuerdo con la realización A30, en la que

$R_5$ es fenilo opcionalmente sustituido con 1, 2, 3, 4 o 5 grupos que son independientemente halogeno, alquilo $C_1$-$C_4$, alcoxi $C_1$-$C_4$, $-CO_2H$, alcoxi $C_1$-$C_4$ carbonilo, alcoxi $C_1$-$C_4$, CHO, $-SO_2NH_2$, haloalcoxi $C_1$-$C_4$, hidroxi $C_1$-$C_4$ alquilo

Realizacion A32 Compuestos de acuerdo con la realización A30, en la que

$R_5$ es fenilo opcionalmente sustituido con 1, 2, 3, 4 o 5 grupos que son independientemente halógeno, alquilo $C_1$-$C_4$, alcoxi $C_1$-$C_4$, $-CO_2H$, -alquilo $C_1$-$C_4$-$NR_{10}R_{11}$ , -alquilo $C_1$-$C_4$-$NR_{12}C(O)NR_{13}R_{14}$, -alquilo $C_1$-$C_4$-$NR_{12}C(O)$-(alquilo $C_1$-$C_4$)-$NR_{13}R_{14}$, -alquilo $C_1$-$C_4$-$NR_{12}C(O)OR_{15}$ o -alquilo $C_1$-$C_4$-$NR_{12}C(O)$-(alquilo $C_1$-$C_4$)-$R_{15}$ o -$OC(O)$alquilo $C_1$-$C_6$ en los que

$R_{12}$ es H o alquilo $C_1$-$C_6$,

$R_{13}$ y $R_{14}$ son independientemente H o alquilo $C_1$-$C_6$, o

$R_{13}$, $R_{14}$ y el nitrógeno al que están acoplados forman un anillo morfolinilo,

$R_{15}$ es alcoxi $C_1$-$C_6$

Realizacion A33 Compuestos de acuerdo con la realizacion A31, en la que

$R_5$ es fenilo opcionalmente sustituido con 1, 2, 3, 4 ó 5 grupos que son independientemente halogeno, alquilo $C_1$-$C_4$, alcoxi $C_1$-$C_4$, -$CO_2H$, -alquilo $C_1$-$C_4$-$NR_{10}R_{11}$, -alquilo $C_1$-$C_4$-$NR_{12}C(O)NR_{13}R_{14}$, -alquilo $C_1$-$C_4$-$NR_{12}C(O)$-(alquilo $C_1$-$C_4$)-$NR_{13}R_{14}$, en los que

$R_{12}$ es H o alquilo $C_1$-$C_6$,

$R_{13}$ y $R_{14}$ son independientemente H o alquilo $C_1$-$C_6$, o

$R_{13}$ y $R_{14}$ y el nitrógeno al que estan acoplados forman un anillo morfolinilo

Realizacion A34 Compuestos de acuerdo con una cualquiera de las realizaciones A30, A31, A32 o A33, en las que el grupo fenilo se sustituye con dos grupos que son meta el uno con el otro

Realizacion A35 Compuestos de acuerdo con una cualquiera de las realizaciones A30, A31, A32 o A33, en las que el grupo fenilo se sustituye con dos grupos que son para el uno con el otro

Realizacion A36 Compuestos de acuerdo con la realizacion A20, en la que

$R_5$ es indolilo, piridilo, piridazinilo, pirimidinilo, indazolilo, quinolinilo, isoquinolinilo, isoindolilo, indol-2-onilo, piridazinilo, pirimidinilo o pirazinilo, cada uno de los cuales no esta sustituido o está sustituido con 1, 2, 3, 4 o 5 grupos que son independientemente alquilo $C_1$-$C_4$, halogeno, $CF_3$, $OCF_3$, -$CO_2CH_3$, hidroxi $C_1$-$C_4$ alquilo, alcoxi $C_1$-$C_4$, -$CO_2$(alquilo $C_1$-$C_5$), benciloxi, $NR_8R_9$,

$NR_6R_7$ alquilo $C_1$-$C_4$, $-C(O)NR_6R_7$ o amidino-oxima, en los que

$R_6$ y $R_7$ son independientemente, en cada aparición, H, alquilo $C_1$-$C_4$, hidroxi $C_1$-$C_4$ alquilo, alcoxi $C_1$-$C_4$, alcoxi $C_1$-$C_4$ alquilo $C_1$-$C_4$, alcanoilo $C_1$-$C_4$, fenilalquilo $C_1$-$C_4$, fenilalcoxi $C_1$-$C_4$ o fenilalcanoilo $C_1$-$C_4$, en el que cada uno no esta sustituido o está sustituido con 1, 2 o 3 grupos que son independientemente halógeno, OH, SH, cicloalquilo $C_3$-$C_6$, alcoxi $C_1$-$C_4$, alquilo $C_1$-$C_4$ OH, $CF_3$ u $OCF_3$, o

$R_6$, $R_7$ y el nitrogeno al cual se acoplan forman un anillo morfolinilo tiomorfolinilo o piperazinilo opcionalmente sustituido con 1 ó 2 grupos que son independientemente alquilo $C_1$-$C_4$, hidroxi, hidroxialquilo $C_1$-$C_4$ o halogeno

Realizacion A38 Compuestos de acuerdo con la realizacion A36, en la que

$R_5$ es indolilo, piridilo, pirimidinilo, indazolilo o pirazinilo, cada uno de los cuales no se sustituye o se sustituye con 1, 2, 3 ó 4 grupos que son independientemente alquilo $C_1$-$C_4$, halogeno, $CF_3$, $OCF_3$, $-CO_2CH_3$, hidroxi $C_1$-$C_4$ alquilo, alcoxi $C_1$-$C_4$, $-CO_2$(alquilo $C_1$-$C_5$), benciloxi, $-C(O)NR_6R_7$, $-NR_8R_9$, $NR_6R_7$ alquilo $C_1$-$C_4$ y amidino-oxima, en los que

$R_6$ y $R_7$ son independientemente, en cada aparicion, H, alquilo $C_1$-$C_4$, hidroxi $C_1$-$C_4$ alquilo, alcoxi $C_1$-$C_4$, alcoxi $C_1$-$C_4$ alquilo $C_1$-$C_4$, alcanoilo $C_1$-$C_4$, fenilalquilo $C_1$-$C_4$, fenilalcoxi $C_1$-$C_4$ o fenilalcanoilo $C_1$-$C_4$, en los que cada uno no está sustituido o está sustituido con 1, 2 o 3 grupos que son independientemente halógeno, OH, SH, cicloalquilo $C_3$-$C_6$, alcoxi $C_1$-$C_4$, alquilo $C_1$-$C_4$ OH, $CF_3$ u $OCF_3$

Realizacion A39 Compuestos de acuerdo con la realización A30, en la que

$R_5$ es indolilo, piridilo o pirazinilo, cada uno de los

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cuales no se sustituye o se sustituye con 1, 2, 3 o 4 grupos que son independientemente alquilo $C_1$-$C_4$, halogeno, $CF_3$, $OCF_3$, $-CO_2CH_3$, hidroxi $C_1$-$C_4$ alquilo, alcoxi $C_1$-$C_4$, $-CO_2$(alquilo $C_1$-$C_5$), benciloxi, $-C(O)NR_6R_7$, $-NR_8R_9$, $NR_6R_7$ alquilo $C_1$-$C_4$ y amidino-oxima, en los que

$R_6$ y $R_7$ son independientemente, en cada aparición, H, alquilo $C_1$-$C_4$, hidroxi $C_1$-$C_4$ alquilo, alcoxi $C_1$-$C_4$, alcoxi $C_1$-$C_4$ alquilo $C_1$-$C_4$, cada uno de los cuales se sustituye opcionalmente con 1, 2 o 3 grupos que son independientemente halógeno, OH, SH, cicloalquilo $C_3$-$C_6$, alcoxi $C_1$-$C_4$, alquilo $C_1$-$C_4$, OH, $CF_3$ u $OCF_3$

Realización A40 Compuestos de acuerdo con la realizacion A36, en la que

$R_5$ es indolilo, piridilo, piridazinilo, pirimidinilo o pirazinilo, cada uno de los cuales no se sustituye o se sustituye con 1, 2, 3, 4 ó 5 grupos que son independientemente alquilo $C_1$-$C_4$, halógeno, $CF_3$, $OCF_3$, $-CO_2CH_3$, hidroxi $C_1$-$C_4$ alquilo, alcoxi $C_1$-$C_4$, $-CO_2$(alquilo $C_1$-$C_5$), benciloxi, $-C(O)NH_2$, $-C(O)NH$(alquilo $C_1$-$C_6$) en los que el grupo alquilo se sustituye opcionalmente con OH o metoxi, $-C(O)N$(alquilo $C_1$-$C_6$) (alquilo $C_1$-$C_6$) en los que cada grupo alquilo se sustituye independiente y opcionalmente con CH o metoxi, $-C(O)NR_6R_7$, $NR_8R_9$, $NR_6R_7$ alquilo $C_1$-$C_4$, -alquilo $C_1$-$C_4$-$NH_2$, -alquilo $C_1$-$C_4$-NH(alquilo $C_1$-$C_6$) en los que cada grupo alquilo se sustituye independiente y opcionalmente con OH o metoxi, -alquilo $C_1$-$C_4$-N(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$) en los que cada grupo alquilo se sustituye independiente y opcionalmente con OH o metoxi y amidino-oxima, en los que

$R_6$, $R_7$ y el nitrogeno al cual se acoplan forman un anillo morfolinilo, tiomorfolinilo o piperazinilo opcionalmente sustituido con 1 ó 2 grupos que son independientemente alquilo $C_1$-$C_4$, hidroxi, hidroxialquilo

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$C_1$-$C_4$ o halogeno

Realización A42 Compuestos de acuerdo con una cualquiera de las realizaciones A37, A38, A39 o A40 en las que

$R_1$ es H, halogeno, metilo o carboxaldehido,

$R_2$ es benciloxi, feniloxi, feniloxialquil($C_1$-$C_6$) o feniltioalcoxi ($C_1$-$C_4$), en el que cada uno de los anteriormente mencionados se sustituye opcionalmente con 1, 2, 3 o 4 grupos que son independientemente halógeno, -alquil($C_1$-$C_6$)-N(R)-$CO_2R_{30}$, $NR_6R_7$, haloalquilo ($C_1$-$C_4$), haloalcoxi ($C_1$-$C_4$), alquilo ($C_1$-$C_6$), $NR_6R_7$alquil($C_1$-$C_6$), piridilo, morfolinilo, tiomorfolinilo, piperazinilo piridilalquil($C_1$-$C_6$), morfolinilalquil($C_1$-$C_6$), tiomorfolinilalquil($C_1$-$C_6$) o piperazinilalquil($C_1$-$C_6$) en los que los anillos piridilo, morfolinilo, tiomorfolinilo y piperazinilo se sustituyen opcionalmente con 1 ó 2 grupos que son independientemente alquilo $C_1$-$C_4$ o halógeno, en los que

$R_6$ y $R_7$ son independientemente, en cada aparición, H, alquilo $C_1$-$C_4$ opcionalmente sustituido con uno o dos grupos que son independientemente OH, halogeno o metoxi, hidroxi $C_1$-$C_4$ alquilo, alcoxi $C_1$-$C_4$, alcoxi $C_1$-$C_4$ alquilo $C_1$-$C_4$, alcanoilo $C_1$-$C_4$, bencilo, benciloxi o fenilalcanoilo $C_1$-$C_4$, en los que cada uno no se sustituye o se sustituye con 1, 2 ó 3 grupos que son independientemente halogeno, OH, SH, cicloalquilo $C_3$-$C_6$, alcoxi $C_1$-$C_4$, alquilo $C_1$-$C_4$, $CF_3$ u $OCF_3$ y

$R_4$ es H, alquilo ($C_1$-C3) opcionalmente sustituido con uno o dos grupos que son independientemente $CO_2H$, -$CO_2$alquilo, -C(O)NRR, -N($R_{30}$)C(O)NRR, -N($R_{30}$)C(O)-alcoxi($C_1$-$C_6$), -$NR_6R_7$, $NR_6R_7$alquilo $C_1$-$C_4$ o hidroxialquil($C_1$-$C_3$)

Realizacion A43 Compuestos de acuerdo con la realizacion A42, en la que

$R_1$ es H o halógeno

Realizacion A44 Compuestos de acuerdo con la realizacion A18, en la que

$R_5$ es fenilalquil($C_1$-$C_6$), alquil($C_1$-$C_6$), piperidinilalquilo ($C_1$-$C_6$), tienilalquilo ($C_1$-$C_6$), indolilalquilo ($C_1$-$C_6$), naftilalquil($C_1$-$C_6$), piridilalquil($C_1$-$C_6$), pirimidilalquil($C_1$-$C_6$), quinolinilalquilo ($C_1$-$C_6$), isoquinolinilalquilo ($C_1$-$C_6$), isoindolilalquilo ($C_1$-$C_6$), indol-2-onilalquilo ($C_1$-$C_6$), piridazinilalquilo ($C_1$-$C_6$), pirazinilalquilo ($C_1$-$C_6$) o pirazinilalquil($C_1$-$C_6$), en el que

cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2, 3, 4 o 5 grupos que son independientemente alquilo, halogeno, alcoxi, benciloxi, hidroxialquilo, tioalcoxi, -$CO_2$(alquilo $C_1$-$C_5$), $CO_2H$, CN, amidino-oxima, $NR_8R_9$, $NR_6R_7$, (alquilo $C_1$-$C_6$)-, -C(O)$NR_6R_7$, amidino, $CF_3$ u $OCF_3$,

$R_8$ es hidrogeno, alquilo $C_1$-$C_6$, alcanoilo $C_1$-$C_6$, fenilalquilo $C_1$-$C_6$ y fenilalcanoilo $C_1$-$C_6$, y

$R_9$ es aminoalquilo, monoalquilo $C_1$-$C_6$ aminoalquilo $C_1$-$C_6$, dialquilo $C_1$-$C_6$ aminoalquilo $C_1$-$C_6$, alquilo $C_1$-$C_6$, alcanoilo $C_1$-$C_6$, fenilalquilo $C_1$-$C_4$, indazolilo y fenilalcanoilo $C_1$-$C_4$

En esta realización, se prefiere que cuando $R_2$ es benciloxi, $R_4$ es H y $R_5$ es bencilo o metilo, $R_1$ no sea hidrógeno, y

no mas de dos de $R_1$, $R_2$, $R_4$ y $R_5$ sean simultaneamente hidrogeno

Realizacion A45 Compuestos de acuerdo con la realización A44, en la que

$R_5$ es fenilalquil($C_1$-$C_6$), que no se sustituye o se sustituye con 1, 2, 3, 4 ó 5 grupos que son independientemente alquilo, halogeno, alcoxi, benciloxi, tioalcoxi, -$CO_2$(alquilo $C_1$-$C_5$), $CO_2H$, CN, amidino-oxima, -

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$NR_8R_9$, $-NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, $-C(O)NR_6R_7$ amidino, $CF_3$ u $OCF_3$, en los que

$R_6$ y $R_7$ son independientemente, en cada aparición, H, alquilo $C_1$-$C_4$, hidroxi $C_1$-$C_4$ alquilo, alcoxi $C_1$-$C_4$, alcoxi $C_1$-$C_4$ alquilo $C_1$-$C_4$, alcanoilo $C_1$-$C_4$, fenilalquilo $C_1$-$C_4$, fenilalcoxi $C_1$-$C_4$ o fenilalcanoilo $C_1$-$C_4$, en los que cada uno no esta sustituido o está sustituido con 1, 2 o 3 grupos que son irdependientemente halogeno, OH, SH, cicloalquilo $C_3$-$C_6$, alcoxi $C_1$-$C_4$, alquilo $C_1$-$C_4$ $CF_3$ u $OCF_3$, o

$R_6$, $R_7$ y el nitrogeno al cual se acoplan forman un anillo morfolinilo, tiomorfolinilo o piperazinilo opcionalmente sustituido con 1 o 2 grupos que son independientemente alquilo $C_1$-$C_4$, hidroxi, hidroxialquilo $C_1$-$C_4$ o halogeno,

$R_8$ es hidrógeno, alquilo $C_1$-$C_6$, alcanoilo $C_1$-$C_6$, fenilalquilo $C_1$-$C_6$ y fenilalcanoilo $C_1$-$C_6$, y

$R_9$ es aminoalquilo, monoalquilo $C_1$-$C_6$ aminoalquilo $C_1$-$C_6$, dialquilo $C_1$-$C_6$ aminoalquilo $C_1$-$C_6$, alquilo $C_1$-$C_6$, alcanoilo $C_1$-$C_6$, fenilalquilo $C_1$-$C_4$, indazolilo y fenilalcanoilo $C_1$-$C_4$

Realizacion A46 Compuestos de acuerdo con la realizacion A45, en la que

$R_5$ es fenilalquil($C_1$-$C_6$), que no se sustituye o se sustituye con 1, 2, 3, 4 o 5 grupos que son independientemente CN, halógeno, alcoxi $C_1$-$C_4$, tioalcoxi $C_1$-$C_4$, haloalquilo $C_1$-$C_4$, alquilo $C_1$-$C_4$, haloalquilo $C_1$-$C_4$, haloalcoxi $C_1$-$C_4$, $-C(O)NR_{20}R_{21}$, en los que

$R_{20}$ y $R_{21}$ son independientemente H, alquilo $C_1$-$C_6$, hidroxi $C_1$-$C_6$ alquilo, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$ o

$R_{20}$, $R_{21}$ y el nitrogeno al cual se acoplan forman un anillo piperazinilo o morfolinilo, el cual esta opcionalmente sustituido con 1 ó 2 grupos que son independientemente alquilo o halogeno

Realizacion A47 Compuestos de acuerdo con la realizacion A46, en la que

$R_5$ es fenilalquil($C_1$-$C_4$), que no se sustituye o se sustituye con 1, 2, 3, 4 ó 5 grupos que son independientemente CN, halógeno, alcoxi $C_1$-$C_4$, haloalquilo $C_1$-$C_4$, alquilo $C_1$-$C_4$, haloalcoxi $C_1$-$C_4$, $-C(O)NR_{20}R_{21}$, en los que

$R_{20}$ y $R_{21}$ son independientemente H, alquilo $C_1$-$C_6$, hidroxi $C_1$-$C_6$ alquilo, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$ o

$R_{20}$, $R_{21}$ y el nitrogeno al cual se acoplan forman un anillo piperazinilo o morfolinilo, cada uno de los cuales está opcionalmente sustituido con 1 ó 2 grupos que son independientemente alquilo o halógeno

Realizacion A48 Compuestos de acuerdo con la realización A47, en la que

$R_5$ es bencilo o fenetilo, cada uno de los cuales no se sustituye o se sustituye con 1, 2, 3, 4 ó 5 grupos que son independientemente CN, halogeno, alcoxi $C_1$-$C_4$, $CF_3$, $OCF_3$, alquilo $C_1$-$C_4$, $-C(O)NR_{20}R_{21}$, en los que

$R_{20}$ y $R_{21}$ son independientemente H, alquilo $C_1$-$C_6$, hidroxi $C_1$-$C_6$ alquilc, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$ o

$R_{20}$, $R_{21}$ y el nitrogeno al cual se acoplan forman un anillo piperazinilo o morfolinilo, cada uno de los cuales esta opcionalmente sustituido con 1 ó 2 grupos que son independientemente alquilo o halógeno

Realización A49 Compuestos de acuerdo con la realizacion A48, en la que

$R_5$ es bencilo o fenetilo, cada uno de los cuales no se sustituye o se sustituye con 1, 2, 3, 4 ó 5 grupos que son independientemente halógeno, metoxi, etoxi, $CF_3$, $OCF_3$, metilo, etilo o , $-C(O)NR_{20}R_{21}$, en los que

$R_{20}$ y $R_{21}$ son independientemente H, alquilo $C_1$-$C_6$, hidroxi $C_1$-$C_6$ alquilo, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$,

Realización A50 Compuestos de acuerdo con la realizacion A48, en la que

$R_5$ es bencilo o fenetilo, cada uno de los cuales no se sustituye o se sustituye con 1, 2, 3, 4 o 5 grupos que son independientemente halogeno, metoxi, etoxi, $CF_3$, $OCF_3$, metilo, etilo o $-C(O)NR_{20}R_{21}$, en los que

$R_{20}$, $R_{21}$ y el nitrógeno al cual se acoplan forman un anillo piperazinilo o morfolinilo, cada uno de los cuales esta opcionalmente sustituido con 1 ó 2 grupos que son independientemente alquilo o halógeno

Realizacion A51 Compuestos de acuerdo con la realizacion A49, en la que

$R_5$ se sustituye en el anillo fenilo con 1, 2, 3, 4 o 5 grupos y en el que existe un grupo en la posición para del fenilo

Realizacion A52 Compuestos de acuerdo con la realizacion A43, en la que

$R_5$ es piperidinilalquilo ($C_1$-$C_6$), tienilalquilo ($C_1$-$C_6$), indolililalquilo ($C_1$-$C_6$), piridilalquil($C_1$-$C_6$), pirimidilalquil($C_1$-$C_6$), quinolinilalquilo ($C_1$-$C_6$), isoquinolinilalquilo ($C_1$-$C_6$), isoindolilalquilo ($C_1$-$C_6$), indol-2-onilalquilo ($C_1$-$C_6$), piridazinilalquilo ($C_1$-$C_6$) o pirazinilalquilo ($C_1$-$C_6$) o pirazinilalquil($C_1$-$C_6$) o pirazinilalquil($C_1$-$C_6$), en el que

cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2, 3, 4 o 5 grupos que son independientemente alquilo $C_1$-$C_6$, halogeno, alcoxi $C_1$-$C_6$, hidroxi $C_1$-$C_6$ alquilo, benciloxi, tioalcoxi $C_1$-$C_6$, $-CO_2$(alquilo $C_1$-$C_5$), $CO_2H$, CN, amidino-oxima, $NR_8R_9$, $NR_6R_7$-(alquilo $C_1$-$C_6$)-, $-C(O)NR_6R_7$, amidino, $CF_3$ u $OCF_3$,

$R_8$ es hidrógeno, alquilo $C_1$-$C_6$, alcanoilo $C_1$-$C_6$, fenilalquilo $C_1$-$C_6$ y fenilalcanoilo $C_1$-$C_6$, y

$R_9$ es aminoalquilo, monoalquilo $C_1$-$C_6$ aminoalquilo $C_1$-

$C_6$, dialquilo $C_1$-$C_6$ aminoalquilo $C_1$-$C_6$, alquilo $C_1$-$C_6$, alcanoilo $C_1$-$C_6$, fenilalquilo $C_1$-$C_4$, indazolilo y fenilalcanoilo $C_1$-$C_4$

En esta realizacion, se prefiere que cuando $R_2$ es benciloxi, $R_4$ es H y $R_5$ es bencilo o metilo, $R_1$ no sea hidrogeno, y

no más de dos de $R_1$, $R_2$, $R_4$ y $R_5$ sean simultaneamente hidrogeno

Realización A53 Compuestos de acuerdo con la realización A52, en la que

$R_5$ es piperidinilalquilo ($C_1$-$C_4$), tienilalquilo ($C_1$-$C_4$), indolilalquilo ($C_1$-$C_4$), piridilalquil($C_1$-$C_4$), pirimidilalquil($C_1$-$C_4$) o pirazinilalquil($C_1$-$C_4$), cada uno de los cuales no se sustituye

Realización A54 Compuestos de acuerdo con la realizacion A52, en la que

$R_5$ es indolilalquilo ($C_1$-$C_4$), pirimidilalquil($C_1$-$C_4$) o pirazinilalquil($C_1$-$C_4$), en el que

cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2, 3 o 4 grupos que son independientemente alquilo $C_1$-$C_6$, halógeno, alcoxi $C_1$-$C_6$, hidroxi $C_1$-$C_6$ alquilo, benciloxi, tioalcoxi $C_1$-$C_6$, -$CO_2$(alquilo $C_1$-$C_5$), $CO_2H$, CN, amidino-oxima, $NR_8R_9$, $NR_6R_7$-(alquilo $C_1$-$C_6$)-, amidino, -C(O)$NR_{20}R_{21}$, $CF_3$ u $OCF_3$, en los que

$R_6$ y $R_7$ son independientemente, en cada aparicion, H, alquilo $C_1$-$C_4$, hidrcxi $C_1$-$C_4$ alquilo, alcoxi $C_1$-$C_4$, alcoxi $C_1$-$C_4$ alquilo $C_1$-$C_4$, alcanoilo $C_1$-$C_4$, bencilo, benciloxi o fenilalcanoilo $C_1$-$C_4$, en los que cada uno no esta sustituido o está sustituido con 1, 2 ó 3 grupos que son independientemente halogeno, OH, SH, cicloalquilo $C_3$-$C_6$, alcoxi $C_1$-$C_4$, alquilo $C_1$-$C_4$ $CF_3$ u $OCF_3$, o

$R_6$, $R_7$ y el nitrogeno al cual se acoplan forman un

anillo morfolinilo, tiomorfolinilo o piperazinilo opcionalmente sustituido con 1 o 2 grupos que son independientemente alquilo $C_1$-$C_4$, hidroxi, hidroxialquilo $C_1$-$C_4$ o halogeno,

$R_8$ es hidrogeno, alquilo $C_1$-$C_6$, alcanoilo $C_1$-$C_6$, fenilalquilo $C_1$-$C_4$ y fenilalcanoilo $C_1$-$C_4$, y

$R_9$ es aminoalquilo, monoalquilo $C_1$-$C_6$ aminoalquilo $C_1$-$C_6$, dialquilo $C_1$-$C$, aminoalquilo $C_1$-$C_6$, alquilo $C_1$-$C_6$, alcanoilo $C_1$-$C_6$, fenilalquilo $C_1$-$C_4$, indazolilo y fenilalcanoilo $C_1$-$C_4$,

$R_{20}$ y $R_{21}$ son independientemente H, alquilo $C_1$-$C_6$, hidroxi $C_1$-$C_6$ alquilo, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$ o

$R_{20}$, $R_{21}$ y el nitrogeno al cual se acoplan forman un anillo piperazinilo o morfolinilo, cada uno de los cuales está opcionalmente sustituido con 1 o 2 grupos que son independientemente alquilo o halogeno

Realizacion A55 Compuestos de acuerdo con la realización A54, en la que

$R_5$ es indolilalquilo ($C_1$-$C_4$) o pirazinilalquil($C_1$-$C_4$), en el que cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2, 3 ó 4 grupos que son independientemente alquilo $C_1$-$C_6$, halógeno, alcoxi $C_1$-$C_6$, hidroxi $C_1$-$C_6$ alquilo, benciloxi, tioalcoxi $C_1$-$C_6$, -$CO_2$(alquilo $C_1$-$C_5$), $CO_2H$, CN, -$C(O)NR_{20}R_{21}$, $CF_3$ u $OCF_3$, en los que

$R_{20}$ y $R_{21}$ son independientemente H, alquilo $C_1$-$C_6$, hidroxi $C_1$-$C_6$ alquilo, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$ o

$R_{20}$, $R_{21}$ y el nitrogeno al cual se acoplan forman un anillo piperazinilo o morfolinilo, cada uno de los cuales esta opcionalmente sustituido con 1 o 2 grupos que son independientemente alquilo o halogeno

Realizacion A56 Compuestos de acuerdo con la realización A52, en la que

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$R_5$ es isoquinolinilo, isoindolilo, indol-2-onilo, quinolinilalquilo ($C_1$-$C_6$), isoquinolinilalquilo ($C_1$-$C_6$), isoindolilalquilo ($C_1$-$C_6$), indol-2-onilalquilo ($C_1$-$C_6$), en el que

cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2, 3, 4 o 5 grupos que son independientemente alquilo $C_1$-$C_6$, halogeno, alcoxi $C_1$-$C_6$, hidroxi $C_1$-$C_6$ alquilo, benciloxi, tioalcoxi $C_1$-$C_6$, -$CO_2$(alquilo $C_1$-$C_5$), $CO_2H$, CN, amidino-oxima, $NR_8R_9$, $NR_6R_7$-(alquilo $C_1$-$C_6$)-, -$C(O)NR_6R_7$ amidino, $CF_3$ u $OCF_3$

Realizacion A57 Compuestos de acuerdo con la realizacion A1, en la que

$R_1$ es H, halogeno, metilo, etilo, alquenilo $C_2$-$C_4$ alquinilo $C_2$-$C_4$ o carboxaldehido,

$R_2$ es benciloxi, OH, feniloxi, feniloxialquil($C_1$-$C_6$) o feniltioalcoxi ($C_1$-$C_4$), en el que cada uno de los anteriormente mencionados se sustituye opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente halogeno, -alquil($C_1$-$C_6$)-N(R)-$CO_2R_{30}$, $NR_6R_7$, -haloalquilo ($C_1$-$C_4$), haloalcoxi ($C_1$-$C_4$), alquilo ($C_1$-$C_6$), piridilo o $NR_6R_7$-(alquilo $C_1$-$C_6$)-, y

$R_4$ es H, alquilo ($C_1$-$C_4$) opcionalmente sustituido con uno o dos grupos que son independientemente $CO_2H$, -$CO_2$alquilo, -C(O)NRR, -N($R_{30}$)C(O)NRR, -N($R_{30}$)C(O)-alcoxi($C_1$-$C_6$) o -$NR_6R_7$ o hidroxialquil($C_1$-$C_4$),

$R_5$ es cicloalquilo $C_3$-$C_7$ o cicloalquilalquilo $C_3$-$C_7$, cada uno de los cuales se sustituye opcionalmente con 1 ó 2 grupos que son independientemente alquilo, alcoxi, halogeno, -$NR_6R_7$ o $NR_6R_7$-(alquilo $C_1$-$C_6$)-, en los que cada uno de los grupos alquilo se sustituye opcionalmente con 1 o 2 grupos que son independientemente OH, metoxi, $NH_2$ o halógeno

Realizacion A58 Compuestos de acuerdo con la

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realizacion A57, en la que

$R_5$ es cicloalquilo $C_3$-$C_7$ o cicloalquilo $C_3$-$C_7$ alquilo $C_1$-$C_4$, cada uno de los cuales se sustituye opcionalmente con 1 ó 2 grupos que son independientemente alquilo $C_1$-$C_4$, alcoxi $C_1$-$C_4$, halogeno, $-NR_6R_7$ o $NR_6R_7$-(alquilo $C_1$-$C_6$)-, en los que cada uno de los grupos alquilo se sustituye opcionalmente con 1 o 2 grupos que son independientemente OH, metoxi o $NH_2$,

$R_6$ y $R_7$ son independientemente, en cada aparicion, H, alquilo $C_1$-$C_4$, hidroxi $C_1$-$C_4$ alquilo, alcoxi $C_1$-$C_4$, alcoxi $C_1$-$C_4$ alquilo $C_1$-$C_4$, alcanoilo $C_1$-$C_4$, bencilo, benciloxi o fenilalcanoilo $C_1$-$C_4$, en los que cada uno no esta sustituido o está sustituido con 1, 2 o 3 grupos que son independientemente halógeno, OH, SH, cicloalquilo $C_3$-$C_6$, alcoxi $C_1$-$C_4$, alquilo $C_1$-$C_4$ $CF_3$ u $OCF_3$, o

$R_6$, $R_7$ y el nitrogeno al cual se acoplan forman un anillo morfolinilo, tiomorfolinilo o piperazinilo opcionalmente sustituido con 1 o 2 grupos que son independientemente alquilo $C_1$-$C_4$, hidroxi, hidroxialquilo $C_1$-$C_4$ o halogeno

Realización A59 Compuestos de acuerdo con la realización A58, en la que

$R_1$ es H, halogeno, metilo, etilo,

$R_2$ es benciloxi, feniloxi, feniloxialquil($C_1$-$C_6$) o feniltioalcoxi ($C_1$-$C_4$), en el que cada uno de los anteriormente mencionados se sustituye opcionalmente con 1, 2, 3 o 4 grupos que son independientemente halógeno, -alquil($C_1$-$C_6$)-N(R)-CO $R_{30}$, amino, mono o dialquilamino, $NR_6R_7$, haloalquilo ($C_1$-$C_4$), haloalcoxi ($C_1$-$C_4$), alquilo ($C_1$-$C_6$) o $NR_6R_7$-(alquilo $C_1$-$C_6$)-, y

$R_4$ es H, metilo, alquil($C_1$-$C_4$) opcionalmente sustituido con uno o dos grupos que son independientemente $CO_2H$, -$CO_2$alquilo, -C(O)NRR, -N($R_{30}$)C(O)NRR, -N($R_{30}$)C(O)-alcoxi($C_1$-

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$C_6$) o $-NR_6R_7$ o hidroxialquil($C_1$-$C_2$)

Realizacion A60 Compuestos de acuerdo con la realizacion A59, en la que

$R_2$ se sustituye con dos halogenos y ademas se sustituye opcionalmente con 1 ó 2 grupos que son independientemente halogeno, -alquil($C_1$-$C_6$)-N(R)-$CO_2R_{30}$, amino, mono o dialquilamino, $-NR_6R_7$, haloalquilo ($C_1$-$C_4$), haloalcoxi ($C_1$-$C_4$), a_quilo ($C_1$-$C_6$) o $NR_6R_7$-(alquilo $C_1$-$C_6$)

Realizacion A61 Compuestos de acuerdo con la realizacion A1, en la que

$R_5$ es H, alquilo opcionalmente sustituido con 1, 2 o 3 grupos que son independientemente fenilalcoxicarbonilo, -$NR_8R_9$, halógeno, $-C(O)NR_8R_9$, alcoxicarbonilo o alcanoilo, alcoxialquilo opcionalmente sustituido con un grupo trimetilsililo, alcoxicarbonilo, amino, hidroxialquilo, alquenilo opcionalmente sustituido con alcoxicarbonilo, alquinilo, $-SO_2$-alquilo o alcoxi opcionalmente sustituido con un grupo trimetilsililo, en los que

cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2, 3, 4 o 5 grupos que son independientemente alquilo, halogeno, alcoxi, fenilalcoxi, tioalcoxi, $-SO_2$alquilo, alcoxicarbonilo, fenilalcoxicarbonilo, $CO_2H$, CN, OH, amidino-oxima, $NR_8R_9$, $NR_6R_7$-(alquilo $C_1$-$C_6$)-, $-C(O)NR_6R_7$, amidino, hidroxialquilo, carboxaldehído, $-NR_6R_7$, haloalquilo o haloalcoxi,

en los que $R_8$ es hidrógeno, alquilo, alcanoilo, fenilalquilo y arilalcanoilo, y

en los que $R_9$ es alquilo, alcanoilo, fenilalquilo, heteroarilo, aminoalquilo, monoalquilaminoalquilo, dialquilaminoalquilo y arilalcanoilo

En esta realizacion, se prefiere que cuando $R_2$ es benciloxi, $R_4$ es H y $R_5$ es bencilo o metilo, $R_1$ no sea hidrógeno, y

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no mas de dos de $R_1$, $R_2$, $R_4$ y $R_5$ sean simultaneamente hidrogeno

Realizacion A62 Compuestos de acuerdo con la realizacion A1, en la que

$R_5$ es H, alquilo opcionalmente sustituido con 1, 2 o 3 grupos que son independientemente fenilalcoxicarbonilo, $-NR_8R_9$, halogeno, $-C(O)NR_8R_9$, alcoxicarbonilo o alcanoilo, alcoxialquilo opcionalmente sustituido con un grupo trimetilsililo, alcoxicarbonilo, amino, hidroxialquilo, alquenilo opcionalmente sustituido con alcoxicarbonilo, alquinilo, $-SO_2$-alquilo, alcoxi opcionalmente sustituido con un grupo trimetilsililo, en los que

cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2, 3, 4 ó 5 grupos que son independientemente alquilo, halogeno, alcoxi, fenilalcoxi, tioalcoxi, $-SO_2$alquilo, alcoxicarbonilo, fenilalcoxicarbonilo, $CO_2H$, CN, OH, amidino-oxima, $NR_8R_9$, $NR_6R_7$-(alquilo $C_1$-$C_6$)-, $-C(O)NR_6R_7$, amidino, hidroxialquilo, carboxaldehido, $-NR_6R_7$, haloalquilo o haloalcoxi,

en los que $R_8$ es hidrogeno, alquilo, alcanoilo, fenilalquilo y arilalcanoilo, y

en los que $R_9$ es alquilo, alcanoilo, fenilalquilo, heteroarilo, aminoalquilo, monoalquilaminoalquilo, dialquilaminoalquilo y arilalcanoilo

En esta realización, se prefiere que cuando $R_2$ es benciloxi, $R_4$ es H y $R_5$ es bencilo o metilo, $R_1$ no sea hidrogeno, y

no más de dos de $R_1$, $R_2$, $R_4$ y $R_5$ sean simultaneamente hidrogeno

Realizacion A63 Compuestos de acuerdo con la realización A62, en la que

$R_1$ es H, halógeno, metilo, etilo, alquenilo $C_2$-$C_4$ alquinilo $C_2$-$C_4$ o carboxaldehido,

$R_2$ es benciloxi, OH, feniloxi, feniloxialquil($C_1$-$C_6$) o feniltioalcoxi ($C_1$-$C_4$), en el que cada uno de los anteriormente mencionados se sustituye opcionalmente con 1, 2, 3 ó 4 grupos que son independientemente halógeno, -alquil($C_1$-$C_6$)-N(R)-$CO_2R_{30}$, $NR_6R_7$, -haloalquilo ($C_1$-$C_4$), haloalcoxi ($C_1$-$C_4$), alquilo ($C_1$-$C_6$), piridilo o $NR_6R_7$-(alquilo $C_1$-$C_6$)-, y

$R_4$ es H, alquilo ($C_1$-$C_4$) opcionalmente sustituido con uno o dos grupos que son independientemente $CO_2H$, -$CO_2$alquilo, -C(O)NRR, -N($R_{30}$)C(O)NRR, -N($R_{30}$)C(O)-alcoxi($C_1$-$C_6$) o -$NR_6R_7$ o hidroxialquil($C_1$-$C_4$)

Realización A64 Compuestos de acuerdo con la realizacion A63, en la que

$R_5$ es H, alquilo opcionalmente sustituido con 1, 2 o 3 grupos que son independientemente fenilalcoxicarbonilo, -$NR_8R_9$, halogeno, -C(O)$NR_8R_9$, alcoxicarbonilo o alcanoilo, alcoxialquilo opcionalmente sustituido con un grupo trimetilsililo, alcoxicarbonilo, amino, hidroxialquilo, alquenilo opcionalmente sustituido con alcoxicarbonilo, alquinilo, -$SO_2$-alquilo, alcoxi opcionalmente sustituido con un grupo trimetilsililo, en el que

$R_8$ es hidrogeno, alquilo $C_1$-$C_4$, alcanoilo $C_1$-$C_4$, fenilalquilo $C_1$-$C_4$ y fenilalcanoilo $C_1$-$C_4$,

en el que $R_9$ es alquilo $C_1$-$C_4$, alcanoilo $C_1$-$C_4$, fenilalquilo $C_1$-$C_4$ piridilo, aminoalquilo, monoalquilaminoalquilo, dialquilaminoalquilo y fenilalcanoilo $C_1$-$C_4$

Realización A65 Compuestos de acuerdo con la realizacion A64, en la que

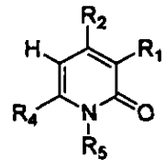
$R_5$ es alquilo $C_1$-$C_6$ opcionalmente sustituido con 1, 2 o 3 grupos que son independientemente fenilalcoxi $C_1$-$C_4$ carbonilo, $NH_2$, monoalquilo $C_1$-$C_4$ amino, dialquilo $C_1$-$C_4$ amino, halogeno, -C(O)$NH_2$, -C(O)NH(alquilo $C_1$-$C_6$) en los que

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el alquilo se sustituye opcionalmente con OH, $NH_2$ o metoxi, -C(O)N (alquilo $C_1$-$C_6$) (alquilo $C_1$-$C_6$) en el que cada alquilo se sustituye opcionalmente con OH, $NH_2$ o metoxi, alcoxi $C_1$-$C_4$ carbonilo y alcanoilo $C_1$-$C_4$ o

$R_5$ es alcoxi $C_1$-$C_4$ alquilo $C_1$-$C_4$, alcoxi $C_1$-$C_4$ carbonilo, amino, hidroxi $C_1$-$C_4$ alquilo, alquenilo $C_2$-$C_4$ opcionalmente sustituido con alcoxi $C_1$-$C_4$ carbonilo, alquinilo $C_2$-$C_4$, $-SO_2-$ alquilo $C_1$-$C_4$ o alcoxi $C_1$-$C_4$

Realización A66 Un compuesto de la formula



o una sal farmacéuticamente aceptable del mismo, en la que

$R_1$ es halogeno, $NO_2$, alquilo, carboxaldehido, hidroxialquilo, arilalcoxi, arilalquilo, CN, arilo, alcanoilo, alcoxi, alcoxialquilo, haloalquilo o arilalcanoilo,

en el que la porcion arilo del arilalcoxi, arilalquilo y arilalcanoilo no se sustituye o se sustituye con 1, 2, 3, 4 ó 5 grupos que son independientemente halogeno, alquil($C_1$-$C_4$), alcoxi ($C_1$-$C_4$), nitro, CN, haloalquilo, haloalcoxi o $CO_2H$,

en el que la porcion alquilo de los grupos alquilo, hidroxialquilo, arilalcoxi, arilalquilo, alcanoilo, alcoxi, alcoxialquilo y arilalcanoilo no se sustituye o se sustituye con 1, 2 ó 3 grupos que son independientemente halógeno, alcoxi $C_1$-$C_4$ , alcoxi $C_1$-$C_4$ carbonilo o espirociclopropilo,

$R_2$ es arilo, heteroarilo, arilalquenilo, arilalcoxi, ariloxialquilo, arilalquilo, OH, alquinilo, ariloxi, ariloxialquilo, ariltioalcoxi, alcoxi, $-OC(O)NH(CH_2)_n$arilo,

-OC(O)N(alquil)$(CH_2)_n$arilo, -$OSO_2$alquil($C_1$-$C_6$), -$OSO_2$arilo, alquilo, alcoxialcoxi, $NR_8R_9$ o $CO_2H$, en el que

n es 0, 1, 2, 3, 4, 5 ó 6,

cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2, 3, 4 o 5 grupos que son independientemente halogeno, -alquil($C_1$-$C_6$)-N(R)-$CO_2R_{30}$, alcoxi, alcoxicarbonilo, CN, $NR_6R_7$, haloalquilo, haloalcoxi, alquilo, heteroarilo, heteroarilalquilo, $NR_6R_7$-(alquilo $C_1$-$C_6$)-, fenilo, -$SO_2$-fenilo en los que los grupos fenilo se sustituyen opcionalmente con 1, 2 ó 3 grupos que son independientemente halógeno o $NO_2$, o -OC(O)$NR_6R_7$, en el que

$R_6$ y $R_7$ son independientemente, en cada aparicion, H, alquilo, alcoxi, alcoxialquilo, alcoxicarbonilo, -$SO_2$-alquilo, OH, hidroxialquilo, -alquil($C_1$-$C_4$)-$CO_2$-alquilo, heteroarilalquilo, alcanoilo, arilalquilo, arilalcoxi o arilalcanoilo, en los que cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2 o 3 grupos que son independientemente halógeno, alcoxi, heterocicloalquilo, OH, SH, cicloalquilo $C_3$-$C_6$, $NH_2$, NH(alquilo), N(alquil)(alquilo), -O-alcanoilo, alquilo, haloalquilo o haloalcoxi, o

$R_6$, $R_7$ y el nitrogeno al cual se acoplan forman un anillo morfolinilo, tiomorfolinilo, piperidinilo, pirrolidinilo o piperazinilo opcionalmente sustituido con 1 o 2 grupos que son independientemente alquilo $C_1$-$C_4$, alcoxi $C_1$-$C_4$ hidroxi, hidroxialquilo $C_1$-$C_4$ o halogeno,

R, en cada aparición, es independientemente H o alquilo $C_1$-$C_6$,

$R_{30}$ es alquilo $C_1$-$C_6$ opcionalmente sustituido con 1 o 2 grupos que son independientemente OH, SH, halogeno, amino, monoalquilamino, dialquilamino o cicloalquilo $C_3$-$C_6$,

$R_4$ es H, alquilo opcionalmente sustituido con uno o

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dos grupos que son independientemente $CO_2H$, $-CO_2$alquilo, $-C(O)NRR$, $-N(R_{30})C(O)NRR$, $-N(R_{30})C(O)$-alcoxi$(C_1-C_6)$ o $-NR_6R_7$ arilalcoxi, arilalquilo, hidroxialquilo, haloalquilo, alcoxi, carboxaldehido, $CO_2H$, alcoxialquilo o alcoxialcoxi, en los que la porción arilo del arilalcoxi, arilalquilo no se sustituye o se sustituye con 1, 2, 3, 4 o 5 grupos que son independientemente halogeno, hidroxi, alcoxi, alquilo, nitro, haloalquilo o haloalcoxi, y

$R_5$ es H, arilalquilo, alquilo, arilo, alcoxi, heterocicloalquilalquilo, heteroarilalquilo, heterocicloalquilo, cicloalquilo, cicloalquilalquilo, -alquil-S-arilo, -alquil-$SO_2$-arilo, -alquilo $(C_1-C_4)$-C(O)-heterocicloalquilo, -$SO_2$-arilo o heteroarilo, en el que

cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2, 3, 4 ó 5 grupos que son independientemente alquilo, halogeno, alcoxi, arilo, arilalcoxi, tioalcoxi, alcoxicarbonilo, arilalcoxicarbonilo, OH, $CO_2H$, CN, amidino-oxima, $NR_8R_9$, $NR_6R_7$-(alquilo $C_1-C_6$)-, $-C(O)NR_6R_7$, -(alquilo $C_1-C_4$)-$C(O)NR_6R_7$ amidino, hidroxialquilo, $-SO_2$alquilo, $-SO_2H$, $-SO_2NR_6R_7$, $-NR_6R_7$, alcanoilo, en los que la porcion alquilo esta opcionalmente sustituida con OH, halogeno o alcoxi, haloalquilo, -(alquilo $C_1-C_4$)$-NR_{15}C(O)NR_{16}R_{17}$, -(alquilo $C_1-C_4$)$-NR_{15}C(O)R_{18}$, $-O-CH_2-O$, $-O-CH_2CH_2-O$- o haloalcoxi, en los que

$R_8$, en cada aparición, es independientemente hidrógeno, alquilo, alcanoilo, arilalquilo y arilalcanoilo, en el que cada uno de los anteriormente mencionados se sustituye opcionalmente con 1, 2, 3, 4 ó 5 grupos que son independientemente alquilo, alcoxi, alcoxicarbonilo, halogeno o haloalquilo, y

$R_9$, en cada aparicion, es independientemente alquilo, alcanoilo, arilalquilo cicloalquilo, alquenilo,

heteroarilo, cicloalquilalquilo, arilalcanoilo, -$SO_2$-fenilo y arilo, en el que cada uno de los anteriormente mencionados se sustituye opcionalmente con 1, 2, 3, 4 o 5 grupos que son independientemente alquilo, alcoxi, alcoxicarbonilo, halogeno o haloalquilo,

$R_{15}$ es H o alquilo $C_1$-$C_6$,

$R_{16}$ y $R_{17}$ son independientemente H o alquilo $C_1$-$C_6$, o

$R_{16}$, $R_{17}$ y el nitrógeno al que están acoplados forman un anillo morfolinilo, y

$R_{18}$ es alquilo $C_1$-$C_6$ opcionalmente sustituido con -O-(alcanoilo $C_2$-$C_6$, hidroxi $C_1$-$C_6$ alquilo, alcoxi $C_1$-$C_6$, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, aminoalquilo $C_1$-$C_6$, mono o dialquilaminoalquilo $C_1$-$C_6$

En esta realización, se prefiere que

$R_6$ y $R_7$ no sean simultaneamente OH,

$R_6$ y $R_7$ no sean simultaneamente -$SO_2$(alquilo $C_1$-$C_6$),

cuando $R_2$ es OH, $R_4$ es metilo y $R_5$ es fenilo, $R_1$ no sea acetilo, y

$R_4$ y $R_5$ no sean simultaneamente hidrogeno

Realizacion A71 Compuestos de acuerdo con la realización A66 en la que

$R_1$ es halogeno, alquilo $C_1$-$C_6$, fenilo, carboxaldehido, hidroxi $C_1$-$C_6$ alquilo, fenilalcoxi $C_1$-$C_6$, fenilalquilo $C_1$-$C_6$, CN, alcanoilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, haloalquilo $C_1$-$C_6$ o fenilalcanoilo $C_1$-$C_6$,

en el que los grupos fenilo anteriormente mencionados no se sustituyen o se sustituyen con 1, 2 ó 3 grupos que son independientemente halógeno, alquil($C_1$-$C_4$), alcoxi ($C_1$-$C_4$), nitro, CN, haloalquilo $C_1$-$C_4$ haloalcoxi $C_1$-$C_4$ o $CO_2H$,

en los que los grupos alquilo anteriormente mencionados no se sustituyen o se sustituyen con 1, 2 o 3 grupos que son independientemente halógeno, metoxi o etoxi,

$R_2$ es fenilalcoxi, OH, feniloxi, feniloxialquil($C_1$-$C_6$),

feniltioalcoxi($C_1$-$C_4$), alcoxi, alquenilo, fenetilo, -OC(O)NH($CH_2$)$_n$fenilo, -OC(O)N(alquil)($CH_2$)$_n$fenilo, alquilo, alcoxialcoxi, $NR_8R_9$, piridilo, pirimidilo, piridazilo, pirazolilo, imidazolilo, pirrolilo, tetrahidroquinolinilo, amino, tetrahidroisoquinolinilo, tetrazolilo, pirazinilo, bencimidazolilo, triazinilo, tetrahidrofurilo, piperidinilo, hexahidropirimidinilo, tiazolilo, tienilo o $CO_2H$, en el que

n es 0, 1, 2 o 3,

cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2, 3, 4 o 5 grupos que son independientemente halogeno, -alquil($C_1$-$C_6$)-N(R)-$CO_2R_{30}$, haloalquilo, haloalcoxi, alquilo, tienilo, piridilo o fenilo opcionalmente sustituido con 1, 2 ó 3 halogenos,

$R_6$ y $R_7$ son independientemente, en cada aparicion, H, alquilo, alcoxi, alcoxialquilo, hidroxialquilo, alcoxicarbonilo, -alquil($C_1$-$C_4$)-$CO_2$-alquilo, alcanoilo, fenilalquilo, fenilalcoxi o fenilalcanoilo, en los que cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2 o 3 grupos que son independientemente halogeno, OH, SH, cicloalquilo $C_3$-$C_6$, alcoxi, $NH_2$, NH(alquilo $C_1$-$C_6$), N(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$), alquilo, $CF_3$ u $OCF_3$, o

$R_6$, $R_7$ y el nitrogeno al cual se acoplan forman un anillo morfolinilo, tiomorfolinilo, piperidinilo, pirrolidinilo o piperazinilo opcionalmente sustituido con 1 ó 2 grupos que son independientemente alquilo $C_1$-$C_4$, hidroxi, hidroxialquilo $C_1$-$C_4$ o halogeno,

$R_4$ es H, alquilo opcionalmente sustituido con uno o dos grupos que son independientemente $CO_2H$, -$CO_2$alquilo, -C(O)NRR, -N($R_{30}$)C(O)NRR, -N($R_{30}$)C(O)-alcoxi($C_1$-$C_6$) o -$NR_6R_7$ fenilalcoxi, fenilalquilo, hidroxialquilo, carboxaldehido, haloalquilo, alcoxi, alcoxialquilo, alcoxialquilo o

alcoxialcoxi, en los que

los grupos fenilo anteriormente mencionados no se sustituyen o se sustituyen con 1, 2 o 3, grupos que son independientemente halogeno, hidroxi, alcoxi, alquilo, nitro, haloalquilo o haloalcoxi, y

$R_5$ es bencilo, fenetilo, alquil($C_1$-$C_6$), fenilo, naftilo, alcoxi, piperidinilo, pirrolidinilo, imidazolidinilo, piperazinilo, isoquinolinilo, tetrahidroisoquinolinilo, indolilo, 1H-indazolilo, piridilo, pirimidilo, piridazilo, pirazinilo, piperidinilalquil($C_1$-$C_6$), pirrolidinilalquil($C_1$-$C_6$), imidazolidinilalquil($C_1$-$C_6$), piperazinilalquil($C_1$-$C_6$), piridilalquil($C_1$-$C_6$), pirimidilalquil($C_1$-$C_6$), piridazilalquil($C_1$-$C_6$), pirazinilalquil($C_1$-$C_6$), isoquinolinilalquil($C_1$-$C_6$), tetrahidroisoquinolinilalquil($C_1$-$C_6$), indolilalquil($C_1$-$C_6$) o 1H-indazolilalquil($C_1$-$C_6$), y en el que

cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2, 3, 4 ó 5 grupos que son independientemente alquilo, halógeno, alcoxi, hidroxialquilo, fenilalcoxi, tioalcoxi, alcoxicarbonilo, fenilalcoxicarbonilo, OH, $CO_2H$, CN, amidino-oxima, $NR_8R_9$, $NR_6R_7$-(alquilo $C_1$-$C_6$) , $-C(O)NR_6R_7$, amidino, piperazinilo, morfolinilo, $-SO_2$ alquilo ($C_1$-$C_6$), $-SO_2NH_2$, $-SO_2NH$alquil($C_1$-$C_6$), $-SO_2N$alquil($C_1$-$C_6$) alquil($C_1$-$C_6$), haloalquilo o haloalcoxi

En esta realizacion, se prefiere que cuando $R_2$ es OH, $R_4$ es metilo y $R_5$ es fenilo, $R_1$ no sea acetilo, y

$R_4$ y $R_5$ no sean simultaneamente hidrogeno

Realización A72 Compuestos de acuerdo con la realización A71, en la que

$R_1$ is halogeno, alquilo, carboxaldehido, hidroxialquilo, fenilalcoxi, fenilo, bencilo, fenetilo,

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fenpropilo, fenbutilo, CN, alcanoil($C_2$-$C_6$), haloalquilo o fenilCO-, fenil$CH_2$CO-, fenil$CH_2CH_2$CO-,

en el que los grupos fenilo anteriormente mencionados no se sustituyen o se sustituyen con 1, 2 ó 3 grupos que son independientemente halógeno, alquil($C_1$-$C_4$), alcoxi ($C_1$-$C_4$), nitro, CN, haloalquilo haloalcoxi o $CO_2H$,

en los que los grupos alquilo anteriormente mencionados no se sustituyen o se sustituyen con 1, 2 ó 3 grupos que son independientemente halógeno, metoxi o etoxi,

$R_2$ es bencilcxi, feneti1oxi, fenpropiloxi, OH, feniloxi, feniloxialquil($C_1$-$C_6$), feniltioalcoxi($C_1$-$C_4$), $NR_8R_9$, alquil($C_1$-$C_6$), alquinilo, fenetilo, -OC(O)N($CH_3$)$CH_2$fenilo, alcoxialcoxi, piridilo, pirimidilo, piridazilo, pirazolilo, imidazolilo, pirrolilo, pirazinilo, piperidinilo, hexahidropirimidinilo, bencimidazolilo o tienilo, en el que

cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2 ó 3 grupos que son independientemente halogeno, -alquil($C_1$-$C_6$)-N(R)-$CO_2R_{30}$, $CF_3$, $OCF_3$, alquil($C_1$-$C_4$), tienilo, piridilo o fenilo opcionalmente sustituido con 1, 2 ó 3 halogenos,

$R_6$ y $R_7$ son independientemente, en cada aparicion, H, alquil($C_1$-$C_6$), alcoxi($C_1$-$C_6$), alcoxi($C_1$-$C_6$)alquil($C_1$-$C_6$), alcoxi($C_1$-$C_6$)carbonilo, hidroxialquil($C_1$-$C_6$), -alquil($C_1$-$C_4$)-$CO_2$-alquilo, alcanoil($C_1$-$C_6$), fenilalquil($C_1$-$C_6$), fenilalcoxi($C_1$-$C_6$) o fenilalcanoil($C_1$-$C_6$), en los que cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2 ó 3 grupos que son independientemente halogeno, alcoxi($C_1$-$C_6$), $NH_2$, OH, SH, cicloalquilo $C_3$-$C_6$, alquil($C_1$-$C_6$), $CF_3$ u $OCF_3$, o

$R_6$, $R_7$ y el nitrogeno al cual se acoplan forman un anillo morfolinilo, piperidinilo, pirrolidinilo o piperazinilo opcionalmente sustituido con 1 ó 2 grupos que

son independientemente alquilo $C_1$-$C_4$, hidroxi, hidroxialquilo $C_1$-$C_4$ o halogeno,

$R_4$ es H, alquilo opcionalmente sustituido con uno o dos grupos que son independientemente $CO_2H$, $-CO_2$alquilo, $-C(O)NRR$, $-N(R_{30})C(O)NRR$, $-N(R_{30})C(O)$-alcoxi($C_1$-$C_6$) o $-NR_6R_7$ benciloxi, fenetiloxi, fenpropiloxi, bencilo, fenetilo, fenpropilo, hidroxialquilo, haloalquil($C_1$-$C_4$), carboxaldehido, alcoxi, alcoxialquilo o alcoxialcoxi, en los que

los grupos fenilo anteriormente mencionados no se sustituyen o se sustituyen con 1, 2 ó 3, grupos que son independientemente halogeno, hidroxi, alcoxi, alquilo, nitro, $CF_3$ u $OCF_3$, y

$R_5$ es bencilo, fenetilo, fenpropilo, fenbutilo, alquil($C_1$-$C_6$), fenilo, piperidinilo, pirrolidinilo, imidazolidinilo, piperidinilalquil($C_1$-$C_6$), pirrolidinilalquil($C_1$-$C_6$), imidazolidinilalquil($C_1$-$C_6$), piridilo, pirimidilo, piridazilo, pirazinilo, piridilalquil($C_1$-$C_6$), pirimidilalquil($C_1$-$C_6$), piridazilalquil($C_1$-$C_6$) o pirazinilalquil($C_1$-$C_6$) en el que

cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2, 3, 4 ó 5 grupos que son independientemente alquilo, halogeno, haloalquilo, $NR_8R_9$, $NR_6R_7$-(alquilo $C_1$-$C_6$)-, carboxaldehido, morfolinilo, $SO_2NH_2$, $SO_2NH$(alquilo), $SO_2N$(alquil)(alquilo), alcoxi, hidroxialquilo, benciloxi, tioalcoxi, OH, $CO_2H$, CN, $-CO_2$(alquilo $C_1$-$C_5$), fenilalcoxicarbonilo, amidino-oxima, amidino, $-C(O)NR_6R_7$, $CF_3$, $CF_2CF_3$, $ClCH_2$ u $OCF_3$

En esta realizacion, se prefiere que cuando $R_2$ es OH, $R_4$ es metilo y $R_5$ es fenilo, $R_1$ no sea acetilo

Realizacion A73 Compuestos de acuerdo con la realizacion A72 en la que

$R_1$ es halogeno, alquilo, carboxaldehido,

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hidroxialquil($C_1$-$C_4$), fenilalcoxi, bencilo, fenetilo, -C(O)$CH_3$, fenilCO- o fenil$CH_2$CO-,

en el que los grupos fenilo anteriormente mencionados no se sustituyen o se sustituyen con 1, 2 o 3 grupos que son independientemente halogeno, alquil($C_1$-$C_4$), alcoxi ($C_1$-$C_4$), nitro, CN, $CF_3$ u $OCF_3$,

en el que los grupos alquilo anteriormente mencionados no se sustituyen o se sustituyen con 1, 2 o 3 grupos que son independientemente halogeno, metoxi o etoxi,

$R_2$ es benciloxi, fenetiloxi, fenpropiloxi, OH, feniloxi, feniloxialquil($C_1$-$C_6$), fenetilo, $NR_8R_9$, -S-bencilo o alquil($C_1$-$C_6$), en el que

cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2 ó 3, grupos que son independientemente halogeno, -alquil($C_1$-$C_6$)-N(R)-$CO_2R_{30}$, $CF_3$ $OCF_3$, alquilo, tienilo o piridilo,

$R_6$ y $R_7$ son independientemente, en cada aparición, H, alquil($C_1$-$C_6$), alccxi($C_1$-$C_6$), alcoxi($C_1$-$C_6$)alquil($C_1$-$C_6$), alcoxi($C_1$-$C_6$)carbonilo, hidroxialquil($C_1$-$C_6$), -alquil($C_1$-$C_4$)-$CO_2$-alquilo, alcanoil($C_1$-$C_6$), fenilalquil($C_1$-$C_6$), fenilalcoxi($C_1$-$C_6$) o fenilalcanoil($C_1$-$C_6$), en los que cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2 ó 3 grupos que son independientemente halógeno, alcoxi($C_1$-$C_6$), $NH_2$, OH, SH, cicloalquilo $C_3$-$C_6$, alquil($C_1$-$C_6$), $CF_3$ u $OCF_3$, o

$R_6$, $R_7$ y el nitrogeno al cual se acoplan forman un anillo morfolinilo, piperidinilo, pirrolidinilo o piperazinilo opcionalmente sustituido con 1 o 2 grupos que son independientemente alquilo $C_1$-$C_4$, hidroxi, hidroxialquilo $C_1$-$C_4$ o halogeno,

$R_4$ es H, alquilo opcionalmente sustituido con uno o dos grupos que son independientemente $CO_2H$, -$CO_2$alquilo, -C(O)NRR, -N($R_{30}$)C(O)NRR, -N($R_{30}$)C(O)-alcoxi($C_1$-$C_6$) o -$NR_6R_7$

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benciloxi, feneti1oxi, fenpropiloxi, bencilo o hidroxialquilo, en los que

los grupos fenilo anteriormente mencionados no se sustituyen o se sustituyen con 1, 2 o 3, grupos que son independientemente halógeno, hidroxi, alcoxi, alquilo, nitro, $CF_3$ u $OCF_3$, y

$R_5$ es bencilo, fenetilo, fenpropilo, fenbutilo, alquil($C_1$-$C_6$), fenilc, piridilo, pirazinilo, pirimidinilo, pirazinilalquil($C_1$-$C_6$), pirimidinilalquil($C_1$-$C_6$) o piridilalquil($C_1$-$C_4$), en el que

cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2, 3, 4 ó 5 grupos que son independientemente alquilo, halogeno, haloalquilo, morfolinilo, -$SO_2$ alquilo ($C_1$-$C_6$), -$SO_2NH_2$, -$SO_2NH$($C_1$-$C_6$), -$SO_2N$($C_1$-$C_6$)($C_1$-$C_6$), alcoxi($C_1$-$C_4$), fenilalcoxi($C_1$-$C_4$), tioalcoxi($C_1$-$C_4$), alcoxi ($C_1$-$C_4$) carbonilo, OH, $CO_2H$, CN, amidino-oxima, amidino, $NR_8R_9$, $NR_6R_7$-(alquilo $C_1$-$C_6$)-, hidroxialquilo, $CONR_6R_7$, $CF_3$ u $OCF_3$

Realizacion A74 Compuestos de acuerdo con la realización A73 en la que

$R_1$ es halogeno, alquilo, carboxaldehido o hidroxialquilo,

$R_2$ es benciloxi, fenetiloxi, fenpropiloxi, OH, feniloxi, feniloxialquil($C_1$-$C_6$), fenetilo, feniltioalcoxi o alquil($C_1$-$C_6$), en el que

cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2 o 3, grupos que son independientemente -alquil($C_1$-$C_6$)-N(R)-$CO_2R_{30}$, $CF_3$ $OCF_3$ alquilo, tienilo o piridilo

$R_4$ es H, alquilo ($C_1$-$C_4$) opcionalmente sustituido con uno o dos grupos que son independientemente $CO_2H$, -$CO_2$alquilo, -C(O)NRR, -N($R_{30}$)C(O)NRR, -N($R_{30}$)C(O)-alcoxi($C_1$-$C_6$) o -$NR_6R_7$ benciloxi o fenetiloxi, en los que

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los grupos ferilo anteriormente mencionados no se sustituyen o se sustituyen con 1, 2 o 3 grupos que son independientemente halógeno, hidroxi, alcoxi($C_1$-$C_4$), alquil($C_1$-$C_4$), nitro, $CF_3$ u $OCF_3$, y

$R_5$ es bencilo, fenetilo, alquil($C_1$-$C_6$), fenilo, indazolilo o piridilo, en el que cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2, 3, 4 o 5 grupos que son independientemente alquil($C_1$-$C_4$), halogeno, OH, $CO_2H$, CN, alcoxi($C_1$-$C_4$), -C(O)pirrolidina, -$SO_2$ alquilo ($C_1$-$C_6$), benciloxi, -$CO_2$(alquilo $C_1$-$C_5$), amidino, tioalcoxi($C_1$-$C_4$), amidino-oxima, $CF_3$, $NR_8R_9$, $NR_6R_7$-(alquilo $C_1$-$C_6$)-, $CONR_6R_7$ u $OCF_3$

Realizacion A75 Compuestos de acuerdo con la realizacion A74, en la que

$R_1$ es cloro, bromo, yodo, metilo, alquenilo $C_2$-C3 alquinilo $C_2$-$C_3$ y

$R_5$ es bencilo, fenetilo, fenpropilo, fenilo o piridilo, cada uno de los cuales no se sustituye o se sustituye con 1, 2 o 3 grupos que son independientemente alquilo, OH, halogeno, alcoxi, $NH_2$, NHalquil($C_1$-$C_6$), N-alquil($C_1$-$C_6$)alquil($C_1$-$C_6$), $NR_8R_9$, $NR_6R_7$-(alquilo $C_1$-$C_6$)-, $CONR_6R_7$ y amidino-oxima, en los que

$R_6$ y $R_7$ son independientemente H, alquilo $C_1$-$C_4$, alcanoilo $C_1$-$C_6$, en los que los grupos alquilo y alcanoilo se sustituyen opcionalmente con 1, 2 ó 3 grupos que son independientemente OH, halogeno o ciclopropilo $C_3$-$C_7$

Realizacion A76 Compuestos de acuerdo con la realizacion A75 en la que

$R_2$ es benciloxi, fenetilo, feniloxialquil($C_1$-$C_6$) o fenetiloxi, cada uno de los cuales no esta sustituido o esta sustituido con 1, 2 o 3 grupos que son independientemente halógeno, -alquil($C_1$-$C_6$)-N(R)-$CO_2R_{30}$, $CF_3$, $OCF_3$ o alquil($C_1$-$C_4$)

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Realizacion A77 Compuestos de acuerdo con la realizacion A66, en la que

$R_5$ es bencilo, fenetilo, tienil(alquilo $C_1$-$C_6$), piperidinilalquil($C_1$-$C_6$), pirrolidinilalquil($C_1$-$C_6$), imidazolidinilalquil($C_1$-$C_6$), piperazinilalquil($C_1$-$C_6$), piridilalquil($C_1$-$C_6$), pirimidilalquil($C_1$-$C_6$), piridazilalquil($C_1$-$C_6$), pirazinilalquil($C_1$-$C_6$), isoquinolinilalquil($C_1$-$C_6$), tetrahidroisoquinolinilalquil($C_1$-$C_6$), indolilalquil($C_1$-$C_6$) o 1H-indazolilalquil($C_1$-$C_6$), en el que

cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2, 3, 4 o 5 grupos que son independientemente alquil($C_1$-$C_6$), halógeno, alcoxi($C_1$-$C_6$), hidroxi($C_1$-$C_6$)alquilo fenilalcoxi($C_1$-$C_6$), tioalcoxi($C_1$-$C_6$), alcoxi($C_1$-$C_6$)carbonilo, fenilalcoxi($C_1$-$C_6$)carbonilo, OH, $CO_2H$, CN, amidino-oxima, $-NR_8R_9$, $-NR_6R_7$, (alquilo $C_1$-$C_6$)-, $-C(O)NR_6R_7$, amidino, piperazinilo, morfolinilo, $-SO_2$ alquilo ($C_1$-$C_6$), $-SO_2NH_2$, $-SO_2NH$alquil($C_1$-$C_6$), $-SO_2N$alquil($C_1$-$C_6$) alquil($C_1$-$C_6$), haloalquil($C_1$-$C_4$) -(alquilo $C_1$-$C_4$)-$NR_{15}C(O)NR_{16}R_{17}$, -(alquilo $C_1$-$C_4$)-$NR_{15}C(O)R_{18}$, $-O-CH_2-O-$, $-O-CH_2CH_2-O-$ o haloalcoxi($C_1$-$C_4$), en los que

$R_6$ y $R_7$ son independientemente, en cada aparicion, H, alquil($C_1$-$C_6$), alcoxi($C_1$-$C_6$), alcoxi($C_1$-$C_6$)alquil($C_1$-$C_6$), alcoxi($C_1$-$C_6$)carbonilo, hidroxi($C_1$-$C_6$)alquilo, -alquil($C_1$-$C_4$)-$CO_2$-alquil($C_1$-$C_6$), alcanoil($C_1$-$C_6$), fenilalquil($C_1$-$C_6$), fenilalcoxi($C_1$-$C_6$) o fenilalcanoil($C_1$-$C_6$), en los que cada uno de los anteriormente mencionados no esta sustituido o esta sustituido con 1, 2 o 3 grupos que son independientemente halogeno, alcoxi($C_1$-$C_4$), $NH_2$, OH, SH, cicloalquilo $C_3$-$C_6$, NH(alquilo $C_1$-$C_6$), N(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$), alquil($C_1$-$C_4$), $CF_3$ u $OCF_3$, o

$R_6$, $R_7$ y el nitrogeno al cual se acoplan forman un anillo morfolinilc, tiomorfolinilo, piperidinilo,

pirrolidinilo o piperazinilo opcionalmente sustituido con 1 o 2 grupos que son independientemente alquilo $C_1$-$C_4$, hidroxi, hidroxialquilo $C_1$-$C_4$ o halógeno, y

$R_{18}$ es alquilo $C_1$-$C_6$ opcionalmente sustituido con -O-(alcanoilo $C_2$-$C_6$, hidroxi $C_1$-$C_6$ alquilo, alcoxi $C_1$-$C_6$, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, aminoalquilo $C_1$-$C_6$, mono o dialquilaminoalquilo $C_1$-$C_6$

En esta realización, se prefiere que $R_6$ y $R_7$ no sean simultaneamente OH, y

$R_6$ y $R_7$ no sean simultaneamente $-SO_2$(alquilo $C_1$-$C_6$)

Realización A78 Compuestos de acuerdo con la realización A77, en la que

$R_1$ es halogeno, metilo, etilo, alquenilo $C_2$-$C_4$ alquinilo $C_2$-$C_4$ o carboxaldehido,

$R_2$ es benciloxi, OH, feniloxi, feniloxialquil($C_1$-$C_6$) o feniltioalcoxi ($C_1$-$C_4$), en el que cada uno de los anteriormente mencionados se sustituye opcionalmente con 1, 2, 3 o 4 grupos que son independientemente halogeno, -alquil($C_1$-$C_6$)-N(R)-$CO_2R_{30}$, $NR_6R_7$, -haloalquilo ($C_1$-$C_4$), haloalcoxi ($C_1$-$C_4$), a quilo ($C_1$-$C_6$) o piridilo, y

$R_4$ es H, alquilo ($C_1$-$C_4$) opcionalmente sustituido con uno o dos grupos que son independientemente $CO_2H$, -$CO_2$alquilo, -C(O)NRR, -N($R_{30}$)C(O)NRR, -N($R_{30}$)C(O)-alcoxi($C_1$-$C_6$) o -$NR_6R_7$ o hidroxialquil($C_1$-$C_4$)

Realizacion A79 Compuestos de acuerdo con la realizacion A78, en la que

$R_5$ es bencilo o fenetilo, en el que cada uno no está sustituido o esta sustituido con 1, 2, 3, 4 ó 5 grupos que son independientemente alquil($C_1$-$C_6$), halogeno, alcoxi($C_1$-$C_6$), hidroxi($C_1$-$C_6$)alquilo, fenilalcoxi($C_1$-$C_6$), tioalcoxi($C_1$-$C_6$), alcoxi($C_1$-$C_6$)carbonilo, fenilalcoxi($C_1$-$C_6$)carbonilo, OH, $CO_2H$, CN, amidino-oxima, $NR_8R_9$, $NR_6R_7$-(alquilo $C_1$-$C_6$)-, -C(O)$NR_6R_7$, -(alquilo $C_1$-$C_4$)-C(O)$NR_6R_7$amidino, piperazinilo,

morfolinilo, $-SO_2$ alquilo ($C_1$-$C_6$), $-SO_2NH_2$, $-SO_2NH$alquil($C_1$-$C_6$), $-SO_2N$alquil($C_1$-$C_6$) alquil($C_1$-$C_6$), haloalquil($C_1$-$C_4$), -(alquilo $C_1$-$C_4$)-$NR_1$,C(O)$R_{18}$, $-O-CH_2-O$, $-O-CH_2CH_2-O-$ o haloalcoxi($C_1$-$C_4$), en los que

$R_6$ y $R_7$ son independientemente, en cada aparicion, H, alquil($C_1$-$C_6$), alcoxi($C_1$-$C_6$), alcoxi($C_1$-$C_6$)alquil($C_1$-$C_6$), alcoxi($C_1$-$C_6$)carbonilo, hidroxi($C_1$-$C_6$)alquilo, -alquil($C_1$-$C_4$)-$CO_2$-alquil($C_1$-$C_6$), alcanoil($C_1$-$C_6$), fenilalquil($C_1$-$C_6$), fenilalcoxi($C_1$-$C_6$) o fenilalcanoil($C_1$-$C_6$), en los que cada uno de los anteriormente mencionados no está sustituido o está sustituido con 1, 2 o 3 grupos que son independientemente halogeno, alcoxi($C_1$-$C_4$), $NH_2$, OH, SH, cicloalquilo $C_3$-$C_6$, NH(alquilo $C_1$-$C_6$), N(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$), alquil($C_1$-$C_4$), $CF_3$ u $OCF_3$, o

$R_6$, $R_7$ y el nitrogeno al cual se acoplan forman un anillo morfolinilo, tiomorfolinilo, piperidinilo, pirrolidinilo o piperazinilo opcionalmente sustituido con 1 o 2 grupos que son independientemente alquilo $C_1$-$C_4$, hidroxi, hidroxialquilo $C_1$-$C_4$ o halógeno, y

$R_{18}$ es alquilo $C_1$-$C_6$ opcionalmente sustituido con -O-(alcanoilo $C_2$-$C_6$, hidroxi $C_1$-$C_6$ alquilo, alcoxi $C_1$-$C_6$, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, aminoalquilo $C_1$-$C_6$ o mono o dialquilaminoalquilo $C_1$-$C_6$

En esta realizacion, se prefiere que $R_6$ y $R_7$ no sean simultaneamente OH, y

$R_6$ y $R_7$ no sean simultaneamente $-SO_2$(alquilo $C_1$-$C_6$)

Realizacion A80 Compuestos de acuerdo con la realización A79, en la que

$R_5$ es bencilo o fenetilo, en el que cada uno esta opcionalmente sustituido con 1, 2, 3, 4 o 5 grupos que son independientemente alquilo $C_1$-$C_6$, -C(O)$NR_6R_7$ -(alquilo $C_1$-$C_4$)-C(O)$NR_6R_7$, $NR_8R_9$, halogeno, alcoxi $C_1$-$C_6$, $CO_2H$, -(alquilo $C_1$-$C_4$)-$CO_2H$, tioalcoxi $C_1$-$C_6$, amidino-oxima, alcoxi $C_1$-$C_6$

carbonilo, -(alquilo $C_1$-$C_4$)-alcoxi $C_1$-$C_6$ carbonilo, hidroxi $C_1$-$C_6$ alquilo, -(alquilo $C_1$-$C_4$)-CN, CN, fenilalcoxi $C_1$-$C_6$, OH, haloalquilo $C_1$-$C_3$, haloalcoxi $C_1$-$C_4$, $NR_6R_7$-(alquilo $C_1$-$C_6$)-, -(alquilo $C_1$-$C_4$)-$NR_{15}C(O)R_{18}$, amidino-oxima, $-SO_2$(alquilo $C_1$-$C_6$), $-O-CH_2-O-$, $-O-CH_2CH_2-O-$, fenilalcoxi $C_1$-$C_4$ o fenilo, en los que

$R_6$ y $R_7$ en cada aparición, son independientemente H, OH, alquilo $C_1$-$C_6$, aminoalquilo $C_1$-$C_4$, NH(alquilo $C_1$-$C_6$)alquilo, N(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$) alquilo $C_1$-$C_6$, hidroxi $C_1$-$C_6$ alquilo, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, $-SO_2$(alquilo $C_1$-$C_6$), cada uno de los cuales se sustituye opcionalmente con 1, 2 ó 3 grupos que son independientemente halógeno, OH, SH, cicloalquilo $C_3$-$C_6$, alcoxi $C_1$-$C_4$, alquilo $C_1$-$C_4$, OH, $CF_3$ u $OCF_3$,

o

$R_6$, $R_7$ y el nitrógeno al cual se acoplan forman un anillo piperidinilo, pirrolidinilo, piperazinilo, morfolinilo, tiomorfolinilo opcionalmente sustituido con 1 ó 2 grupos que son independientemente alquilo, hidroxi, hidroxialquilo $C_1$-$C_4$ o halogeno,

$R_{18}$ es alquilo $C_1$-$C_6$ opcionalmente sustituido con -O-(alcanoilo $C_2$-$C_6$, hidroxi $C_1$-$C_6$ alquilo, alcoxi $C_1$-$C_6$, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, aminoalquilo $C_1$-$C_6$, mono o dialquilamino alquilo $C_1$-$C_6$

En esta realizacion, se prefiere que $R_6$ y $R_7$ no sean simultaneamente OH, y

$R_6$ y $R_7$ no sean simultaneamente $-SO_2$(alquilo $C_1$-$C_6$)

Realización A81 Compuestos de acuerdo con la realizacion A80, en la que

$R_5$ es bencilo o fenetilo, en el que cada uno esta opcionalmente sustituido con 1, 2, 3, 4 ó 5 grupos que son independientemente alquilo $C_1$-$C_6$, $-C(O)NR_6R_7$ -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$, halógeno, alcoxi $C_1$-$C_6$, $CO_2H$, -(alquilo $C_1$-

$C_4$)-$CO_2H$, tioalcoxi $C_1$-$C_6$, amidino-oxima, alcoxi $C_1$-$C_6$ carbonilo, -(alquilo $C_1$-$C_4$)-alcoxi $C_1$-$C_6$ carbonilo, hidroxi $C_1$-$C_6$ alquilo, -(alquilo $C_1$-$C_4$)-CN, CN, fenilalcoxi $C_1$-$C_6$, OH, haloalquilo $C_1$-$C_4$, haloalcoxi $C_1$-$C_4$, $NR_6R_7$-(alquilo $C_1$-$C_6$)-, $NR_8R_9$ -(alquilo $C_1$-$C_4$)-$NR_{15}C(O)R_{18}$, amidino-oxima, -$SO_2$(alquilo $C_1$-$C_6$), O-$CH_2$-O-, -O-$CH_2CH_2$-O-, fenilalcoxi $C_1$-$C_4$ o fenilo, en los que

$R_6$ y $R_7$ en cada aparicion, son independientemente H, OH, alquilo $C_1$-$C_6$, aminoalquilo $C_1$-$C_4$, NH(alquilo $C_1$-$C_6$)alquilo, N(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$) alquilo $C_1$-$C_6$, hidroxi $C_1$-$C_6$ alquilo, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$ -$SO_2$(alquilo $C_1$-$C_6$), cada uno de los cuales se sustituye opcionalmente con 1, 2 o 3 grupos que son independientemente halógeno, OH, SH, cicloalquilo $C_3$-$C_6$, alcoxi $C_1$-$C_4$, alquilo $C_1$-$C_4$, OH, $CF_3$ u $OCF_3$, y

$R_{18}$ es alquilo $C_1$-$C_6$ opcionalmente sustituido con -O-(alcanoilo $C_2$-$C_6$, hidroxi $C_1$-$C_6$ alquilo, alcoxi $C_1$-$C_6$, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, aminoalquilo $C_1$-$C_6$, mono o dialquilaminoalquilo $C_1$-$C_6$

En esta realización, se prefiere que $R_6$ y $R_7$ no sean simultaneamente OH, y

$R_6$ y $R_7$ no sean simultaneamente -$SO_2$(alquilo $C_1$-$C_6$)

Realizacion A82 Compuestos de acuerdo con la realización A81, en la que

$R_5$ es bencilo opcionalmente sustituido con 1, 2, 3, 4 o 5 grupos que son independientemente alquilo $C_1$-$C_4$, -$C(O)NR_6R_7$ -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$, halogeno, alcoxi $C_1$-$C_4$, $CO_2H$, tioalcoxi $C_1$-$C_4$, alcoxi $C_1$-$C_4$ carbonilo, hidroxi $C_1$-$C_6$ alquilo, CN, OH, $NR_6R_7$-(alquilo $C_1$-$C_6$)-, $NR_8R_9$, -$SO_2$(alquilo $C_1$-$C_6$) o benciloxi, en los que

$R_6$ y $R_7$ en cada aparición, son independientemente H, OH, alquilo $C_1$-$C_6$, aminoalquilo $C_1$-$C_4$, NH(alquilo $C_1$-$C_6$)alquilo, N(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$) alquilo $C_1$-$C_6$,

hidroxi $C_1$-$C_6$ alquilo, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, -$SO_2$(alquilo $C_1$-$C_6$), cada uno de los cuales se sustituye opcionalmente con 1, 2 o 3 grupos que son independientemente halógeno, OH, SH, cicloalquilo $C_3$-$C_6$, alcoxi $C_1$-$C_4$, alquilo $C_1$-$C_4$, OH, $CF_3$ u $OCF_3$,

En esta realizacion, se prefiere que $R_6$ y $R_7$ no sean simultaneamente OH, y

$R_6$ y $R_7$ no sean simultáneamente -$SO_2$(alquilo $C_1$-$C_6$)

Realización A83 Compuestos de acuerdo con la realización A82, en la que

$R_5$ es bencilo opcionalmente sustituido con 1, 2, 3, 4 o 5 grupos que son independientemente alquilo $C_1$-$C_4$, -$C(O)NR_6R_7$ -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$, halogeno, alcoxi $C_1$-$C_4$, tioalcoxi $C_1$-$C_4$, alcoxi $C_1$-$C_4$ carbonilo, hidroxi $C_1$-$C_6$ alquilo, CN, $NR_8R_9$ o $NR_6R_7$-(alquilo $C_1$-$C_6$)-, en los que

$R_6$ y $R_7$ en cada aparición, son independientemente H, OH, alquilo $C_1$-$C_6$, aminoalquilo $C_1$-$C_4$, NH(alquilo $C_1$-$C_6$)alquilo, N(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$) alquilo $C_1$-$C_6$, hidroxi $C_1$-$C_6$ alquilo o alcoxi $C_1$-$C_4$ alquilo $C_1$-$C_4$, cada uno de los cuales se sustituye opcionalmente con 1, 2 ó 3 grupos que son independientemente halogeno, OH, SH, cicloalquilo $C_3$-$C_6$, alcoxi $C_1$-$C_4$, alquilo $C_1$-$C_4$, OH, $CF_3$ u $OCF_3$

En esta realizacion, se prefiere que $R_6$ y $R_7$ no sean simultaneamente OH

Realizacion A84 Compuestos de acuerdo con la realización A83, en la que

el grupo $R_5$ se disustituye con dos grupos que son meta entre si

Realizacion A86 Compuestos de acuerdo con la realización A80, en la que

$R_5$ es bencilo opcionalmente sustituido con 1, 2, 3, 4 o 5 grupos que son independientemente alquilo $C_1$-$C_4$, -

$C(O)NR_6R_7$ -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$, $NR_8R_9$, $NR_6R_7$-(alquilo $C_1$-$C_6$)-, halogeno, alcoxi $C_1$-$C_4$, $CO_2H$, -(alquilo $C_1$-$C_4$)-$CO_2H$, -(alquilo $C_1$-$C_4$)-alcoxi $C_1$-$C_6$ carbonilo, -(alquilo $C_1$-$C_4$)-CN, CN, fenilalcoxi $C_1$-$C_6$, $CF_3$, $OCF_3$, -(alquilo $C_1$-$C_4$)-$NR_{15}C(O)R_{18}$, amidino-oxima, $-O-CH_2-O-$, $-O-CH_2CH_2-O-$ o fenilo, en los que

$R_6$ y $R_7$ en cada aparición, son independientemente H, alquilo $C_1$-$C_4$, aminoalquilo $C_1$-$C_4$, NH(alquilo $C_1$-$C_4$)alquilo, N(alquilo $C_1$-$C_4$)(alquilo $C_1$-$C_6$) alquilo $C_1$-$C_4$, hidroxi $C_1$-$C_6$ alquilo, alcoxi $C_1$-$C_4$ alquilo $C_1$-$C_4$ u OH, cada uno de los cuales se sustituye opcionalmente con 1, 2 o 3 grupos que son independientemente halogeno, OH, SH, cicloalquilo $C_3$-$C_6$, alcoxi $C_1$-$C_4$, alquilo $C_1$-$C_4$, OH, $CF_3$ u $OCF_3$, y

$R_{18}$ es alquilo $C_1$-$C_6$, hidroxi $C_1$-$C_6$ alquilo, alcoxi $C_1$-$C_6$, alcoxi $C_1$-$C_4$ alquilo $C_1$-$C_6$, aminoalquilo $C_1$-$C_6$, mono o dialquilaminoalquilo $C_1$-$C_6$

En esta realizacion, se prefiere que $R_6$ y $R_7$ no sean simultaneamente OH

Realizacion A87 Compuestos de acuerdo con la realización A80, en la que

$R_5$ es bencilo o fenetilo, en el que cada uno está opcionalmente sustituido con 1, 2, 3, 4 o 5 grupos que son independientemente alquilo $C_1$-$C_6$, $-C(O)NR_6R_7$ -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$, halogeno, alcoxi $C_1$-$C_6$, $CO_2H$, -(alquilo $C_1$-$C_4$)-$CO_2H$, tioalcoxi $C_1$-$C_6$, amidino-oxima, alcoxi $C_1$-$C_6$ carbonilo, -(alquilo $C_1$-$C_4$)-alcoxi $C_1$-$C_6$ carbonilo, hidroxi $C_1$-$C_6$ alquilo, -(alquilo $C_1$-$C_4$)-CN, CN, fenilalcoxi $C_1$-$C_6$, OH, haloalquilo $C_1$-$C_4$, haloalcoxi $C_1$-$C_4$, $NR_8R_9$ $NR_6R_7$-(alquilo $C_1$-$C_6$)-, -(alquilo $C_1$-$C_4$)-$NR_{15}C(O)R_{18}$, amidino-oxima, $-SO_2$(alquilo $C_1$-$C_6$), $-O-CH_2-O-$, $-O-CH_2CH_2-O-$, fenilalcoxi $C_1$-$C_4$ o fenilo, en los que

$R_6$, $R_7$ y el nitrógeno al cual se acoplan forman un anillo piperidinilo, pirrolidinilo, piperazinilo,

morfolinilo, tiomorfolinilo opcionalmente sustituido con 1 o 2 grupos que son independientemente alquilo, hidroxi, hidroxialquilo $C_1$-$C_4$ o halógeno,

$R_{18}$ es alquilo $C_1$-$C_6$ opcionalmente sustituido con -O-(alcanoilo $C_2$-$C_6$, hidroxi $C_1$-$C_6$ alquilo, alcoxi $C_1$-$C_6$, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, aminoalquilo $C_1$-$C_6$, mono o dialquilaminoalquilo $C_1$-$C_6$

En esta realizacion, se prefiere que $R_6$ y $R_7$ no sean simultáneamente OH, y

$R_6$ y $R_7$ no sean simultáneamente -$SO_2$(alquilo $C_1$-$C_6$)

Realización A88 Compuestos de acuerdo con la realización A87, en _a que

$R_5$ es bencilo opcionalmente sustituido con 1, 2, 3, 4 o 5 grupos que son independientemente alquilo $C_1$-$C_4$, -C(O)$NR_6R_7$ -(alquilo $C_1$-$C_4$)-C(O)$NR_6R_7$, halogeno, alcoxi $C_1$-$C_4$, $CO_2H$, tioalcoxi $C_1$-$C_4$, alcoxi $C_1$-$C_4$ carbonilo, hidroxi $C_1$-$C_6$ alquilo, CN, OH, $NR_6R_7$-(alquilo $C_1$-$C_6$)-, -$SO_2$(alquilo $C_1$-$C_6$) o benciloxi, en los que

$R_6$ y $R_7$ en cada aparición, son independientemente H, OH, alquilo $C_1$-$C_6$, aminoalquilo $C_1$-$C_4$, NH(alquilo $C_1$-$C_6$)alquilo, N(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$) alquilo $C_1$-$C_6$, hidroxi $C_1$-$C_6$ alquilo, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$ o -$SO_2$(alquilo $C_1$-$C_6$), cada uno de los cuales se sustituye opcionalmente con 1, 2 ó 3 grupos que son independientemente halogeno, OH, SH, cicloalquilo $C_3$-$C_6$, alcoxi $C_1$-$C_4$, alquilo $C_1$-$C_4$, OH, $CF_3$ u $OCF_3$

En esta realización, se prefiere que $R_6$ y $R_7$ no sean simultaneamente OH, y

$R_6$ y $R_7$ no sean simultaneamente -$SO_2$(alquilo $C_1$-$C_6$)

Realización A89 Compuestos de acuerdo con la realizacion A80, en la que

$R_5$ es bencilo opcionalmente sustituido con 1, 2, 3, 4 o 5 grupos que son independientemente alquilo $C_1$-$C_4$, -

$C(O)NR_6R_7$ -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$ $NR_6R_7$-(alquilo $C_1$-$C_6$)-, $NR_8R_9$, halogeno, alcoxi $C_1$-$C_4$, tioalcoxi $C_1$-$C_4$, alcoxi $C_1$-$C_4$ carbonilo, hidroxi $C_1$-$C_6$ alquilo o CN, en los que

$R_6$ y $R_7$ en cada aparición, son independientemente H, OH, alquilo $C_1$-$C_6$, aminoalquilo $C_1$-$C_4$, NH(alquilo $C_1$-$C_6$)alquilo, N(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$) alquilo $C_1$-$C_6$, hidroxi $C_1$-$C_6$ alquilc o alcoxi $C_1$-$C_4$ alquilo $C_1$-$C_4$, cada uno de los cuales se sustituye opcionalmente con 1, 2 ó 3 grupos que son independientemente halogeno, OH, SH, cicloalquilo $C_3$-$C_6$, alcoxi $C_1$-$C_4$, alquilo $C_1$-$C_4$, OH, $CF_3$ u $OCF_3$

En esta realizacion, se prefiere que $R_6$ y $R_7$ no sean simultáneamente OH

Realizacion A90 Compuestos de acuerdo con la realización A89, en la que el grupo $R_5$ se disustituye con dos grupos que son meta entre si

Realizacion A91 Compuestos de acuerdo con la realización A78, en la que

$R_5$ es fenilo, opcionalmente sustituido con 1, 2, 3, 4 ó 5 grupos que son independientemente alquilo $C_1$-$C_4$, -$C(O)NR_6R_7$, -$NR_6R_7$, $NF_6R_7$(alquilo $C_1$-$C_6$), $NR_8R_9$, hidroxi $C_1$-$C_6$ alquilo, halogeno, alcoxi $C_1$-$C_4$, $CO_2H$, OH, alcoxi $C_1$-$C_6$ carbonilo, carboxaldehido, haloalquilo $C_1$-$C_4$, -(alquilo $C_1$-$C_4$)-$NR_{15}C(O)NR_{16}R_{17}$, -(alquilo $C_1$-$C_4$)-$NR_{15}C(O)R_{18}$, en los que

$R_6$ y $R_7$, en caca aparición, son independientemente H, OH, alquilo $C_1$-$C_6$, aminoalquilo $C_1$-$C_4$, NH(alquilo $C_1$-$C_6$)alquilo, N(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$) alquilo $C_1$-$C_6$, hidroxi $C_1$-$C_6$ alquilo, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, -$SO_2$(alquilo $C_1$-$C_6$), -$SO_2NH_2$, -$SO_2NH$(alquilo $C_1$-$C_6$), -$SO_2N$(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$) o alcanoilo $C_1$-$C_6$, cada uno de los cuales se sustituye opcionalmente con 1, 2 o 3 grupos que son independientemente halogeno, OH, SH, cicloalquilo $C_3$-$C_6$, alcoxi $C_1$-$C_4$, alquilo $C_1$-$C_4$, OH, $CF_3$ u

$OCF_3$ o

$R_6$, $R_7$ y el nitrogeno al cual se acoplan forman un anillo piperidinilo, pirrolidinilo, piperazinilo o morfolinilo, tiomorfolinilo opcionalmente sustituido con 1 o 2 grupos que son independientemente alquilo, hidroxi, hidroxialquilo $C_1$-$C_4$ o halógeno,

$R_{15}$ es H o alquilo $C_1$-$C_6$,

$R_{16}$ y $R_{17}$ son incependientemente H o alquilo $C_1$-$C_6$, o

$R_{16}$, $R_{17}$ y el nitrogeno al que están acoplados forman un anillo morfolinilo,

$R_{18}$ es alquilo $C_1$-$C_6$ opcionalmente sustituido con -O-(alcanoilo $C_2$-$C_6$, hidroxi $C_1$-$C_6$ alquilo, alcoxi $C_1$-$C_6$, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, aminoalquilo $C_1$-$C_6$, mono o dialquilaminoalquilo $C_1$-$C_6$

En esta realización, se prefiere que $R_6$ y $R_7$ no sean simultaneamente OH

Realización A92 Compuestos de acuerdo con la realizacion A91, en la que

$R_5$ es fenilo, opcionalmente sustituido con 1, 2, 3, 4 o 5 grupos que son independientemente alquilo $C_1$-$C_4$, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$ $-C(O)NR_6R_7$, $-NR_6R_7$, $NR_6R_7$(alquilo $C_1$-$C_6$), $NR_8R_9$, hidroxi $C_1$-$C_6$ alquilo, halogeno, alcoxi $C_1$-$C_4$, $CO_2H$, OH, alcoxi $C_1$-$C_6$ carbonilo, carboxaldehido, haloalquilo $C_1$-$C_4$, -(alquilo $C_1$-$C_4$)-$NR_{15}C(O)NR_{16}R_{17}$, -(alquilo $C_1$-$C_4$)-$NR_{15}C(O)R_{18}$, en los que

$R_6$ y $R_7$, en cada aparicion, son independientemente H, OH, alquilo $C_1$-$C_6$, aminoalquilo $C_1$-$C_4$, NH(alquilo $C_1$-$C_6$)alquilo, N(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$) alquilo $C_1$-$C_6$, hidroxi $C_1$-$C_6$ alquilo, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, -$SO_2$(alquilo $C_1$-$C_6$), $-SO_2NH_2$, $-SO_2NH$(alquilo $C_1$-$C_6$), $-SO_2N$(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$) o alcanoilo $C_1$-$C_6$, cada uno de los cuales se sustituye opcionalmente con 1, 2 o 3 grupos que son independientemente halogeno, OH, SH,

cicloalquilo $C_3$-$C_6$, alcoxi $C_1$-$C_4$, alquilo $C_1$-$C_4$, OH, $CF_3$ u $OCF_3$,

$R_{15}$ es H o alquilo $C_1$-$C_6$,

$R_{16}$ y $R_{17}$ son independientemente H o alquilo $C_1$-$C_6$, o

$R_{16}$, $R_{17}$ y el nitrogeno al que estan acoplados forman un anillo morfolinilo,

$R_{18}$ es alquilo $C_1$-$C_6$ opcionalmente sustituido con -O-(alcanoilo $C_2$-$C_6$, hidroxi $C_1$-$C_6$ alquilo, alcoxi $C_1$-$C_6$, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, aminoalquilo $C_1$-$C_6$, mono o dialquilaminoalquilo $C_1$-$C_6$

Realización A93 Compuestos de acuerdo con la realizacion A92, en a que

$R_1$ es halogeno, metilo, etilo, alquenilo $C_2$-$C_4$ alquinilo $C_2$-$C_4$ o carboxaldehido,

$R_2$ es benciloxi, OH, feniloxi, feniloxialquil($C_1$-$C_6$) o feniltioalcoxi ($C_1$-$C_4$), en el que cada uno de los anteriormente mencionados se sustituye opcionalmente con 1, 2, 3 o 4 grupos que son independientemente halogeno, -alquil($C_1$-$C_6$)-N(R)-$CO_2R_{30}$, $NR_6R_7$, -haloalquilo ($C_1$-$C_4$), haloalcoxi ($C_1$-$C_4$), alquilo ($C_1$-$C_6$), piridilo o $NR_6R_7$-(alquilo $C_1$-$C_6$)-, y

$R_4$ es H, alquilo ($C_1$-$C_4$) opcionalmente sustituido con uno o dos grupos que son independientemente $CO_2H$, -$CO_2$alquilo, -C(O)NRR, -N($R_{30}$)C(O)NRR, -N($R_{30}$)C(O)-alcoxi($C_1$-$C_6$) o -$NR_6R_7$ o hidroxialquil($C_1$-$C_4$)

Realización A94 Compuestos de acuerdo con la realizacion A93, en la que

$R_5$ es fenilo, opcionalmente sustituido con 1, 2, 3, 4 ó 5 grupos que son independientemente alquilo $C_1$-$C_4$, -C(O)$NR_6R_7$, -(alquilo $C_1$-$C_4$)-C(O)$NR_6R_7$ -$NR_6R_7$, $NR_6R_7$(alquilo $C_1$-$C_6$), hidroxi $C_1$-$C_6$ alquilo, halógeno, alcoxi $C_1$-$C_4$, $CO_2H$, OH, alcoxi $C_1$-$C_6$ carbonilo, carboxaldehido, halolalquilo $C_1$-$C_4$, en los que

$R_6$ y $R_7$, en cada aparición, son independientemente H, OH, alquilo $C_1$-$C_6$, aminoalquilo $C_1$-$C_4$, NH(alquilo $C_1$-$C_6$)alquilo, N(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$) alquilo $C_1$-$C_6$, hidroxi $C_1$-$C_6$ alquilo, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, -$SO_2$(alquilo $C_1$-$C_6$), -$SO_2NH_2$, -$SO_2$NH(alquilo $C_1$-$C_6$), -$SO_2$N(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$) o alcanoilo $C_1$-$C_6$, cada uno de los cuales se sustituye opcionalmente con 1, 2 ó 3 grupos que son independientemente halogeno, OH, SH, cicloalquilo $C_3$-$C_6$, alcoxi $C_1$-$C_4$, alquilo $C_1$-$C_4$, OH, $CF_3$ u $OCF_3$,

Realización A101 Compuestos de acuerdo con la realización A66, en la que

$R_5$ es tienil(alquilo $C_1$-$C_6$), piperidinilalquil($C_1$-$C_6$), pirrolidinilalquil($C_1$-$C_6$), imidazolidinilalquil($C_1$-$C_6$), piperazinilalquil($C_1$ $C_6$), piridilalquil($C_1$-$C_6$), pirimidilalquil($C_1$-$C_6$), piridazilalquil($C_1$-$C_6$), pirazinilalquil($C_1$-$C_6$), isoquinolinilalquil($C_1$-$C_6$), tetrahidroisoquinolinilalquil($C_1$-$C_6$), indolilalquil($C_1$-$C_6$), 1H-indazolilalquil($C_1$-$C_6$), dihidroindolonil(alquilo $C_1$-$C_6$), indolinil(alquilo $C_1$-$C_6$), dihidroisoindolilal(alquilo $C_1$-$C_6$), dihidrobencimdazolil(alquilo $C_1$-$C_6$) o dihidrobenzoimidazolonil(alquilo $C_1$-$C_6$), en el que

cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2, 3, 4 o 5 grupos que son independientemente alquil($C_1$-$C_6$), halógeno, alcoxi($C_1$-$C_6$), hidroxi($C_1$-$C_6$)alquilo, fenilalcoxi($C_1$-$C_6$), tioalcoxi($C_1$-$C_6$), alcoxi($C_1$-$C_6$)carbonilo, fenilalcoxi($C_1$-$C_6$)carbonilo, OH, $CO_2H$, CN, amidino-oxima, -$NR_8R_9$, $NR_6R_7$-(alquilo $C_1$-$C_6$)-, -C(O)$NR_6R_7$, -(alquilo $C_1$-$C_4$)-C(O)$NR_6R_7$ amidino, piperazinilo, morfolinilo, -$SO_2$ alquilo ($C_1$-$C_6$), -$SO_2NH_2$, -$SO_2$NHalquil($C_1$-$C_6$), -$SO_2$Nalquil($C_1$-$C_6$) alquil($C_1$-$C_6$), haloalquil($C_1$-$C_4$), -(alquilo $C_1$-$C_4$)-$NR_{15}$C(O)$NR_{16}R_{17}$, -(alquilo $C_1$-$C_4$)-$NR_{15}$C(O)$R_{18}$, -O-$CH_2$-O, -O-$CH_2CH_2$-O- o haloalcoxi($C_1$-

$C_4$), en los que

$R_6$ y $R_7$ son independientemente, en cada aparicion, H, alquil($C_1$-$C_6$), alcoxi($C_1$-$C_6$), alcoxi($C_1$-$C_6$)alquil($C_1$-$C_6$), alcoxi($C_1$-$C_6$)carbonilo, hidroxi($C_1$-$C_6$)alquilo, -alquil($C_1$-$C_4$)-$CO_2$-alquil($C_1$-$C_6$), alcanoil($C_1$-$C_6$), fenilalquil($C_1$-$C_6$), fenilalcoxi($C_1$-$C_6$) o fenilalcanoil($C_1$-$C_6$), en los que cada uno de los anteriormente mencionados no esta sustituido o está sustituido con 1, 2 ó 3 grupos que son independientemente halogeno, alcoxi($C_1$-$C_4$), OH, SH, cicloalquilo $C_3$-$C_6$, $NH_2$, NH(alquilo $C_1$-$C_6$), N(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$), alquil($C_1$-$C_4$), $CF_3$ u $OCF_3$, o

$R_6$, $R_7$ y el nitrogeno al cual se acoplan forman un anillo morfolinilo, tiomorfolinilo, piperidinilo, pirrolidinilo o piperazinilo opcionalmente sustituido con 1 o 2 grupos que son independientemente alquilo $C_1$-$C_4$, hidroxi, hidroxialquilo $C_1$-$C_4$ o halogeno, y

$R_{18}$ es alquilo $C_1$-$C_6$ opcionalmente sustituido con -O-(alcanoilo $C_2$-$C_6$, hidroxi $C_1$-$C_6$ alquilo, alcoxi $C_1$-$C_6$, alcoxi $C_1$-$C_6$ alquilo $C_1$ $C_6$, aminoalquilo $C_1$-$C_6$, mono o dialquilaminoalquilo $C_1$-$C_6$

En esta realización, se prefiere que $R_6$ y $R_7$ no sean simultáneamente OH, y

$R_6$ y $R_7$ no sean simultáneamente -$SO_2$(alquilo $C_1$-$C_6$)

Realización A102 Compuestos de acuerdo con la realizacion A101, en la que

$R_1$ es halógeno, metilo, etilo, alquenilo $C_2$-$C_4$ alquinilo $C_2$-$C_4$ o carboxaldehido,

$R_2$ es benciloxi, OH, feniloxi, feniloxialquil($C_1$-$C_6$) o feniltioalcoxi ($C_1$-$C_4$), en el que cada uno de los anteriormente mencionados se sustituye opcionalmente con 1, 2, 3 ó 4 grupos que son independientemente halogeno, -alquil($C_1$-$C_6$)-N(R)-$CO_2R_{30}$, $NR_6R_7$, -haloalquilo ($C_1$-$C_4$), haloalcoxi ($C_1$-$C_4$), alquilo ($C_1$-$C_6$), piridilo o $NR_6R_7$-

(alquilo $C_1$-$C_6$)-, y

$R_4$ es H, alquilo ($C_1$-$C_4$) opcionalmente sustituido con uno o dos grupos que son independientemente $CO_2H$, -$CO_2$alquilo, -C(O)NRR, -N($R_{30}$)C(O)NRR, -N($R_{30}$)C(O)-alcoxi($C_1$-$C_6$) o -$NR_6R_7$ o hidroxialquil($C_1$-$C_4$)

Realizacion A103 Compuestos de acuerdo con la realizacion A102, en la que

$R_5$ es tienil(alquilo $C_1$-$C_6$), indolil(alquilo $C_1$-$C_6$), piridinil(alquilo $C_1$-$C_6$), piperazinil(alquilo $C_1$-$C_6$) o pirazinil(alquilo $C_1$-$C_6$), cada uno de los cuales esta opcionalmente sustituido con 1, 2 o 3 grupos que son independientemente alquilo $C_1$-$C_4$, hidroxi $C_1$-$C_4$ alquilo, halógeno, -C(O)$NR_6R_7$, -(alquilo $C_1$-$C_4$)-C(O)$NR_6R_7$ alcoxi $C_1$-$C_6$ carbonilo, -$NR_6R_7$, $NR_6R_7$-(alquilo $C_1$-$C_6$)-, haloalquilo, alcanoilo $C_1$-$C_6$,

$R_6$ y $R_7$, en cada aparición, son independientemente H, alquilo $C_1$-$C_6$ opcionalmente sustituido con 1, 2 o 3 grupos que son independientemente alcoxi $C_1$-$C_4$ carbonilo, halogeno, cicloalquilo $C_3$-$C_6$, OH, SH o alcoxi $C_1$-$C_4$,

O

$R_6$, $R_7$ y el nitrogeno al cual se acoplan forman un anillo piperidinilo, pirrolidinilo, piperazinilo o morfolinilo, tiomorfolinilo opcionalmente sustituido con 1 ó 2 grupos que sor independientemente alquilo, hidroxi, hidroxialquilo $C_1$-$C_4$ o halógeno

Realizacion A104 Compuestos de acuerdo con la realizacion A103, en la que

$R_5$ es tienil(alquilo $C_1$-$C_6$), indolil(alquilo $C_1$-$C_6$), piridinil(alquilo $C_1$-$C_6$), piperazinil(alquilo $C_1$-$C_6$) o pirazinil(alquilo $C_1$-$C_6$)

Realización A105 Compuestos de acuerdo con la realización A103, en la que

R4 es H, metilc, etilo o -$CH_2OH$,

$R_5$ es piridinil(alquilo $C_1$-$C_6$) o pirazinil(alquilo $C_1$-$C_6$), cada uno de los cuales está opcionalmente sustituido con 1, 2 o 3 grupos que son independientemente alquilo $C_1$-$C_4$, hidroxi $C_1$-$C_4$ alquilo, halogeno, -C(O)$NR_6R_7$, -(alquilo $C_1$-$C_4$)-C(O)$NR_6R_7$ alcoxi $C_1$-$C_6$ carbonilo, -$NR_6R_7$, $NR_6R_7$-(alquilo $C_1$-$C_6$)-, $CF_3$, alcanoilo $C_1$-$C_6$, en los que

$R_6$ y $R_7$, en cada aparicion, son independientemente H, alquilo $C_1$-$C_6$ opcionalmente sustituido con 1, 2 o 3 grupos que son independ entemente alcoxi $C_1$-$C_4$ carbonilo, halogeno, cicloalquilo $C_3$-$C_6$, OH, SH o alcoxi $C_1$-$C_4$,

o

$R_6$, $R_7$ y el nitrogeno al cual se acoplan forman un anillo piperidinilo, pirrolidinilo, piperazinilo o morfolinilo, tiomorfolinilo opcionalmente sustituido con 1 ó 2 grupos que son independientemente alquilo, hidroxi, hidroxialquilo $C_1$-$C_4$ o halógeno

Realizacion A106 Compuestos de acuerdo con la realizacion A105, en la que

$R_4$ es H, alquilo opcionalmente sustituido con uno o dos grupos que son independientemente $CO_2H$, -$CO_2$-(alquilo $C_1$-$C_6$), -C(O)NRR, -N($R_{30}$)C(O)NRR, -N($R_{30}$)C(O)-alcoxi($C_1$-$C_6$) o -$NR_6R_7$

Realizacion A112 Compuestos de acuerdo con la realización 16, en la que

$R_1$ es halogeno o metilo,

$R_2$ es benciloxi, opcionalmente sustituido con 1, 2, 3 o 4 grupos que son independientemente halogeno, -alquil($C_1$-$C_6$)-N(R)-$CO_2R_{30}$, $CF_3$, $OCF_3$ o alquilo ($C_1$-$C_4$), y

$R_4$ es H, metilc, etilo, -$CH_2OH$, -$CH_2CO_2$-(alquilo $C_1$-$C_4$) o hidroxi $C_2$ alquilo

Realizacion A113 Compuestos de acuerdo con una cualquiera de las realizaciones A85, A95, A97, A98, A99, A100, 16 o 17, en las que

$R_1$ es halogeno o metilo,

$R_2$ es benciloxi, opcionalmente sustituido con 1, 2, 3 o 4 grupos que son independientemente halógeno, -alquil($C_1$-$C_6$)-N(R)-$CO_2R_{30}$, $CF_3$, $OCF_3$ o alquilo ($C_1$-$C_4$), y

$R_4$ es alquilo opcionalmente sustituido con un grupo que es $CO_2H$, -$CO_2$-alquil($C_1$-$C_6$), -C(O)NRR, -N($R_{30}$)C(O)NRR, -N($R_{30}$)C(O)-alcoxi($C_1$-$C_6$) o -$NR_6R_7$

Realización A114 Compuestos de acuerdo con la realización A66, en la que

$R_5$ es isoquinolinil(alquilo $C_1$-$C_6$), tetrahidroisoquinolinil(alquilo $C_1$-$C_6$), 1H-indazolil(alquilo $C_1$-$C_6$), dihidroindolonil(alquilo $C_1$-$C_6$), indolinil(alquilo $C_1$-$C_6$), dihidroisoindolil(alquilo $C_1$-$C_6$), dihidrobencimdazolil(alquilo $C_1$-$C_6$), dihidrobenzoimidazolonil(alquilo $C_1$-$C_6$), cada uno de los cuales no se sustituye o se sustituye con 1, 2 o 3 grupos que son independientemente alquilo, alcoxi, halógeno, alcoxi $C_1$-$C_6$ carbonilo, alcanoilo opcionalmente sustituido con 1 o 2 grupos que se seleccionan independientemente entre el grupo que consiste en OH, $NH_2$, NH(alquilo $C_1$-$C_6$) y N(alquilo $C_1$-$C_6$) (alquilo $C_1$-$C_6$), -C(O)$NR_6R_7$, -(alquilo $C_1$-$C_4$)-C(O)$NR_6R_7$ $NR_6R_7$-(alquilo $C_1$-$C_6$)-, -$NR_6R_7$ o $SO_2H$, o

piperidinilalquilo $C_1$-$C_4$ opcionalmente sustituido con 1, 2 o 3 grupos que son independientemente alquilo $C_1$-$C_4$, alcoxi $C_1$-$C_4$, halógeno, -C(O)$NR_6R_7$, -(alquilo $C_1$-$C_4$)-C(O)$NR_6R_7$ $NR_6R_7$-(alquilo $C_1$-$C_6$)- o -$NR_6R_7$ o alcoxi $C_1$-$C_6$ carbonilo

Realizacion A115 Compuestos de acuerdo con la realización A114, en la que

$R_5$ es isoquinolinil(alquilo $C_1$-$C_4$), piperidinilalquilo $C_1$-$C_4$, tetrahidroisoquinolinil(alquilo $C_1$-$C_4$), 1H-indazolil(alquilo $C_1$-$C_4$), dihidroindolonil(alquilo $C_1$-$C_4$), indolinil(alquilo $C_1$-$C_4$), dihidroisoindolil(alquilo $C_1$-$C_4$),

dihidrobencimdazolil(alquilo $C_1$-$C_4$) o dihidrobenzoimidazolonil(alquilo $C_1$-$C_4$)

Realización A116 Compuestos de acuerdo con la realizacion A114, en la que

$R_5$ es piperidinilalquilo $C_1$-$C_4$ opcionalmente sustituido con 1, 2 o 3 grupos que son independientemente alquilo $C_1$-$C_4$, alcoxi $C_1$-$C_4$, halógeno o alcoxi $C_1$-$C_6$ carbonilo

Realizacion A11' Compuestos de acuerdo con la realización A66, en la que

$R_5$ es pirimidilo, indolinilo, indolilo, 1H-isoindolilo, isoquinolinilo, tetrahidroisoquinolinilo, bencimidazolilo, dihidro-1H-bencimidazolilo, pirrolilo, imidazolilo o cada uno de ellos se sustituye opcionalmente con 1, 2 ó 3 grupos independientemente seleccionados entre el grupo que consiste en

alcoxi $C_1$-$C_6$ carbonilo, tioalcoxi $C_1$-$C_4$, cada uno de los cuales no esta sustituido o esta sustituido con 1, 2 o 3 grupos que son independientemente $-C(O)NR_6R_7$, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$ $NR_6R_7$-(alquilo $C_1$-$C_6$)-, $-NR_6R_7$, alquilo, alcoxi, halogeno, alcoxi $C_1$-$C_6$ carbonilo o alcanoilo opcionalmente sustituido con 1 ó 2 grupos que se seleccionan independientemente entre el grupo que consiste en OH, $NH_2$, NH(alquilo $C_1$-$C_6$) y N(alquilo $C_1$-$C_6$) (alquilo $C_1$-$C_6$) y $SO_2H$, o

piridilo, pirazolilo, opcionalmente sustituido con 1, 2 ó 3 grupos que son independientemente $-C(O)NR_6R_7$, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$ $NR_6R_7$-(alquilo $C_1$-$C_6$)-, $-NR_6R_7$, alquilo $C_1$-$C_4$, hidroxi $C_1$-$C_4$ alquilo, halógeno, alcoxi $C_1$-$C_6$ carbonilo, $-NR_6R_7$, $NR_6R_7$-(alquilo $C_1$-$C_6$)-, $CF_3$, alcanoilo $C_1$-$C_6$, en los que

$R_6$ y $R_7$, en cada aparicion, son independientemente H, alquilo $C_1$-$C_6$ opcionalmente sustituido con 1, 2 o 3 grupos que son independientemente alcoxi $C_1$-$C_4$ carbonilo,

halogeno, cicloalquilo $C_3$-$C_6$, OH, SH o alcoxi $C_1$-$C_4$,

O

$R_6$, $R_7$ y el nitrogeno al cual se acoplan forman un anillo piperidinilo, pirrolidinilo, piperazinilo o morfolinilo, tiomorfolinilo opcionalmente sustituido con 1 o 2 grupos que son independientemente alquilo, hidroxi, hidroxialquilo $C_1$-$C_4$ o halogeno

Realizacion A118 Compuestos de acuerdo con la realización A117, en la que

$R_5$ es pirimidilc, pirrolilo, imidazolilo o pirazolilo, cada uno de los cuales esta opcionalmente sustituido con 1, 2 o 3 grupos independientemente seleccionados entre alcoxi $C_1$-$C_6$ carbonilo, tioalcoxi $C_1$-$C_4$, cada uno de los cuales no se sustituye o se sustituye con 1, 2 o 3 grupos que son independientemente

alquilo, alcoxi, halogeno, alcoxi $C_1$-$C_6$ carbonilo, $-C(O)NR_6R_7$, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$ $NR_6R_7$-(alquilo $C_1$-$C_6$)- o $-NR_6R_7$ o alcanoilo $C_1$-$C_4$ opcionalmente sustituido con 1 o 2 grupos que se seleccionan independientemente entre el grupo que consiste en OH, $NH_2$, NH(alquilo $C_1$-$C_6$) y N(alquilo $C_1$-$C_6$) (alquilo $C_1$-$C_6$) o $SO_2H$

Realizacion A119 Compuestos de acuerdo con la realizacion A117, en la que

$R_5$ es piridilo o pirazolilo, opcionalmente sustituido con 1, 2 o 3 grupos que son independientemente alquilo $C_1$-$C_4$, hidroxi $C_1$-$C_4$ alquilo, halógenno, $-C(O)NR_6R_7$, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$ $NR_6R_7$-(alquilo $C_1$-$C_6$)- o $-NR_6R_7$, alcoxi $C_1$-$C_6$ carbonilo, $-NR_6R_7$, $NR_6R_7$-(alquilo $C_1$-$C_6$)-, $CF_3$, alcanoilo $C_1$-$C_6$, en los que

$R_6$ y $R_7$, en cada aparición, son independientemente H, alquilo $C_1$-$C_6$ opcionalmente sustituido con 1, 2 ó 3 grupos que son independientemente alcoxi $C_1$-$C_4$ carbonilo, halógeno, cicloalquilo $C_3$-$C_6$, OH, SH o alcoxi $C_1$-$C_4$,

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o

$R_6$, $R_7$ y el nitrógeno al cual se acoplan forman un anillo piperidinilo, pirrolidinilo, piperazinilo, morfolinilo, opcionalmente sustituido con 1 o 2 grupos que son independientemente alquilo, hidroxi, hidroxialquilo $C_1$-$C_4$ o halógeno

Realizacion A120 Compuestos de acuerdo con la realizacion A119, en la que

$R_5$ es piridilo o pirazolilo, opcionalmente sustituido con 1, 2 ó 3 grupos que son independientemente alquilo $C_1$-$C_4$, hidroxi $C_1$-$C_4$ alquilo, halogeno, $-C(O)NR_6R_7$, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$ $NR_6R$-(alquilo $C_1$-$C_6$)-, $-NR_6R_7$, alcoxi $C_1$-$C_6$ carbonilo, $-CF_3$, alcanoilo $C_1$-$C_6$, en los que

$R_6$ y $R_7$, en cada aparicion, son independientemente H, alquilo $C_1$-$C_6$ opcionalmente sustituido con 1, 2 o 3 grupos que son independientemente alcoxi $C_1$-$C_4$ carbonilo, halógeno, cicloalquilo $C_3$-$C_6$, OH, SH o alcoxi $C_1$-$C_4$

Realizacion A121 Compuestos de acuerdo con la realización A119, en la que

$R_5$ es piridilo o pirazolilo, opcionalmente sustituido con 1, 2 o 3 grupos que son independientemente alquilo $C_1$-$C_4$, hidroxi $C_1$-$C_4$ alquilo, halógeno, $-C(O)NR_6R_7$, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$ $NR_6R_7$-(alquilo $C_1$-$C_6$)-, $-NR_6R_7$, alcoxi $C_1$-$C_6$ carbonilo, $-CF_3$, alcanoilo $C_1$-$C_6$, en los que

$R_6$, $R_7$ y el nitrógeno al cual se acoplan forman un anillo piperidinilo, pirrolidinilo, piperazinilo, morfolinilo, opcionalmente sustituido con 1 ó 2 grupos que son independientemente alquilo, hidroxi, hidroxialquilo $C_1$-$C_4$ o halógeno

Realizacion A122 Compuestos de acuerdo con una cualquiera de las realizaciones A114, A115, A116 o A117, en las que

$R_1$ es halógeno, metilo, etilo, alquenilo $C_2$-$C_4$

alquinilo $C_2$-$C_4$ o carooxaldehido,

$R_2$ es bencciloxi, OH, feniloxi, feniloxialquil($C_1$-$C_6$) o feniltioalcoxi ($C_1$-$C_4$), en el que cada uno de los anteriormente mencionados se sustituye opcionalmente con 1, 2, 3 ó 4 grupos que son independientemente halogeno, -alquil($C_1$-$C_6$)-N(R)-$CO_2R_{30}$, $NR_6R_7$, -haloalquilo ($C_1$-$C_4$), haloalcoxi ($C_1$-$C_4$), alquilo ($C_1$-$C_6$), piridilo o $NR_6R_7$-(alquilo $C_1$-$C_6$)-, y

$R_4$ es H, alquilc ($C_1$-$C_4$) sustituido con un grupo que es $CO_2H$, -$CO_2$-alquil($C_1$-$C_6$), -C(O)NRR, -N($R_{30}$)C(O)NRR, -N($R_{30}$)C(O)-alcoxi($C_1$-$C_6$) o -$NR_6R_7$, hidroxialquil($C_1$-$C_4$)

Realizacion A123 Compuestos de acuerdo con la realización A66, en la que

$R_5$ es alquilo $C_-$-$C_6$ opcionalmente sustituido con 1 ó 2 grupos que son independientemente alcoxi $C_1$-$C_4$ carbonilo o halogeno, o

$R_5$ es alcoxi $C_1$-$C_4$, etilo, metilo, ciclopropilmetilo, cicloalquilo o alquinilo, o

$R_5$ es alquenilo $C_2$-$C_6$ opcionalmente sustituido con alcoxi $C_1$-$C_4$ carbonilo o ciclohexilo

Realizacion A124 Compuestos de acuerdo con la realización A123, en la que

$R_1$ es halogeno, metilo, etilo, alquenilo $C_2$-$C_4$ alquinilo $C_2$-$C_4$ o carboxaldehido,

$R_2$ es bencciloxi, OH, feniloxi, feniloxialquil($C_1$-$C_6$) o feniltioalcoxi ($C_1$-$C_4$), en el que cada uno de los anteriormente mencionados se sustituye opcionalmente con 1, 2, 3 o 4 grupos que son independientemente halogeno, -alquil($C_1$-$C_6$)-N(R)-$CO_2R_{30}$, $NR_6R_7$, -haloalquilo ($C_1$-$C_4$), haloalcoxi ($C_1$-$C_4$), alquilo ($C_1$-$C_6$), piridilo o $NR_6R_7$-(alquilo $C_1$-$C_6$)-, y

$R_4$ es H, alquilo ($C_1$-$C_4$) sustituido con un grupo que es $CO_2H$, -$CO_2$-alquil($C_1$-$C_6$), -C(O)NRR, -N($R_{30}$)C(O)NRR, -

$N(R_{30})C(O)$-alcoxi$(C_1-C_6)$ o $-NR_6R_7$, hidroxialquil$(C_1-C_4)$, en el que

$R_6$ y $R_7$, en cada aparición, son independientemente H, alquilo $C_1-C_6$ opcionalmente sustituido con 1, 2 o 3 grupos que son independientemente alcoxi $C_1-C_4$ carbonilo, halogeno, cicloalquilo $C_3-C_6$, OH, SH o alcoxi $C_1-C_4$,

O

$R_6$, $R_7$ y el nitrogeno al cual se acoplan forman un anillo piperidinilo, pirrolidinilo, piperazinilo, morfolinilo opcionalmente sustituido con 1 ó 2 grupos que son independientemente alquilo, hidroxi, hidroxialquilo $C_1-C_4$ o halógeno

Realizacion A125 Compuestos de acuerdo con la realización A124, en la que

$R_5$ es alquilo $C_1-C_6$ opcionalmente sustituido con 1 o 2 grupos que son independientemente alcoxi $C_1-C_4$ carbonilo o halogeno, o

$R_5$ es alcoxi $C_1-C_4$, etilo, metilo, ciclopropilmetilo, ciclohexilo, ciclopentilo, alquinilo $C_2-C_6$ o

$R_5$ es alquenilo $C_2-C_6$ opcionalmente sustituido con alcoxi $C_1-C_4$ carbonilo o ciclohexilo

Realización A126 Compuestos de acuerdo con la realizacion A66, en la que

$R_2$ es fenilalquinilo, $-OC(O)NH(CH_2)_n$arilo, $-OC(O)N$(alquil)$(CH_2)_n$arilo, $-OSO_2$alquil$(C_1-C_6)$, $-OSO_2$arilo o $NR_8R_9$, en el que

n es 0, 1, 2, 3, 4, 5 o 6,

cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2, 3, 4 ó 5 grupos que son independientemente halogeno, -alquil$(C_1-C_6)$-$N(R)$-$CO_2R_{30}$, alcoxi, alcoxicarbonilo, CN, $NR_6R_7$, haloalquilo, haloalcoxi, alquilo, heteroarilo, heteroarilalquilo, $NR_6R_7$-(alquilo $C_1-C_6$)-, fenilo, $-SO_2$-fenilo en los que los grupos

fenilo se sustituyen opcionalmente con 1, 2 o 3 grupos que son independientemente halógeno o $NO_2$, o $-OC(O)NR_6R_7$, en los que

$R_6$ y $R_7$ son independientemente, en cada aparicion, H, alquilo, alcoxi, alcoxialquilo, alcoxicarbonilo, $-SO_2$-alquilo, OH, hidroxialquilo, -alquil($C_1$-$C_4$)-$CO_2$-alquilo, heteroarilalquilo, alcanoilo, arilalquilo, arilalcoxi o arilalcanoilo, en los que cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2 ó 3 grupos que son independientemente halogeno, alcoxi, heterocicloalquilo, OH, $NH_2$, cicloalquilo $C_3$-$C_6$, NH(alquilo), N(alquil)(alquilo), -O-alcanoilo, alquilo, haloalquilo $C_1$-$C_4$ o haloalcoxi $C_1$-$C_4$, o

$R_6$, $R_7$ y el nitrogeno al cual se acoplan forman un anillo morfolinilo, tiomorfolinilo, piperidinilo, pirrolidinilo o piperazinilo opcionalmente sustituido con 1 o 2 grupos que son independientemente alquilo $C_1$-$C_4$, alcoxi $C_1$-$C_4$ hidroxi, hidroxialquilo $C_1$-$C_4$ o halógeno

Realizacion A127 Compuestos de acuerdo con la realizacion A126, en la que

$R_1$ es halogeno, metilo, etilo, alquenilo $C_2$-$C_4$ alquinilo $C_2$-$C_4$ o carboxaldehido, y

$R_4$ es H, alquilo ($C_1$-$C_4$) sustituido con un grupo que es $CO_2H$, $-CO_2$-alquil($C_1$-$C_6$), $-C(O)NRR$, $-N(R_{30})C(O)NRR$, $-N(R_{30})C(O)$-alcoxi($C_1$-$C_6$), $-NR_6R_7$, $NR_6R_7$-(alquilo $C_1$-$C_6$)- o hidroxialquil($C_1$-$C_4$)

Realizacion A128 Compuestos de acuerdo con la realización A127, en la que

$R_5$ es fenilo, opcionalmente sustituido con 1, 2, 3, 4 o 5 grupos que son independientemente halógeno, alquilo $C_1$-$C_4$, alcoxi $C_1$-$C_4$, $CF_3$, $OCF_3$, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$ $NR_6R_7$-(alquilo $C_1$-$C_6$)-, $-NR_6R_7$ o $C(O)NR_6R_7$, en los que

$R_6$ y $R_7$ son independientemente, en cada aparicion, H,

alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$ carbonilo, OH, hidroxi $C_1$-$C_6$ alquilo, -alquil($C_1$-$C_4$)-$CO_2$-alquilo, piridilalquilo $C_1$-$C_6$, alcanoilo $C_1$-$C_6$, bencilo, fenilalcoxi $C_1$-$C_6$ o fenilalcanoilo $C_1$-$C_6$, en los que cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2 o 3 grupos que son independientemente halogeno, alcoxi $C_1$-$C_6$, piperidinilalquilo $C_1$-$C_6$, morfolinilalquilo $C_1$-$C_6$, piperazinilalquilo $C_1$-$C_6$, OH, SH, cicloalquilo $C_3$-$C_6$, $NH_2$, NH(alquilo), N(alquil)(alquilo), -O-alcanoilo $C_1$-$C_4$, alquilo $C_1$-$C_4$, $CF_3$ u $OCF_3$, o

$R_6$, $R_7$ y el nitrogeno al cual se acoplan forman un anillo morfolinilo, tiomorfolinilo, piperidinilo, pirrolidinilo o pipeiazinilo opcionalmente sustituido con 1 o 2 grupos que son independientemente alquilo $C_1$-$C_4$, alcoxi $C_1$-$C_4$ hidroxi, hidroxialquilo $C_1$-$C_4$ o halógeno, o

$R_5$ es bencilo, opcionalmente sustituido con 1, 2, 3, 4 o 5 grupos que son independientemente halogeno, alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$, CN, $CF_3$, $OCF_3$, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$ $NR_6R_7$-(alquilo $C_1$-$C_6$)-, $-NR_6R_7$ o $C(O)NR_6R_7$

Realizacion A129 Compuestos de acuerdo con la realización A128, en la que

$R_2$ es $NR_8R_9$ o $NR_8R_9$-(alquilo $C_1$-$C_4$)-, en el que

$R_8$, en cada aparición, es independientemente hidrógeno, alquilo $C_1$-$C_6$, alcanoilo $C_1$-$C_6$, fenilalquil($C_1$-$C_6$) o fenilalcanoil($C_1$-$C_6$) en el que cada uno de los anteriormente mencionados esta opcionalmente sustituido con 1, 2, 3, 4 ó 5 grupos que son independientemente alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$, alcoxi $C_1$-$C_6$ carbonilo, halógeno o haloalquilo $C_1$-$C_4$ y

$R_9$, en cada aparición, es independientemente alquilo $C_1$-$C_6$, alcanoilo $C_1$-$C_6$, fenilalquil($C_1$-$C_6$), cicloalquilo $C_3$-$C_7$, alquenilo $C_2$-$C_6$, piridilo, piridazinilo, pirimidinilo,

pirazinilo, imidazolilo, cicloalquilo $C_3$-$C_7$alquil($C_1$-$C_6$), fenilalcanoil($C_1$-$C_6$), -$SO_2$-fenilo y fenilo, en el que cada uno de los anteriormente mencionados se sustituye opcionalmente con 1, 2, 3, 4 o 5 grupos que son independientemente alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$, alcoxi $C_1$-$C_6$ carbonilo, halogeno o haloalquilo $C_1$-$C_4$

Realización A130 Compuestos de acuerdo con la realizacion A129, en la que

$R_8$ es H

Realizacion A131 Compuestos de acuerdo con la realizacion A130, en la que

$R_2$ es -NH-bencilo opcionalmente sustituido con 1, 2 o 3 grupos que son independientemente halógeno, alquilo $C_1$-$C_4$, alcoxi $C_1$-$C_4$, $CF_3$, $OCF_3$,

O

$R_2$ es -NH-C(O)fenilo, en el que el grupo fenilo está opcionalmente sustituido con 1, 2 o 3 grupos que son independientemente halogeno, alquilo $C_1$-$C_4$ o alcoxi $C_1$-$C_4$, o $R_2$ es -NH-alilo

Realización A132 Compuestos de acuerdo con la realizacion A131, en la que

$R_1$ es cloro, bromo, yodo o metilo, y

$R_5$ es bencilo opcionalmente sustituido con 1 ,2 3, 4 ó 5 grupos que son independientemente halogeno, -(alquilo $C_1$-$C_4$)-C(O)$NR_6R_7$ $NR_6R_7$-(alquilo $C_1$-$C_6$)-, -$NR_6R_7$, alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$, CN, $CF_3$ $OCF_3$ o C(O)$NR_6R_7$

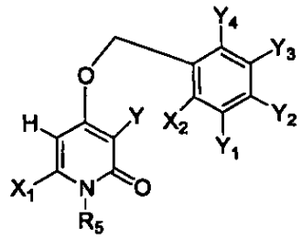
Realización A133 Compuestos de acuerdo con la realización A131, en la que

$R_1$ es cloro, bromo, yodo o metilo, y

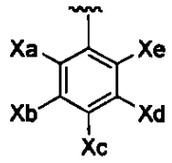
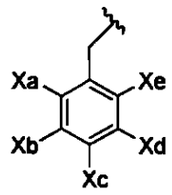
$R_5$ es fenilo opcionalmente sustituido con 1 2 3 4 6 5 grupos que son independientemente halógeno, -(alquilo $C_1$-$C_4$)-C(O)$NR_6R_7$ $NR_6R_7$-(alquilo $C_1$-$C_6$)-, -$NR_6R_7$, alquilo $C_1$-$C_4$, alcoxi $C_1$-$C_4$, $CF_3$ $OCF_3$ o C(O)$NR_6R_7$

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Realizacion A134 Un compuesto de la formula



o sus sales farmaceuticamente aceptables, en la que

$R_5$ es  o  , en la que

$X_1$, $X_2$, $X_a$, $X_b$, $X_c$, $X_d$, y $X_e$ se seleccionan independientemente entre $-C(O)NR_6R_7$, $-NR_6R_7$, hidroxialquil($C_1$-$C_4$), H, OH, halogeno, haloalquilo, alquilo, haloalcoxi, heteroarilo, heterocicloalquilo, cicloalquilo $C_3$-$C_7$, $NR_6R_7$-(alquilo $C_1$-$C_6$)-, $-CO_2$-alquil($C_1$-$C_6$), $-N(R)C(O)NR_6R_7$, $-N(R)C(O)$-alcoxi($C_1$-$C_6$), $CO_2H$-(alquilo $C_1$-$C_6$)- o $-SO_2NR_6R_7$, en los

los grupos heteroarilo y heterocicloalquilo se sustituyen opcionalmente con $-NR_6R_7$, $-C(O)NR_6R_7$, $NR_6R_7$-(alquilo $C_1$-$C_6$)-, alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$ o halógeno,

$R_6$ y $R_7$ son independientemente, en cada aparición, H, alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$ carbonilo, OH, hidroxi $C_1$-$C_6$ alquilo, tiohidroxi $C_1$-$C_6$ alquilo, -alquil($C_1$-$C_4$)-$CO_2$-alquilo, piridilalquilo $C_1$-$C_6$, alcanoilo $C_1$-$C_6$, bencilo, fenilalcoxi $C_1$-$C_6$ o fenilalcanoilo $C_1$-$C_6$, en los que cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2 o 3 grupos que son independientemente halogeno, cicloalquilo $C_3$-$C_6$, alcoxi $C_1$-$C_6$, piperidinilalquilo $C_1$-$C_6$, morfolinilalquilo $C_1$-$C_6$, piperazinilalquilo $C_1$-$C_6$, OH, SH, $NH_2$, NH(alquilo), N(alquil)(alquilo), -O-alcanoilo $C_1$-$C_4$,

alquilo $C_1$-$C_4$, $CF_3$ u $OCF_3$, o

$R_6$, $R_7$ y el nitrógeno al cual se acoplan forman un anillo morfolinilo, tiomorfolinilo, piperidinilo, pirrolidinilo o piperazinilo opcionalmente sustituido con 1 o 2 grupos que son independientemente alquilo $C_1$-$C_4$, alcoxi $C_1$-$C_4$ hidroxi, hidroxialquilo $C_1$-$C_4$ o halógeno,

R, en cada aparicion, es independientemente H o alquilo $C_1$-$C_6$, y

Y, $Y_1$, $Y_2$, $Y_3$, y $Y_4$ se seleccionan independientemente entre H, halógeno, alquilo, carboxaldehido, hidroxialquilo, alquenilo, alquinilo, CN, alcanolilo, alcoxi, alcoxialquilo, haloalquilo y carboxilo

Realizacion A134 Compuestos de acuerdo con la realizacion A134, en la que

$Y_2$, $Y_4$, y Y son independientemente halógeno, y

$Y_1$ y $Y_3$ son ambos hidrogeno

Realización A135 Compuestos de acuerdo con la realizacion A135, en la que

$X_1$ es H, metilo, $-NR_6R_7$, $NR_6R_7$-(alquilo $C_1$-$C_6$)-, $-C(O)NR_6R_7$, hidroxi $C_1$-$C_6$ alquilo o -(alquilo $C_1$-$C_4$)-morfolinilo

Realizacion A137 Compuestos de acuerdo con la realización A136, en la que

$X_a$ y $X_e$ sor independientemente halogeno, $NH_2$, NH(alquilo $C_1$-$C_6$), N(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$) o metilo

Realizacion A138 Compuestos de acuerdo con la realización A137, en la que

$X_b$ o $X_c$ es $-NR_6R_7$, $NR_6R_7$-(alquilo $C_1$-$C_6$)-, $-C(O)NR_6R_7$, $-SO_2NR_6R_7$ o halógeno, en el que

$R_6$ y $R_7$ son incependientemente, en cada aparición, H, alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$ carbonilo, OH, hidroxi $C_1$-$C_6$ alquilo, -alquil($C_1$-$C_4$)-$CO_2$-alquilo, piridilalquilo $C_1$-$C_6$, alcanoilo

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$C_1$-$C_6$, bencilo, fenilalcoxi $C_1$-$C_6$ o fenilalcanoilo $C_1$-$C_6$, en los que cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2 ó 3 grupos que son independientemente halógeno, cicloalquilo $C_3$-$C_6$, alcoxi $C_1$-$C_6$, piperidinilalquilo $C_1$-$C_6$, morfolinilalquilo $C_1$-$C_6$, piperazinilalquilo $C_1$-$C_6$, OH, SH, $NH_2$, NH(alquilo), N(alquil)(alquilo), O-alcanoilo $C_1$-$C_4$, alquilo $C_1$-$C_4$, $CF_3$ u $OCF_3$, o

$R_6$, $R_7$ y el nitrógeno al cual se acoplan forman un anillo morfolinilo, tiomorfolinilo, piperidinilo, pirrolidinilo o pipe-azinilo opcionalmente sustituido con 1 ó 2 grupos que son independientemente alquilo $C_1$-$C_4$, alcoxi $C_1$-$C_4$ hidroxi, hidroxialquilo $C_1$-$C_4$ o halogeno

Realización A139 Compuestos de acuerdo con la realizacion A138, en la que

$R_6$, $R_7$ y el nitrogeno al cual se acoplan forman un anillo morfolinilo, tiomorfolinilo, piperidinilo, pirrolidinilo o piperazinilo opcionalmente sustituido con 1 o 2 grupos que son independientemente alquilo $C_1$-$C_4$, alcoxi $C_1$-$C_4$ hidroxi, hidroxialquilo $C_1$-$C_4$ o halógeno

Realización A140 Compuestos de acuerdo con la realizacion A138, en la que

$R_6$, $R_7$ y el nitrogeno al cual se acoplan forman un anillo piperazinilo opcionalmente sustituido con 1 ó 2 grupos que son independientemente alquilo $C_1$-$C_4$, alcoxi $C_1$-$C_4$ hidroxi, hidroxialquilo $C_1$-$C_4$ o halogeno

Realización A141 Compuestos de acuerdo con la realizacion A138, en la que

$R_6$ y $R_7$ son independientemente, en cada aparicion, H, alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$ carbonilo, OH, hidroxi $C_1$-$C_6$ alquilo, -alquil($C_1$-$C_4$)-$CO_2$-alquilo, piridiloalquilo $C_1$-$C_6$, alcanoilo $C_1$-$C_6$, bencilo, fenilalcoxi $C_1$-$C_6$ o fenilalcanoilo $C_1$-$C_6$, en

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los que cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2 ó 3 grupos que son independientemente halógeno, cicloalquilo $C_3$-$C_6$, alcoxi $C_1$-$C_6$, piperidinilalquilo $C_1$-$C_6$, morfolinilalquilo $C_1$-$C_6$, piperazinilalquilo $C_1$-$C_6$, OH, $NH_2$, NH(alquilo), N(alquil)(alquilo), O-alcanoilo $C_1$-$C_4$, alquilo $C_1$-$C_4$, $CF_3$ u $OCF_3$

Realizacion A142 Compuestos de acuerdo con la realizacion A138, en la que

$R_6$ y $R_7$ son independientemente, en cada aparición, H, alquilo $C_1$-$C_6$, hidroxi $C_1$-$C_6$ alquilo, alcoxi $C_1$-$C_6$, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$ o alcanoilo $C_1$-$C_6$, en los que cada uno de los anteriormente mencionados se sustituye opcionalmente con 1, 2 ó 3 grupos que son independientemente OH, SH, halogeno o cicloalquilo $C_3$-$C_6$

Realizacion A143 Compuestos de acuerdo con la realizacion A137, en la que

$X_a$ y $X_e$ son independientemente fluoro, cloro o metilo, y

$X_c$ es hidrógeno o halogeno

Realizacion A144 Compuestos de acuerdo con la realizacion A137, en la que

$X_a$ es halogeno,

$X_e$ es $NH_2$, NH(alquilo $C_1$-$C_6$) o N(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$)

$X_b$ y $X_d$ son ambcs hidrogeno

Realización A145 Compuestos de acuerdo con la realizacion A144, en la que

$X_c$ es $-NR_6R_7$, $NR_6R_7$ alquilo $C_1$-$C_6$ $-SO_2NR_6R_7$ o halogeno, en el que

$R_6$ y $R_7$ son independientemente, en cada aparicion, H, alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$ carbonilo, OH, hidroxi $C_1$-$C_6$ alquilo, -

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alquil($C_1$-$C_4$)-$CO_2$-alquilo, piridilalquilo $C_1$-$C_6$, alcanoilo $C_1$-$C_6$, bencilo, fenilalcoxi $C_1$-$C_6$ o fenilalcanoilo $C_1$-$C_6$, en los que cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2 o 3 grupos que son independientemente halogeno, cicloalquilo $C_3$-$C_6$, alcoxi $C_1$-$C_6$, piperidinilalquilo $C_1$-$C_6$, morfolinilalquilo $C_1$-$C_6$, piperazinilalquilo $C_1$-$C_6$, OH, SH, $NH_2$, NH(alquilo), N(alquil)(alquilo), -O-alcanoilo $C_1$-$C_4$, alquilo $C_1$-$C_4$, $CF_3$ u $OCF_3$, o

$R_6$, $R_7$ y el nitrógeno al cual se acoplan forman un anillo morfolinilo, tiomorfolinilo, piperidinilo, pirrolidinilo o piperazinilo opcionalmente sustituido con 1 ó 2 grupos que son independientemente alquilo $C_1$-$C_4$, alcoxi $C_1$-$C_4$ hidroxi, hidroxialquilo $C_1$-$C_4$ o halogeno

Realización A146 Compuestos de acuerdo con la realizacion A145, en la que

$X_c$ es fluoro, cloro, $-NH_2$, -NH(alquilo $C_1$-$C_6$), -N(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$), $-SO_2NH_2$, $-SO_2$NH(alquilo $C_1$-$C_6$), $-SO_2$N(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$) o piperazinilo, en el que el grupo piperazinilo se sustituye opcionalmente con 1 o 2 grupos que son independientemente alquilo $C_1$-$C_4$, alcoxi $C_1$-$C_4$, hidroxi, hidroxialquilo $C_1$-$C_4$ o halogeno

Realización A147 Compuestos de acuerdo con cualquiera de las realizaciones A137 o A144, en la que

$X_c$ es $-C(O)NR_6R_7$, -(alquilo $C_1$-$C_6$)-$C(O)NR_6R_7$, $-NR_6R_7$ o $NR_6R_7$-(alquilo $C_1$-$C_6$)- en el que

$R_6$ y $R_7$ son independientemente, en cada aparición, H, alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$ carbonilo, OH, hidroxi $C_1$-$C_6$ alquilo, -alquil($C_1$-$C_4$)-$CO_2$-alquilo, piridilalquilo $C_1$-$C_6$, alcanoilo $C_1$-$C_6$, bencilo, fenilalcoxi $C_1$-$C_6$ o fenilalcanoilo $C_1$-$C_6$, en los que cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2 o 3 grupos que son

independientemente halogeno, cicloalquilo $C_3$-$C_6$, alcoxi $C_1$-$C_6$, piperidinilalquilo $C_1$-$C_6$, morfolinilalquilo $C_1$-$C_6$, piperazinilalquilo $C_1$-$C_6$, OH, $NH_2$, NH(alquilo), N(alquil)(alquilo), -O-alcanoilo $C_1$-$C_4$, alquilo $C_1$-$C_4$, $CF_3$ u $OCF_3$, o

$R_6$, $R_7$ y el nitrógeno al cual se acoplan forman un anillo morfolinilo, tiomorfolinilo, piperidinilo, pirrolidinilo o piperazinilo opcionalmente sustituido con 1 ó 2 grupos que son independientemente alquilo $C_1$-$C_4$, alcoxi $C_1$-$C_4$ hidroxi, hidroxialquilo $C_1$-$C_4$ o halógeno

Realizacion A148 Compuestos de acuerdo con la realizacion A147, en la que

$R_6$ es hidrógeno, y

$R_7$ es alquilo $C_1$-$C_6$ o alcanoilo $C_1$-$C_6$, cada uno de los cuales se sustituye opcionalmente con 1, 2 o 3 grupos que son independientemente $NH_2$, NH(alquilo $C_1$-$C_6$), N(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$), OH, SH, ciclopropilo o alcoxi $C_1$-$C_4$

Realizacion A148a Compuestos de acuerdo con la realizacion A148, en la que

$R_7$ es alcanoilo $C_1$-$C_6$ opcionalmente sustituido con 1, 2 ó 3 grupos que son independientemente OH, ciclopropilo o $NH_2$

Realizacion A149 Compuestos de acuerdo con la realizacion A135, en la que

$X_a$ es hidrogeno,

$X_b$, $X_c$ o $X_d$ es $-C(O)NR_6R_7$ -(alquilo $C_1$-$C_6$)-$C(O)NR_6R_7$, $-NR_6R_7$, $NR_6R_7$-(alquilo $C_1$-$C_6$)- o $-CO_2$-alquil($C_1$-$C_6$), en el que

$R_6$ y $R_7$ son independientemente, en cada aparicion, H, alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$ carbonilo, OH, hidroxi $C_1$-$C_6$ alquilo, -alquil($C_1$-$C_4$)-$CO_2$-alquilo, piridilalquilo $C_1$-$C_6$, alcanoilo $C_1$-$C_6$, bencilo, fenilalcoxi $C_1$-$C_6$ o fenilalcanoilo $C_1$-$C_6$, en los que cada uno de los anteriormente mencionados no se

sustituye o se sustituye con 1, 2 ó 3 grupos que son independientemente halogeno, cicloalquilo $C_3$-$C_6$, alcoxi $C_1$-$C_6$, piperidinilalquilo $C_1$-$C_6$, morfolinilalquilo $C_1$-$C_6$, piperazinilalquilo $C_1$-$C_6$, OH, $NH_2$, NH(alquilo), N(alquil)(alquilo), -O-alcanoilo $C_1$-$C_4$, alquilo $C_1$-$C_4$, $CF_3$ u $OCF_3$, o

$R_6$, $R_7$ y el nitrógeno al cual se acoplan forman un anillo morfolinilo, piperidinilo, pirrolidinilo o piperazinilo opcionalmente sustituido con 1 ó 2 grupos que son independientemente alquilo $C_1$-$C_4$, alcoxi $C_1$-$C_4$ hidroxi, hidroxialquilo $C_1$-$C_4$ o halogeno, y

$X_e$ es hidrogeno, metilo, alcoxi $C_1$-$C_2$ o halógeno

Realizacion A150 Compuestos de acuerdo con la realización A149, en la que

$X_b$ es $-NR_6R_7$ o $NR_6R_7$-(alquilo $C_1$-$C_6$)-, $-C(O)NR_6R_7$ o $-CO_2$-alquil($C_1$-$C_6$), en el que

$R_6$ es hidrogeno o alquilo $C_1$-$C_4$,

$R_7$ es OH, alquilo $C_1$-$C_6$ o alcanoilo $C_1$-$C_6$, en el que el los grupos alquilo y alcanoilo se sustituyen con 1, 2 o 3 grupos que son independientemente $NH_2$, NH(alquilo $C_1$-$C_6$), N(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$), cicloalquilo $C_3$-$C_6$, OH o alcoxi $C_1$-$C_4$

Realizacion A151 Compuestos de acuerdo con la realizacion A137, en la que

$X_a$ es halógeno,

$X_b$ es $-NR_6R_7$ o $NR_6R_7$-(alquilo $C_1$-$C_6$)-, $-C(O)NR_6R_7$ o $-CO_2$-alquil($C_1$-$C_6$),

$X_c$ es $-NR_6R_7$, $NR_6R_7$-(alquilo $C_1$-$C_6$)-, $-C(O)NR_6R_7$, halógeno, $-CO_2$-alquil($C_1$-$C_6$), $NH_2$, NH(alquilo $C_1$-$C_6$), N(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$), $-SO_2NH_2$, $-SO_2NH$(alquilo $C_1$-$C_6$), $-SO_2N$(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$) o piperazinilo, en el que el grupo piperazinilo se sustituye opcionalmente con 1 ó 2 grupos que son independientemente alquilo $C_1$-$C_4$,

alcoxi $C_1$-$C_4$, hidroxi, hidroxialquilo $C_1$-$C_4$ o halogeno,

$X_d$ es hidrogeno,

$X_e$ es H, metilo, $NH_2$, NH(alquilo $C_1$-$C_6$) o N(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$)

Realización A152 Compuestos de acuerdo con la realización A135, en la que

$X_1$, $X_2$, $X_a$, $X_b$, $X_c$, $X_d$, y $X_e$ se seleccionan independientemente entre H, OH, halogeno, $CF_3$, alquilo, $OCF_3$, piridilo, piridazinilo, pirimidilo, pirazinilo, tienilo, furilo, pirrolilo, piperidinilo, piperazinilo o cicloalquilo $C_3$-$C_7$, en los que cada uno de los anteriormente mencionados se sustituye opcionalmente con -$NR_6R_7$, -C(O)$NR_6R_7$, $NR_6R_7$-(alquilo $C_1$-$C_6$)-, alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$ o halógeno

Realizacion A153 Compuestos de acuerdo con la realización A152, en la que al menos tres de $X_1$, $X_2$, $X_a$, $X_b$, $X_c$, $X_d$, y $X_e$ son hidrógeno

Realización A154 Un compuesto de la formula




o una sal farmaceuticamente aceptable del mismo, en la que

$R_1$ es alcanoilo, halógeno, arilalcanoilo, arilalquilo, alcoxialquilo, hidroxialquilo o carboxaldehido, en el que

la porcion arilo del arilalquilo y arilalcanoilo no se sustituye o se sustituye con 1, 2, 3, 4 o 5 grupos que son independientemente halógeno, alquilo $C_1$-$C_4$, alcoxi $C_1$-$C_4$, nitro, CN, haloalquilo, haloalcoxi o $CO_2H$,

la porcion alquilo de los grupos hidroxialquilo, arilalquilo, alcanoilo, alcoxialquilo y arilalcanoilo no se sustituye o se sustituye con 1, 2 o 3 grupos que son

independientemente halogeno, metoxi, etoxi o espirociclopropilo,

$R_2$ es arilalcoxi, ariloxi, feniloxialquil($C_1$-$C_6$), OH, halógeno, ariltioalcoxi, alcoxi, -OC(O)NH($CH_2$)$_n$arilo, -OC(O)N(alquil)($CH_2$)$_n$arilo, alquilo, alcoxialcoxi, dialquilamino, piridilo, pirimidilo, piridazilo, pirazolilo, imidazolilo, pirrolilo, tetrahidroquinolinilo, tetrahidroisoquinolirilo, tetrazolilo, pirazinilo, bencimidazolilo, triazinilo, tetrahidrofurilo, piperidinilo, hexahidropirimidinilo, tiazolilo, tienilo o $CO_2H$, en el que

n es 0, 1, 2, 3, 4, 5 ó 6,

la porcion arilo del arilalcoxi, ariloxi, ariltioalcoxi, -OC(O)NH($CH_2$)$_n$arilo y -OC(O)N(alquil)($CH_2$)$_n$arilo o los grupos heteroarilo y heterocicloalquilo no se sustituyen o se sustituyen con 1, 2, 3, 4 ó 5 grupos que son independientemente halogeno, -alquil($C_1$-$C_6$)-N(R)-$CO_2R_{30}$, haloalquilo, heteroarilo, heteroarilalquilo, $NR_6R_7$, $NR_6R_7$-(alquilo $C_1$-$C_6$)-, -OC(O)$NR_6R_7$, en los que

$R_6$ y $R_7$ son independientemente, en cada aparicion, H, alquilo, alcoxi, alcanoilo, arilalquilo, arilalcoxi, arilalcanoilo, en los que cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2 ó 3 grupos que son independientemente OH, SH, cicloalquilo $C_3$-$C_6$ alcoxi, alquilo, haloalquilo o haloalcoxi, o

$R_6$, $R_7$ y el nitrógeno al cual se acoplan forman un anillo morfolinilo, tiomorfolinilo, tiomorfolinilo S-óxido, tiomorfolinilo S,S-dióxido, piperidinilo o piperazinilo opcionalmente sustituido con 1 ó 2 grupos que son independientemente alquilo $C_1$-$C_4$, alcoxicarbonilo, hidroxilo, hidroxialquilo o halogeno,

R, en cada aparición, es independientemente H o

alquilo $C_1$-$C_6$,

$R_{30}$ es alquilo $C_1$-$C_6$ opcionalmente sustituido con 1 o 2 grupos que son independientemente OH, SH, halogeno, amino, monoalquilamino, dialquilamino o cicloalquilo $C_3$-$C_6$,

$R_3$ es halógeno, arilalcoxicarbonilo, ariloxicarbonilo, arilalquilo, $-OC(O)NH(CH_2)_n$arilo, arilalcoxi, $-OC(O)N(alquil)(CH_2)_n$arilo, ariloxi, ariltio, tioalcoxi, ariltioalcoxi, alquenilo, $-NR_6R_7$, $NR_6R_7$-(alquilo $C_1$-$C_6$) o alquilo, en el que

la porcion arilo del arilalcoxicarbonilo, ariloxicarbonilo, arilalquilo, $-OC(O)NH(CH_2)_n$arilo, arilalcoxi, $-OC(O)N(alquil)(CH_2)_n$arilo y ariltioalcoxi no esta sustituida o esta sustituida con 1, 2 o 3 grupos que son independientemente halógeno, alcoxi, alquilo, haloalquilo o haloalcoxi,

en los que n es 0, 1, 2, 3, 4, 5 ó 6, o

$R_4$ es H, alquilo opcionalmente sustituido con un grupo seleccionado entre $CO_2H$, $-CO_2$-alquil($C_1$-$C_6$), $-C(O)NRR$, $-N(R_{30})C(O)NRR$, $-N(R_{30})C(O)$-alcoxi($C_1$-$C_6$) y $-NR_6R_7$, arilalcoxi, arilalquilo, hidroxialquilo, haloalquilo, alcoxi, alcoxialquilo o alcoxialcoxi, en el que

la porcion arilo del arilalcoxi, arilalquilo no se sustituye o se sustituye con 1, 2, 3, 4 o 5 grupos que son independientemente halogeno, hidroxi, alcoxi, alquilo, nitro, haloalquilo o haloalcoxi, y

$R_5$ es arilalquilo, alquilo, arilo, alcoxi, heterocicloalquilalquilo, heteroarilalquilo, ariltioalquilo, heterocicloalquilo o heteroarilo, en el que

cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2, 3, 4 ó 5 grupos que son independientemente alquilo, halógeno, alcoxi, arilalcoxi, tioalcoxi, alcoxicarbonilo, arilalcoxicarbonilo, $CO_2H$, CN, OH, amidino-oxima, $NR_6R_7$, $NR_6R_7$-(alquilo $C_1$-$C_6$)-, $-C(O)NR_6R_7$,

amidino, haloalquilo o haloalcoxi

Realización A160 Compuestos de acuerdo con la realizacion A154, en la que

$R_1$ es haloçeno, alcanoil($C_1$-$C_6$), fenilalcanoil($C_1$-$C_6$), naftilalcanoil($C_1$-$C_6$), naftilalquil($C_1$-$C_6$), fenilalquil($C_1$-$C_6$), alcoxialquilo, hidroxialquilo o carboxaldehido, en el que

las porciones fenilo y naftilo de los anteriormente mencionados no se sustituyen o se sustituyen con 1, 2, 3, 4 o 5 grupos que son independientemente halógeno, alquilo $C_1$-$C_4$, alcoxi $C_1$-$C_4$, nitro, CN, $CF_3$, $OCF_3$ o $CO_2H$,

la porción alquilo de los grupos anteriormente mencionados no se sustituye o se sustituye con 1, 2 ó 3 grupos que son independientemente halogeno, metoxi o etoxi

$R_2$ es fenilalcoxi, ariloxi, feniloxialquil($C_1$-$C_6$), OH, halogeno, feniltioalcoxi, alcoxi, alquilo, alcoxialcoxi, -OC(O)NH$(CH_2)_n$fenilo, -OC(O)N(alquil)$(CH_2)_n$fenilo, piridilo, pirimidilo, piridazilo, pirazolilo o tienilo, en el que

n es 0, 1, 2, 3 o 4, y

los grupos anteriormente mencionados no se sustituyen o se sustituyen con 1, 2, 3, 4 ó 5 grupos que son independientemente halogeno, -alquil($C_1$-$C_6$)-N(R)-$CO_2R_{30}$, haloalquil($C_1$-$C_4$) o tienilo

$R_3$ es halogeno, fenilalcoxicarbonilo, feniloxicarbonilo, fenilalquil($C_1$-$C_6$), fenilalcoxi, feniloxi, feniltio, tioalcoxi, ariltioalcoxi, alquenil($C_2$-$C_6$), $NR_6R_7$, $NR_6R_7$-(alquilo $C_1$-$C_6$)- o alquilo, en el que

las porciones fenilo, naftilo y arilo del arilalcoxicarbonilo, ariloxicarbonilo, arilalquilo, -OC(O)NH$(CH_2)_n$arilo, ariltioalcoxi, arilalcoxi y-OC(O)N(alquil)$(CH_2)_n$arilo no se sustituyen o se sustituyen con 1, 2 ó 3 grupos que son independientemente halógeno, alcoxi, alquilo, $CF_3$ u $OCF_3$,

en los que n es 0, 1, 2, 3, 4, 5 o 6, o

$R_4$ es H, alquilo ($C_1$-$C_6$) sustituido con un grupo que es $CO_2H$, $-CO_2$-alquil($C_1$-$C_6$), $-C(O)NRR$, $-N(R_{30})C(O)NRR$, $-N(R_{30})C(O)$-alcoxi($C_1$-$C_6$) o $-NR_6R_7$, fenilalcoxi, fenilalquil($C_1$-$C_6$), hidroxialquilo, haloalquilo, alcoxialquilo o alcoxialcoxi, en el que

la porcion fenilo de los grupos anteriormente mencionados no se sustituye o se sustituye con 1, 2, 3, 4 o 5 grupos que son independientemente halogeno, hidroxi, alcoxi, alquilo, nitro, $CF_3$ u $OCF_3$

$R_5$ es fenilalquil($C_1$-$C_6$), alquil($C_1$-$C_6$), fenilo, naftilo, piridilo, alcoxi($C_1$-$C_6$), piperidinilalquil($C_1$-$C_6$), pirrolilalquil($C_1$-$C_6$), imidazolidinilalquil($C_1$-$C_6$), pirazolilalquil($C_1$-$C_6$), imidazolilalquil($C_1$-$C_6$), tetrahidropiridinilalquil($C_1$-$C_6$), tienilalquil($C_1$-$C_6$), feniltioalquil($C_1$-$C_6$) o piridilalquil($C_1$-$C_6$), en el que cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2 o 3 grupos que son independientemente alquil($C_1$-$C_4$), fluoro, cloro, bromo, alcoxi($C_1$-$C_4$), fenilalcoxi($C_1$-$C_4$), tioalcoxi($C_1$-$C_4$), alcoxi ($C_1$-$C_4$)carbonilo, fenilalcoxi($C_1$-$C_4$)carbonilo, $CO_2H$, CN, amidino-oxima, $NR_6R_7$, $NR_6R_7$-(alquilo $C_1$-$C_6$)-, $-C(O)NR_6R_7$, amidino, $CF_3$, $-CF_2CF_3$, $OCF_3$ u $OCF_2CF_3$

Realizacion A161 Compuestos de acuerdo con la realización A160, en la que

$R_1$ es halógeno, alcanoil($C_1$-$C_4$), fenilalcanoil($C_1$-$C_4$), bencilo, fenetilo, fenpropilo, hidroxialquilo o carboxaldehido, en el que

los grupos fenilo anteriormente mencionados no se sustituyen o se sustituyen con 1, 2 ó 3 grupos que son independientemente halogeno, alquilo $C_1$-$C_4$, alcoxi $C_1$-$C_4$, nitro, CN, $CF_3$, $OCF_3$ o $CO_2H$

la porcion alquilo de los grupos anteriormente

mencionados no se sustituye o se sustituye con 1, 2 o 3 grupos que son independientemente halógeno, metoxi o etoxi,

$R_2$ es benciloxi, fenetiloxi, fenpropiloxi, fenbutiloxi, feniloxi, feniloxialquil($C_1$-$C_6$), OH, halogeno, feniltioalcoxi, alcoxi, alquilo, alcoxialcoxi, en el que

n es 0, 1, 2, 3 ó 4 y

los grupos anteriormente mencionados no se sustituyen o se sustituyen con 1, 2 ó 3 grupos que son independientemente halogeno, -alquil($C_1$-$C_6$)-N(R)-$CO_2R_{30}$, haloalquil($C_1$-$C_4$) o tienilo,

$R_3$ es halógeno, fenilalcoxicarbonilo, feniloxicarbonilo, fenilalquil($C_1$-$C_6$), fenilalcoxi, feniloxi, feniltio, tioalcoxi, feniltioalcoxi, alquenil($C_2$-$C_6$), $NR_6R_7$, $NR_6R_7$ alquilo $C_1$-$C_6$ o alquilo, en el que

los grupos fenilo anteriormente mencionados no se sustituyen o se sustituyen con 1, 2 ó 3 grupos que son independientemente halogeno, alcoxi, alquil($C_1$-$C_4$), $CF_3$ u $OCF_3$

$R_4$ es H, alquilo ($C_1$-$C_6$) sustituido con un grupo que es $CO_2H$, -$CO_2$-alquil($C_1$-$C_6$), -C(O)NRR, -N($R_{30}$)C(O)NRR, -N($R_{30}$)C(O)-alcoxi($C_1$-$C_6$) o -$NR_6R_7$, fenilalcoxi, bencilo, fenetilo, hidroxialquilo, haloalquilo, alcoxialquilo o alcoxialcoxi, en el que

la porción fenilo de los grupos anteriormente mencionados no se sustituye o se sustituye con 1, 2 o 3 grupos que son independientemente halogeno, hidroxi, alcoxi($C_1$-$C_4$), alquil($C_1$-$C_4$), nitro, $CF_3$, u $OCF_3$

$R_5$ es bencilo, fenetilo, fenpropilo, fenbutilo, alquil($C_1$-$C_6$), fenilo o piridilo, en el que cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2 ó 3 grupos que son independientemente alquil($C_1$-$C_4$), fluoro, cloro, bromo, alcoxi($C_1$-$C_4$), fenilalcoxi($C_1$-$C_4$), tioalcoxi($C_1$-$C_4$, alcoxi($C_1$-$C_4$)carbonilo, $CO_2H$, CN,

amidino-oxima, $NR_6R_7$, $NR_6R_7$-(alquilo $C_1$-$C_6$)-, -C(O)$NR_6R_7$, amidino, $CF_3$ u $OCF_3$

Realizacion A162 Compuestos de acuerdo con la realización A161, en la que

$R_1$ es bromo, fenilalcanoil($C_1$-$C_4$), bencilo, fenetilo, fenpropilo, hidroxialquilo o carboxaldehido, en el que

los grupos fenilo anteriormente mencionados no se sustituyen o se sustituyen con 1, 2 o 3 grupos que son independientemente halogeno, alquilo $C_1$-$C_4$, alcoxi $C_1$-$C_4$, nitro, CN, $CF_3$, $OCF_3$ o $CO_2H$,

$R_2$ es benciloxi, fenetiloxi, fenpropiloxi, fenbutiloxi, feniloxi, feniloxialquil($C_1$-$C_6$), OH, halogeno o feniltioalcoxi, en el que

n es 0, 1, 2, 3 o 4, y

los grupos anteriormente mencionados no se sustituyen o se sustituyen con 1, 2 ó 3 grupos que son independientemente halogeno, -alquil($C_1$-$C_6$)-N(R)-$CO_2R_{30}$, haloalquil($C_1$-$C_4$) o t enilo,

$R_3$ es bromo, fenilalcoxicarbonilo, feniloxicarbonilo, fenilalquil($C_1$-$C_6$), fenilalcoxi, feniloxi, feniltio, tioalcoxi, feniltioalcoxi, alquenil($C_2$-$C_6$), $NR_6R_7$, $NR_6R_7$ alquilo $C_1$-$C_6$ o alqui o, en el que

los grupos fenilo anteriormente mencionados no se sustituyen o se sustituyen con 1, 2 o 3 grupos que son independientemente halogeno, alcoxi, alquil($C_1$-$C_4$), $CF_3$ u $OCF_3$

$R_4$ es H, alquilo ($C_1$-$C_6$) sustituido con un grupo que es $CO_2H$, -$CO_2$-alquil($C_1$-$C_6$), -C(O)NRR, -N($R_{30}$)C(O)NRR, -N($R_{30}$)C(O)-alcoxi($C_1$-$C_6$) o -$NR_6R_7$, fenilalcoxi, bencilo o fenetilo, en el que

la porcion fenilo de los grupos anteriormente mencionados no se sustituye o se sustituye con 1, 2 ó 3 grupos que son independientemente halógeno, hidroxi,

alcoxi($C_1$-$C_4$), alquil($C_1$-$C_4$), nitro, $CF_3$ u $OCF_3$

$R_5$ es bencilo, fenetilo, fenpropilo, alquil($C_1$-$C_6$), fenilo o piridilo, en el que cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2 o 3 grupos que son independientemente alquil($C_1$-$C_4$), fluoro, cloro, bromo, alcoxi($C_1$-$C_4$), $CO_2H$, CN, amidino-oxima, amidino, $CF_3$, $OCF_3$ $NR_6R_7$, $NR_6R_7$-(alquilo $C_1$-$C_6$)- o $-C(O)NR_6R_7$ en los que

$R_6$ y $R_7$ son independientemente hidrogeno, OH, alcoxi $C_1$-$C_4$, alcanoilo $C_1$-$C_6$ o alquilo $C_1$-$C_6$, en los que cada uno de los anteriormente mencionados se sustituye opcionalmente con 1 o 2 grupos que son independientemente OH, $NH_2$, cicloalquilo $C_3$-$C_6$ o halogeno, o

$R_6$, $R_7$ y el nitrogeno al cual se acoplan forman un anillo morfolinilo piperidinilo, pirrolidinilo o piperazinilo opcionalmente sustituido con 1 ó 2 grupos que son independientemente alquilo $C_1$-$C_4$, alcoxi $C_1$-$C_4$ hidroxi, hidroxialquilo $C_1$-$C_4$ o halogeno

Realización A163 Compuestos de la fórmula




o sus sales farmaceuticamente aceptables, en la que

$R_1$ es H, halogeno, alquilo, carboxaldehido, hidroxialquilo, arilalcoxi, arilalquilo, CN, alcanoilo, alcoxi, alcoxialquilc o arilalcanoilo,

en el que la porción arilo del arilalcoxi, arilalquilo y arilalcanoilo no se sustituye o se sustituye con 1, 2, 3, 4 o 5 grupos que son independientemente halogeno, alquilo $C_1$-$C_4$, alcoxi $C_1$-$C_4$, nitro, CN, haloalquilo, haloalcoxi o $CO_2H$,

en el que la porcion alquilo de los grupos alquilo,

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hidroxialquilo, arilalcoxi, arilalquilo, alcanoilo, alcoxi, alcoxialquilo y arilalcanoilo no se sustituye o se sustituye con 1, 2 o 3 grupos que son independientemente halogeno, metoxi, etcxi o espirociclopropilo,

$R_2$ es H, ariltio, $-OC(O)NH(CH_2)_n$arilo, arilalquilo, $-OC(O)N(alquil)(CH_2)_n$arilo o ariltioalcoxi, en el que n es 1, 2, 3, 4 o 5, en el que los grupos arilo se sustituyen opcionalmente con 1, 2, 3, 4 ó 5 grupos que son independientemente halogeno, $-alquil(C_1-C_6)-N(R)-CO_2R_{30}$, alcoxi $C_1-C_4$, alquilo $C_1-C_4$, $CF_3$ u $OCF_3$,

R, en cada aparicion, es independientemente H o alquilo $C_1-C_6$,

$R_{30}$ es alquilo $C-C_6$ opcionalmente sustituido con 1 o 2 grupos que son independientemente OH, SH, halogeno, amino, monoalquilamino, dialquilamino o cicloalquilo $C_3-C_6$,

$R_3$ es halogeno, alcoxicarbonilo, arilalcoxicarbonilo, ariloxicarbonilo, arilalquilo, $-OC(O)NH(CH_2)_n$arilo, arilalcoxi, $-OC(O)N(alquil)(CH_2)_n$arilo, ariloxi, ariltio, tioalcoxi, ariltioalcoxi, alquenilo, $-NR_6R_7$ alquilo $C_1-C_6$, $NR_6R_7$ o alquilo, en e que

la porcion arilo del arilalcoxicarbonilo, ariloxicarbonilo, arilalquilo, $-OC(O)NH(CH_2)_n$arilo, arilalcoxi, $-OC(O)N(alquil)(CH_2)_n$arilo y ariltioalcoxi no esta sustituida o esta sustituida con 1, 2 ó 3 grupos que son independientemente halogeno, alcoxi, alquilo, haloalquilo o haloalcoxi,

en los que n es 0, 1, 2, 3, 4, 5 ó 6, o

$R_4$ es H, alquilo sustituido con un grupo que es $CO_2H$, $-CO_2-alquil(C_1-C_6)$, $-C(O)NRR$, $-N(R_{30})C(O)NRR$, $-N(R_{30})C(O)-alcoxi(C_1-C_6)$ o $-NR_6R_7$, arilalcoxi, arilalquilo, hidroxialquilo, haloalquilo, alcoxi, alcoxialquilo o alcoxialcoxi, en el que

la porción arilo del arilalcoxi, arilalquilo no se

sustituye o se sustituye con 1, 2, 3, 4 ó 5 grupos que son independientemente halogeno, hidroxi, alcoxi, alquilo, nitro, haloalquilo o haloalcoxi, y

$R_5$ es arilalquilo, alquilo, arilo, alcoxi, heterocicloalquilalquilo, heteroarilalquilo, ariltioalquilo, heterocicloalquilo o heteroarilo, en el que cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2, 3, 4 ó 5 grupos que son independientemente alquilo, halogeno, alcoxi, arilalcoxi, tioalcoxi, alcoxicarbonilo, arilalcoxicarbonilo, $CO_2H$, CN, amidino-oxima, $NR_6R_7$, $NR_6R_7$-(alquilo $C_1$-$C_6$)-, $-C(O)NR_6R_7$, amidino, haloalquilo o haloalcoxi, en los que

$R_6$ y $R_7$ son independientemente, en cada aparición, H, alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$ carbonilo, OH, hidroxi $C_1$-$C_6$ alquilo, -alquil($C_1$-$C_4$)-$CO_2$-alquilo, piridilalquilo $C_1$-$C_6$, alcanoilo $C_1$-$C_6$, bencilo, fenilalcoxi $C_1$-$C_6$ o fenilalcanoilo $C_1$-$C_6$, en los que cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2 ó 3 grupos que son independientemente halogeno, cicloalquilo $C_3$-$C_6$, alcoxi $C_1$-$C_6$, piperidinilalquilo $C_1$-$C_6$, morfolinilalquilo $C_1$-$C_6$, piperazinilalquilo $C_1$-$C_6$, OH, SH, $NH_2$, NH(alquilo), N(alquil)(alquilo), -O-alcanoilo $C_1$-$C_4$, alquilo $C_1$-$C_4$, $CF_3$ u $OCF_3$, o

$R_6$, $R_7$ y el nitrogeno al cual se acoplan forman un anillo morfolinilo, tiomorfolinilo, piperidinilo, pirrolidinilo o piperazinilo opcionalmente sustituido con 1 o 2 grupos que son independientemente alquilo $C_1$-$C_4$, alcoxi $C_1$-$C_4$ hidroxi, hidroxialquilo $C_1$-$C_4$ o halógeno

Realización A168 Compuestos de acuerdo con la realizacion A163, en la que

$R_5$ es bencilo, fenetilo, fenpropilo, fenbutilo, alquilo, fenilo alcoxi, piridilalquil($C_1$-$C_6$),

feniltioalquil($C_1$-$C_6$), pirrolilo, pirrolilalquil($C_1$-$C_6$) o piridilo, en el que cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2 o 3 grupos que son independientemente alquil($C_1$-$C_6$), halógeno, alcoxi($C_1$-$C_6$), fenilalcoxi($C_1$-$C_6$), tio($C_1$-$C_6$)alcoxi, alcoxicarbonilo, $CO_2H$, CN, amidino-oxima, amidino, $CF_3$ u $OCF_3$

Realización A169 Compuestos de acuerdo con la realización A163, en la que

$R_1$ es H, Cl, Br, alquil($C_1$-$C_6$), carboxaldehido, hidroxialquil($C_1$-$C_6$),

en el que la porcion alquilo de los anteriormente mencionados no se sustituye o se sustituye con 1, 2 o 3 grupos que son independientemente halógeno, metoxi o etoxi

$R_2$ es H, feniltio, -OC(O)NH$(CH_2)_n$arilo, fenilalquilo, -OC(O)N(alquil)$(CH_2)_n$arilo o feniltioalcoxi($C_1$-$C_6$), en el que n es 1, 2, 3 o 4

en el que los grupos arilo se sustituyen opcionalmente con 1, 2, 3, 4 ó 5 grupos que son independientemente halogeno, -alquil($C_1$-$C_6$)-N(R)-$CO_2R_{30}$, alcoxi $C_1$-$C_4$, alquilo $C_1$-$C_4$, $CF_3$ u $OCF_3$,

$R_3$ es bromo, alcoxicarbonilo, fenialcoxicarbonilo, feniloxicarbonilo, fenilalquilo, fenilalcoxi, feniloxi, feniltio, tioalcoxi feniltioalcoxi, alquenilo, $NR_6R_7$ o alquilo, en el que

la porción fenilo de los anteriormente mencionados no se sustituye o se sustituye con 1, 2 o 3 grupos que son independientemente halógeno, alcoxi($C_1$-$C_4$), alquil($C_1$-$C_4$), haloalquil($C_1$-$C_4$) o haloalcoxi($C_1$-$C_4$),

en los que n es 0, 1, 2, 3 o 4,

$R_4$ es H, alquilo sustituido con un grupo que es $CO_2H$, -$CO_2$-alquil($C_1$-$C_6$), -C(O)NRR, -N($R_{30}$)C(O)NRR, -N($R_{30}$)C(O)-alcoxi($C_1$-$C_6$) o -$NR_6R_7$, fenilalcoxi, fenilalquilo,

hidroxialquilo, haloalquilo, alcoxi, alcoxialquilo, o en el que

la porcion fenilo del fenilalcoxi, fenilalquilo no se sustituye o se sustituye con 1, 2 ó 3 grupos que son independientemente halogeno, hidroxi, alcoxi, alquilo, nitro, haloalquilo o haloalcoxi

$R_5$ es bencilo, fenetilo, fenpropilo, fenbutilo, alquilo, fenilo, feniltioalquil($C_1$-$C_6$), pirrolilo o piridilo, en el que cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2 o 3 grupos que son independientemente alquil($C_1$-$C_6$), halógeno, alcoxi($C_1$-$C_6$), benciloxi, tioalcoxi($C_1$-$C_6$), alcoxicarbonilo, $CO_2H$, CN, amidino-oxima, amidino, $CF_3$ u $OCF_3$,

$R_6$ y $R_7$ son independientemente hidrógeno, OH, alcoxi $C_1$-$C_4$, alcanoilo $C_1$-$C_6$ o alquilo $C_1$-$C_6$, en los que cada uno de los anteriormente mencionados se sustituye opcionalmente con 1 o 2 grupos que son independientemente OH, $NH_2$, cicloalquilo $C_3$-$C_6$ o halógeno, o

$R_6$, $R_7$ y el nitrogeno al cual se acoplan forman un anillo morfolinilo, piperidinilo, pirrolidinilo o piperazinilo opcionalmente sustituido con 1 o 2 grupos que son independientemente alquilo $C_1$-$C_4$, alcoxi $C_1$-$C_4$ hidroxi, hidroxialquilo $C_1$-$C_4$ o halogeno

Realizacion A170 Compuestos de acuerdo con la realizacion 1




o una sal farmaceuticamente aceptable de los mismos, en la que

$R_1$ es H, halogeno, alquilo, carboxaldehido, hidroxialquilo, arilalcoxi, arilalquilo, CN, alcanoilo,

alcoxi, alcoxialquilc o arilalcanoilo,

en el que la porcion arilo del arilalcoxi, arilalquilo y arilalcanoilo no se sustituye o se sustituye con 1, 2, 3, 4 o 5 grupos que son independientemente halógeno, alquilo $C_1$-$C_4$, alcoxi $C_1$-$C_4$, nitro, CN, haloalquilo, haloalcoxi o $CO_2H$,

en los que la porción alquilo de los grupos alquilo, hidroxialquilo, arilalcoxi, arilalquilo, alcanoilo, alcoxi, alcoxialquilo y arilalcanoilo no se sustituye o se sustituye con 1, 2 o 3 grupos que son independientemente halogeno, metoxi, etoxi o espirociclopropilo,

$R_2$ es arilalcoxi, ariloxi, ariloxialquilo, OH, halógeno, ariltioalcoxi, alcoxi, -OC(O)NH$(CH_2)_n$arilo, -OC(O)N(alquil)$(CH_2)_n$arilo, alquilo, alcoxialcoxi, dialquilamino, o $CO_2H$, en el que

n es 0, 1, 2, 3, 4, 5 ó 6,

la porcion arilo del arilalcoxi, ariloxi, ariltioalcoxi, -OC(O)NH$(CH_2)_n$arilo y -OC(O)N(alquil)$(CH_2)_n$arilo o los grupos heteroarilo y heterocicloalquilo no se sustituyen o se sustituyen con 1, 2, 3, 4 o 5 grupos que son independientemente halogeno, -alquil($C_1$-$C_6$)-N(R)-$CO_2R_{30}$, haloalquilo, heteroarilo, heteroarilalquilo, $NR_6R_7$, $NR_6R_7$-(alquilo $C_1$-$C_6$)-, -OC(O)$NR_6R_7$, en los que

$R_6$ y $R_7$ son independientemente, en cada aparicion, H, alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$ carbonilo, OH, hidroxi $C_1$-$C_6$ alquilo, -alquil($C_1$-$C_4$)-$CO_2$-alquilo, piridilalquilo $C_1$-$C_6$, alcanoilo $C_1$-$C_6$, bencilo, fenilalcoxi $C_1$-$C_6$ o fenilalcanoilo $C_1$-$C_6$, en los que cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2 ó 3 grupos que son independientemente halógeno, cicloalquilo $C_3$-$C_6$, alcoxi $C_1$-$C_6$, piperidinilalquilo $C_1$-$C_6$, morfolinilalquilo $C_1$-$C_6$,

piperazinilalquilo $C_1$-$C_6$, OH, SH, $NH_2$, NH(alquilo), N(alquil)(alquilo), -O-alcanoilo $C_1$-$C_4$, alquilo $C_1$-$C_4$, $CF_3$ u $OCF_3$, o

$R_6$, $R_7$ y el nitrogeno al cual se acoplan forman un anillo morfolinilo, tiomorfolinilo, piperidinilo, pirrolidinilo o piperazinilo opcionalmente sustituido con 1 o 2 grupos que son independientemente alquilo $C_1$-$C_4$, alcoxi $C_1$-$C_4$ hidroxi, hidroxialquilo $C_1$-$C_4$ o halógeno,

R, en cada aparicion, es independientemente H o alquilo $C_1$-$C_6$,

$R_{30}$ es alquilo $C_1$-$C_6$ opcionalmente sustituido con 1 o 2 grupos que son independientemente OH, SH, halógeno, amino, monoalquilamino, dialquilamino o cicloalquilo $C_3$-$C_6$,

$R_3$ es halógeno, alcoxicarbonilo, arilalcoxicarbonilo, ariloxicarbonilo, arilalquilo, $-OC(O)NH(CH_2)_n$arilo, arilalcoxi, $-OC(O)N(alquil)(CH_2)_n$arilo, ariloxi, ariltio, tioalcoxi, ariltioalcoxi, alquenilo, $-NR_6R_7$, alquilo $C_1$-$C_6$, $NR_6R_7$ o alquilo, en el que

la porción arilo del arilalcoxicarbonilo, ariloxicarbonilo, arilalquilo, $-OC(O)NH(CH_2)_n$arilo, arilalcoxi, $-OC(O)N(alquil)(CH_2)_n$arilo y ariltioalcoxi no esta sustituida o esta sustituida con 1, 2 ó 3 grupos que son independientemente halogeno, alcoxi, alquilo, haloalquilo o haloalcoxi,

en los que n es 0, 1, 2, 3, 4, 5 ó 6, o

$R_4$ es H, alquilo sustituido con un grupo que es $CO_2H$, $-CO_2$-alquil($C_1$-$C_6$), $-C(O)NRR$, $-N(R_{30})C(O)NRR$, $-N(R_{30})C(O)$-alcoxi($C_1$-$C_6$) o $-NR_6R_7$, arilalcoxi, arilalquilo, hidroxialquilo, haloalquilo, alcoxi, alcoxialquilo o alcoxialcoxi, en el que

la porción arilo del arilalcoxi, arilalquilo no se sustituye o se sustituye con 1, 2, 3, 4 o 5 grupos que son independientemente halogeno, hidroxi, alcoxi, alquilo,

nitro, haloalquilo o haloalcoxi, y

$R_5$ es arilo, heterocicloalquilalquilo, heteroarilalquilo, ariltioalquilo, heterocicloalquilo o heteroarilo, en el que cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2, 3, 4 o 5 grupos que son independientemente alquilo, halógeno, alcoxi, arilalcoxi, tioalcoxi, alcoxicarbonilo, arilalcoxicarbonilo, $CO_2H$, CN, amidino-oxima, $NR_6R_7$, $NR_6R_7$-(alquilo $C_1$-$C_6$)-, $-C(O)NR_6R_7$, amidino, haloalquilo o haloalcoxi

Realización A173 Compuestos de acuerdo con la realizacion A170, en la que

$R_1$ es H, halogeno, alquilo, carboxaldehido, hidroxialquilo, benciloxi, feneciloxi, fenpropiloxi, bencilo, fenetilo, fenpropilo, CN, alcanoilo, alcoxi o fenilC(O)-, fenil$CH_2$C(O)- o fenil$CH_2CH_2$C(O),

en el que los grupos fenilo anteriormente mencionados no se sustituyen o se sustituyen con 1, 2 o 3 grupos que son independientemente halógeno, alquilo $C_1$-$C_4$, alcoxi $C_1$-$C_4$, nitro, CN, $CF_3$, $CCF_3$ o $CO_2H$,

en los que los grupos alquilo anteriormente mencionados no se sustituyen o se sustituyen con 1, 2 o 3 grupos que son independientemente halogeno, metoxi o etoxi,

$R_2$ es benciloxi, feneciloxi, fenpropiloxi, feniloxi, feniloxialquil($C_1$-$C_6$), OH, halógeno, feniltioalcoxi, alquilo, alcoxi, $-OC(O)NH(CH_2)_n$fenilo, $-OC(O)N$(alquil)$(CH_2)_n$fenilo, dialquilamino o $CO_2H$, en el que

n es 0, 1, 2, 3 ó 4,

los grupos arilo anteriormente mencionados no se sustituyen o se sustituyen con 1, 2, 3, 4 o 5 grupos que son independientemente halogeno, -alquil($C_1$-$C_6$)-N(R)-$CO_2R_{30}$, $CF_3$, piridilo, tienilo, $NR_6R_7$ o $NR_6R_7$-(alquilo $C_1$-$C_6$)-, en los que

$R_6$ y $R_7$ son independientemente, en cada aparición, H, alquilo, alcanoilo, bencilo o fenilC(O)-, en los que la porcion fenilo de los anteriormente mencionados no se sustituye o se sustituye con 1, 2 ó 3 grupos que son independientemente halogeno, OH, cicloalquilo $C_3$-$C_6$, alcoxi, alquilo, $CF_3$ u $OCF_3$

$R_3$ es halogeno, alcoxicarbonilo, fenilalcoxicarbonilo, feniloxicarbonilo, fenilalquilo, $-OC(O)NH(CH_2)_n$fenilo, fenilalcoxi, $-OC(O)N(alquil)(CH_2)_n$fenilo, feniloxi, feniltio, tioalcoxi, feniltioalcoxi, alquenilo, $NR_6R_7$ o alquilo, en el que

la porcion fenilo de los anteriormente mencionados no se sustituye o se sustituye con 1, 2 o 3 grupos que son independientemente halogeno, alcoxi, alquilo, haloalquilo o haloalcoxi,

en el que n es 0, 1, 2, 3 o 4,

$R_4$ es H, alquilo sustituido con un grupo que es $CO_2H$, $-CO_2$-alquil($C_1$-$C_6$), $-C(O)NRR$, $-N(R_{30})C(O)NRR$, $-N(R_{30})C(O)$-alcoxi($C_1$-$C_6$) o $-NR_6R_7$, fenilalcoxi, fenilalquilo, hidroxialquilo, haloalquilo, alcoxi, alcoxialquilo o alcoxialcoxi, en el que

la porcion fenilo de los anteriormente mencionados no se sustituye o se sustituye con 1, 2 o 3 grupos que son independientemente halogeno, hidroxi, alcoxi, alquilo, nitro, haloalquilo o haloalcoxi, y

$R_5$ es fenilo, naftilo, pirrolilalquilo, piperidinilalquilo piridinilalquilo, pirimidinilalquilo, feniltioalquilo, pirrolilo, piperidinilo, piridilo o tienilalquilo, en el que cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2 ó 3 grupos que son independientemente alquilo, halogeno, alcoxi, fenilalcoxi, tioalcoxi, alcoxicarbonilo, fenilalcoxicarbonilo, $CO_2H$, CN, amidino-oxima, $NR_6R_7$, $NR_6R_7$-

(alquilo $C_1$-$C_6$)-, -C(O)$NR_6R_7$, amidino, haloalquilo o haloalcoxi

Realización A174 Compuestos de acuerdo con la realización A173, en la que

$R_1$ es H, halogeno, alquilo, carboxaldehido, hidroxialquilo, benciloxi, feneciloxi, bencilo, fenetilo, CN, alcanoil($C_1$-$C_6$), alcoxi o fenilC(O)- o fenil$CH_2$C(O)-,

en el que los grupos fenilo anteriormente mencionados no se sustituyen o se sustituyen con 1, 2 ó 3 grupos que son independientemente halogeno, alquilo $C_1$-$C_4$, alcoxi $C_1$-$C_4$, nitro, CN, $CF_3$, $OCF_3$ o $CO_2H$,

$R_2$ es benciloxi feneciloxi, fenpropiloxi, feniloxi, feniloxialquil($C_1$-$C_6$), halógeno, feniltioalcoxi($C_1$-$C_4$), -OC(O)NH$(CH_2)_n$fenilo, -OC(O)N(alquil)$(CH_2)_n$fenilo o dialquilamino, en el que

n es 0, 1, 2, 3 o 4,

los grupos fenilo anteriormente mencionados no se sustituyen o se sustituyen con 1, 2 ó 3 grupos que son independientemente halogeno, $CF_3$, $NR_6R_7$ o $NR_6R_7$-(alquilo $C_1$-$C_6$)-, en los que

$R_6$ y $R_7$ son independientemente, en cada aparicion, H, alquil($C_1$-$C_6$), acetilo, bencilo o fenilC(O)-, en los que la porcion fenilo de los anteriormente mencionados no se sustituye o se sustituye con 1, 2 o 3 grupos que son independientemente halogeno, OH, ciclopropilo, alcoxi, alquilo, $CF_3$ u $OCF_3$,

$R_3$ es halógeno, alcoxicarbonilo, fenilalcoxicarbonilo, feniloxicarbonilo, fenilalquilo, fenilalcoxi, feniloxi, feniltio, tioalcoxi, feniltioalcoxi, alquenilo, $NR_6R_7$ o alquilo, en el que

la porcion fenilo de los anteriormente mencionados no se sustituye o se sustituye con 1, 2 o 3 grupos que son independientemente halogeno, alcoxi, alquilo, haloalquilo o

haloalcoxı,

en los que n es 0, 1, 2, 3 o 4,

$R_4$ es H, alquılc sustıtuıdo con un grupo que es $CO_2H$, $-CO_2$-alquıl($C_1$-$C_6$), -C(O)NRR, $-N(R_{30})C(O)NRR$, $-N(R_{30})C(O)$-alcoxı($C_1$-$C_6$) o $-NR_6R_7$, fenılalcoxı, fenılalquılo, hıdroxıalquılo, halɔalquılo, alcoxı, alcoxıalquılo o alcoxıalcoxı, en el que

la porcıon fenılo de los anterıormente mencıonados no se sustıtuye o se sustituye con 1, 2 o 3 grupos que son ındependıentemente halógeno, hıdroxı, alcoxı, alquılo, nıtro, haloalquılo o haloalcoxı, y

$R_5$ es fenılo, fenıltıoalquıl($C_1$-$C_4$), pırıdılo o tıenılalquıl($C_1$-$C_4$), en el que cada uno de los anterıormente mencıonados no se sustıtuye o se sustituye con 1, 2 o 3 grupos que son ındependıentemente alquıl($C_1$-$C_4$), fluoro, cloro, bromo, alcoxı($C_1$-$C_4$), CN, amıdıno-oxıma, amıdıno, $CF_3$ u $OCF_3$

Realızacıon A175 Compuestos de acuerdo con la realızacıon A174, en la que

$R_5$ se sustıtuye con al menos un grupo seleccıonado entre fluoro, cloro, bromo y metılo

En otro aspecto, la ınvencıón provee composıcıones farmacéutıcas que comprenden al menos un vehıculo, dısolvente, adyuvante o excıpıente farmacéutıcamente aceptable y un compuesto de formula I, realızacıón A66 o realızacıon A154

La ınvencıón prcvee ademas composıcıones farmaceutıcas que comprenden al menos un vehıculo, dısolvente, adyuvante o excıpıente farmacéutıcamente aceptable y compuestos de acuerdo con cualquıera de las realızacıones precedentes

Como se observo previamente, la ınvencıon abarca metodos para tratar un trastorno mediado por FNT, un trastorno, ınflamacıcn y/o artrıtıs mediado por p38 quınasa

en un sujeto, comprendiendo el metodo tratar a un sujeto que padece o es susceptible a dicho trastorno o afeccion con una cantidad terapeuticamente eficaz de un compuesto de fórmula I o de la realización A1

Mas especificamente, la invencion provee metodos para tratar o prevenir inflamacion, artritis, artritis reumatoidea, espondilartropatias, artritis gotosa, osteoartritis, lupus sistemico eritematoso, artritis juvenil y otras afecciones artriticas, neuroinflamación, alergia, enfermedades mediadas por Th2, dolor, dolor neuropatico, fiebre, trastornos pulmonares, inflamación pulmonar, sindrome de distres respiratorio del adulto, sarcoidosis pulmonar, asma, silicosis, enfermedad inflamatoria pulmonar crónica y enfermedad pulmonar obstructiva crónica (EPOC), enfermedad cardiovascular, arteriosclerosis, infarto de miocardio (incluyendo indicaciones post-infarto de miocardio), trombosis, insuficiencia cardiaca congestiva, lesion por reperfusión cardiaca, como asi tambien complicaciones asociadas con hipertensión y/o insuficiencia cardiaca, como daño vascular de organos, restenosis cardiomiopatia, accidente cerebrovascular, incluyendo accidente isquemico y hemorragico, lesion por reperfusion, reperfusion renal, isquemia, incluyendo accidente cerebrovascular e isquemia como consecuencia de derivacion cardiaca/coronaria, neurotrauma y trauma cerebral, incluyendo lesion cefalica cerrada, edema cerebral, trastornos neurodegenerativos, enfermedad hepat ca y nefritis, afecciones gastrointestinales, enfermedad intestinal inflamatoria, enfermedad de Crohn, gastritis, sindrome de intestino irritable, colitis ulcerosa, enfermedades ulcerosas, ulceras gástricas, enfermedades oftalmicas, retinitis, retinopatias, uveitis, fotofobia ocular, lesion aguda al

tejido ocular y traumas oculares tales como glaucoma post-traumatico, neuropatia óptica traumática y oclusión de la arteria central de la retina, enfermedad periodontal, afecciones oftalmologicas, retinitis, retinopatias (incluyendo retinopatia diabética), uveitis, fotofobia ocular, atrofia no glaucomatosa del nervio optico y degeneracion macular relacionada con la edad (DMRE) (forma atrofica de DMRE ), rechazo de injerto en cornea, neovascularizacion ocular, neovascularizacion retinal, neovascularizacion posterior a lesion o infeccion, fibroplasia retrolenticular, glaucoma neovascular, glaucoma, incluyendo glaucoma primario de ángulo abierto (GPAA), glaucoma primario de angulo abierto juvenil, glaucoma de cierre de ángulo, glaucoma seudoexfoliativo, glaucoma, neuropatia optica isquémica anterior (NOIA), hipertension ocular, sindrome de Reiger, glaucoma de tension normal, glaucoma neovascular, inflamacion ocular y glaucoma inducido por corticosteroides, diabetes, nefropatia diabetica, afecciones relacionadas con la piel, soriasis, eczema, cuemaduras, dermatitis, formacion de queloides, formacion de tejido cicatricial, trastornos angiogenicos, infecciones virales y bacterianas, sepsis, choque septico, sepsis por gram negativo, paludismo, meningitis, infección VIH, infecciones oportunistas, caquexia secundaria a infeccion o malignidad, caquexia secundaria a sindrome de inmunodeficiencia adquirida (sida), sida, CRS (complejo relacionado con sida), neumonia, herpes virus, mialgias debidas a infeccion, gripe, choque endotóxico sindrome de choque toxico enfermedad autoinmune, reacción del hospedante frente al injerto y rechazo de injertos tratamiento de enfermedades de resorcion osea, osteoporosis, esclerosis multiple, trastornos del sistema reproductor femenino, endometriosis,

hemangiomas, hemangiomas infantiles, angiofibroma de la nasofaringe, necrosis avascular de los huesos, neoplasia/tumores benignos y malignos, cancer, cancer colorrectal, cancer cerebral, cáncer de huesos, neoplasia epitelial (carcinoma epitelial), carcinoma basocelular, adenocarcinoma, cancer gastrointestinal, cancer de labio, cancer de la cavidad bucal, cancer de esofago, cancer de intestino delgado, cancer de estomago, cáncer de colon, cancer de higado, cancer de vejiga, cancer de pancreas, cancer de ovario, carcer cervical, cáncer de pulmón, cáncer de mama, cáncer de piel, cáncer de celulas escamosas y/o células basales, cancer de próstata, carcinoma celular renal y otros canceres conocidos que afectan las celulas epiteliales de todo el cuerpo, leucemia, linfoma, lupus eritematoso sistemico (LES), angiogenesis, incluyendo neoplasia, metástasis, trastornos del sistema nervioso central, trastornos del sistema nervioso central que tienen componentes inflamatorios o apoptoticos, enfermedad de Alzheimer, enfermedad de Parkinson, enfermedad de Huntington, esclerosis lateral amiotrofica, lesion de la médula espinal y neuropatia periferica, linfoma de celulas B caninas Los compuestos de la invención también son utiles para prevenir la producción o expresion de ciclo-oxigenasa-2 o la actividad de la ciclo-oxigenasa-2

En este aspecto, la invención abarca metodos para tratar un trastorno mediado por p38 quinasa o FNT-alfa, que comprende administrar a un paciente en necesidad de los mismos, una cantidad terapeuticamente eficaz de los compuestos de acuerdo con la realizacion 1 y al menos un vehiculo, adyuvante, disolvente o excipiente farmaceuticamente aceptable

Los compuestos representativos de la invencion son

1-bencil-4-(benciloxi)-3-bromopiridin-2(1*H*)-ona,

3-bromo-1-(4-fluorobencil)-4-[(4-fluorobencil)oxi]piridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-(dimetilfenil)-6-metilpiridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-(4-fluorobencil)piridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-(3-(fluorobencil)piridir-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-(piridin-3-ilmetil)piridin-2(1*H*)-ona,

4-bromo-2-(2,6-diclorofenil)-5-[(2,4-difluorobencil)oxi]piridazin-3(2*H*)-ona,

3-bromo-1-(2,6-diclorofenil)-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

3-bromo-1-(3-fluorobencil)-4-[(3-metilbencil)oxi]piridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-(piridin-4-ilmetil)piridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-(3-fluorobencil)piridin-2(1*H*)-ona,

1-bencil-4-(benciloxi)-3-bromo-6-metilpiridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2-metoxi-6-metilfenil)-6-metilpiridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2-(fluorobencil)piridin-2(1*H*)-ona,

3-bromo-4-[(4-fluorobencil)oxi]-6-metil-1-(piridin-3-ilmetil)piridin-2(1*H*)-ona,

3-bromo-1-(2,6-diclorofenil)-4-[(4-fluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-(4-metilbencil)piridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-(4-clorobencil)piridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-(3-(metoxibencil)piridin-2(1*H*)-ona,

Ácido 4-{[4-(benciloxi)-3-bromo-2-oxopiridin-1(2*H*)-il]metil}benzoico

4-(benciloxi)-3-bromo-1-(2-fluorobencil)piridin-2(1*H*)-ona,

3-bromo-1-(2,6-cimetilfenil)-4-[(4-fluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-[4-(metiltio)bencil]piridin-2(1*H*)-ona,

1-bencil-4-(benciloxi)-3-cloropiridin-2(1*H*)-ona,

4-{[4-(benciloxi)-3-bromo-2-oxopiridin-1(2*H*)-il]metil}-*N*-hidroxibencenocarboximidamida,

4-{[4-(benciloxi)-3-bromo-2-oxopiridin-1(2*H*)-il]metil}benzoato de metilo,

3-bromo-4-[(3-clorobencil)oxi]-1-(3-fluorobencil)piridin-2(1*H*)-ona,

3-bromo-1-(3-fluorobencil)-4-[(4-fluorobencil)oxi]piridin-2(1*H*)-ona

4-{[4-(benciloxi)-3-bromo-2-oxopiridin-1(2*H*)-il]metil}benzonitrilo,

4-(benciloxi)-3-bromo-1-(2,6-diclorofenil)-6-metilpiridin-2(1*H*)-ona,

3-bromo-4-[(4-fluorobencil)oxi]-1-(piridin-4-ilmetil)piridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-(4-bromobencil)piridin-2(1*H*)-ona,

4-{[3-bromo-4-[(4-fluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}benzonitrilo,

1-(3-fluorobencil)-4-[(4-fluorobencil)oxi]-3-yodopiridin-2(1*H*)-ona,

4-bromo-2-(2,6-diclorofenil)-5-{[2-(hidroximetil)bencil]oxi}pridazin-3(2*H*)-ona,

3-bromo-4-[(4-fluorobencil)oxi]-1-(piridin-3-ilmetil)piridin-2(1*H*)-ona,

3-bromo-1-(2,4-difluorobencil)-4-[(2,4-difluorobencil)oxi]piridin-2(1*H*)-ona,

3-bromo-4-[(4-fluorobencil)oxi]-6-metil-1-(piridin-2-ilmetil)piridin-2(1*H*)-ona, o una sal farmaceuticamente aceptable de los mismos

Realizacion 57 Compuestos de acuerdo con la realización 1 o la realizacion A1, que es

3-bromo-4-[(4-clorobencil)oxi]-1-(4-fluorobencil)piridin-2(1*H*)-ona,

1-bencil-3-bromc-4-[(-4-clorobencil)oxi]piridin-2(1*H*)-ona,

3-bromo-1-(4-clcrobencil)-4-[(4-clorobencil)oxi]piridin-2(1*H*)-ona,

3-bromo-4-[(4-clorobencil)oxi]-1-[2-(feniltio)etil]piridin-2(1*H*)-ona,

3-bromo-4-[(4-clorobencil)oxi]-1-(2-(feniletil)piridin-2(1*H*)-ona,

3-bromo-4-hidroxi-1-(4-hidroxibencil)piridin-2(1*H*)-ona,

hidrocloruro de 4-(benciloxi)-3-bromo-1-(piperidin-3-ilmetil)piridin-2(1*H*)-ona,

3-bromo-1-(4-metoxibencil)-4-fenoxipiridin-2(1*H*)-ona,

1-bencil-2-oxo-4-fenoxi-1,2-dihidropiridina-3-carbaldehido,

3-bromo-4-[(4-clorobencil)oxi]-1-(4-(metoxibencil)piridin-2(1*H*)-ona,

3-bromo-4-[(4-fluorobencil)oxi]-1-(3-(fenilpropil)piridin-2(1*H*)-ona,

4-(benciloxi)-1-[4-(benciloxi)bencil]-3-bromopiridin-

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2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-[2-(trifluorometil)bencil)]piridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-[3-(trifluorometil)bencil)]piridin-2(1*H*)-ona,

hidrocloruro de 4-(benciloxi)-3-bromo-1-(piperidin-4-ilmetil)piridin-2(1*H*)-ona,

1-bencil-3-bromo-4-{[2-(trifluorometil)bencil]oxi}piridin-2(1*H*)-ona,

1-bencil-4-[(2,6-diclorobencil)oxi]piridin-2(1*H*)-ona,

1-bencil-4-(benciloxi)-3-)hidroximetil)piridin-2(1*H*)-ona,

1-bencil-3-bromo-4-[(2,6-diclorobencil)oxi]piridin-2(1*H*)-ona,

1-bencil-4-[(3-clorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

1-bencil-3-bromo-4-[(3-clorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

1-bencil-3-bromo-4-[(-2-clorobencil)oxi]piridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-etilpiridin-2(1*H*)-ona,

4-(benciloxi)-1-(4-bromobencil)piridin-2(1*H*)-ona,

3-bromo-1-(4-metilbencil)-4-[(4-metilbencil)oxi]piridin-2(1*H*)-ona,

4-{[4-(benciloxi)-3-bromo-2-oxopiridin-1(2*H*)-il]metil}benzoato de metilo,

4-(benciloxi)-3-bromo-1-(2-tien-3-iletil)piridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-(2-tien-2-iletil)piridin-2(1*H*)-ona,

1-bencil-4-[(3-clorobencil)oxi]piridin-2(1*H*)-ona,

3-bromo-1-(4-fluorobencil)-4-[(4-fluorobencil)oxi]piridin-2(1*H*)-ona,

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4-(benciloxi)-1-(3-fluorobencil)piridin-2(1*H*)-ona,

4-(benciloxi)-1-(2-fluorobencil)piridin-2(1*H*)-ona,

hidrobromuro de 4-(benciloxi)-3-bromo-1-metilpiridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-metilpiridin-2(1*H*)-ona,

3-bromo-1-(3-clorobencil)-4-[(4-clorobencil)oxi]piridin-2(1*H*)-ona,

3-bromo-1-(3-clorobencil)-4-[(4-fluorobencil)oxi]piridin-2(1*H*)-ona,

4-(benciloxi)-1-(4-clorobencil)piridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-[4-(trifluorometoxi)bencil)]piridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-(4-*terc*-butilbencil)piridin-2(1*H*)-ona,

1-bencil-4-(benciloxi)-6-metilpiridin-2(1*H*)-ona,

1-bencil-4-(benciloxi)-3,5-dibromo-6-metilpiridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-[4-(trifluorometil)bencil)]piridin-2(1*H*)-ona,

1-bencil-4-[(2-clorobencil)oxi]piridin-2(1*H*)-ona,

1-(2-bromobencil)-3-[(2-bromobencil)oxi]piridin-2(1*H*)-ona,

metil 5-cloro-1-(4-clorobencil)-6-oxo-1,6-dihidropiridina-3-carboxilato,

3-bencil-4-hidroxi-1-(2-feniletil)piridin-2(1*H*)-ona,

5-bromo-1-(2-cloro-6-fluorobencil)-3-metilpiridin-2(1*H*)-ona,

1-(2-bromobencil)-3-[(2-bromobencil)oxi]piridin-2(1*H*)-ona,

1-bencil-4-(benciloxi)piridin-2(1*H*)-ona,

1-bencil-4-(benciloxi)-3-bromopiridin-2(1*H*)-ona,

1-bencil-4-(benciloxi)-2-oxo-1,2-dihidropiridina-3-carbaldehido,

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1-bencil-4-cloro-2-oxo-1,2-dihidropiridina-3-carbaldehido,

1-bencil-4-hidroxi-2-oxo-1,2-dihidropiridina-3-carbaldehido,

1-bencil-4-(benciloxi)-3-metilpiridin-2(1*H*)-ona,

4-(benciloxi)-1-(4-fluorobencil)piridin-2(1*H*)-ona,

1-bencil-4-(benciloxi)-3,5-dibromopiridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-[4-(metiltio)bencil)]piridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-(4-fluorobencil)piridin-2(1*H*)-ona,

1-bencil-4-(benciloxi)-3-cloropiridin-2(1*H*)-ona,

3-bromo-1-(4-fluorobencil)-4-[(4-fluorobencil)oxi]piridin-2(1*H*)-ona,

1-bencil-3-bromo-2-oxo-1,2-dihidropiridin-4-il metil(fenil)carbamato,

1-bencil-3-bromo-4-(2-feniletil)piridin-2(1*H*)-ona,

1-bencil-3-bromo-4-(3-fenilpropil)piridin-2(1*H*)-ona,

1-bencil-3-metil-4-(2-feniletil)piridin-2(1*H*)-ona,

1-bencil-3-metil-4-(3-fenilpropil)piridin-2(1*H*)-ona,

1-bencil-4-(benciltio)-3-metilpiridin-2(1*H*)-ona,

1-bencil-4-(benciltio)-3-bromopiridin-2(1*H*)-ona,

1-bencil-2-oxo-1,2-dihidropiridin-4-il metanosulfonato,

3-acetil-4-hidroxi-6-metil-1-[cloro]fenilpiridin-2(1*H*)-ona,

6-(benciloxi)-1-metil-2-oxo-1,2-dihidropiridina-3-carbonitrilo,

3-benzoil-6-(benciloxi)-1-metilpiridin-2(1*H*)-ona,

3-bencil-6-(benciloxi)-1-metilpiridin-2(1*H*)-ona,

1-bencil-4-hidroxipiridin-2(1*H*)-ona,

1-bencil-4-(benciltio)piridin-2(1*H*)-ona

4-amino-1-bencilpiridin-2(1*H*)-ona,

1-bencil-4-(benciloxi)piridin-2(1*H*)-ona,

1-bencil-4-hidroxipiridin-2(1*H*)-ona,

1-bencil-2-oxo-1,2-dihidropiridin-4-il metil(fenil)carbamato,

o una sal farmaceuticamente aceptable de los mismos

Realizacion 58 Compuestos de acuerdo con la realización 1 o la realización A1, que es

4-(benciloxi)-1 (4-metilbencil)piridin-2(1*H*)-ona,

4-(benciloxi)-3-bromopiridin-2(1*H*)-ona,

4-{[4-(benciloxi)-2-oxopiridin-1(2*H*)-il]metil}benzoato de metilo,

4-{[4-(benciloxi)-3-bromo-2-oxopiridin-1(2*H*)-il]metil}benzoato de metilo,

4-{[4-(benciloxi)-2-oxopiridin-1(2*H*)-il]metil} benzonitrilo,

4-(benciloxi)-1 (4-*terc*-butilbencil)piridin-2(1*H*)-ona,

4-(benciloxi)-1-[4-(trifluorometil)bencil)]piridin-2(1*H*)-ona,

4-(benciloxi)-3 bromo-1-[4-(trifluorometil)bencil)]piridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-[3-(trifluorometil)bencil)]piridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-[2-(trifluorometil)bencil)]piridin-2(1*H*)-ona,

4-(benciloxi)-1-[4-(trifluorometoxi)bencil]piridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-[4-(trifluorometoxi)bencil)]piridin-2(1*H*)-ona,

1-bencil-4-hidroxi-6-metilpiridin-2(1H)-ona,

1-bencil-6-metil-2-oxo-1,2-dihidropiridin-4-il 4-bromobencenosulfonato,

1-bencil-3-bromo-4-[(3-clorobencil)oxi]-6-metilpiridin-2(1H)-ona,

1-bencil-6-metil-2-oxo-1,2-dihidropiridin-4-il 4-bromobencenosulfonato,

1-bencil-3-bromo-4-[(3-clorobencil)oxi]-6-metilpiridin-2(1H)-ona,

1-bencil-4-[(2,6-diclorobencil)oxi]piridin-2(1H)-ona,

4-[(2,6-diclorobencil)oxi]piridina-1-óxido,

4-[(2,6-diclororbencil)oxi]piridina 1-oxido,

1-bencil-3-bromo-4-[2,6-(diclorobencil)oxi]piridin-2(1H)-ona,

1-bencil-3-bromo-4-[(-4-metilbencil)oxi]piridin-2(1H)-ona,

1-bencil-4-[benciltio]-3-bromopiridin-2(1*H*)-ona,

1-bencil-4-(benciloxi)-3-yodopiridin-2(1H)-ona,

1-bencil-4-(benciloxi)-3-vinilpiridin-2(1H)-ona,

1-bencil-4-(benciloxi)-3-etilpiridin-2(1H)-ona,

3-acetil-4-(benciloxi)-1-(2-clorofenil)-6-metilpiridin-2(1H)-ona,

3-acetil-1-(2-clorofenil)-4-hidroxi-6-metilpiridin-2(1H)-ona,

1-bencil-3-bromo-4-hidroxipiridin-2(1H)-ona,

1-bencil-3-bromo-2-oxo-1,2-dihidropiridin-4-il trifluorometanosulfonato,

1-bencil-3-bromo-4-(feniletinil)piridin-2(1H)-ona,

3-bromo-1-(3-fluorobencil)-6-metil-4-(2-feniletil)piridin-2(1H)-ona,

1-(3-fluorobencil)-4-hidroxi-6-metilpiridin-2(1H)-ona

3-bromo-1-(3-fluorobencil)-4-hidroxi-6-metilpiridin-2(1H)-ona

3-bromo-1-(3-fluorobencil)-6-metil-2-oxo-1,2-dihidropiridin-4-il trifluorometanosulfonato,

3-bromo-1-(3-fluorobencil)-6-metil-4-(feniletinil)piridin-2(1H)-ona,

3-acetil-1-(2,6-diclorofenil)-4-hidroxi-6-

metilpiridin-2(1H)-ona,

1-(2,6-diclorofenil)-4-hidroxi-6-metilpiridin-2(1H)-ona,

4-(benciloxi)-1-(2,6-diclorofenil)-6-metilpiridin-2(1H)-ona,

3-bromo-1-(3-fluorobencil)-4-(2-feniletil)piridin-2(1H)-ona,

3-bromo-1-(3-fluorobencil)-4-hidroxipiridin-2(1H)-ona,

3-bromo-1-(3-fluorobencil)-2-oxo-1,2-dihidropiridin-4-il trifluorometanosulfonato,

3-bromo-1-(3-fluorobencil)-4-(feniletinil)piridin-2(1H)-ona,

4-(benciloxi)-3-etinil-1-(3-fluorobencil)piridin-2(1H)-ona,

4-(benciloxi)-1 (3-fluorobencil)-3-yodopiridin-2(1*H*)-ona,

4-(benciloxi)-1 (3-fluorobencil)-3-[(trimetilsilil)etinil]piridin-2(1H)-ona,

4-(bencilamino)-3-bromo-1-(3-fluorobencil)piridin-2(1H)-ona,

1-(3-fluorobencil)-4-hidroxipiridin-2(1H)-ona,

4-(bencilamino) 1-(3-fluorobencil)piridin-2(1H)-ona,

o una sal farmaceuticamente aceptable de los mismos

Realizacion 59 Compuestos de acuerdo con la realizacion 1 o la realización A1, que es

3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2-(fluorobencil)piridin-2(1*H*)-ona,

3-bromo-4-[(4-fluorobencil)oxi]-6-metil-1-(piridin-3-ilmetil)piridin-2(1*H*)-ona,

3-bromo-4-[(4-fluorobencil)oxi]-6-metil-1-(piridin-4-ilmetil)piridin-2(1*H*)-ona,

3-bromo-1-(2,6-diclorofenil)-4-[(4-fluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-(3-(metoxibencil)piridin-2(1*H*)-ona,

3-bromo-1-(2,6-dimetilfenil)-4-[(4-fluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

3-bromo-4-[(3-clorobencil)oxi]-1-(3-fluorobencil)piridin-2(1*H*)-ona,

3-bromo-4-[(4-fluorobencil)oxi]-1-(piridin-4-ilmetil)piridin-2(1*H*)-ona,

3-bromo-1-(3-fluorobencil)-4-[(4-fluorobencil)oxi]piridin-2(1*H*)-ona,

4-{[3-bromo-4-[(4-fluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}benzonitrilo,

1-(3-fluorobencil)-4-[(4-fluorobencil)oxi]-3-yodopiridin-2(1*H*)-ona,

3-bromo-4-[(4-fluorobencil)oxi]-1-(piridin-3-ilmetil)piridin-2(1*H*)-ona,

3-bromo-1-(2,4-difluorobencil)-4-[(2,4-difluorobencil)oxi]piridin-2(1*H*)-ona,

3-bromo-4-[(4-fluorobencil)oxi]-6-metil-1-(piridin-2-ilmetil)piridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-(3-(fluorobencil)piridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-(piridin-3-ilmetil)piridin-2(1*H*)-ona,

3-bromo-1-(2,6-diclorofenil)-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

3-bromo-1-(3-fluorobencil)-4-[(3-metilbencil)oxi]piridin-2-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-(piridin-4-ilmetil)piridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2-metoxi-6-metilfenil)-6-metilpiridin-2(1*H*)-ona,

o una sal farmaceuticamente aceptable de los mismos

Realizacion 60 Compuestos de acuerdo con la realización 1, que es:

1-(1-acetil-2,3-dihidro-1*H*-indol-5-il)-3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-(1-glicoloil-2,3-dihidro-1*H*-indol-5-il)-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[1-(2-hidroxi-2-metilpropanoil)-2,3-dihidro-1*H*-indol-5-il]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-1-[1-(*N*-metilglicil)-2,3-dihidro-1*H*-indol-5-il]piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[1-(3-hidroxipropanoil)-2,3-dihidro-1*H*-indol-5-il]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[1-(3-hidroxi-3-metilbutanoil)-2,3-dihidro-1*H*-indol-5-il]-6-metilpiridin-2(1*H*)-ona,

5-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]indolina-1-carboxamida,

3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-1-[1-(metilsulfonil)-2,3-dihidro-1*H*-indol-5-il]piridin-2(1*H*)-ona,

1-(1-acetil-1*H*-indol-5-il)-3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-(1-glicoloil-1*H*-indol-5-il)-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[1-(2-hidroxi-2-metilpropanoil)-1*H*-indol-5-il]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-1-[1-(*N*-metilglicil)-1*H*-indol-5-il]piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[1-(3-hidroxipropanoil)-1*H*-indol-5-il]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[1-(3-hidroxi-3-metilbutanoil)-1*H*-indol-5-il]-6-metilpiridin-2(1*H*)-ona,

5-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]indol-1-carboxamida,

3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-1-[1-(metilsulfonil)-1*H*-indol-5-il]piridin-2(1*H*)-ona,

1-(2-acetil-2,3-dihidro-1*H*-isoindol-5-il)-3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-(2-glicoloil-2,3-dihidro-1*H*-isoindol-5-il)-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[2-(2-hidroxi-2-metilpropanoil)-2,3-dihidro-1*H*-isoindol-5-il]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-1-[2-(*N*-metilglicil)-2,3-dihidro-1*H*-isoindol-5-il]piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[2-(3-hidroxipropanoil)-2,3-dihidro-1*H*-isoindol-5-il]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[2-(3-hidroxi-3-metilbutanoil)-2,3-dihidro-1*H*-isoindol-5-il]-6-metilpiridin-2(1*H*)-ona,

5-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-1,3-dihidro-2*H*-isoindol-2-carboxamida,

3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-1-[2-(metilsulfonil)-2,3-dihidro-1*H*-isoindol-5-il]piridin-2(1*H*)-ona,

1-(2-acetil-1,2,3,4-tetrahidroisoquinolin-6-il)-3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-(2-glicoloil-1,2,3,4-tetrahidroisoquinolin-6-il)-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[2-(2-hidroxi-2-metilpropanoil)-1,2,3,4-tetrahidroisoquinolin-6-il]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-1-[2-(*N*-metilglicil)-1,2,3,4-tetrahidroisoquinolin-6-il]piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[2-(3-hidroxipropanoil)-1,2,3,4-tetrahidroisoquinolin-6-il]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[2-(3-hidroxi-3-metilbutanoil)-1,2,3,4-tetrahidroisoquinolin-6-il]-6-metilpiridin-2(1*H*)-ona,

6-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-3,4-dihidroisoquinolina-2(1*H*)-carboxamida,

3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-1-[2-(metilsulfonil)-1,2,3,4-tetrahidroisoquinolin-6-il]piridin-2(1*H*)-ona,

1-(2-acetil-1,2,3,4-tetrahidroisoquinolin-7-il)-3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona

3-cloro-4-[(2,4-difluorobencil)oxi]-1-(2-glicoloil-1,2,3,4-tetrahidroisoquinolin-7-il)-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[2-(2-hidroxi-2-metilpropanoil)-1,2,3,4-tetrahidroisoquinolin-7-il]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-1-[2-(*N*-metilglicil)-1,2,3,4-tetrahidroisoquinolin-7-il]piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[2-(3-hidroxipropanoil)-1,2,3,4-tetrahidroisoquinolin-7-il]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[2-(3-hidroxi-3-

metilbutanoil)-1,2,3,4-tetrahidroisoquinolin-7-il]-6-metilpiridin-2(1*H*)-ona,

7-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-3,4-dihidroisoquinolina-2(1*H*)-carboxamida,

3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-1-[2-(metilsulfonil)-1,2,3,4-tetrahidroisoquinolin-7-il]piridin-2(1*H*)-ona,

1-(1-acetil-1*H*-bencimidazol-5-il)-3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-(1-glicoloil-1*H*-bencimidazol-5-il)-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[1-(2-hidroxi-2-metilpropanoil)-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-1-[1-(*N*-metilglicil)-1*H*-bencimidazol-5-il]piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[1-(3-hidroxipropanoil)-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[1-(3-hidroxi-3-metilbutanoil)-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona,

5-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-1*H*-bencimidazol-1-carboxamida,

3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-1-[1-(metilsulfonil)-1*H*-bencimidazol-5-il]piridin-2(1*H*)-ona,

3-cloro-1-(1,3-diacetil-2,3-dihidro-1*H*-bencimidazol-5-il)-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

1-(3-acetil-1-glicoloil-2,3-dihidro-1*H*-bencimidazol-5-il)-3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

1-[3-acetil-1-(2-hidroxi-2-metilpropanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]-3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

1-[3-acetil-1-(*N*-metilglicil)-2,3-dihidro-1*H*-bencimidazol-5-il]-3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

1-[3-acetil-1-(3-hidroxipropanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]-3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

1-[3-acetil-1-(3-hidroxi-3-metilbutanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]-3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

3-acetil-5-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

1-(1-acetil-1-glicoloil-2,3-dihidro-1*H*-bencimidazol-5-il)-3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-

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2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-(1,3-diglicoloil-2,3-dihidro-1*H*-bencimidazol-5-il)-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[3-glicoloil-1-(2-hidroxi-2-metilpropanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[3-glicoloil-1-(*N*-metilglicil)-2,3-dihidro-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[3-glicoloil-1-(3-hidroxipropanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona,

5-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-3-glicoloil-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[3-glicoloil-1-(3-hidroxi-3-metilbutanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[3-glicoloil-1-(metilsulfonil)-2,3-dihidro-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona,

1-[1-acetil-3-(2-hidroxi-2-metilpropanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]-3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[1-glicoloil-3-(2-hidroxi-2-metilpropanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona,

1-[1,3-bis(2-hidroxi-2-metilpropanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]-3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[3-(2-hidroxi-2-metilpropanoil)-1-(*N*-metilglicil)-2,3-dihidro-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[3-(2-hidroxi-2-metilpropanoil)-1-(3-hidroxipropanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[1-(3-hidroxi-3-metilbutanoil)-3-(2-hidroxi-2-metilpropanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona,

5-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-3-(2-hidroxi-2-metilpropanoil)-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[3-(2-hidroxi-2-metilpropanoil)-1-(metilsulfonil)-2,3-dihidro-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona,

1-[1-acetil-3-(*N*-metilglicil)-2,3-dihidro-1*H*-bencimidazol-5-il]-3 cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

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3-cloro-4-[(2,4-difluorobencil)oxi]-1-[1-glicoloil-3-(*N*-metilglicil)-2,3-dihidro-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[1-(2-hidroxi-2-metilpropanoil)-3-(*N*-metilglicil)-2,3-dihidro-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona,

1-[1,3-bis(*N*-metilglicil)-2,3-dihidro-1*H*-bencimidazol-5-il]-3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[1-(3-hidroxipropanoil)-3-(*N*-metilglicil)-2,3-dihidro-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[1-(3-hidroxi-3-metilbutanoil)-3-(*N*-metilglicil)-2,3-dihidro-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona,

5-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-3-(*N*-metilglicil)-2,3-dihidro-1*H*-bencimidazol-1-carbcxamida,

3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-1-[3-(*N*-metilglicil)-1-(metilsulfonil)-2,3-dihidro-1*H*-bencimidazol-5-il]piridin-2(1*H*)-ona,

1-[1-acetil-3-(3-hidroxipropanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]-3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[1-glicoloil-3-(3-hidroxipropanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[1-(2-hidroxi-2-metilpropanoil)-3-(3-hidroxipropanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[3-(3-hidroxipropanoil)-1-(*N*-metilglicil)-2,3-dihidro-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona,

1-[1,3-bis(3-hidroxipropanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]-3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[1-(3-hidroxi-3-metilbutanoil)-3-(3-hidroxipropanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona,

5-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-3-(3-hidroxipropanoil)-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[3-(3-hidroxipropanoil)-1-(metilsulfonil)-2,3-dihidro-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona,

1-[1-acetil-3-(3-hidroxi-3-metilbutanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]-3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[1-glicoloil-3-

(3-hidroxi-3-metilbutanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[3-(3-hidroxi-3-metilbutanoil)-1-(2-hidroxi-2-metilpropanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[3-(3-hidroxi-3-metilbutanoil)-1-(*N*-metilglicil)-2,3-dihidro-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[3-(3-hidroxi-3-metilbutanoil)-1-(3-hidroxipropanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona,

1-[1,3-bis(3-hidroxi-3-metilbutanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]-3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

5-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-3-(3-hidroxi-3-metilbutanoil)-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[3-(3-hidroxi-3-metilpropanoil)-1-(metilsulfonil)-2,3-dihidro-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona,

3-acetil-6-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

6-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-3-glicoloil-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

6-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-3-(2-hidroxi-2-metilpropanoil)-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

6-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-3-(*N*-metilglicil)-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

6-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-3-(3-hidroxipropanoil)-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

6-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-3-(3-hidroxi-3-metilbutanoil)-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

5-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-1*H*-bencimidazol-1,3(2*H*)-dicarboxamida,

6-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-3-(metilsulfonil)-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

1-(1-acetil-3-(metilsulfonil)-2,3-dihidro-1*H*-bencimidazol-5-il)-3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[1-glicoloil-3-(metilsulfonil)-2,3-dihidro-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[1-(2-hidroxi-2-metilpropanoil)-3-(metilsulfonil)-2,3-dihidro-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-1-[1-(*N*-metilglicil)-3-(metilsulfonil)-2,3-dihidro-1*H*-bencimidazol-5-il]piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[1-(3-hidroxipropanoil)-3-(metilsulfonil)-2,3-dihidro-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[1-(3-hidroxi-3-metilbutanoil)-3-(metilsulfonil)-2,3-dihidro-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona,

5-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-3-(metilsulfonil)-2,3-dihidro-1*H*-bencimidazol-1-carbcxamida,

1-[1,3-bis(metilsulfonil)-2,3-dihidro-1*H*-bencimidazol-5-il]-3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

1-(3-acetil-1-(metilsulfonil)-2,3-dihidro-1*H*-bencimidazol-5-il)-3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

1-(1-acetil-1*H*-pirrol-3-il)-3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-(1-glicoloil-1*H*-pirrol-3-il)-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[1-(2-hidroxi-2-metilpropanoil)-1*H*-pirrol-3-il]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-1-[1-(*N*-metilglicil)-1*H*-pirrol-3-il]piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[1-(3-hidroxipropanoil)-1*H*-pirrol-3-il]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[1-(3-hidroxi-3-metilbutanoil)-1*H*-pirrol-3-il]-6-metilpiridin-2(1*H*)-ona,

3-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-1*H*-pirrol-1-carboxamida,

3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-1-[1-(metilsulfonil)-1*H*-pirrol-3-il]piridin-2(1*H*)-ona,

1-(1-acetil-1*H*-imidazol-4-il)-3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-(1-glicoloil-1*H*-imidazol-4-il)-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[1-(2-hidroxi-2-metilpropanoil)-1*H*-imidazol-4-il]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-1-[1-(*N*-metilglicil)-1*H*-imidazol-4-il]piridin-2(1*H*)-ona,

3-cloro-4-[(2,4 difluorobencil)oxi]-1-[1-(3-hidroxipropanoil)-1*H*-imidazol-4-il]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4 difluorobencil)oxi]-1-[1-(3-hidroxi-3-

metılbutanoıl)-1*H*-ımıdazol-4-ıl]-6-metılpırıdın-2(1*H*)-ona,

4-[3-cloro-4-[(2,4-dıfluorobencıl)oxı]-6-metıl-2-oxopırıdın-1(2*H*)-ıl)-1*H*-ımıdazol-1-carboxamıda,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-6-metıl-1-[1-(metılsulfonıl)-1*H*-ımıdazol-4-ıl]pırıdın-2(1*H*)-ona,

1-(1-acetıl-1*H*-pırazol-4-ıl)-3-cloro-4-[(2,4-dıfluorobencıl)oxı]-6-metılpırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-(1-glıcoloıl-1*H*-pırazol-4-ıl)-6-metılpırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-[1-(2-hıdroxı-2-metılpropanoıl)-1*H*-pırazol-4-ıl]-6-metılpırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-6-metıl-1-[1-(*N*-metılglıcıl)-1*H*-pırazol-4-ıl]pırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-[1-(3-hıdroxıpropanoıl)-1*H*-pırazol-4-ıl]-6-metılpırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-[1-(3-hıdroxı-3-metılbutanoıl)-1*H*-pırazol-4-ıl]-6-metılpırıdın-2(1*H*)-ona,

4-[3-cloro-4-[(2,4-dıfluorobencıl)oxı]-6-metıl-2-oxopırıdın-1(2*H*)-ıl]-1*H*-pırazol-1-carboxamıda,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-6-metıl-1-[1-(metılsulfonıl)-1*H*-pırazol-4-ıl]pırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-ısoquınolın-7-ıl-6-metılpırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-(ısoquınolın-6-ılmetıl)pırıdın-2(1*H*)-ona,

5-{[3-cloro-4-[(2,4-dıfluorobencıl)oxı]-2-oxopırıdın-1(2*H*)-ıl]metıl}-1,3-dıhıdro-2*H*-ındol-2-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-(2,3-dıhıdro-1*H*-ındol-5-ılmetıl)pırıdın-2(1*H*)-ona,

1-[(1-acetıl-2,3-dıhıdro-1*H*-ındol-5-ıl)metıl]-3-cloro-4-[(2,4-dıfluorobencıl)oxı]pırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-(1-glıcoloıl-2,3-dıhıdro-1*H*-ındol-5-ıl)metıl]pırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-{[1-(2-hıdroxı-2-metılpropanoıl)-2,3-dıhıdro-1*H*-ındol-5-ıl]metıl}pırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-{[1-(*N*-metılglıcıl)-2,3-dıhıdro-1*H*-ındol-5-ıl]metıl}pırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-{[1-(3-hıdroxıpropanoıl)-2,3-dıhıdro-1*H*-ındol-5-ıl]metıl}pırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-{[1-(3-hıdroxı-3-metılbutanoıl)-2,3-dıhıdro-1*H*-ındol-5-ıl]metıl}pırıdın-2(1*H*)-ona,

5-[3-cloro-4-[(2,4-dıfluorobencıl)oxı]-2-oxopırıdın-1(2*H*)-ıl]metıl}ındolına-1-carboxamıda,

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3-cloro-4-[(2,4-difluorobenzil)oxi]-1-{[1-(metilsulfonil)-2,3-dihidro-1*H*-indol-5-il]metil}piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobenzil)oxi]-1-(2,3-dihidro-1*H*-isoindol-5-ilmetil)piridin-2(1*H*)-ona,

1-[(2-acetil-2,3-dihidro-1*H*-isoindol-5-il)metil]-3-cloro-4-[(2,4-difluorobenzil)oxi]piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobenzil)oxi]-1-[(2-glicoloil-2,3-dihidro-1*H*-indol-5-il)metil]piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobenzil)oxi]-1-{[2-(2-hidroxi-2-metilpropanoil)-2,3-dihidro-1*H*-isoindol-5-il]metil}piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobenzil)oxi]-1-{[2-(*N*-metilglicil)-2,3-dihidro-1*H*-isoindol-5-il]metil}piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobenzil)oxi]-1-{[2-(3-hidroxipropanoil)-2,3-dihidro-1*H*-isoindol-5-il]metil}piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobenzil)oxi]-1-{[2-(3-hidroxi-3-metilbutanoil)-2,3-dihidro-1*H*-isoindol-5-il]metil}piridin-2(1*H*)-ona,

5-{[3-cloro-4-[(2,4-difluorobenzil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1,3-dihidro-2*H*-isoindol-2-carboxamida,

3-cloro-4-[(2,4-difluorobenzil)oxi]-1-{[2-(metilsulfonil)-2,3-dihidro-1*H*-isoindol-5-il]metil}piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobenzil)oxi]-1-(1,2,3,4-tetrahidroisoquinolin-6-ilmetil)piridin-2(1*H*)-ona

1-[(2-acetil-1,2,3,4-tetrahidroisoquinolin-6-il)metil]-3-cloro-4-[(2,4-difluorobenzil)oxi]-piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobenzil)oxi]-1-[(2-glicoloil-1,2,3,4-tetrahidroisoquinolin-6-il)metil]piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobenzil)oxi]-1-{[2-(2-hidroxi-2-metilpropanoil)-1,2,3,4-tetrahidroisoquinolin-6-il]metil}piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobenzil)oxi]-1-{[2-(*N*-metilglicil)-1,2,3,4-tetrahidroisoquinolin-6-il]metil}piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobenzil)oxi]-1-{[2-(3-hidroxipropanoil)-1,2,3,4-tetrahidroisoquinolin-6-il]metil}piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobenzil)oxi]-1-{[2-(3-hidroxi-3-metilbutanoil)-1,2 3,4-tetrahidroisoquinolin-6-il]metil}piridin-2(1*H*)-ona,

6-{[3-cloro-4-[(2,4-difluorobenzil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3,4-dihidroisoquinolina-2(1*H*)-carboxamida,

3-cloro-4-[(2,4 difluorobenzil)oxi]-1-{[2-(metilsulfonil)-1,2, 3,4-tetrahidroisoquinolin-6-

ıl]metıl}pırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-(1,2,3,4-tetrahıdroısoquınolın-5-ılmetıl)pırıdın-2(1*H*)-ona,

1-[(2-acetıl-1,2,3,4-tetrahıdroısoquınolın-5-ıl)metıl]-3-cloro-4-[(2,4-dıfluorobencıl)oxı]-pırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-[(2-glıcoloıl-1,2,3,4-tetrahıdroısoquınolın-5-ıl)metıl]pırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-{[2-(2-hıdroxı-2-metılpropanoıl)-1,2,3,4-tetrahıdroısoquınolın-5-ıl]metıl}pırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-{[2-(*N*-metılglıcıl)-1,2,3,4-tetrahıdroısoquınolın-5-ıl]metıl}pırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-{[2-(3-hıdroxıpropanoıl)-1,2,3,4-tetrahıdroısoquınolın-5-ıl]metıl}pırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-{[2-(3-hıdroxı-3-metılbutanoıl)-1,2,3,4-tetrahıdroısoquınolın-5-ıl]metıl}pırıdın-2(1*H*)-ona,

5-{[3-cloro-4-[(2,4-dıfluorobencıl)oxı]-2-oxopırıdın-1(2*H*)-ıl]metıl}-3,4-dıhıdroısoquınolına-2(1*H*)-carboxamıda,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-{[2-(metılsulfonıl)-1,2,3,4-tetrahıdroısoquınolın-5-ıl]metıl}pırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-(2,3-dıhıdro-1*H*-bencımıdazol-5-ılmetıl)pırıdın-2(1*H*)-ona,

1-[(1-acetıl-2,3-dıhıdro-1*H*-bencımıdazol-5-ıl)metıl]-3-cloro-4-[(2,4-dıfluorobencıl)oxı]pırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-(1-glıcoloıl-2,3-dıhıdro-1*H*-bencımıdazol-5-ıl)metıl]pırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-{[1-(2-hıdroxı-2-metılpropanoıl)-2,3-dıhıdro-1*H*-bencımıdazol-5-ıl]metıl}pırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-{[1-(*N*-metılglıcıl)-2,3-dıhıdro-1*H*-bencımıdazol-5-ıl]metıl}pırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-{[1-(3-hıdroxıpropanoıl)-2,3-dıhıdro-1*H*-bencımıdazol-5-ıl]metıl}pırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-{[1-(3-hıdroxı-3-metılbutanoıl)-2,3-dıhıdro-1*H*-bencımıdazol-5-ıl]metıl}pırıdın-2(1*H*)-ona,

5-{[3-cloro-4-[(2,4-dıfluorobencıl)oxı]-2-oxopırıdın-1(2*H*)-ıl]metıl}-2,3-dıhıdro-1*H*-bencımıdazol-1-carboxamıda,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-{[1-(metılsulfonıl)-2,3-dıhıdro-1*H*-bencımıdazol-5-ıl]metıl}pırıdın-2(1*H*)-ona

1-[(3-acetıl-2,3-dıhıdro-1*H*-bencımıdazol-5-ıl)metıl]-

3-cloro-4-[(2,4-difluorobencil)oxi]piridin-2(1*H*)-ona,

3-cloro-1-[(1,3-diacetil-2,3-dihidro-1*H*-bencimidazol-5-il)metil]-4-[(2,4-difluorobencil)oxi]piridin-2(1*H*)-ona,

1-[(3-acetil-1-glicoloil-2,3-dihidro-1*H*-bencimidazol-5-il)metil]-3-cloro-4-[(2,4-difluorobencil)oxi]piridin-2(1*H*)-ona,

1-{[3-acetil-1-(2-hidroxi-2-metilpropanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}-3-cloro-4-[(2,4-difluorobencil)oxi]piridin-2(1*H*)-ona,

1-{[3-acetil-1-(*N*-metilglicil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}-3-cloro-4-[(2,4-difluorobencil)oxi]piridin-2(1*H*)-ona,

1-{[3-acetil-1-(3-hidroxipropanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}-3-cloro-4-[(2,4-difluorobencil)oxi]piridin-2(1*H*)-ona,

1-{[3-acetil-1-(3-hidroxi-2-metilbutanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}-3-cloro-4-[(2,4-difluorobencil)oxi]piridin-2(1*H*)-ona,

3-acetil-5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

1-{[3-acetil-1-(metilsulfonil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}-3-cloro-4-[(2,4-difluorobencil)oxi]piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-(3-glicoloil-2,3-dihidro-1*H*-bencimidazol-5-il)metil]piridin-2(1*H*)-ona,

1-[(1-acetil-3-glicoloil-2,3-dihidro-1*H*-bencimidazol-5-il)metil]-3-cloro-4-[(2,4-difluorobencil)oxi]piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi}-1-(1,3-diglicoloil-2,3-dihidro-1*H*-bencimidazol-5-il)metil]piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[3-glicoloil-1-(2-hidroxi-2-metilpropanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[3-glicoloil-1-(*N*-metilglicil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[3-glicoloil-1-(3-hidroxipropanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[3-glicoloil-1-(3-hidroxi-3-metilbutanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}piridin-2(1*H*)-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-glicoloil-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[3-glicoloil-1-(metilsulfonil)-2,3-dihidro-1*H*-bencimidazol-5-

ıl]metıl}pırıdın-2( *H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-{[3-(2-hıdroxı-2-metılpropanoıl)-2,3-dıhıdro-1*H*-bencımıdazol-5-ıl]metıl}pırıdın-2( *H*)-ona,

1-{[1-acetıl-3 (2-hıdroxı-2-metılpropanoıl)-2,3-dıhıdro-1*H*-bencımıdazol-5-ıl]metıl}-3-cloro-4-[(2,4-dıfluorobencıl)oxı]pırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-{[1-glıcoloıl-3-(2-hıdroxı-2-metılpı opanoıl)-2,3-dıhıdro-1*H*-bencımıdazol-5-ıl]metıl}pırıdın-2( *H*)-ona,

1-{[1,3-bıs(2-hıdroxı-2-metılpropanoıl)-2,3-dıhıdro-1*H*-bencımıdazol-5-ı ]metıl}-3-cloro-4-[(2,4-dıfluorobencıl)oxı]pırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-{[3-(2-hıdroxı-2-metılpropanoıl)-1 (*N*-metılglıcıl)-2,3-dıhıdro-1*H*-bencımıdazol-5-ıl]metıl}pırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-{[3-(2-hıdroxı-2-metılpropanoıl)-1 (3-hıdroxıpropanoıl)-2,3-dıhıdro-1*H*-bencımıdazol-5-ıl]me tıl}pırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-{[1-(3-hıdroxı-3-metılbutanoıl)-3-(2-hıdroxı-2-metılpropanoıl)-2,3-dıhıdro-1*H*-bencımıdazol-5-ıl]metıl}pırıdın-2(1*H*)-ona,

5-{[3-cloro-4- (2,4-dıfluorobencıl)oxı]-2-oxopırıdın-1(2*H*)-ıl]metıl}-3-( )-hıdroxı-2-metılpropanoıl)-2,3-dıhıdro-1*H*-bencımıdazol-1-carboxamıda,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-{[3-(2-hıdroxı-2-metılpropanoıl)-1 (metılsulfonıl)-2,3-dıhıdro-1*H*-bencımıdazol-5-ıl]metıl}pırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-{[3-(*N*-metılglıcıl)-2,3-dıhıdro-1*H*-bencımıdazol-5-ıl]metıl}pırıdın-2( l*H*)-ona,

1-{[1-acetıl-1 (*N*-metılglıcıl)-2,3-dıhıdro-1*H*-bencımıdazol-5-ıl]metıl}-3-cloro-4-[(2,4-dıfluorobencıl)oxı]pırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-{[1-glıcoloıl-3-(*N*-metılglıcıl)-2,3 dıhıdro-1*H*-bencımıdazol-5-ıl]metıl}pırıdın-2( l*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-{[1-(2-hıdroxı-2-metılpropanoıl)-3 (*N*-metılglıcıl)-2,3-dıhıdro-1*H*-bencımıdazol-5-ıl]metıl}pırıdın-2(1*H*)-ona,

1-{[1,3-bıs(*N*-metılglıcıl)-2,3-dıhıdro-1*H*-bencımıdazol-5-ıl]metıl}-3-cloro-4-[(2,4-dıfluorobencıl)oxı]pırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-{[1-(3-hıdroxıpropanoıl)-3 (*N*-metılglıcıl)-2,3-dıhıdro-1*H*-bencımıdazol-5-ıl]me tıl}pırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-{[1-(3-hıdroxı-3-metılbutanoıl)-3-(*N*-metılglıcıl)-2,3-dıhıdro-1*H*-bencımıdazol-5-ıl]me tıl}pırıdın-2(1*H*)-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(*N*-metilglicil)-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[3-(*N*-metilglicil)-1-(metilsulfonil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[3-(3-hidroxipropanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}piridin-2(1*H*)-ona,

1-{[1-acetil-3-(3-hidroxipropanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}-3-cloro-4-[(2,4-difluorobencil)oxi]piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[1-glicoloil-3-(3-hidroxipropanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[1-(2-hidroxi-2-metilpropanoil)-3-(3-hidroxipropanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[3-(3-hidroxipropanoil)-1-(*N*-metilglicil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}piridin-2(1*H*)-ona,

1-{[1,3-bis(3-hidroxipropanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}-3-cloro-4-[(2,4-difluorobencil)oxi]piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[1-(3-hidroxi-3-metilbutanoil)-3-(3-hidroxipropanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}piridin-2(1*H*)-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(3-hidroxipropanoil)-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[3-(3-hidroxipropanoil)-1-(metilsulfonil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[3-(3-hidroxi-3-metilbutanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}piridin-2(1*H*)-ona,

1-{[1-acetil-3-(3-hidroxi-3-metilbutanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}-3-cloro-4-[(2,4-difluorobencil)oxi]piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[1-glicoloil-3-(3-hidroxi-3-metilbutanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[3-(3-hidroxi-3-metilbutanoil)-1-(2-hidroxi-2-metilpropanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[3-(3-hidroxi-3-metilbutanoil)-1-(*N*-metilglicil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[3-(3-hidroxi-

3-metilbutanoil)-1-(metilsulfonil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}piridin-2(1*H*)-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(3-hidroxi-3-metilbutanoil)-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

1-{[1,3-bis(3-hidroxi-3-metilbutanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}-3-cloro-4-[(2,4-difluorobencil)oxi]piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[3-(3-hidroxi-3-metilbutanoil)-1-(3-hidroxipropanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}piridin-2(1*H*)-ona,

6-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

3-acetil-6-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

6-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-glicoloil-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

6-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(2-hidroxi-2-metilpropanoil)-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

6-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(*N*-metilglicil)-2,3-dihidro-1*H*-bencimidazol-1-carbcxamida,

6-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(3-hidroxipropanoil)-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

6-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(3-hidroxi-3-metilbutanoil)-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1*H*-bencimidazol-1,3(2*H*)-dicarboxamida,

6-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(metilsulfonil)-2,3-dihidro-1*H*-bencimidazol-1-carboxamida

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[3-(metilsulfonil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}piridin-2(1*H*)-ona,

1-{[1-acetil-3-(metilsulfonil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}-3-cloro-4-[(2,4-difluorobencil)oxi]piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[1-glicoloil-3-(metilsulfonil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[1-(2-hidroxi-2-metilpropanoil)-3-(metilsulfonil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[1-(*N*-metilglicil)-3-(metilsulfonil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[1-(3-hidroxipropanoil)-3-(metilsulfonil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[1-(3-hidroxi-3-metilbutanoil)-3-(metilsulfonil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}piridin-2(1*H*)-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(metilsulfonil)-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

1-{[1,3-bis(metilsulfonil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}-3-cloro-4-[(2,4-difluorobencil)oxi]piridin-2(1*H*)-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1,3-dihidro-2*H*-bencimidazol-2-ona,

1-acetil-5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1,3-dihidro-2*H*-bencimidazol-2-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1-glicoloil-1,3-dihidro-2*H*-bencimidazol-2-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1-(2-hidroxi-2-metilpropanoil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1-(*N*-metilglicil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1-(3-hidroxipropanoil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1-(3-hidroxi-3-metilbutanoil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-2-oxo-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1-(metilsulfonil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

1-acetil-6-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1,3-dihidro-2*H*-bencimidazol-2-ona,

1,3-diacetil-5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1,3-dihidro-2*H*-bencimidazol-2-ona,

3-acetil-5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1-glicoloil-1,3-dihidro-2*H*-bencimidazol-2-ona,

3-acetil-5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1-(2-hidroxi-2-metilpropanoil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

3-acetil-5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1-(*N*-metilglicil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

3-acetil-5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1-(3-hidroxipropanoil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

3-acetil-5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1-(3-hidroxi-3-metilbutanoil)-

1,3-dihidro-2*H*-bencimidazol-2-ona,

3-acetil-5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-2-oxo-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

3-acetil-5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1-(metilsulfonil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

6-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1-glicoloil-1,3-dihidro-2*H*-bencimidazol-2-ona,

1-acetil-5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-glicoloil-1,3-dihidro-2*H*-bencimidazol-2-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1,3-diglicoloil-1,3-dihidro-2*H*-bencimidazol-2-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-glicoloil-1-(2-hidroxi-2-metilpropanoil)-1,3-dihidro-2*H*-bencimidazol-2-ona

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-glicoloil-1-(*N*-metilglicil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-glicoloil-1-(3-hidroxipropanoil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-glicoloil-1-(3-hidroxi-3-metilbutanoil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-glicoloil-2-oxo-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-

1(2*H*)-il]metil}-3-glicoloil-1-(metilsulfonil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

6-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1-(2-hidroxi-2-metilpropanoil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

1-acetil-5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(2-hidroxi-2-metilpropanoil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1-glicoloil-3-(2-hidroxi-2-metilpropanoil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1,3-bis(2-hidroxi-2-metilpropanoil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(2-hidroxi-2-metilpropanoil)-1-(*N*-metilglicil)-1,3-dihidro-2*H*-bencimidazol-2-ona

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(2-hidroxi-2-metilpropanoil)-1-(3-hidroxipropanoil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1-(3-hidroxi-3-metilbutanoil)-3-(2-hidroxi-2-metilpropanoil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(2-hidroxi-2-metilpropanoil)-2-oxo-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(2-hidroxi-2-metilpropanoil)-1-(metilsulfonil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

6-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1-(*N*-metilglicil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

1-acetil-5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il|metil}-3-(*N*-metilglicil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1-glicoloil-3-(*N*-metilglicil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

5-{[3-cloro-4-|(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1-(2-hidroxi-2-metilpropanoil)-3-(*N*-metilglicil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1,3-bis(*N*-metilglicil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

5-{[3-cloro-4-|(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1-(2-hidroxipropanoil)-3-(*N*-metilglicil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1-(2-hidroxi-3-metilbutanoil)-3-(*N*-metilglicil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(*N*-metilglicil)-2-oxo-2,3-dihidro-1*H*-bencimidazol-1-carbcxamida,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(N-metilglicil)-1-(metilsulfonil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

6-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1-(3-hidroxipropanoil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

1-acetil-5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(3-hidroxipropanoil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1-glicoloil-3-(3-hidroxipropanoil)-1,3-

dihidro-2*H*-bencimidazol-2-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1-(2-hidroxi-2-metilpropanoil)-3-(3-hidroxipropanoil)-1 3-dihidro-2*H*-bencimidazol-2-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(3-hidroxipropanoil)-1-(*N*-metilglicil)-1,3-dihidro-2*H*-benc midazol-2-ona,

5-{[3-cloro-4-,(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1,3-bis(3-hidroxipropanoil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

5-{[3-cloro-4-|(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1-(3-hidroxi-3-metilbutanoil)-3-(3-hidroxipropanoil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(3-hidroxipropanoil)-2-oxo-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(3-hidroxipropanoil)-1-(metilsulfonil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

6-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1-(3-hidroxi-3-metilbutanoil)-1,3-dihidro-2*H*-bencimidazol-2-ona

1-acetil-5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(3-hidroxi-3-metilbutanoil)-1,3-dihidro-2*H*-bencimidazol-2-ona

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1-glicoloil-3-(3-hidroxi-3-metilbutanoil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(3-hidroxi-3-metilbutanoil)-1-(2-hidroxi-2-metilpropanoil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-

1(2*H*)-il]metil}-3-(3-hidroxi-3-metilbutanoil)-1-(*N*-metilglicil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(3-hidroxi-3-metilbutanoil)-1-(3-hidroxipropanoil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1,3-bis(3-hidroxi-3-metilbutanoil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(3-hidroxi-3-metilbutanoil)-2-oxo-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(3-hidroxi-3-metilbutanoil)-1-(metilsulfonil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

6-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-2-oxo-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

3-acetil-6-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-2-oxo-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

6-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-glicoloil-2-oxo-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

6-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(2-hidroxi-2-metilpropanoil)-2-oxo-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

6-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(*N*-metilglicil)-2-oxo-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

6-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(3 hidroxipropanoil)-2-oxo-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

6-{[3-cloro-4- (2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(3-hidroxi-3-metilbutanoil)-2-oxo-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

5-{[3-cloro-4-|(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-2-oxo-1*H*-bencimidazol-1,3-dicarboxamida

6-{[3-cloro-4-|(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(metilsulfonil)-2-oxo-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

6-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1-(metilsulfonil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

1-acetil-5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(metilsulfonil)-1,3-dihidro-2*H*-bencimidazol-2-ona

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1-glicoloil-3-(metilsulfonil)-1,3-dihidro-2*H*-bencimidazol-2-ona

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1-(2-hidroxi-2-metilpropanoil)-3-(metilsulfonil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1-(*N*-metilglicil)-3-(metilsulfonil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1-(3-hidroxipropanoil)-3-(metilsulfonil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1-(3-hidroxi-3-metilbutanoil)-3-(metilsulfonil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(metilsulfonil)-2-oxo-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1,3 bis(metilsulfonil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

3-bencil-4-hidroxi-1-(2-feniletil)piridin-2(1*H*)-ona,

1-bencil-4-hydroxy-2-oxo-1,2-dihidropiridina-3-carbaldehido,

1-bencil-4-cloro-2-oxo-1,2-dihidropiridina-3-carbaldehído,

5-cloro-1-(4-clorobencil)-6-oxo-1,6-dihidropiridina-3-carboxilato de metilo,

5-bromo-1-(2-cloro-6-fluorobencil)-3-metilpiridin-2(1*H*)-ona,

3-bromo-1-(2,6-diclorofenil)-4-[(4-fluorofenil)etinil]-6-metilpiridin-2(1*H*)-ona,

3-bromo-1-(2,6-diclorofenil)-4-[(4-fluorofenil)etinil]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]benzoato de metilo,

4-[(2,4-difluorobencil)oxi]-1-(3-fluorobencil)-2-oxo-1,2-dihidropiridina-3-carbonitrilo,

4-[(2,4-difluorobencil)oxi]-6-(hidroximetil)-1-(2,4,6-trifluorofenil)piridin-2(1*H*)-ona,

4-[(2,4-difluorobencil)oxi]-6-metil-1-[2-(trifluorometil)fenil]piridin-2(1*H*)-ona,

3-[4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]benzaldehido,

4-[(2,4-difluorobencil)oxi]-1-(2,6-difluoro-4-morfolina-4-ilfenil)-6-metilpiridin-2(1*H*)-ona,

4-[(2,4-difluorobencil)oxi]-1-[2,6-difluoro-4-(4-metilpiperazin-1-il)fenil]-6-metilpiridin-2(1*H*)-ona,

acido 3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]benzoico,

4-[(2,4-difluorobencil)oxi]-1-[4-(dimetilamino)-2,6-difluorofenil]-6-metilpiridin-2(1*H*)-ona,

4-[(2,4-difluorobencil)oxi]-1-{2,6-difluoro-4-[(2-hidroxietil)(metil)amino]fenil}-6-metilpiridin-2(1*H*)-ona,

3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]benzoato de metilo,

acido 3-[4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-4-metilbenzoico,

4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorofenil)-6-(hidroximetil)piridin-2(1*H*)-ona,

3-bromo-1-{[5-(clorometil)pirazin-2-il]metil}-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

1-[2-cloro-5-(hidroximetil)fenil]-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

4-[(2,4-difluorobencil)oxi]-1-(2,6-difluoro-4-hidroxifenil)-6-metilpiridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-[4-(hidroximetil)-2-metoxifenil]-6-metilpiridin-2(1*H*)-ona,

3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]4-metilbenzoato de metilo,

3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-{3-[(4-(metilpiperazin-1-il)carbonil]fenil}piridin-2(1*H*)-ona,

3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-*N*-[2-dimetilamino)etil]benzamida,

3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-*N*-(2-metoxietil)benzamida,

3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-*N*-[2-dimetilamino)etil]-*N*-metilbenzamida,

3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-*N*-(2-hidroxietil)-*N*-metilbenzamida,

3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-

oxopirıdın-1(2*H*)-ıl|-*N*-(2-metoxıetıl)-*N*-metılbenzamıda,

4-[3-bromo-4-[(2,4-dıfluorobencıl)oxı]-6-metıl-2-oxopırıdın-1(2*H*)-ıl|benzamıda,

3-[3-cloro-4-[(2,4-dıfluorobencıl)oxı]-6-metıl-2-oxopırıdın-1(2*H*)-ıl -4-fluorobenzoato de metılo,

acıdo 4-[4-[(2,4-dıfluorobencıl)oxı]-6-metıl-2-oxopırıdın-1(2*H*)-ıl]-3-metılbenzoıco,

1-(4-bromo-2-metılfenıl)-4-[(2,4-dıfluorobencıl)oxı]-6-metılpırıdın-2(1*H*)-ona,

1-[(1-acetıl-1*H*-ındol-5-ıl)metıl]-3-cloro-4-[(2,4-dıfluorobencıl)oxı]pırıdın-2(1*H*)-ona,

3-bromo-4-[(2,4-dıfluorobencıl)oxı]-6-metıl-1-[(5-metılpırazın-2-ıl)metıl]pırıdın-2(1*H*)-ona,

2-({[3-bromo-1-(2,6-dıfluorofenıl)-6-metıl-2-oxo-1,2-dıhıdropırıdın-4-ıl]oxy}metıl)-3,5-dıfluorobencılcarbamato de metılo,

3-bromo-4-[(2,4-dıfluorobencıl)oxı]-1-{[5-(hıdroxımetıl)pırazın-2-ıl]metıl}-6-metılpırıdın-2(1*H*)-ona,

4-{[3-bromo-4-[(2,4-dıfluorobencıl)oxı]-6-metıl-2-oxopırıdın-1(2*H*)-ıl]metıl}-*N*,*N*-dımetılbenzamıda,

3-[3-bromo-4-[(2,4-dıfluorobencıl)oxı]-6-metıl-2-oxopırıdın-1(2*H*)-ıl]-*N*-(2-hıdroxıetıl)-4-metılbenzamıda,

3-bromo-4-[(2,4-dıfluorobencıl)oxı]-6-metıl-1-{4-[(4-(metılpıperazın-1-ıl)carbonıl]bencıl}pırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-(1*H*-ındol-5-ılmetıl)pırıdın-2(1*H*)-ona,

3-[3-bromo-4-[(2,4-dıfluorobencıl)oxı]-6-metıl-2-oxopırıdın-1(2*H*)-ıl]-*N*-metılbenzamıda,

3-[3-bromo-4-[(2,4-dıfluorobencıl)oxı]-6-metıl-2-oxopırıdın-1(2*H*)-ıl]benzamıda,

3-cloro-4-[(2,4 dıfluorobencıl)oxı]-1-{[5-(hıdroxımetıl)pırazın-2-ıl]metıl}-6-metılpırıdın-2(1*H*)-ona,

3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-*N*-(2-metoxietil)-4-metilbenzamida,

3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-*N*,4-dimetilbenzamida,

3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il -*N*,*N*,4-trimetilbenzamida,

3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-[2-metil-5-(morfolin-4-ilcarbonil)fenil]piridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-[5-(1-hidroxi-1-metiletil)-2-metilfenil]-6-metilpiridin-2(1*H*)-ona,

1-(2-bromobencil)-3-[(2-bromobencil)oxi]piridin-2(1*H*)-ona,

1-(2-bromobencil)-3-[(2-bromobencil)oxi]piridin-2(1*H*)-ona,

3-bromo-1-(4-metoxibencil)-4-fenoxipiridin-2(1*H*)-ona,

1-bencil-2-oxo-4-fenoxi-1,2-dihidropiridina-3-carbaldehido,

3-bromo-4-(2,4-difluoro-benciloxi)-1-(3-dimetilaminometil-bencil)-6-metil-1H-piridin-2-ona,

N-{3-[3-bromo-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-ilmetil]-bencil}-2-hidroxi-acetamida

3-bromo-4-(2,4-difluoro-benciloxi)-6-metil-1-[4-(piperidina-1-carbonil)-bencil]-1H-piridin-2-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorofenil)-6-[(etoxiamino)metil]piridin-2(1*H*)-ona,

4-[3-bromo-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-ilmetil]-N-isopropil-benzamida,

hidrocloruro de *N*-(3-aminopropil)-4-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]metil}benzamida,

3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-*N*,4-dimetilbenzamida,

4-[3-bromo-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-ilmetil]-N-N-bis-(2-hidroxi-etil)-benzamida,

3-bromo-4-(2,4-difluoro-benciloxi)-6-metil-1-[4-(pirrolidina-1-carbonil)-bencil]-1H-piridin-2-ona,

4-[3-bromo-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-ilmeti ]-N-hidroxi-benzamida,

4-[3-bromo-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-ilmetil]-N-metil-benzamida,

4-[3-bromo-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-ilmeti]]-N-(2-dimetilamino-etil)-benzamida,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-(1*H*-indazol-5-ilmetil)piridin-2(1*H*)-ona,

3-bromo-4-(2,4-difluoro-benciloxi)-6-metil-1-[4-(4-metil-piperazina-1-carbonil)-bencil]-1H-piridin-2-ona,

3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-4-metilbenzaldehido,

3-bromo-4-(2,4-difluoro-benciloxi)-1-(4-dimetilaminometil-bencil)-6-metil-1H-piridin-2-ona,

3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-*N*-(2-metoxietil)-4-metilbenzamida,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-[2-(dimetilamino)-4,6-difluorofenil]-6-metilpiridin-2(1*H*)-ona,

hidrocloruro de *N*-(2-aminoetil)-4-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]metil}benzamida,

4-[3-bromo-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-ilmetil]-N-(2-hidroxi-etil)-benzamida,

3-bromo-4-(2,4-difluoro-benciloxi)-1-(4-hidroximetil-bencil)-6-metil-1H-piridin-2-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[2,6-difluoro-4-(4-metilpiperazin-1-il)fenil]-6-metilpiridin-2(1*H*)-ona,

3-bromo-4-[(2,4 difluorobencil)oxi]-1-[2-

(dimetilamino)-4,6-difluorofenil]-6-metilpiridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-[2,6-difluoro-4-(4-metilpiperazin-1-il)fenil]-6-metilpiridin-2(1*H*)-ona,

4-[3-bromo-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-ilmetil]-N-(2-metoxi-etil)-benzamida,

3-bromo-4-(2,4 difluoro-benciloxi)-1-{4-[(2-hidroxi-etilamino)-metil]-bencil}-6-metil-1H-piridin-2-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorofenil)-6-[(dimetilamino)metil]piridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-[2-metil-5-(morfolin-4-ilcarbonil)fenil]piridin-2(1*H*)-ona,

3-bromo-4-(2,4-difluoro-benciloxi)-6-metil-1-(4-metilaminometil-bencil)-1H-piridin-2-ona,

3-bromo-4-(2,4-difluoro-benciloxi)-6-metil-1-[4-(morfolina-4-carbonil)-bencil]-1H-piridin-2-ona,

*N*-(2-aminoetil)-3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il] benzamida,

hidrocloruro de *N*-(3-aminopropil)-3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]benzamida,

4-[3-bromo-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-ilmetil]-N-(2-metoxi-etil)-N-metil-benzamida,

1-(4-aminometil-bencil)-3-bromo-4-(2,4-difluoro-benciloxi)-6-metil-1H-piridin-2-ona,

hidrocloruro de 3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-[4-(piperazin-1-ilcarbonil)bencil]piridin-2(1*H*)-ona,

3-bromo-4-(2,4-difluoro-benciloxi)-1-[4-(isopropilamino-metil)bencil]-6-metil-1H-piridin-2-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-(dimetilfenil)-6-met_lpiridin-2(1*H*)-ona,

3-bromo-4-(2,4-difluoro-benciloxi)-1-{3-[(2-hidroxi-etilamino)-metil]-bencil}-6-metil-1H-piridin-2-ona,

1-(3-aminometil-bencil)-3-bromo-4-(2,4-difluoro-benciloxi)-6-metil-1H-piridin-2-ona,

3-bromo-4-(2,4 difluoro-benciloxi)-1-(4-hidroxi-bencil)-6-metil-1H-piridin-2-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorofenil)-6-[(dimetilamino)metil]piridin-2(1*H*)-ona,

N-{3-[3-bromo-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-ilmetil]-bencil}-acetamida,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-{2,6-difluoro-4-[(2-hidroxietil)(metil)amino]fenil}-6-metilpiridin-2(1*H*)-ona,

3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]benzoato de etilo,

trifluoroacetato de 1-[3-(aminometil)bencil]-3-bromo-4-[(2,4-difluorobencil)oxi]piridin-2(1*H*)-ona,

1-(3-{[Bis(2-hidroxi-etil)-amino]-metil}-bencil)-3-bromo-4-(2,4-difluoro-benciloxi)-6-metil-1H-piridin-2-ona,

3-bromo-4-(2,4-difluoro-benciloxi)-1-[3-(isopropilamino-metil)bencil]-6-metil-1H-piridin-2-ona,

éster terc-butílico de acido {3-[3-bromo-4-(2,4-difluoro-benciloxi)-2-oxo-2H-piridin-1-ilmetil]-bencil}-carbamico,

3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]benzamida,

3-bromo-4-(2,4-difluoro-benciloxi)-1-[4-(1-hidroxi-1-metil-etil)-bencil]-6-metil-1H-piridin-2-ona,

3-bromo-4-(2,4-difluoro-benciloxi)-1-(3-dimetilaminometil-bencil)-1H-piridin-2-ona,

3-bromo-4-(2,4-difluoro-benciloxi)-6-metil-1-(3-piperidin-1-ilmetil-bencil)-1H-piridin-2-ona,

3-bromo-4-[(2,4-difluorobenzil)oxi]-1-(2,6-difluorofenil)-6-{[(2-metoxietil)amino]metil}piridin-2(1*H*)-ona,

3-[3-bromo-4-[(2,4-difluorobenzil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-*N*-metilbenzamida,

3-bromo-4-[(2,4-difluorobenzil)oxi]-1-{2,4-difluoro-6-[(2-hidroxietil) (metil)amino]fenil}-6-metilpiridin-2(1*H*)-ona,

3-bromo-4-(2,4-difluoro-benziloxi)-6-metil-1-(3-morfolin-4-ilmetil-benzil)-1H-piridin-2-ona

3-bromo-1-(2,6-dimetilfenil)-6-metil-4-[(2,4,6-trifluorobenzil)oxi]piridin-2(1*H*)-ona,

3-bromo-1-(2,6-dimetilfenil)-6-metil-4-[(2,4,6-trifluorobenzil)oxi]piridin-2(1*H*)-ona,

1-(4-{[Bis(2-hidroxi-etil)-amino]-metil}-benzil)-3-bromo-4-(2,4-difluoro-benziloxi)-6-metil-1H-piridin-2-ona,

3-bromo-4-[(2,4-difluorobenzil)oxi]-1-(2,6-difluoro-4-morfolin-4-ilfenil)-6-metilpiridin-2(1*H*)-ona,

4-benziloxi-3-bromo-1-(4-fluoro-benzil)-1H-piridin-2-ona,

4-[3-cloro-4-(2,4-difluoro-benziloxi)-2-oxo-2H-piridin-1-ilmetil]-benzamida,

3-[3-bromo-4-[(2,4-difluorobenzil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-*N*,*N*,4-trimetilbenzamida,

3-[3-bromo-4-[(2,4-difluorobenzil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-*N*-isopropilbenzamida,

4-[3-bromo-4-(2,4-difluoro-benziloxi)-6-metil-2-oxo-2H-piridin-1-ilmetil]-benzamida,

4-[3-bromo-4-(2,4-difluoro-benziloxi)-6-metil-2-oxo-2H-piridin-1-ilmetil]-benzonitrilo,

3-bromo-4-(2,4-difluoro-benziloxi)-6-metil-1-(3-piperazin-1-ilmetil-benzil)-1H-piridin-2-ona,

4-[3-bromo-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-ilmetil]-N-(2-hidroxi-etil)-N-metil-benzamida

4-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il|-3-clorobenzoato de metilo,

3-bromo-4-(2,4-difluoro-benciloxi)-6-metil-1-[3-(morfolina-4-carbon_l)-bencil]-1H-piridin-2-ona,

3-[3-bromo-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-ilmeti]]-N-N-bis-(2-hidroxi-etil)-benzamida,

ester metílicc de acido 4-[3-bromo-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-ilmetil]-benzoico,

3-[3-bromo-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-ilmetil}-N-hidroxi-benzamida,

3-bromo-4-(2,4-difluoro-benciloxi)-1-(3-hidroximetil-bencil)-6-metil-1H-piridin-2-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-(3-fluorobencil)piridin-2(1*H*)-ona,

3-bromo-4-(2,4-difluoro-benciloxi)-1-(3-fluoro-bencil)-1H-piridin-2-ona,

N-{3-[3-bromo-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-ilmetil]-bencil}-metanosulfonamida,

3-bromo-4-(2,4-difluoro-benciloxi)-6-metil-1-[3-(pirrolidina-1-carbonil)-bencil]-1H-piridin-2-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-(piridin-3-ilmetil)piridin-2(1*H*)-ona,

hidrocloruro de *N*-(3-aminopropil)-3-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]metil}benzamida,

3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-(piridin-3-ilmetil)piridin-2(1*H*)-ona,

3-bromo-4-(2,4-difluoro-benciloxi)-1-(3-metilaminometil-bencil)-1H-piridin-2-ona,

4-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-

oxopiridin-1(2*H*)-il]-3,5-diclorobencenosulfonamida,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-[4-(dimetilamino)-2,6-difluorofenil]-6-metilpiridin-2(1*H*)-ona,

3-bromo-4-(2,4-difluoro-benciloxi)-6-metil-1-(4-piperidin-1-ilmetil bencil)-1H-piridin-2-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-(piridin-4-ilmetil)piridin-2(1*H*)-ona,

hidrocloruro de *N*-(2-aminoetil)-3-{[3-bromo-4-[(2,4-difluorobencil)oxi] 6-metil-2-oxopiridin-1(2*H*)-il]metil}benzamida,

3-bromo-1-[2-cloro-5-(hidroximetil)fenil]-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-(difluorofenil)-6-metilpiridin-2(1*H*)-ona,

3-cloro-1-[2-cloro-5-(hidroximetil)fenil]-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-*N*-(2-hidroxietil)-4-metilbenzamida,

2-{3-[3-bromo-4-(2,4-difluoro-benciloxi)-2-oxo-2H-piridin-1-ilmetil]-fenil}-acetamida,

hidrocloruro de 3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-[3-(piperazin-1-ilcarbonil)bencil]piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-(2,6-(difluorofenil)-6-metilpiridin-2(1*H*)-ona,

ester metilico de acido 4-[3-bromo-4-(2,4-difluoro-benciloxi)-2-oxo-2H-piridin-1-ilmetil]-benzoico,

1-(3-aminometil-2-fluoro-bencil)-3-bromo-4-(2,4-difluoro-benciloxi)-1H-piridin-2-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorofenil)-6-(morfolin-4-ilmetil)piridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-(4-fluorobencil)piridin-2(1*H*)-

ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-(1*H*-indol-5-ilmetil)piridin-2(1*H*)-ona,

trifluoroacetato de 1-[3-(aminometil)bencil]-3-bromo-4-[(4-fluorobencil)oxi]piridin-2(1*H*)-ona,

trifluoroacetato de 1-[3-(2-aminoetil)bencil]-3-bromo-4-[(2,4-difluorobencil)oxi]piridin-2(1*H*)-ona,

1-[3-(aminometil)bencil]-3-bromo-4-[(4-fluorobencil)oxi]piridin-2(1*H*)-ona,

3-bromo-1-(2,6-diclorofenil)-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-*N*-(2-hidroxietil)benzamida,

3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-(piridin-4-ilmetil)piridin-2(1*H*)-ona,

3-bromo-4-(2,4-difluoro-benciloxi)-1-(4-metoxi-bencil)-6-metil-1H-piridin-2-ona,

4-[3-bromo-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-ilmetil]-N,N-dimetil-benzamida,

3-bromo-6-metil-1-(piridin-4-ilmetil)-4-[(2,4,6-trifluorobencil)oxi]piridin-2(1*H*)-ona,

4-[3-bromo-4-(2,4-difluoro-benciloxi)-2-oxo-2H-piridin-1-ilmetil]-benzamida,

3-[3-bromo-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-ilmetil]-N-metil-benzamida,

ester metílico de ácido {3-[3-bromo-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-ilmetil]-bencil}-carbamico,

3-bromo-4-[(2,6-difluorobencil)oxi]-1-(2,6-(dimetilfenil)-6-metilpiridin-2(1*H*)-ona,

4-[3-bromo-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-ilmetil]-benzonitrilo,

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3-bromo-4-[(2,4-difluorobenzil)oxi]-6-metil-1-(piridin-4-ilmetil)piridin-2(1*H*)-ona,

1-benzil-4-(benziloxi)-3-bromo-6-metilpiridin-2(1*H*)-ona,

1-benzil-4-benziloxi-3-bromo-6-metil-1H-piridin-2-ona,

1-benzil-4-(benziloxi)-3-bromo-6-metilpiridin-2(1*H*)-ona,

1-benzil-3-bromo-4-(2,4-difluoro-benziloxi)-6-metil-1H-piridin-2-ona,

{3-[3-bromo-4-(2,4-difluoro-benziloxi)-2-oxo-2H-piridin-1-ilmetil]-fenil}-acetonitrilo,

3-[3-bromo-4-(2,4-difluoro-benziloxi)-6-metil-2-oxo-2H-piridin-1-ilmetil]-N-(2-hidroxi-etil)-benzamida,

3-cloro-4-(2,4-difluoro-benziloxi)-1-(3-fluoro-benzil)-1H-piridin-2-ona,

1-alil-3-cloro-4-(2,4-difluoro-benziloxi)-6-metil-1H-piridin-2-ona,

3-cloro-4-(2,4-difluoro-benziloxi)-1-[4-isopropilamino-metil)benzil]-1H-piridin-2-ona,

3-[3-cloro-4-[(2,4-difluorobenzil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]4-metilbenzoato de metilo,

3-bromo-4-[(2,4-difluorobenzil)oxi]-6-(hidroximetil)-1-(2,4,6-trifluorofenil)piridin-2(1*H*)-ona,

3-bromo-4-(2,4-difluoro-benziloxi)-6-metil-1-(4-piperazin-1-ilmetil-benzil)-1H-piridin-2-ona,

3-bromo-4-[(2,4-difluorobenzil)oxi]-1-(2,6-(difluorofenil)-6-(hidroximetil)piridin-2(1*H*)-ona,

3-[3-bromo-4-(2 4-difluoro-benziloxi)-6-metil-2-oxo-2H-piridin-1-ilmetil]-N,N-dimetil-benzamida,

3-bromo-1-(3-fluorobenzil)-4-[(3-metilbenzil)oxi]piridin-2(1*H*)-ona,

3-bromo-1-(3-fluoro-benzil)-4-(3-metil-benziloxi)-1H-

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pirıdın-2-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-(1,2,3,4-tetrahıdroısoquınol·n-5-ılmetıl)pırıdın-2(1*H*)-ona,

3-bromo-1-(3-f_uorobencıl)-4-[(3-metılbencıl)oxı]pırıdın-2(1*H*)-ona,

trıfluoroacetato de 3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-(ısoquınolın-5-ılmetıl)pırıdın-2(1*H*)-ona,

3-[3-bromo-4-(2,4-dıfluoro-bencıloxı)-6-metıl-2-oxo-2H-pırıdın-1-ılmetıl]-benzamıda,

trıfluoroacetato de 3-bromo-4-[(2,4-dıfluorobencıl)oxı]-6-metıl-1-({5-[(4-(metılpıperazın-1-ıl)carbonıl]pırazın-2-ıl}metıl)pırıdın-2(1*H*)-ona,

3-bromo-4-[(2,4-dıfluorobencıl)oxı]-1-[5-(hıdroxımetıl)-2-metılfenıl]-6-metılpırıdın-2(1*H*)-ona,

1-alıl-3-bromo-4-[(2,4-dıfluorobencıl)oxı]-6-metılpırıdın-2(1*H*)-ona,

3-bromo-4-[(2,4-dıfluorobencıl)oxı]-1-(pırıdın-3-ılmetıl)pırıdın-2(1*H*)-ona,

3-bromo-4-[(2,4-dıfluorobencıl)oxı]-1-(2-metoxı-6-metılfenıl)-6-metılpırıdın-2(1*H*)-ona,

3-bromo-4-[(2,4-dıfluorobencıl)oxı]-1-(2-metoxı-6-metılfenıl)-6-metılpırıdın-2(1*H*)-ona,

3-[3-bromo-4-(2,4-dıfluoro-bencıloxı)-2-oxo-2H-pırıdın-1-ılmetıl]-bənzamıda,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-6-(hıdroxımetıl)-1-(2,4,6-trıfluorofenıl)pırıdın-2(1*H*)-ona,

3-bromo-4-[(2,4-dıfluorobencıl)oxı]-6-metıl-1-[2-(trıfluorometıl)fenıl]pırıdın-2(1*H*)-ona,

ácıdo 4-[3-bromo-4-(2,4-dıfluoro-bencıloxı)-6-metıl-2-oxo-2H-pırıdın-1-ılmetıl]-benzoıco,

3-bromo-4-(2,4-dıfluoro-bencıloxı)-6-metıl-1-(4-morfolın-4-ılmetıl-bencıl)-1H-pırıdın-2-ona,

4-(2,4-difluoro-benciloxi)-1-(3-fluoro-bencil)-3-yodo-1H-piridin-2-ona

3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-(2,4,6-trifluorofenil)piridin-2(1*H*)-ona,

3-[3-bromo-4-[ 2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-*N*-hidroxibenzamida,

3-bromo-1-(2,6-diclorofenil)-4-[(2,6-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

3-(4-benciloxi-3-bromo-2-oxo-2H-piridin-1-ilmethil)-benzonitrilo,

3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-[3-(pirrolidin-1-ilcarbonil)fenil]piridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2-fluorobencil)piridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-(4-metilbencil)piridin-2(1*H*)-ona,

3-{[3-cloro-4-[(2,4-difluorobencil)amino]-6-metil-2-oxopiridin-1(2*H*)-il]metil}benzonitrilo,

3-[3-bromo-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-ilmetil]-N-isopropil-benzamida,

3-bromo-1-(4-bromo-2,6-difluorofenil)-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

3-bromo-4-[(4-fluorobencil)oxi]-6-metil-1-(piridin-3-ilmetil)piridin-2(1*H*)-ona,

3-bromo-4-[(4-fluorobencil)oxi]-6-metil-1-(piridin-4-ilmetil)piridin-2(1*H*)-ona,

3-bromo-4-[(4-fluorobencil)oxi]-6-metil-1-(piridin-4-ilmetil)piridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-(4-clorobencil)piridin-2(1*H*)-ona

4-benciloxi-3-bromo-1-(4-cloro-bencil)-1H-piridin-2-ona,

3-bromo-1-(4-fluorobencil)-4-[(4-fluorobencil)oxi]piridin-2(1*H*)-ona,

3-bromo-1-(2,6-diclorofenil)-4-[(4-fluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

3-bromo-1-(4-fluoro-bencil)-4-(4-fluoro-benciloxi)-1H-piridin-2-ona,

4-[3-bromo-4-[ 2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]benzoato de metilo,

acido 4-(4-benciloxi-3-bromo-2-oxo-2H-piridin-1-ilmethil)-benzoico,

acido 4-{[4-(benciloxi)-3-bromo-2-oxopiridin-1(2*H*)-il]metil}benzoico,

3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-1-(2,4,6-trifluorofenil)piricin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-(2-fluorobencil)piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-(2,6-(difluorofenil)-6-(hidroximetil)piridin-2(1*H*)-ona,

hidrocloruro de *N*-(2-aminoetil)-4-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]benzamida,

4-benciloxi-3-bromo-1-(4-metilsulfanil-bencil)-1H-piridin-2-ona,

1-bencil-4-benciloxi-3-cloro-1H-piridin-2-ona,

4-(benciloxi)-3-bromo-1-[4-(metiltio)bencil)]piridin-2(1*H*)-ona,

1-bencil-4-(benciloxi)-3-cloropiridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-{[5-(hidroximetil)pirazin-2-il]metil}-6-metilpiridin-2(1*H*)-ona,

3-bromo-1-(2,6-dimetilfenil)-4-[(4-fluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

3-bromo-1-(2,6-dimetilfenil)-4-[(4-fluorobencil)oxi]-

6-metilpiridin-2(1*H*)-ona,

3-bromo-4-(2,4 difluoro-benciloxi)-1-[3-isopropilamino-metil)bencil]-1H-piridin-2-ona,

3-[3-cloro-4-(2,4-difluoro-benciloxi)-2-oxo-2H-piridin-1-ilmetil]-2-fluoro-benzamida,

5-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]metil}-*N*-(2,3-hidroxipropil)pirazin-2-carboxamida,

éster etílico de acido {3-[3-bromo-4-(2,4-difluoro-benciloxi)-2-oxo-2H-piridin-1-ilmetil]-fenil}-acetico,

4-(4-benciloxi-3-bromo-2-oxo-2H-piridin-1-ilmethil)-N-hidroxi-benzamidina,

4-{[4-(benciloxi)-3-bromo-2-oxopiridin-1(2*H*)-il]metil}-*N*-hidroxibencenocarboximidamida,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]metil}pirazina-2-carboxilato de etilo,

3-bromo-4-(2,4-difluoro-benciloxi)-1-(3-metoxi-bencil)-1H-piridin-2-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-[(5-metilpirazin-2-il)metil]piridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-(3-(metoxibencil)piridin-2(1*H*)-ona,

éster metílico de ácido 4-(4-benciloxi-3-bromo-2-oxo-2H-piridin-1-ilmetil)-benzoico,

3-bromo-4-(2,4-difluoro-benciloxi)-1-(4-dimetilaminometil-bencil)-1H-piridin-2-ona,

3-cloro-4-(2,4-difluoro-benciloxi)-1-(3-metanosulfonil-bencil)-1H-piridin-2-ona,

ester metílico de acido 4-(4-benciloxi-3-bromo-2-oxo-2H-piridin-1-ilmethil)-benzoico,

4-{[4-(benciloxi)-3-bromo-2-oxopiridin-1(2*H*)-il]metil}benzoato de metilo,

5-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]metil}pirazina-2-carboxilato de etilo,

4-{[4-(benciloxi)-3-bromo-2-oxopiridin-1(2*H*)-il]metil}benzonitrilo,

4-(4-benciloxi 3-bromo-2-oxo-2H-piridin-1-ilmethil)-benzonitrilo,

ester terc-butílico de acido {3-[3-bromo-4-(4-fluoro-benciloxi)-2-oxo-2H piridin-1-ilmetil]-bencil}-carbamico,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-[5-(1-hidroxi-1-metiletil)-2-metilfenil]-6-metilpiridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-(2,6-diclorofenil)-6-metilpiridin-2(1*H*)-ona,

1-(3-aminometil-bencil)-4-benciloxi-3-bromo-1H-piridin-2-ona,

3-bromo-4-[(4-fluorobencil)oxi]-1-(piridin-4-ilmetil)piridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-(4-bromobencil)piridin-2(1*H*)-ona,

4-benciloxi-3-bromo-1-(4-bromo-bencil)-1H-piridin-2-ona,

5-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-(difluorofenil)-6-oxo-1,6-dihidropiridina-2-carbaldehido,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[5-(hidroximetil)pirazin-2-il]metil}-6-metilpiridin-2(1*H*)-ona,

4-(4-benciloxi-3-bromo-2-oxo-2H-piridin-1-ilmethil)-benzamida,

hidrocloruro de 3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-[3-(piperazin-1-ilcarbonil)fenil]piridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)amino]-1-(3-(fluorobencil)piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-1-[(5-metilpirazin-2-il)metil]piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[5-(hidroximetil)-2-metilfenil]-6-metilpiridin-2(1*H*)-ona,

3-bromo-1-(3-fluorobencil)-4-[(4-fluorobencil)oxi]piridin-2(1*H*)-ona,

3-bromo-1-(3-fluoro-bencil)-4-(4-fluoro-benciloxi)-1H-piridin-2-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-[3-(morfolin-4-ilcarbonil)fenil]piridin-2(1*H*)-ona,

ester metilico de acido 3-(4-benciloxi-3-bromo-2-oxo-2H-piridin-1-ilmethil)-benzoico,

3-bromo-1-(3-fluorobencil)-4-{[2-(hidroximetil)bencil]oxi}piridin-2(1*H*)-ona,

3-bromo-1-(3-fluoro-bencil)-4-(2-hidroximetil-benciloxi)-1H-piridin-2-ona,

1-benzo[1,3]dicxol-5-ilmetil-3-bromo-4-(2,4-difluoro-benciloxi)-1H-piridin-2-ona,

3-bromo-4-[(2,6-difluorobencil)oxi]-6-metil-1-(piridin-4-ilmetil)piridin-2(1*H*)-ona,

3-bromo-4-[(3-clorobencil)oxi]-1-(3-fluorobencil)piridin-2(1*H*)-ona,

3-bromo-4-[(3-clorobencil)oxi]-1-(3-fluorobencil)piridin-2(1*H*)-ona,

3-bromo-4-(3-cloro-benciloxi)-1-(3-fluoro-bencil)-1H-piridin-2-ona,

4-(benciloxi)-3-bromo-1-(3-fluorobencil)piridin-2(1*H*)-ona,

4-benciloxi-3-bromo-1-(3-fluoro-bencil)-1H-piridin-2-ona,

3-bromo-4-(2,4-difluoro-benciloxi)-6-metil-1-[3-(piperidina-1-carbonil)-bencil]-1H-piridin-2-ona,

3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il] *N*,*N*-dimetilbenzamida,

éster metílico de acido 3-[3-cloro-4-(2,4-difluoro-benciloxi)-2-oxo-2H-piridin-1-ilmetil]-2-fluoro-benzoico,

1-(3-fluorobencil)-4-[(4-fluorobencil)oxi]-3-yodopiridin-2(1*H*)-ona,

1-(3-fluoro-bencil)-4-(4-fluoro-benciloxi)-3-yodo-1H-piridin-2-ona,

hidrocloruro de *N*-(3-aminopropil)-4-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]benzamida,

4-{[3-bromo-4-[(4-fluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}benzonitrilo,

4-[3-bromo-4-(4-fluoro-benciloxi)-2-oxo-2H-piridin-1-ilmetil]-benzonitrilo,

3-bromo-1-(3-fluoro-bencil)-4-(2,3,4-trifluoro-benciloxi)-1H-piridin-2-ona,

1-bencil-4-(benciloxi)-3-bromopiridin-2(1*H*)-ona,

5-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]metil}-*N*-(2-hidroxietil)-*N*-metilpirazina-2-carboxamida,

4-(4-benciloxi-3-bromo-2-oxo-2H-piridin-1-ilmetil)-benzonitrilo,

3-bromo-1-(2,4-difluorobencil)-4-[(2,4-difluorobencil)oxi]piridin-2(1*H*)-ona,

3-bromo-1-(2,4-difluoro-bencil)-4-(2,4-difluoro-benciloxi)-1H-piridin-2-ona,

4-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-*N*-(2-hidroxietil)benzamida,

3-bromo-4-[(4-fluorobencil)oxi]-1-(piridin-3-ilmetil)piridin-2(1*H*)-ona,

1-bencil-4-benciloxi-3-bromo-1H-piridin-2-ona,

3-bromo-1-(ciclopropilmetil)-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

1-(4-aminometil-bencil)-4-benciloxi-3-bromo-1H-piridin-2-ona,

3-bromo-1-(4-fluorobencil)-4-[(4-fluorobencil)amino]-6-metilpiridin-2(1*H*-ona,

éster metílico de ácido 3-[3-bromo-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-ilmetil]-benzoico,

5-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]metil}-*N*,*N*-dimetilpirazina-2-carboxamida,

3-bromo-4-[(4-fluorobencil)oxi]-6-metil-1-(piridin-2-ilmetil)piridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-(dimetilfenil)-6-metilpiridin-2(1*H*)-ona,

3-bromo-1-(2,6-diclorofenil)-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

4-(benciloxi)-1-(4-bromobencil)piridin-2(1*H*)-ona,

3-bromo-4-hidroxi-1-(4-hidroxibencil)piridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-[2-(trifluorometil)bencil)]piridin-2(1*H*)-ona,

1-bencil-4-[(3-clorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

hidrocloruro de 4-(benciloxi)-3-bromo-1-(piperidin-3-ilmetil)piridin-2(1*H*)-ona,

1-benzil-3-bromo-2-oxo-1,2-dihidropiridin-4-il metil(fenil)carbamato,

4-(bencilamino)-1-(3-fluorobencil)-6-metil-3-nitropiridin-2(1*H*)-ona,

4-[3-bromo-1-(3-fluorobencil)-2-oxo-1,2-dihidropiridin-4-il]piperazina-1-carboxilato *terc*-butílico

,

[4-(benciloxi)-3-bromo-2-oxopiridin-1(2*H*)-

ıl]metıl}acetato de etılo,

*N*- [3-bromo-1-(3-fluorobencıl)-2-oxo-1,2-dıhıdropırıdın-4-ıl]bencenosulfonamıda,

3-bromo-4-[(4-*terc*-butılbencıl)oxı]-1-(3-(fluorobencıl)pırıdın-2(1*H*)-ona,

*N*- [3-bromo-1-(3-fluorobencıl)-2-oxo-1,2-dıhıdropırıdın-4-ıl]-1-fenılmetılmetanosulfonamıda,

1-(bıfenıl-2-ılmetıl)-3-bromo-4-[(4-fluorobencıl)oxı]pırıdın-2(1*H*)-ona,

4-(bıfenıl-2- ılmetoxı)-3-bromo-1-(3-fluorobencıl)pırıdın-2(1*H*)-ona,

3-bromo-4-[(2,4-dıfluorofenıl)amıno]-1-(3-(fluorobencıl)pırıdın-2(1*H*)-ona,

4-(anılıno)-3-bromo-1-(3-fluorobencıl)pırıdın-2(1*H*)-ona,

4-{[3-bromo-1-(3-fluorobencıl)-2-oxo-1,2-dıhıdropırıdın-4-ıl]-1-amıno}benzoato de metılo,

3-bromo-1-(3-fluorobencıl)-4-[(3,4,5trımetoxıfenıl)amıno]pırıdın-2(1*H*)-ona,

3-bromo-1-(3-fluorobencıl)-4-[4-(4-fluorofenıl)pıperazın-1-ıl]pırıdın-2(1*H*)-ona,

trıfluoroacetato de 3-bromo-1-(3-fluorobencıl)-4-(4-metılpıperazın-1-ıl)pırıdın-2(1*H*)-ona,

*N*- [3-bromo-1-(3-fluorobencıl)-2-oxo-1,2-dıhıdropırıdın-4-ıl]-2,5-dıfluorobenzamıda,

*N*- [3-bromo-1-(3-fluorobencıl)-2-oxo-1,2-dıhıdropırıdın-4-ıl]-2,4-dıfluorobenzamıda,

3-bromo-1-(cıclohexılmetıl)-4-[(4-fluorobencıl)oxı]pırıdın-2(1*H*)-ona,

ácıdo 3-[4-(bencıloxı)-3-bromo-2-oxopırıdın-1(2*H*)-ıl]propanoıco,

*N*- [3-bromo-1-(3-fluorobencıl)-2-oxo-1,2-

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dihidropiridin-4-il]-*N*-(2,4-difluorofenil)urea,

3-[4-(benciloxi)-3-bromo-2-oxopiridin-1(2*H*)-il]propanamida

4-(benciloxi)-3-bromo-1-(3-morfolin-4-il-3-oxopropyl)piridin-2(1*H*)-ona,

hidrocloruro de *N*-(3-aminopropil)-3-[4-(benciloxi)-3-bromo-2-oxopiridin-1(2*H*)-il]propanamida,

hidrocloruro de 4-(benciloxi)-3-bromo-1-(3-oxo-3-piperazin-1-ilpropil)piridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-(2-morfolin-4-iletil)piridin-2(1*H*)-ona,

3-bromo-1-(3-fluorobencil)-4-{[4-fluoro-2-(trifluorometil)bencil]amino}piridin-2(1*H*)-ona,

hidrocloruro de *N*-(2-aminoetil)-3-[4-(benciloxi)-3-bromo-2-oxopiridin-1(2*H*)-il]propanamida

acido [3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]acetico

3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-(tetrahidrofuran-2-ilmetil)piridin-2(1*H*)-ona,

4-[(2,4-difluorobencil)oxi]-6-metil-1-(tetrahidrofuran-2-ilmetil)piridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridina-1(2*H*)-carboxilato de metilo,

1-alil-3-(2,4-difluorobencil)-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

4-(benciloxi)-1-(2,2-dietoxietil)piridin-2(1*H*)-ona,

*N*-acetil-3-[4-(benciloxi)-2-oxopiridin-1(2*H*)-il]alaninato de metilo,

*N*-acetil-3-[4-(benciloxi)-2-oxopiridin-1(2*H*)-il]alaninato de bencilo,

*N*-[(benciloxi)carbonil]-3[4-(benciloxi)-2-oxopiridin-1(2*H*)-il]alaninato de bencilo,

4-(benciloxi)-1-(2-oxopropil)piridin-2(1*H*)-ona,

5-{[4-(benciloxi)-2-oxopiridin-1(2*H*)-il]metil}-5-metilimidazolina-2,4-diona,

[4-(benciloxi)-2-oxopiridin-1(2*H*)-il] acetato de etilo,

2-[4-(benciloxi)-2-oxopiridin-1(2*H*)-il]acetamida,

1-bencil-4-(benciloxi)-3,5-dibromopiridin-2(1*H*)-ona,

4-(benciloxi)-1-etilpiridin-2(1*H*)-ona,

4-(benciloxi)-1-(4-*terc*-butilbencil)piridin-2(1*H*)-ona,

4-{[4-(benciloxi)-2-oxopiridin-1(2*H*)-il]metil} benzonitrilo,

3-{[4-(benciloxi)-2-oxopiridin-1(2*H*)-il]metil}piperidina-1-carboxilato *terc*-butílico,

1,3-dibencil-4-hidroxi-6-metilpiridin-2(1*H*)-ona,

1-bencil-6-metil-2-oxo-1,2-dihidropiridin-4-il metanosulfonato,

4-(benciloxi)-1-(4-bromobencil)piridin-2(1*H*)-ona,

4-(benciloxi)-3-bromopiridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-[2-(trifluorometil)bencil)]piridin-2(1*H*)-ona,

1-bencil-4-(1-naftilmetoxi)piridin-2(1*H*)-ona,

1-bencil-4-(benciltio)-3,5-dibromopiridin-2(1*H*)-ona,

1-bencil-4-[(2,6-diclorobencil)oxi]piridin-2(1*H*)-ona,

1-bencil-3-[(bencilamino)metil]-4-(benciloxiy)piridin-2(1*H*)-ona,

1-bencil-4-(benciloxi)-3-{[(2-ciclohexiletil)amino]metil}piridin-2(1*H*)-ona,

1-bencil-4-(benciltio)-5-metilpiridin-2(1*H*)-ona,

1-bencil-3-bromo-6-metil-2-oxo-1,2-dihidropiridin-4-il metanosulfonato,

1-bencil-3-bromo-6-metil-4-{[2-(trifluorometil)bencil]oxi}piridin-2(1*H*)-ona,

1-bencil-6-metil-2-oxo-1,2-dihidropiridin-4-il 4-bromobencenosulfonato,

1-bencil-4-[(3-clorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

1-bencil-3-bromo-6-metil-2-oxo-1,2-dihidropiridin-4-il 4-bromobencenosulfonato,

4-fenoxi-1-{[2-(trimetilsilil)etoxi]metil}piridin-2(1*H*)-ona,

1-bencil-4-fenoxipiridin-2(1*H*)-ona,

1-(4-metoxibencil)-4-fenoxipiridin-2(1*H*)-ona,

hidrocloruro de 3-bromo-4-hidroxi-1-(4-hidroxibencil)piridin-2(1*H*)-ona,

hidrocloruro de 4-(benciloxi)-3-bromo-1-(piperidin-3-ilmetil)piridin-2(1*H*)-ona,

1-bencil-4-[(2,6-diclorobencil)oxi]piridin-2(1*H*)-ona,

1-bencil-4-(benciloxi)-3,5-dibromopiridin-2(1*H*)-ona,

3-bromo-1-(3-fluorobencil)-4-[(*E*)-2-(4-fluorofenil)vinil]piridin-2(1*H*)-ona,

1-bencil-4-(benciloxi)-2-oxo-1,2-dihidropiridina-3-carbaldehido,

1-bencil-4-(benciloxi)piridin-2(1*H*)-ona,

1-bencil-4-(benciloxi)piridin-2(1*H*)-ona,

1-bencil-4-(benciltio)piridin-2(1*H*)-ona,

4-[3-cloro-4-[(2,4-difluorobencil)oxi] -2-oxopiridin-1(2*H*)-il]benzoato de metilo,

(5-nitro-2,6-dioxo-3,6-dihidropirimidin-1(2*H*)-il)acetato de bencilo,

3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxo-2*H*-1,2'-bipiridina-5'-carboxilato de etilo,

4-(benciloxi)-1-(4-metilbencil)piridin-2(1*H*)-ona,

carbamato de [5-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorofenil)-2-metil-6-oxo-1,6-dihidropiridin-3-

ıl]metılo,

4-(bencıloxı)-1-(4-clorobencıl)pırıdın-2(1*H*)-ona,

(2*E*)-4-[4-[(2,4-dıfluorobencıl)oxı]-6-metıl-2-oxopırıdın-1(2*H*)-ıl]but-2-enoato de metılo,

4-(bencıloxı)-1-(2-fluorobencıl)pırıdın-2(1*H*)-ona,

4-{[4-(bencıloxı)-3-bromo-2-oxopırıdın-1(2*H*)-ıl]metıl}pıperıdına-1-carboxılato *terc*-butılıco,

4-(bencıloxı)-1-(3-fluorobencıl)pırıdın-2(1*H*)-ona

3-bromo-4-[(2,4-dıfluorobencıl)oxı]-1-(2,6-(dıfluorofenıl)-5-(1,2-dıhıdroxıetıl)-6-metılpırıdın-2(1*H*)-ona,

1-bencıl-4-hıdroxı-6-metılpırıdın-2(1*H*)-ona,

4-({[3-bromo-1-(3-fluorobencıl)-2-oxo-1,2-dıhıdropırıdın-4-ıl]oxı}metıl)benzonıtrılo,

1-bencıl-4-(bencıloxı)-6-metılpırıdın-2(1*H*)-ona,

5-bromo-4-[(2,4-dıfluorobencıl)oxı]-1-(2,6-(dıfluorofenıl)-2-metıl-6-oxo-1,6-dıhıdropırıdına-3-carbaldehıdo oxıma,

1-bencıl-4-(bencıltıo)-3-metılpırıdın-2(1*H*)-ona,

1-bencıl-4-[(4-metılbencıl)oxı]pırıdın-2(1*H*)-ona,

1-bencıl-4-(bencıloxı)-3,5-dıbromo-6-metılpırıdın-2(1*H*)-ona,

1-bencıl-4-(bencıloxı)-3,5-dıbromo-6-metılpırıdın-2(1*H*)-ona,

3-bromo-1-(3-fluorobencıl)-4-(1-fenıletoxı)pırıdın-2(1*H*)-ona,

4-(bencıloxı)-1-[4-(trıfluorometıl)bencıl)]pırıdın-2(1*H*)-ona,

2-({[3-bromo-2-oxo-1-(pırıdın-3-ılmetıl)-1,2-dıhıdropırıdın-4-ıl]oxı}metıl)-5-fluorobenzonıtrılo,

5-bromo-4-[(2,4-dıfluorobencıl)oxı]-1-(2,6-(dıfluorofenıl)-2-metıl-6-oxo-1,6-dıhıdropırıdına-3-

carbonitrilo,

4-(benciloxi)-1-(3-fluorobencil)-3-(trifluorometil)piridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorofenil-6-metil-5-oxiran-2-ilpiridin-2(1*H*)-ona,

1-bencil-4-[(3-clorobencil)oxi]piridin-2(1*H*)-ona,

1-bencil-4-[(3-clorobencil)oxi]piridin-2(1*H*)-ona,

5-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-(difluorofenil)-2-metil-6-oxo-1,6-dihidropiridina-3-carbaldehido,

3-{[4-(benciloxi)-3-bromo-2-oxopiridin-1(2*H*)-il]metil}piperidina-1-carboxilato *terc*-butílico,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-(difluorofenil)-6-metil-5-vinilpiridin-2(1*H*)-ona,

4-(benciloxi)-1-[4-(trifluorometoxi)bencil]piridin-2(1*H*)-ona,

3-bromo-4-[(4-clorobencil)oxi]-1-[3-(fenoltio)etil]piridin-2(1*H*)-ona,

3-bromo-4-(4-cloro-benciloxi)-1-(2-fenilsulfanil-etil)-1H-piridin-2-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-(2-morfolin-4-iletil)piridin-2(1*H*)-ona,

4-[(2,4-difluorobencil)oxi]-6-(hidroximetil)-1-(piridin-3-ilmetil)piridin-2(1*H*)-ona,

trifluoroacetato de 4-{[2-(aminometil)-4-fluorobencil]oxi}-3-bromo-1-(2,6-difluorofenil)-6-metilpiridin-2(1H)-ona,

4-(benciloxi)-1-(4-fluorobencil)piridin-2(1*H*)-ona,

4-(benciloxi)-1-(4-fluorobencil)piridin-2(1*H*)-ona,

4-benciloxi-3-bromo-1-metanosulfonil-1H-piridin-2-ona,

4-[4-(benciloxi)-3-bromo-2-oxopiridin-1(2*H*)-il] piperidina-1-carboxilato *terc*-butílico,

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1-bencil-4-(benciloxi)-3-vinilpiridin-2(1*H*)-ona,

4-(benciloxi)-1-[4-(metiltio)bencil]piridin-2(1*H*)-ona,

3-bromo-4-(2,4-difluoro-benciloxi)-1-(2-metil-4-metilamino-pirimidin-5-ilmetil)-1H-piridin-2-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

1-bencil-3-bromo-4-{[2-(trifluorometil)bencil]oxi}piridin-2(1*H*)-ona,

1-bencil-3-bromo-4-{[2-(trifluorometil)bencil]oxi}piridin-2(1*H*)-ona,

4-[(2,4-difluorobencil)oxi]-1-[5-(hidroximetil)-2-metilfenil]-6-metilpiridin-2(1*H*)-ona,

4-(benciloxi)-1-[4-(metilsulfonil)bencil]piridin-2(1*H*)-ona,

4-fenoxi-1H-piridin-2-ona,

1-bencil-4-[(2-clorobencil)oxi]piridin-2(1*H*)-ona,

1-bencil-4-[(2-clorobencil)oxi]piridin-2(1*H*)-ona,

4-{[4-(benciloxi)-2-oxopiridin-1(2*H*)-il]metil}benzoato de metilo,

4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorofenil)-6-metilpiridin-2(1*H*)-ona,

1-(3-fluorobencil)-4-(feniletinil)piridin-2(1*H*)-ona,

hidrocloruro de 4-(benciloxi)-3-bromo-1-(piperidin-4-ilmetil)piridin-2(1*H*)-ona,

hidrocloruro de 4-(benciloxi)-3-bromo-1-(piperidin-4-ilmetil)piridin-2(1*H*)-ona

3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-[2-(metiltio)pirimidin-4-il]piridin-2(1*H*)-ona,

hidrocloruro de 4-(benciloxi)-3-bromo-1-piperidin-4-ilpiridin-2(1*H*)-ona,

4-benciloxi-1-difluorometil-1H-piridin-2-ona,

4-benciloxi-3-bromo-1-(2-cloro-fenil)-6-metil-1H-

pirıdın-2-ona,

3-bromo-6-metıl-1-pırıdın-3-ılmetıl-4-[(pırıdın-3-ılmetıl)-amıno-]-1H-pırıdın-2-ona,

(2,4-dıfluoro-fenıl)-amıda de ácıdo 1-(3,4-dıcloro-bencıl)-6-oxo-1,6-dıhıdro-pırıdına-3-carboxılıco,

(2,4-dıfluoro-fenıl)-amıda de ácıdo 1-(2,6-dıcloro-bencıl)-6-oxo-1,6-dıhıdro-pırıdına-3-carboxılıco

2,4-dıfluoro-fenıl)-amıda de acıdo 5-cloro-1-(2,6-dıcloro-bencıl)-6-oxo-1,6-dıhıdro-pırıdına-3-carboxılıco,

metıl-fenıl-amıda de ácıdo 5-cloro-1-(2,6-dıcloro-bencıl)-6-oxo-1,6-dıhıdro-pırıdına-3-carboxılıco,

bencılamıda de acıdo 1-(2,6-dıcloro-bencıl)-6-oxo-1,6-dıhıdro-pırıdına-3-carboxılıco,

(3-dımetılamıno-propıl)-amıda de acıdo 1-(2,6-dıcloro-bencıl)-6-oxo-1,6-dıhıdro-pırıdına-3-carboxılıco,

2-morfolın-4-ıl-etıl)-amıda de acıdo 1-(2,6-dıcloro-bencıl)-6-oxo-1,6-dıhıdro-pırıdına-3-carboxılıco,

N-[5-Acetıl-1-(4-cloro-bencıl)-6-metıl-2-oxo-1,2-dıhıdro-pırıdın-3-ıl]-4-cloro-benzamıda,

z'-(3-cloro-5-trıfluorometıl-pırıdın-2-ıl)-hıdracıda de acıdo 1-(2,6-dıcloro-bencıl)-6-oxo-1,6-dıhıdro-pırıdına-3-carboxılıco,

*N*-alıl-2-[(1-bencıl-6-oxo-1,6-dıhıdropırıdın-3-ıl)carbonıl]hıdrazınacarbotıoamıda,

1-bencıl-5-[5-(3,4-dıcloro-bencılsulfanıl)-[1,3,4]oxadıazol-2-ıl]-1H-pırıdın-2-ona,

*N'*-{[(1-bencıl-6-oxo-1,6-dıhıdropırıdın-3-ıl)carbonıl]oxı}pırıdına-4-carboxımıdamıda,

3-trıfluorometıl-bencılamıda de acıdo 1-(,6-dıcloro-bencıl)-6-oxo-1,6-dıhıdro-pırıdına-3-carboxılıco,

(2-morfolın-4-ıl-etıl)-amıda de ácıdo 1-bencıl-6-oxo-1,6-dıhıdro-pırıdına-3-carboxılıco,

5-[4-(3-cloro-fenil)-piperazina-1-carbonil]-1-(3,4-dicloro-benzil)-1H-piridin-2-ona,

benzilamida de acido 5-cloro-1-(2,6-dicloro-benzil)-6-oxo-1,6-dihidro-piridina-3-carboxílico,

1-(4-cloro-benzil)-5-[3-(4-cloro-fenil)-[1,2,4]oxadiazol-5-il]-1H-piridin-2-ona,

1-(4-cloro-benzil)-5-[3-(4-cloro-fenil)-[1,2,4]oxadiazol-5-il]-1H-piridin-2-ona,

2-cloro-N-[1-(2,6-dicloro-benzil)-6-oxo-5-trifluorometil-1,6-dihidro-piridin-3-il]-4-fluoro-benzamida

N-[1-(2,6-dicloro-benzil)-6-oxo-5-trifluorometil-1,6-dihidro-piridin-3-il]-4-isopropoxi-benzamida,

(4-trifluorometoxi-fenil)-amida de acido 1-(2,6-dicloro-benzil)-6-oxo-1,6-dihidro-piridina-3-carboxílico

(3-trifluorometil-fenil)-amida de acido 1-(2,6-dicloro-benzil)-6-oxo-1,6-dihidro-piridina-3-carboxílico,

3-trifluorometil-fenil)-amida de ácido 5-cloro-1-(2,6-dicloro-benzil)-6-oxo-1,6-dihidro-piridina-3-carboxílico

(4-cloro-fenil)-amida de ácido 1-(2,6-dicloro-benzil)-6-oxo-1,6-dihidro-piridina-3-carboxílico,

(2-dimetilamino-etil)-amida de ácido 1-(2,6-dicloro-benzil)-6-oxo-1,6-dihidro-piridina-3-carboxílico,

5-metil-1-fenil-1H-piridin-2-ona,

3-bromo-1-(3-fluoro-benzil)-4-(3-metoxi-fenil)-1H-piridin-2-ona,

3-bromo-1-(3-fluoro-benzil)-4-(3-isopropil-fenil)-1H-piridin-2-ona,

3'-bromo-1'-(3-fluoro-benzil)-6-metoxi-1'H-[3,4']bipiridinil-2'-ona,

4-benzo[1,3]dioxol-5-il-3-bromo-1-(3-fluoro-benzil)-1H-piridin-2-ona

3-bromo-1-(3-fluoro-bencil)-4-tiofen-3-il-1H-piridin-2-ona,

3-bromo-1-(3-fluoro-bencil)-4-(3-trifluorometil-fenil)-1H-piridin-2-ona,

3-bromo-1-(3-fluoro-bencil)-4-naftalen-2-il-1H-piridin-2-ona,

3-bromo-1-(3-fluoro-bencil)-4-(4-fluoro-fenil)-1H-piridin-2-ona,

1-bencenosulfonil-4-benciloxi-3-bromo-1H-piridin-2-ona,

4-[3-amino-1-(2,4-difluoro-fenil)-propoxi]-3-bromo-6-metil-1-piridin-3-ilmetil-1H-piridin-2-ona,

1-(4-bromo-2,6-difluoro-fenil)-4-(2,4-difluoro-benciloxi)-6-metil-1H-piridin-2-ona,

2-[1-(4-amino-2-metil-pirimidin-5-ilmetil)-3-bromo-6-metil-2-oxo-1,2-dihidro-piridin-4-iloximetil]-5-fluoro-benzonitrilo,

4-(2,4-difluoro-benciloxi)-6-metil-1-(2,4,6-trifluoro-fenil)-1H-piridin-2-ona,

1-(2-cloro-4-hidroxi-fenil)-4-(2,4-difluoro-benciloxi)-6-metil-1H-piridin-2-ona,

éster metílico de acido 3-[4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-il]-benzoico,

3-bromo-1-(2,6-difluoro-fenil)-4-metoxi-6-metil-5-vinil-1H-piridin-2-ona,

3-bromo-1-(2,6-difluoro-fenil)-4-metoxi-6-metil-5-estiril-1H-piridin-2-ona

1-(2,6-difluorc-fenil)-4-metoxi-6-metil-5-fenetil-1H-piridin-2-ona,

3-bromo-1-(2,6-difluoro-fenil)-4-metoxi-6-metil-5-fenetil-1H-piridin-2-ona,

1-(1*H*-indazol-5-il)-4-(1*H*-indazol-5-ilamino)-6-

metilpiridin-2(1*H*)-ona,

5-bromo-4-(2,4-difluoro-benciloxi)-1-(2,6-difluoro-fenil)-2-[2-(2,4-difluoro-fenil)-etil]-6-oxo-1,6-dihidro-piridina-3-carbaldehido,

4-[3-bromo-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-ilmetil]-pirimidine-2-cabonitrilo,

ácido 3-bromo-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-[1,2']bipiridinil-5'-carboxílico,

ácido 3-bromo-4-(5-carboxi-piridin-2-iloxi)-6-metil-2-oxo-2H-[1,2']bipiridinil-5'-carboxilico,

3-bromo-4-(2,4-difluoro-benciloxi)-6,6-dimetil-2-oxo-2H-[1,2']bipiridinil-3'-carbonitrilo,

metilamida ce acido 3-bromo-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-[1,2']bipiridinil-5'-carboxilico,

(2-hidroxi-etil)-amida de ácido 3-bromo-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-[1,2']bipiridinil-5'-carboxilico,

(2-metoxi-etil)-amida de acido 3-Bromo-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-[1,2']bipiridinil-5'-carboxilico,

3-bromo-1-(2,6-difluoro-fenil)-4-metoxi-6-metil-5-)4-metil-bencil)-1H-piridin-2-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-(difluorofenil)-5-(1,2-dihidroxi-2-feniletil)-6-metilpiridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-5'-(1-hidroxi-1-metiletil)-6-metil-2*H*-1,2'-bipiridin-2-ona,

4-benciloxi-1H-piridin-2-ona,

4-benciloxi-3-metil-1H-piridin-2-ona,

2-oxo-6-fenetil-1,2-dihidro-piridina-3-carbonitrilo,

2-oxo-6-fenil-1,2-dihidro-piridina-3-carbonitrilo,

6-oxo-1,6-dihidro-[2,3']bipiridinil-5-carbonitrilo,

ácido 6-oxo-1,6-dihidro-[2,3']bipiridinil-5-carboxílico,

3-{[4-(benciloxi)-3-bromo-2-oxopiridin-1(2*H*)-il]metil}benzamida

3-bromo-4-[(4-fluorobencil)oxi]-1-(4-(metoxibencil)piridin-2(1*H*)-ona,

3-bromo-4-[(4-fluorobencil)oxi]-1-(4-(metoxibencil)piridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-[2-fluoro-5-(hidroximetil)fenil]-6-metilpiridin-2(1*H*)-ona,

3-cloro-1-(4-fluorobencil)-4-[(4-fluorobencil)oxi]piridin-2(1*H*)-ona,

3-cloro-1-(4-fluorobencil)-4-[(4-fluorobencil)oxi]piridin-2(1*H*)-ona,

3-bromo-1-(3-clorobencil)-4-[(4-fluorobencil)oxi]piridin-2(1*H*)-ona,

3-bromo-4-[(3,4-difluorobencil)oxi]-1-(3-fluorobencil)piridin-2(1*H*)-ona

ácido 3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-4-metilbenzoico

3-bromo-1-(3-clorobencil)-4-[(4-fluorobencil)oxi]piridin-2(1*H*)-ona,

3-bromo-1-(3-clorobencil)-4-[(4-fluorobencil)oxi]piridin-2(1*H*)-ona,

trifluoroacetato de 4-{[3-cloro-4-[(2,4-difluorobencil)amino]-6-metil-2-oxopiridin-1(2*H*)-il]metil}benzonitrilo,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-{[5-(1-hidroxi-1-metiletil)pirazin-2-il]metil}-6-metilpiridin-2(1*H*)-ona,

4-(bencilamino)-3-bromo-1-(3-fluorobencil)piridin-2(1*H*)-ona,

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4-(bencilamino) 3-bromo-1-(3-fluorobencil)piridin-2(1*H*)-ona

2-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]metil}benzonitrilo,

trifluoroacetato de 3-bromo-4-[(2,4-difluorobencil)oxi]-1-[2-fluoro-6-(4-metilpiperazin-1-il)fenil]-6-metilpiridin-2(1*H*)-ona,

4-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-*N*-metilbenzamida,

1-[2-(aminometil)bencil]-3-bromo-4-[(2,4-difluorobencil)oxi]piridin-2(1*H*)-ona,

3-bromo-1-(4-fluorobencil)-4-[(4-fluorobencil)oxi]piridin-2(1*H*)-ona,

1-[2-(aminometil)bencil]-3-bromo-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-[3-(piperidin-1-ilcarbonil)fenil]piridin-2(1*H*)-ona

1-bencil-3-bromo-4-[(-4-clorobencil)oxi]piridin-2(1*H*)-ona,

4-[(2,4-difluorobencil)oxi]-1-(3-fluorobencil)-3-metilpiridin-2(1*H*)-ona,

4-(benciloxi)-1-[4-(benciloxi)bencil]-3-bromopiridin-2(1*H*)-ona,

4-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-*N*-hidroxibenzamida,

4-(benciloxi)-3-bromo-1-[4-(trifluorometil)bencil]piridin-2(1*H*)-ona,

3-bromo-1-(ciclopropilmetil)-4-[(4-fluorobencil)oxi]piridin-2(1*H*)-ona,

3-bromo-1-(ciclopropilmetil)-4-[(4-fluorobencil)oxi]piridin-2(1*H*)-ona,

1-bencil-3-bromo-4-[(3-clorobencil)oxi]-6-

metilpirıdın-2(1*H*)-ona,

1-bencil-3-bromo-4-[(3-clorobencil)oxi]-6-metilpirıdın-2(1*H*)-ona,

1-bencil-3-bromo-4-[(3-clorobencil)oxi]-6-metilpirıdın-2(1*H*)-ona,

2-{[3-bromo-4- (2,4-difluorobencil)oxi]-2-oxopirıdın-1(2*H*)-il]metil}benzonitrilo,

trifluoroacetato de 3-bromo-4-[(2,4-difluorobencil)oxi] 6-metil-1-({5-[(metilamino)metil]pirazin-2-il}metil)pirıdın-2(1*H*)-ona,

3-bromo-1-(3-fluorobencil)-4-[(2-metilbencil)oxi]pir_dın-2(1*H*)-ona,

3-bromo-1-(3-fluorobencil)-4-[(2-metilbencil)oxi]pirıdın-2(1*H*)-ona,

3-{[3-bromo-4-|(2,4-difluorobencil)oxi]-2-oxopirıdın-1(2*H*)-il]metil}benzoato de metilo,

3-bromo-1-(3-fluorobencil)-6-metil-4-(2-feniletil)pirıdın-2(1*H*)-ona,

3-bromo-1-(3-fluorobencil)-6-metil-4-(2-feniletil)pirıdın-2(1*H*)-ona,

1-bencil-3-bromo-4-[(-4-metilbencil)oxi]pirıdın-2(1*H*)-ona,

4-(benciloxi)-1-(3-fluorobencil)-3-yodopirıdın-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-[3-(hidroximetil)fenil]-6-metilpirıdın-2(1*H*)-ona,

4-(benciloxi)-1-(3-fluorobencil)-3-yodopirıdın-2(1*H*)-ona,

acido 3-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopirıdın-1(2*H*)-il]metil}benzoico,

3-bromo-4-[(4-fluorobencil)oxi]-1-[2-(hidroximetil)bencil]pirıdın-2(1*H*)-ona,

trifluoroacetato de 3-bromo-4-[(2,4-difluorobencil)oxi]-1-[(5-{[(2-hidroxietil)(metil)amino]metil}pirazin-2-il)metil]-6-metilpiridin-2(1*H*)-ona (sal),

4-(benciloxi)-3-bromo-1-[(6-fluoropiridin-3-il)metil]piridin-2(1*H*)-ona,

3-bromo-4-[(4-clorobencil)oxi]-1-(4-fluorobencil)piridin-2(1*H*)-ona,

3-bromo-4-[(4-cloro-2-fluorobencil)amino]-1-(3-fluorobencil)piridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-etilpiridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-etilpiridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-etilpiridin-2(1*H*)-ona,

2-(2-{[3-bromo-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}fenil) acetamida,

1-bencil-3-bromo-4-[(-2-clorobencil)oxi]piridin-2(1*H*)-ona,

1-bencil-3-bromo-4-[(-2-clorobencil)oxi]piridin-2(1*H*)-ona,

2-{[3-bromo-4-[(4-fluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}benzoato de metilo,

3-bromo-1-(2,6-diclorofenil)-4-[2-(4-fluorofenil)etil]-6-metilpiridin-2(1*H*)-ona,

3-bromo-1-(2,6-diclorofenil)-4-[2-(4-fluorofenil)etil]-6-metilpiridin-2(1*H*)-ona,

hidrocloruro de 3-bromo-4-[(2,4-difluorobencil)oxi]-1-{5-[(isopropilamino)metil]-2-metilfenil}-6-metilpiridin-2(1*H*)-ona,

3-bromo-1-(3-fluorobencil)-4-(2-feniletil)piridin-2(1*H*)-ona,

*N*-{3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]bencil}-*N*'-metilurea,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[3-(hidroximetil)fenil]-6-metilpiridin-2(1*H*)-ona,

3-bromo-1-(3-fluorobencil)-4-[(3-fluorobencil)oxi]piridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-[2-(2-tienil)etil]piridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-[2-(2-tienil)etil]piridin-2(1*H*)-ona,

trifluoroacetato de 3-bromo-4-[(2,4-difluorobencil)amino]-1-(2,6-(difluorofenil)-6-metilpiridin-2(1*H*)-ona,

trifluoroacetato de 3-bromo-4-[(2,4-difluorobencil)amino]-1-(2,6-(difluorofenil)-6-metilpiridin-2(1*H*)-ona,

3-bromo-4-[(4-clorobencil)oxi]-1-(4-metoxibencil)piridin-2(1*H*)-ona,

3-bromo-4-[(4-clorobencil)oxi]-1-(4-metoxibencil)piridin-2(1*H*)-ona,

3-bromo-1-(4-clorobencil)-4-[(4-clorobencil)oxi]piridin-2(1*H*)-ona,

3-bromo-1-(3-fluorobencil)-4-[(4-metoxibencil)oxi]piridin-2(1*H*)-ona,

3-bromo-1-(3,5 dibromo-2,6 difluoro-4-hidroxifenil)-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-[4-(trifluorometoxi)bencil]piridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-[4-(trifluorometoxi)bencil]piridin-2(1*H*)-ona,

*N*'-{3-[3-bromo 4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]bencil}-*N*,*N*-dimetilurea,

3-bromo-4-[(4-fluorobencil)oxi]-1-[4-(trifluorometil)bencil]piridin-2(1*H*)-ona,

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2-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]metil} benzamida

*N*-{3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]bencil}morfolina-4-carboxamida,

*N*-{3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]bencil} metanosulfonamida,

4-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-*N*-isopropilbenzamida,

4-(alilamino)-3-bromo-1-(2,6-difluorofenil)-5-yodo-6-metilpiridin-2(1*H*)-ona,

4-(alilamino)-3-bromo-1-(2,6-difluorofenil)-5-yodo-6-metilpiridin-2(1*H*)-ona,

ácido (4-{[4 (benciloxi)-3-bromo-2-oxopiridin-1(2*H*)-il]metil}fenil)acetico,

3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-[4-(pirrolidin-1-ilcarbonil)fenil]piridin-2(1*H*)-ona,

1-bencil-4-(benciloxi)-3-yodopiridin-2(1*H*)-ona,

1-(bifenil-4-ilmetil)-3-bromo-4-[(4-fluorobencil)oxi]piridin-2(1*H*)-ona,

acido 4-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il] benzoico,

4-(benciloxi)-3-bromo-1-[2-(3-tienil)etil]piridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-[2-(3-tienil)etil]piridin-2(1*H*)-ona,

3-bromo-4-[(4-fluorobencil)oxi]-1-[3-(trifluorometil)bencil]piridin-2(1*H*)-ona,

*N*-[3-bromo-1-(3-fluorobencil)-2-oxo-1,2-dihidropiridin-4-il]-4-fluorobenzamida,

3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]bencilcarbamato de metilo,

1-bencil-4-(benciltio)-3-bromopiridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-(4-*terc*-butilbencil)piridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-(4-*terc*-butilbencil)piridin-2(1*H*)-ona,

*N*-{3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]bencil}-2- metoxiacetamida,

trifluoroacetato de 3-bromo-4-[(2,4-difluorobencil)oxi] 1-({5-[(dimetilamino)metil]pirazin-2-il}metil)-6-metilpiridin-2(1*H*)-ona,

hidrocloruro de 3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-[4-(piperazin-1-ilcarbonil)fenil]piridin-2(1*H*)-ona,

4-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-*N*,*N*-bis(2-hidroxietil)benzamida,

hidrocloruro de 3-bromo-4-[(2,4-difluorobencil)oxi]-1-{5-[(dimetilamino)metil]-2-metilfenil}-6-metilpiridin-2(1*H*)-ona,

1-bencil-3-bromo-4-(2-feniletil)piridin-2(1*H*)-ona,

1-(3-fluorobencil)-4-[(4-fluorobencil)oxi]-3-metilpiridin-2(1*H*)-ona,

trifluorocaetato de 4-(benciloxi)-1-(piperidin-3-ilmetil)piridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-[4-(morfolin-4-ilcarbonil)fenil]piridin-2(1*H*)-ona,

4-(benciloxi)-1-(3-fluorobencil)-3-metilpiridin-2(1*H*)-ona,

hidrocloruro de $N^1$-{3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]bencil}glicinamida,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorofenil)-5-yodo-6-metilpiridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-[4-(piperidin-1-ilcarbonil)fenil]piridin-2(1*H*)-ona,

*N*- [3-bromo-1-(3-fluorobencil)-2-oxo-1,2-dihidropiridin-4-il]-2,6-difluorobenzamida,

2-{[4-(benciloxi)-3-bromo-2-oxopiridin-1(2*H*)-il]metil}benzonitrilo,

5-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]metil}-*N*-metilpirazina-2-carboxamida,

3-cloro-4-[(2,4-difluorobencil)amino]-1-(2,6-difluorofenil)-6-metilpiridin-2(1*H*)-ona,

acido 3-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]benzoico,

3-bromo-1-(3-fluorobencil)-4-[(3-fluorobencil)amino]piridin-2(1*H*)-ona,

3-bromo-1-(3-fluorobencil)-4-[(3-metoxibencil)oxi]piridin-2(1*H*)-ona,

3-bromo-1-(2,4-*terc*-butilbencil)-4-[(2,4-difluorobencil)oxi]piridin-2(1*H*)-ona,

*N*-{3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]bencil} acetamida,

acetato de 2-({3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]bencil}amino)-2-oxoetilo,

1-bencil-4-(benciloxi)-3-metilpiridin-2(1*H*)-ona,

*N*-{3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]bencil}urea,

1-bencil-4-(benciloxi)-3-etilpiridin-2(1*H*)-ona,

*N*-{3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]bencil}-2- hidroxiacetamida,

3-bromo-4-[(4-clorobencil)oxi]-1-(2-feniletil)piridin-2(1*H*)-ona,

3-bromo-1-(3-clorobencil)-4-[(4-clorobencil)oxi]piridin-2(1*H*)-ona,

1-[3-(aminometil)fenil]-3-bromo-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

2-{[4-(benciloxi)-3-bromo-2-oxopiridin-1(2*H*)-il]metil}benzamida,

1-(4-fluorobencil)-4-[(4-fluorobencil)oxi]piridin-2(1*H*)-ona,

1-[2-(aminoetil)bencil]-4-(benciloxi)-3-bromopiridin-2(1*H*)-ona,

3-[4-(benciloxi)-3-bromo-2-oxopiridin-1(2*H*)-il]propanoato de metilo,

1-bencil-4-(benciloxi)-3-metilpiridin-2(1*H*)-ona,

4-(alilamino)-1-(2,6-difluorofenil)-5-yodo-6-metilpiridin-2(1*H*)-ona,

4-(alilamino)-1-(2,6-difluorofenil)-5-yodo-6-metilpiridin-2(1*H*)-ona,

3-bromo-1-(3-fluorobencil)-4-(feniletinil)piridin-2(1*H*)-ona,

4-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-*N*,*N*-dimetilbenzamida,

acido {4-[({4-(benciloxi)-3-bromo-1-[4-(carboximetil)bencil]-1,2-dihidropiridin-2-il}oxi)metil]fenil}acético,

4-(benciloxi)-3-bromo-1-[3-(trifluorometil)bencil]piridin-2(1*H*)-ona,

4-(benciloxi)-3-etinil-1-(3-fluorobencil)piridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-{3-[(dimetilamino)metil]fenil}-6-metilpiridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-metilpiridin-2(1*H*)-ona,

1-bencil-3-bromo-4-(feniletinil)piridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-metilpiridin-2(1*H*)-ona,

3-bromo-1-(3-fluorobencil)-4-{[4-(trifluorometil)bencil]oxi}piridin-2(1*H*)-ona,

4-(bencilamino)-3-bromo-1-(2,6-difluorofenil)-5-yodo-

6-metilpiridin-2(1*H*)-ona,

4-[(2,4-difluorobencil)oxi]-1-(4-metoxibencil)-6-metilpiridin-2(1*H*)-ona,

hidrobromuro de 4-(benciloxi)-3-bromo-1-metilpiridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-[4-(morfolin-4-ilcarbonil)fenil]piridin-2(1*H*)-ona,

acido 5-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-(difluorofenil)-6-oxo-1,6-dihidropiridina-2-carboxilico,

1-bencil-3-bromo-4-[(2,6-diclorobencil)oxi]piridin-2(1*H*)-ona,

acido 3-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-2-metilbenzoico,

acido 4-[4-(benciloxi)-3-bromo-2-oxopiridin-1(2*H*)-il]benzoico,

*N*-(5-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]metil}-2-metilpirimidin-4-il)glicinato trifluoroacetato de etilo,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorofenil)-6-metil-5-[(*E*)-2-fenilvinil]piridin-2(1*H*)-ona,

3-bromo-1-(3-fluorobencil)-4-{[3-(trifluorometil)bencil]amino}piridin-2(1*H*)-ona,

3-bromo-4-[(4-fluorobencil)oxi]-1-(3-fenilpropil)piridin-2(1*H*)-ona,

3-bromo-1-(4-*terc*-butilbencil)-4-[(4-fluorobencil)oxi]piridin-2(1*H*)-ona,

4-(alilamino)-3-bromo-1-(2,6-difluorofenil)-6-metilpiridin-2(1*H*)-ona,

1-ciclohexil-4-[(2,4-difluorobencil)oxi]-3,6-dimetilpiridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-

difluorofenil)-5-(hidroximetil)-6-metilpiridin-2(1*H*)-ona,

1-bencil-4-(benciloxi)-2-oxo-1,2-dihidropiridina-3-carbaldehido,

4-[(2,4-difluorobencil)oxi]-6-metil-1-prop-2-in-1-ilpiridin-2(1*H*)-ona,

3-[4-(benciloxi)-3-bromo-2-oxopiridin-1(2*H*)-il]propanoato de etilo,

1-bencil-4-(benciloxi)-3-(hidroximetil)piridin-2(1*H*)-ona,

o una sal aceptable para el uso farmacéutico

3-cloro-4-(2,4-difluoro-benciloxi)-6-metil-1-(5-metil-pirazin-2-ilmetil)-1H-piridin-2-ona,

3-cloro-4-(2,4-difluoro-benciloxi)-1-(5-hidroximetil-pirazin-2-ilmetil)-6-metil-1H-piridin-2-ona,

3-bromo-4-(2,4-difluoro-benciloxi)-1-(2,3-dihidro-1H-indol-5-ilmetil)-1H-piridin-2-ona,

3-bromo-4-(2,4-difluoro-benciloxi)-1-[1-(2-hidroxi-acetil)-2,3-dihidro-1H-indol-5-ilmetil]-6-metil-1H-piridin-2-ona,

3-bromo-4-(2,4-difluoro-benciloxi)-6-metil-1-(1H-pirazol-3-ilmetil)-1H-piridin-2-ona,

3-[3-cloro-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-il]-4,N-dimetil-benzamida,

3-[3-cloro-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-il]-4-metil-benzamida,

3-[3-cloro-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-il]-4-fluoro-N-metil-benzamida,

4-cloro-3-[3-cloro-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-il]-N-metil-benzamida,

3-[3-cloro-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-il]-4-fluoro-benzamida,

4-[3-cloro-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-

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2H-pirıdın-1-il]-3,N-dımetıl-benzamıda,

3-cloro-4-(2,4-dıfluoro-bencıloxı)-1-[4-(1,2-dıhıdroxı-etıl)-2-metıl-fenıl]-6-metıl-1H-pırıdın-2-ona,

N-{4-[3-Cloro-4-(2,4-dıfluoro-bencıloxı)-6-metıl-2-oxo-2H-pırıdın-1-ılmetıl]-fenıl}-2-hıdroxı-acetamıda,

acıdo 1-hıdroxı-cıclopropanocarboxılıco 4-[3-cloro-4-(2,4-dıfluoro-bencıloxı)-6-metıl-2-oxo-2H-pırıdın-1-ılmetıl]-bencılamıda,

N-{4-[3-Cloro-4-(2,4-dıfluoro-bencıloxı)-6-metıl-2-oxo-2H-pırıdın-1-ılmetıl]-bencıl}-2-hıdroxı-acetamıda,

N-{4-[3-Cloro-4-(2,4-dıfluoro-bencıloxı)-6-metıl-2-oxo-2H-pırıdın-1-ılmetıl]-fenıl}-acetamıda,

ester etılıco de acıdo {2-[3-Bromo-1-(2,6-dıfluoro-fenıl)-6-metıl-2-oxo-1,2-dıhıdro-pırıdın-4-ıloxımetıl]-5-fluoro-bencıl}-carbamıco

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Los nombres anteriores se generaron con *ChemDraw Ultra*, versión 6 0 2, producido por CambridgeSoft com, de Cambridge, Ma, o *ACD* Namepro, versión 5 09, producido por ACDlabs com

Definiciones

Tal como se usa en la presente invención, el término "alquenilo" se refiere a un hidrocarburo lineal o ramificado de un numero designado de atomos de carbono que contienen por lo menos un enlace doble carbono-carbono Ejemplos de "alquenilos" incluyen vinilo, alilo y 2-metil-3-hepteno

El término "alcoxi" representa un alquilo acoplado al resto molecular madre por medio de un puente de oxigeno Ejemplos de grupos alcoxi incluyen, por ejemplo, metoxi, etoxi, propoxi e isopropoxi

El termino 'tioalcoxi" representa un alquilo acoplado al resto molecular madre por medio de un átomo de azufre Ejemplos de grupos tioalcoxi incluyen, por ejemplo, tiometoxi, tioetoxi, tiopropoxi y tioisopropoxi

Tal como se usa en la presente invencion, el termino "alquilo" incluye aquellos grupos alquilo de un numero designado de átomos de carbono Los grupos alquilo pueden ser lineales o ramificados Ejemplos de "alquilo" incluyen metilo, etilo, prop lo, isopropilo, butilo, iso-, sec- y terc-butilo, pentilo, hexilo, heptilo, 3-etilbutilo y similares "Alquilo Cx-Cy" representa un grupo alquilo del numero especificado de carbonos Por ejemplo, el alquilo $C_1$-$C_4$ abarca todos los grupos alquilo que incluyen por lo menos uno, y no más de cuatro, atomos de carbono Tambien contiene subgrupos, tales como, alquilo $C_2$-$C_3$ o alquilo $C_1$-$C_3$

El termino "arilo" se refiere a un sistema de anillo aromatico de hidrocarburos que contiene por lo menos un

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anillo aromatico El anillo aromatico puede estar fusionado o acoplado de otra manera a otros anillos aromaticos de hidrocarburos o anillos no aromaticos de hidrocarburos Ejemplos de grupos arilo incluyen, por ejemplo, fenilo, naftilo, 1,2,3,4-tetrahidronaftaleno, indanilo y bifenilo Los ejemplos preferidos de grupos arilo incluyen fenilo y naftilo El grupo arilo mas preferido es el fenilo Los grupos arilo de la presente invencion son no sustituidos o, segun se especifica, sustituidos en una o más posiciones sustituibles con diversos grupos Asi, tales grupos arilo pueden ser sustituidos opciona_mente con grupos tales como, por ejemplo, alquilo $C_1$ $C_6$, alcoxi $C_1$-$C_6$, halógeno, hidroxi, ciano, nitro, amino, mono- o di-alquil($C_1$-$C_6$)amino, alquenilo $C_2$-$C_6$, alquinilo $C_2$-$C_6$, haloalquilo $C_1$-$C_6$, haloalcoxi $C_1$-$C_6$, aminoalquilo($C_1$-$C_6$), mono- o di-alquil($C_1$-$C_6$)aminoalquilo($C_1$-$C_6$)

El termino "arilalquilo" se refiere a un grupo arilo, tal como se defin ó anteriormente, acoplado al resto molecular madre por medio de un grupo alquilo, tal como se definió anteriormente Los grupos arilalquilo preferidos incluyen bencilo, fenetilo, fenpropilo y fenbutilo Los grupos arilalquilo mas preferidos incluyen bencilo y fenetilo El grupo arilalquilo mas preferido es el bencilo Las porciones arilo de estos grupos son no sustituidas o, como se especifica, sustituidas en una o más posiciones sustituibles con diversos grupos Así, tales grupos arilo pueden ser sustituidos opcionalmente con grupos tales como, por ejemplo, alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$, halógeno, hidroxi, ciano, nitro, amino, mono- o di-alquil($C_1$-$C_6$)amino, alquenilo $C_2$-$C_6$, alquinilo $C_2$-$C_6$, haloalquilo $C_1$-$C_6$, haloalcoxi $C_1$-$C_6$, aminoalquilo($C_1$-$C_6$), mono- o di-alquil($C_1$-$C_6$)aminoalquilo($C_1$-$C_6$)

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El término "arilalcoxi" se refiere a un grupo arilo, tal como se definió anteriormente, acoplado al resto molecular madre por medio de un grupo alcoxi, tal como se definió anteriormente. Los grupos arilalcoxi preferidos incluyen benciloxi, feneticloxi, fenpropiloxi y fenbutiloxi. El grupo arilalcoxi mas preferido es el benciloxi.

El termino "cicloalquilo" se refiere a un hidrocarburo $C_3$-$C_8$ cíclico. Ejemplos de cicloalquilos incluyen ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo y ciclooctilo. Los grupos cicloalquilos mas preferidos incluyen el ciclopropilo.

El termino "cicloalquilalquilo", tal como se usa en la presente invención, se refiere a un grupo cicloalquilo $C_3$-$C_8$ acoplado al resto molecular madre por medio de un grupo alquilo, tal como se definió anteriormente. Ejemplos de grupos cicloalquilalquilo incluyen ciclopropilmetil y ciclopentiletil.

Los terminos "halógeno" o "halo" indican fluor, cloro, bromo o yodo.

El termino "heterocicloalquilo" se refiere a un sistema de anillo no aromático que contiene por lo menos un heteroátomo seleccionado entre nitrogeno, oxigeno y azufre, en el que el heterociclo no aromatico esta acoplado al nucleo. El anillo heterocicloalquilo puede estar opcionalmente fusionado o acoplado de otra manera a otros anillos heterocicloalquilos, heterociclos aromaticos, hidrocarburos aromaticos y/o anillos no aromaticos de hidrocarburos. Los grupos heterocicloalquilo preferidos tienen de 3 a 7 miembros. Ejemplos de grupos heterocicloalquilo incluyen, por ejemplo, piperazina, 1,2,3,4-tetrahidroisoquinolina, morfolina, piperidina, tetrahidrofurano, pirrolidina y pirazola. Los grupos heterocicloalquilo preferidos incluyen piperidinilo,

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piperazinilo, morfolinilo y pirolidinilo Los grupos heterocicloalquilo de la presente invención son no sustituidos o, como se especifica, sustituidos en una o mas posiciones sustituibles con diversos grupos Así, tales grupos heterocicloalquilo pueden ser sustituidos opcionalmente con grupos tales como, por ejemplo, alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$, halogeno, hidroxi, ciano, nitro, amino, mono- o di-alquil($C_1$-$C_6$)amino, alquenilo $C_2$-$C_6$, alquinilo $C_2$-$C_6$, haloalquilo $C_1$-$C_6$, haloalcoxi $C_1$-$C_6$, aminoalquilo($C_1$-$C_6$), mono- o di-alquil($C_1$-$C_6$)amino alquilo($C_1$-$C_6$)

El termino "heteroarilo" se refiere a un sistema de anillo aromático que contiene por lo menos un heteroatomo seleccionado entre nitrógeno, oxigeno y azufre El anillo heteroarilo puede estar fusionado o acoplado de otra manera a uno o más anillos heteroarilos, anillos aromaticos o no aromáticos de hidrocarburos o anillos heterocicloalquilos Ejemplos de grupos heteroarilo incluyen, por ejemplo, piridina, furano, tiofeno, 5,6,7,8-tetrahidroisoquinolina y pirimidina Ejemplos preferidos de grupos heteroarilo incluyen tienilo, benzotienilo, piridilo, quinolilo, pirazinilo, pirimidilo, imidazolilo, bencimidazolilo, furanilo, benzofuranilo, tiazolilo, benzotiazolilo, isoxazolilo, oxadiazolilo, isotiazolilo, bencisotiazolilo, triazolilo, tetrazolilo, pirrolilo, indolilo, pirazolilo y and benzopirazolilo Los grupos heteroarilo preferidos incluyen el piridilo Los grupos heteroarilo de la presente invencion son no sustituidos o, segun se especifica, sustituidos en una o más posiciones sustituibles con diversos grupos Asi, tales grupos heteroarilo pueden ser sustituidos opcionalmente con grupos tales como, por ejemplo, alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$, halógeno, hidroxi, ciano, nitro, amino, mono- o di-alquil($C_1$-$C_6$)amino, alquenilo $C_2$-$C_6$, alquinilo $C_2$-$C_6$,

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haloalquilo $C_1$-$C_6$, haloalcoxi $C_1$-$C_6$, aminoalquilo($C_1$-$C_6$), mono- o di-alquil($C_1$-$C_6$)amino alquilo($C_1$-$C_6$)

El término "heteroarilalquilo" se refiere a un grupo heteroarilo, tal como se definio anteriormente, acoplado al resto molecular madre por medio de un grupo alquilo, tal como se definió anteriormente Los grupos heteroalquilo preferidos incluyen pirazolmetilo, pirazoletilo, piridilmetilo, piridiletilo, tiazolmetilo, thiazoletilo, imidazolmetilo, imidazoletilo, tienilmetilo, tieniletilo, furanilmetilo, furaniletilo, isoxazolmetilo, isoxazoletilo, pirazinmetilo y pirazinetilo Los grupos heteroarilalquilo mas preferidos incluyen piridilmetilo y piridiletilo Las porciones heteroarilo de estos grupos son no sustituidas o, segun se especifica, sustituidas en una o mas posiciones sustituibles con diversos grupos Asi, tales grupos heteroarilo pueden ser sustituidos opcionalmente con grupos tales como, por ejemplo, alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$, halógeno, hidroxi, ciano, nitro, amino, mono- o di-alquil($C_1$-$C_6$)amino, alquenilo $C_2$-$C_6$, alquinilo $C_2$-$C_6$, haloalquilo $C_1$-$C_6$, haloalcoxi $C_1$-$C_6$, aminoalquilo($C_1$-$C_6$), mono- o di-alquil($C_1$-$C_6$)amino alquilo($C_1$-$C_6$)

Si dos o más de los mismos sustituyentes están en un mismo átomo, por ejemplo di-alquil($C_1$-$C_6$)amino, se entiende que la naturaleza de cada grupo es independiente de la otra

Tal como se usa en la presente invención, el termino "trastorno mediado por p38" se refiere a todo y cualquier trastorno y estado de enfermedad en los que el p38 tiene un papel, ya sea por control del p38 mismo o porque el p38 causa que otro factor sea liberado, tal como, pero sin carácter limitativo, el IL-1, IL-6 o IL-8 Un estado de enfermedad en el que, por ejemplo, la IL-1 constituye un componente principal, y su produccion o accion se ve

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exarcebada o segregada en respuesta al p38 se podría consıderar, en consecuencıa, un trastorno mediado por p38

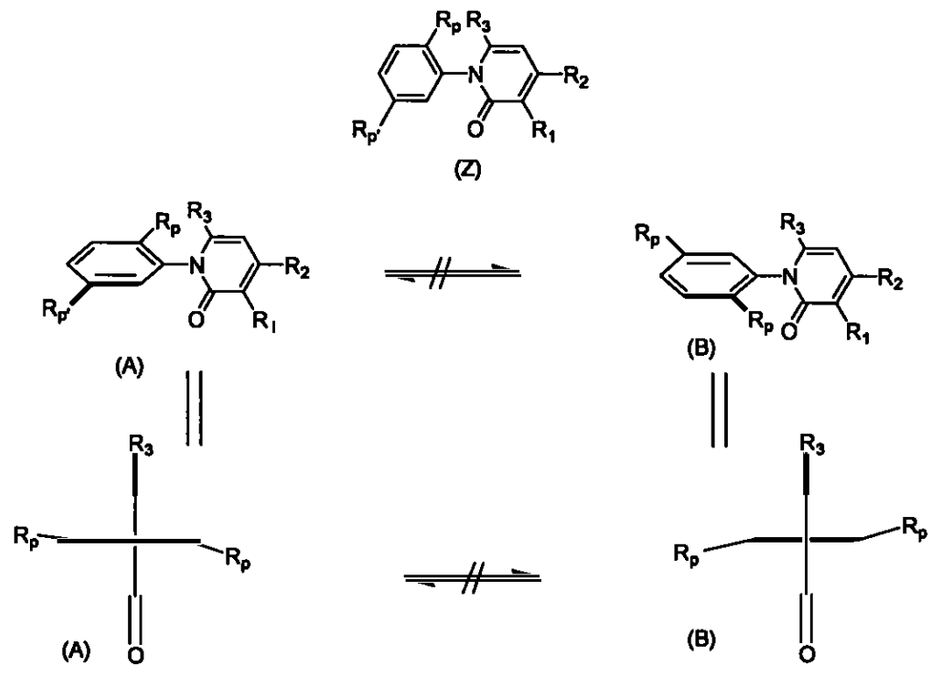
Dado que el FNT-beta tıene una homologıa estructural cercana al FNT-alfa (tambıen conocıdo como caquectına) y como ambos ınducen respuestas bıologıcas sımılares y se enlazan al mısmo receptor celular, la sıntesıs tanto del FNT-alfa como del FNT-beta son ınhıbıdas por los compuestos de la presente ınvencıon y, por eso, en la presente memorıa nos referımos a ellos colectıvamente como "FNT" salvo que se descrıba especıfıcamente de otra manera

Las sales no toxıcas aceptables para uso farmaceutıco ıncluyen, sın caracter lımıtatıvo, sales de acıdos ınorgánıcos, tales como clorhıdrıco, sulfurıco, fosfórıco, dıfosfórıco, bromhıcrıco y nıtrıco o sales de ácıdos orgánıcos tales como fórmıco, cıtrıco, malıco, maleıco, fumarıco, tartárico, succınico, acético, láctico, metanosulfonıco, p-toluenosulfonıco, 2-hıdroxıetılsulfonıco, salicílico y esteárico De modo sımlar, los catıones aceptables para uso farmacéutıco ıncluyen, sın carácter lımıtatıvo, sodıo, potasıo, calcıo, aluminıo, lıtıo y amonıo Los expertos en la tecnica reconoceran una gran varıedad sales para adıcıonar, no tóxıcas, aceptables para uso farmaceutıco

Los compuestos de esta ınvención pueden contener uno o más átomos de carbono asımetrıcos, de modo que los compuestos pueden exıstır en dıstıntas formas esteroısomerıcas Estos compuestos pueden ser, por ejemplo, racematos, quırales no racemıcos o dıastereomeros En estas sıtuacıones, los enantıómeros aıslados, es decır, formas óptımamente actıvas, se pueden obtener por sıntesıs asımetrıca o por resolucıon de los racematos La resolucıon de los racematos se puede lograr, por ejemplo, por métodos convencıonales tales como la crıstalızacıon en

la presencia de un agente de resolucion, la cromatografia, usando, por ejemplo, una columna de HPLC (cromatografia liquida de alto rendimiento) quiral, o derivatizando la mezcla racémica con un reactivo de resolución para generar diastereomeros, separando los diastereomeros mediante cromatografia o cristalización selectiva y eliminando el agente de resolucion para generar el compuesto original de forma enantioméricamente enriquecida Cualquiera de los procedimientos anteriores se puede repetir a fin de incrementar la pureza enantiomerica de un compuesto

Los compuestos de la invencion pueden existir como atropoisómeros, es decir, isómeros rotacionales quirales La invencion abarca los atropoisomeros racemicos y los resueltos La siguiente ilustracion muestra genericamente un compuesto (Z) que puede existir como atropoisómeros así como sus dos atropoisomeros posibles (A) y (B) Esta ilustracion tambien muestra cada uno de los atropoisómeros (A) y (B) en una proyeccion de Fischer En esta ilustración, $R_1$, $R_2$ y $R_4$ llevan las mismas definiciones establecidas para la Formula I, $R_p$ es un sustituyente en la definicion de $R_5$, y $R_p$ es un sustituyente no hidrógeno en la definición de $R_5$



Cuando los compuestos que se describen en esta patente contienen enlaces olefínicos dobles u otros centros de asimetría geométrica, y salvo que se especifique lo contrario, los compuestos incluyen las configuraciones cis, trans, Z- y E- Del mismo modo, están incluidas todas las formas tautoméricas

Los compuestos de la Fórmula general I se pueden administrar por vía oral, tópica, parenteral, por inhalación o espray o por vía rectal en formulaciones para unidades de dosificación que contengan portadores, adyuvantes y vehículos no tóxicos aceptables para uso farmacéutico El término parenteral, tal como se usa en la presente memoria, incluye técnicas de infusión o inyección percutánea, subcutánea, intravascular (por ejemplo, intravenosa), intramuscular o intratecal y similares Además, se proporciona una formulación farmacéutica que comprende un compuesto de la Fórmula general I y un

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portador aceptable para uso farmacéutico Uno o más compuestos de la Formula general I pueden estar presentes asociados con uno o mas portadores y/o diluyentes y/o adyuvantes no tóxicos aceptables para uso farmaceutico y, si se desea, con otros ingredientes activos Las composiciones farmacéuticas que contienen compuestos de la Formula general I pueden tener una presentación adecuada para el uso oral, por ejemplo, tabletas, trociscos, pastillas desleibles, suspensiones acuosas u oleosas, granulos o polvos dispersibles, emulsión, capsulas duras o blandas, o jarabes o elixires

Para la administracion oral, la composición farmacéutica puede tener la presentacion de, por ejemplo, una tableta, una capsula dura o blanda, una pastilla, polvos dispersibles, una suspension o un liquido La composicion farmaceutica está hecha, preferentemente, con la presentacion de una unidad de dosificacion que contiene una cantidad particular del ingrediente activo Ejemplos de tales unidades de dosificacion son las tabletas o las capsulas

Las composiciones destinadas al uso oral se pueden preparar siguiendo cualquier metodo conocido en la tecnica para la elaboración de composiciones farmaceuticas y dichas composiciones pueden contener uno o mas agentes seleccionados del grupo que consiste en agentes edulcorantes, agentes saborizantes, agentes colorantes y agentes conservantes a fin de suministrar preparaciones farmaceuticamente elegantes y de buen sabor Las tabletas contienen el ingrediente activo mezclado con excipientes no toxicos aceptables para uso farmacéutico que son adecuados para la elaboracion de tabletas Estos excipientes pueden ser, por ejemplo, diluyentes inertes, tales como carbonato de calcio, carbonato de sodio, lactosa, fosfato de calcio o

fosfato de sodio, agentes granulantes y desintegrantes, por ejemplo, almidón de maiz o acido alginico, agentes aglutinantes, por ejemplo, almidon, gelatina o acacia, y agentes lubricantes, por ejemplo, estearato de magnesio, ácido estearico o talco Las tabletas pueden ser no recubiertas o estar recubiertas mediante técnicas conocidas En algunos casos, dichos recubrimientos se pueden preparar con técnicas conocidas con el fin de demorar la desintegración y absorcion en el tracto gastrointestinal y asi proporcionar una acción sostenida durante un periodo más largo Por ejemplo, se puede emplear un material que demora el tiempo de absorcion tal como monoestearato de glicerilo o diestearato de glicerilo

Las formulaciores para uso oral también se pueden presentar como capsulas de gelatina dura, en las que el ingrediente activo se mezcla con un diluyente solido inerte, por ejemplo, carbonato de calcio, fosfato de calcio o caolín, o como capsulas de gelatina blanda, en las que el ingrediente activo se mezcla con agua o con un medio oleoso, por ejemplo, aceite de cacahuete, parafina liquida o aceite de oliva

Las formulaciones para uso oral tambien se pueden presentar como pastillas desleibles

Las suspensiones acuosas contienen el material activo mezclado con excipientes adecuados para la elaboracion de suspensiones acuosas Tales excipientes son agentes de suspension, por ejemplo, carboximetilcelulosa de sodio, metilcelulosa, hidropropil-metilcelulosa, alginato de sodio, polivinilpirrolidona, goma tragacanto y goma de acacia, agentes de dispersion o humectantes pueden ser un fosfatido natural, por ejemplo, lecitina, o productos de condensación de un óxido de alquileno con ácidos grasos, por ejemplo, estearato de polioxietileno, o productos de

condensación del oxido de etileno con alcoholes alifaticos de cadena larga, por ejemplo, heptadecaetilenoxicetanol, o productos de condensacion del óxido de etileno con esteres parciales derivados de acidos grasos y un hexitol tal como monooleato de sorbitol polioxietileno, o productos de condensacion del óx do de etileno con ésteres parciales derivados de anhidridos de hexitol y acidos grasos, por ejemplo, monooleato de sorbitan polietileno Las suspensiones acuosas pueden contener tambien uno o mas conservantes, por ejemplo, etilo o n-propil p-hidrobenzoato, uno o mas agentes colorantes, uno o más agentes saborizantes y uno o mas agentes edulcorantes, tales como sucrosa o sacarina

Las suspensiones oleosas pueden estar formuladas mediante la suspension del ingrediente activo en un aceite vegetal, por ejemplo, aceite de cacahuate, aceite de oliva, aceite de sesamo o aceite de coco, o en un aceite mineral tal como la parafina líquida Las suspensiones oleosas pueden contener un aceite espesante, por ejemplo, cera de abejas, parafina dura o alcohol cetilico Los agentes endulzantes y los agentes saborizantes se pueden agregar para proporcionar preparaciones orales con buen sabor Estas composiciones ,e pueden conservar mediante la adicion de in antioxidante tal como el acido ascorbico

Los granulos y polvos dispersibles adecuados para la preparacion de una suspension acuosa mediante la adición de agua proporcionan el ingrediente activo mezclado con un agente de dispersion o humectante, un agente de suspensión y uno o mas conservantes Los agentes de dispersión o humectantes o los agentes de suspensión adecuados estan ejemplificados por aquellos que se mencionaron anteriormente Los excipientes adicionales, por ejemplo,

760

agentes edulcorantes, saborizantes y colorantes pueden estar presentes también

Las composiciones farmaceuticas de la invención también pueden tener la forma de emulsiones de aceite en agua La fase oleosa puede ser un aceite vegetal o un aceite mineral o una mezcla de ambas Los agentes emulsionantes adecuados pueden ser gomas naturales, por ejemplo, goma de acacia o goma tragacanto, fosfatidos naturales, por ejemplo, haba de soja, lecitina y esteres o esteres parciales derivados de ácidos grasos y hexitol, anhidridos, por ejemplo, monooleato de sorbitan, y productos de condensacion de los mencionados ésteres parciales con oxido de etileno, por ejemplo, monooleato de sorbitán polioxietileno Las emulsiones pueden contener también agentes edulcorantes y saborizantes

Los jarabes y elixires pueden estar formulados con agentes edulcorantes, por ejemplo, glicerol, propilenglicol, sorbitol, glucosa o sucrosa Dichas formulaciones pueden contener tambien un demulcente, un conservante y agentes saborizantes y colorantes Las composiciones farmaceuticas pueden presentarse en la forma de una suspension inyectable, estéril, acuosa u oleaginosa Esta suspension puece estar formulada de acuerdo con la tecnica conocida usando aquellos agentes de dispersion o humectantes y agentes de suspensión adecuados que se mencionaron anteriormente La preparación inyectable estéril puede ser también una suspension o disolucion esteril inyectable en un diluyente o disolvente no tóxico parenteralmente aceptable, por ejemplo, una disolución en 1,3-butanodiol Entre los vehiculos y disolventes aceptables que se pueden emplear se encuentran el agua, la disolución de Ringer y la disolucion isotonica de cloruro de sodio Además, convencionalmente se emplean aceites

fijos, esteriles, como un disolvente o medio de suspension Para este proposito se puede emplear cualquier aceite fijo neutro incluyendo mono- o di-gliceridos sintéticos Ademas, acidos grasos tal como el ácido oleico son de utilidad en la preparación de inyectables

Los compuestos de la Fórmula general I también se pueden administrar en forma de supositorios, por ejemplo, para la administracion rectal de la droga Estas composiciones se pueden preparar mezclando la droga con un excipiente adecuado, que no irrite, que sea solido a temperatura normal pero liquido a temperatura rectal y, por lo tanto, se funda en el recto a fin de liberar la droga Tales materiales incluyen manteca de cacao y polietilenglicoles

Los compuestos de la Fórmula general I se pueden administrar parenteralmente en un medio esteril Segun cual sea el vehiculo y la concentración que se usen, la droga podra estar en suspensión o disuelta en el vehiculo Ventajosamente, adyuvantes tales como anestésicos locales, conservantes y agentes amortiguadores se pueden disolver en el vehículo

Tambien es posible administrar el ingrediente activo por medio de una inyeccion (IV, IM, subcutánea o a chorro) como una composicion en la que, por ejemplo, se pueden usar disolucion salina, dextrosa o agua como un portador adecuado Si fuera recesario, se puede ajustar el pH de la composicion con un acido, una base o un tampon adecuados Tambien se pueden incluir en la composicion agentes de carga, de dispersion, humectantes o de suspension, incluyendo el manitol y PEG 400 Una composición parenteral adecuada puede inclu_r también un compuesto formulado como una sustancia solida estéril, incluyendo polvo liofilizado, en viales de inyección Se puede agregar una disolucion

acuosa para disolver el compuesto antes de aplicar la inyección

Para trastornos de los ojos u otros tejidos externos, por ejemplo, boca y piel, las formulaciones se aplican preferentemente como una crema, un gel, un espray o un ungüento tópicos, o como un supositorio, que contienen los ingredientes activos en una cantidad total de, por ejemplo 0,075 a 30% peso/peso, preferiblemente 0,2 a 20% peso/peso y mas preferiblemente 0,4 a 15% peso/peso Cuando estan formulados en un unguento, los ingredientes activos se pueden emplear ya sea con una base de unguento parafinica o miscible en agua

Alternativamente, los ingredientes activos pueden estar formulados en una crema con una base de crema de aceite en agua Si se desea, la fase acuosa de la base de la crema puede incluir, por ejemplo, al menos 30% peso/peso de un alcohol polihidrico tales como propilenglicol, butano-1,3-diol, manitol, sorbitol, glicerol, polietilenglicol y sus mezclas La formulación tópica puede incluir, deseablemente, un compuesto, lo que aumenta la absorcion o penetracion del ingrediente activo a traves de la piel o de otras zonas afectadas Ejemplos de tales intensificadores de la penetracion dermica incluyen dimetilsulfoxido y compuestos analogos relacionados Los compuestos de esta invencion tambien se pueden administrar mediante un dispositivo transdérmico Preferiblemente, la administración topica sera realizara usando un parche, ya sea del tipo de reservorio y membrana porosa o de una variedad de matriz solida En ambos casos, el agente activo es liberado continuamente desde el reservorio o las microcapsulas a través de la membrana y hacia el adhesivo permeable al agente activo que esta en contacto con la piel o la mucosa del receptor Si el agente activo resulta

absorbido por la piel, se administra un flujo controlado y predeterminado del agente activo al receptor En el caso de las microcápsulas, el agente que encapsula puede funcionar tambien como membrana El parche transdérmico puede incluir el compuesto en un sistema disolvente con sistema adhesivo adecuados, tales como una emulsion acrilica y un parche de poliester La fase oleosa de las emulsiones de esta invencion se puede constituir a partir de ingredientes conocidos y de una manera conocida Si bien la fase puede comprender tan solo un emulsionante, puede comprender una mezcla de por lo menos un emulsionante con una grasa o un aceite, o con una grasa y un aceite Preferiblemente se incluye un emulsionante hidrofilico junto con un emulsionante lipofilico, que actua como un estabilizante También es preferible incluir tanto un aceite como una grasa Juntos, el(los) emulsionante(s) con o sin estabilizante(s) constituyen la llamada cera emulsionante, y la cera junto con el aceite y la grasa constituyen la llamada base de unguento emulsionante, que forma la fase dispersada, oleosa, de las formulaciones en crema Estabilizantes de emulsión y emulsionantes adecuados para ser usados en las formulaciones de la presente invención incluyen Tween 60, Span 80, alcohol cetoestearilico, alcohol miristilico, monoestearato de glicerilo y laurilsulfato de socio, entre otros La elección de los aceites o las grasas adecuados para la formulacion se basa en lograr las propiedades cosmeticas deseadas, dado que la solubilidad del compuesto activo en la mayoria de los aceites aptos para usar en las formulaciones de emulsiones farmaceuticas es muy baja Asi, la crema deberia ser preferentemente un producto no graso, que no manche y lavable, con una consistencia adecuada para evitar que se derrame de los tubos o de otros envases Se pueden usar

esteres de alquilo mono- o di-básicos, de cadena lineal o ramificada, tales como di-isoadipato, estearato de isocetilo, diester de propilenglicol de ácidos grasos de coco, miristato de isopropilo, oleato de decilo, palmitato de isopropilo, estearato de butilo, 2-etilhexil palmitato o una mezcla de ésteres de cadena ramificada Éstos se pueden usar solos o en combinación dependiendo de las propiedades que se requieran Alternativamente, se pueden usar lipidos con un punto de fusión alto, tal como la parafina líquida blanca, y/u otros aceites minerales

Las formulaciones adecuadas para la administración topica en el ojo también incluyen gotas oftalmicas en las que los ingredientes activos estan disueltos o suspendidos en un portador adecuado, especialmente un disolvente acuoso para los ingredientes activos Los ingredientes activos antiinflamatorios están presentes en dichas formulaciones, preferentemente, en una concentracion de 0,5 a 20%, ventajosamente 0,5 a 10% y particularmente alrededor de 1,5% peso/peso Para fines terapeuticos, los compuestos activos de esta invencion de combinacion se combinan habitualmente con uno o mas adyuvantes apropiados para la via de administración indicada Si se administran per os, estos compuestos se pueden mezclar con lactosa, sucrosa, polvo de almidón, ésteres de celulosa de ácidos alcanoicos, alquil-ésteres de celulosa, talco, acido esteárico, estearato de magnesio, oxido de magnesio, sal de sodio y de calcio de ácidos fosforico y sulfurico, gelatina, goma de acacia, alginato de sodio, polivinilpirrolidona, y/o alcohol polivinilico, y despues darles la forma de tableta o de capsula para hacer más conveniente su administración Dichas capsulas o tabletas pueden contener una formulación de liberación controlada tal como la que se puede proporcionar en una dispersión de compuesto activo en

hidroxi-propilmetil celulosa Las formulaciones para administracion parenteral pueden presentarse en forma de suspensiones o soluciones de inyeccion estériles, isotonicas, acuosas o no acuosas Estas soluciones y suspensiones se pueden preparar a partir de gránulos o polvos esteriles que tengan uno o mas de los portadores o diluyentes mencionados para usar en las formulaciones que se administran por via oral Estos compuestos se pueden disolver en agua, polietilenglicol, polipropilenglicol, etanol, aceite de maiz, aceite de semillas de algodón, aceite de cacahuete, aceite de sésamo, alcohol bencilico, cloruro de sodio y/o diversos tampones Hay otros adyuvantes y modos de administración que son ampliamente conocidos en la tecnica farmaceutica

La cantidad de compuestos terapéuticamente activos que se administran y el iegimen de dosificación para tratar una enfermedad con los compuestos y/o las composiciones de esta invención dependen de una variedad de factores, incluyendo la edad, el peso, el sexo y la condicion medica del sujeto, la gravedad de la inflamación o del trastorno relacionado con la inflamacion, la via y frecuencia de administración, y el compuesto en particular que se emplea y, por lo tanto, pueden variar ampliamente Las composiciones farmacéuticas pueden contener ingredientes activos en el intervalo de alrededor de 0,1 a 1 000 mg, preferentemente en el intervalo de alrededor de 7,0 a 350 mg Una dosis diaria de alrededor de 0,01 a 100 mg/kg de peso corporal, preferentemente, entre alrededor de 0,1 y alrededor de 50 mg/kg de peso corporal y, más preferentemente, entre alrededor de 0,5 a 30 mg/kg de peso corporal puede ser la apropiada Se puede administrar la dosis diaria en una a cuatro dosis por dia En el caso de afecciones de la piel, quiza sea preferible aplicar una preparación tópica de

compuestos de esta invención dos a cuatro veces por día en la zona afectada

Se entenderá, no obstante, que el nivel de la dosis específica para cualquier paciente en particular dependerá de una diversidad de factores, incluyendo la actividad del compuesto específico empleado, la edad, el peso corporal, el estado de salud en general, el sexo, el tiempo de administración, la vía de administración y la velocidad de excreción, la combinación de drogas y la gravedad de la enfermedad en particular que es objeto de la terapia

Para la administración a animales no humanos, se podrá añadir la composición al alimento o al agua dulce del animal Quiza sea conveniente formular las composiciones de alimento y agua dulce de manera tal que el animal ingiera una cantidad terapéuticamente apropiada de la composición junto con la dieta Quiza sea conveniente también presentar la composición como una premezcla para agregar al alimento o al agua

En esta solicitud de patente, las descripciones de todos los artículos y las referencias, incluyendo patentes, están incorporadas por referencia

Esta invención esta ilustrada, además, por los siguientes ejemplos, que no deberan ser interpretados como limitando la invención en alcance o en espíritu a los procedimientos específicos descritos en ellos

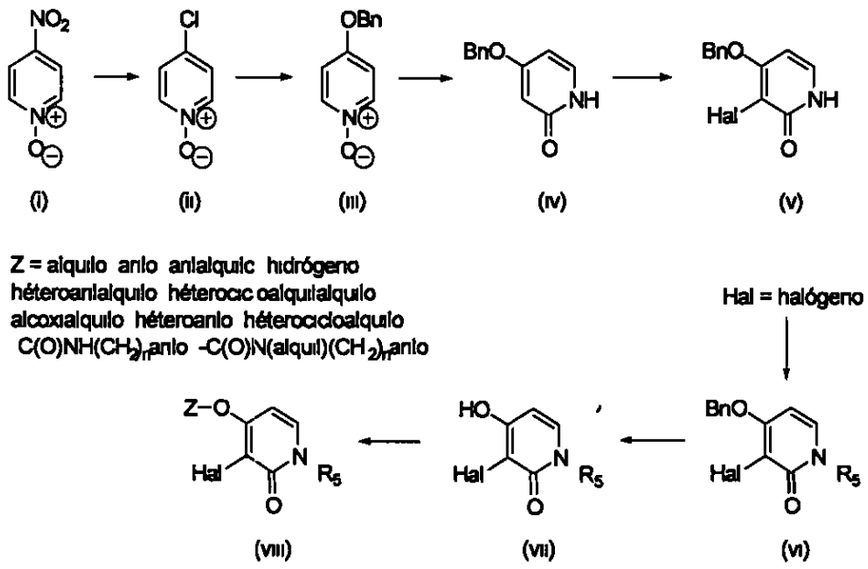
Los materiales de inicio y diversos intermedios se pueden obtener de fuentes comerciales, preparados a partir de compuestos disponibles comercialmente o preparados usando métodos sintéticos bien conocidos

Los nombres de los compuestos en esta solicitud de patente se crearon usando los programas informáticos ACD Name Pro, versión 5 09, o ChemDraw ultra versión 6 0 2

Procedimientos sinteticos generales

Procedimientos representativos para la preparacion de los compuestos de la invencion se delinean mas adelante en los Esquemas Los materiales de inicio se pueden adquirir o preparar usando metodos conocidos por los expertos en la tecnica De modo similar, la preparación de los diversos intermedios se puede lograr usando metodos conocidos en la técnica Los materiales de inicio pueden ser variados y se pueden emplear etapas adicionales para producir los compuestos que abarca la invencion, tal como se demuestra con los siguientes ejemplos Además, para obtener las transformaciones anteriores se pueden usar distintos disolventes y reactivos Para lograr las transformaciones anteriores quiza sea necesaria la proteccion de los grupos reactivos En general, la necesidad de grupos protectores, asi como las condiciones necesarias para acoplar y eliminar tales grupos, sera evidente para los expertos en la técnica de la sintesis orgánica Cuando se emplea un grupo protector, en general se requerira la desprotección Los grupos protectores adecuados y la metodologia para la protección y la desproteccion tales como los descritos en *Protecting Groups in Organic Synthesis* de Green y Wuts son conocidos y apreciados por los expertos en la tecnica

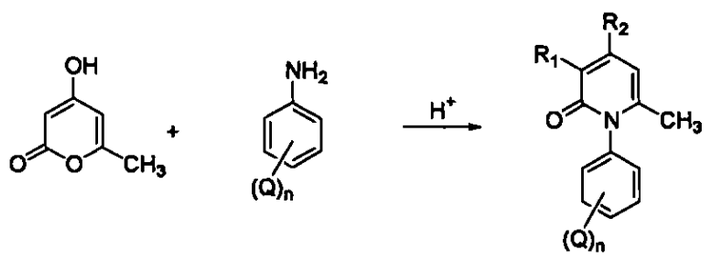
Esquema 1




En este esquema, $R_5$ es tal como se definió anteriormente

Alternativamente, los compuestos de la presente invencion se pueden preparar de acuerdo con el metodo esbozado en el Esquema 2

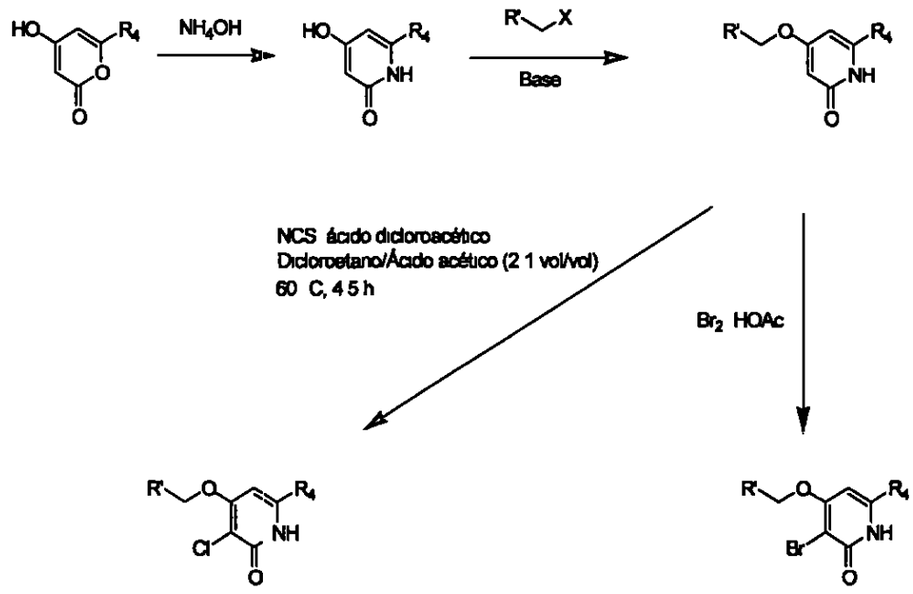
Esquema 2



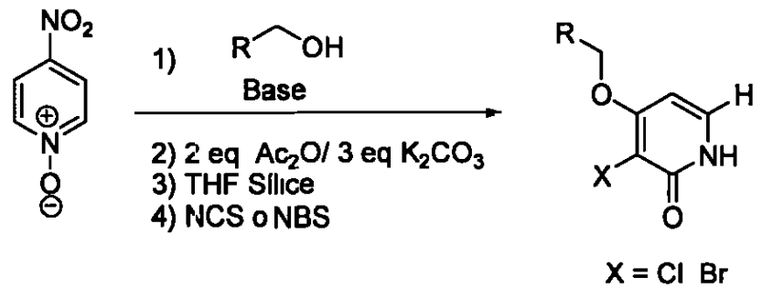

En el esquema 2, en cada aparición Q es independientemente alquilo, halogeno, alcoxi, arilalquilo, tioalcoxi, alcoxicarbonilo, $CO_2H$, CN, amidinooxima, $NR_6R_7$, $NR_6R_7$alquilo, $-C(O)NR_6R_7$, amidino, haloalquilo o haloalcoxi, y n es 0, 1, 2, 3, 4 ó 5

Alternativamente, los compuestos de la invención se pueden preparar usando los procedimientos esbozados en los Esquemas 3-25 En los Esquemas 3-25, los sustituyentes X, X', R, R' y R'' en grupos tales como arilo, heteroarilo, amino y alquilo llevan la misma definicion descrita anteriormente para sustituyentes en estos grupos

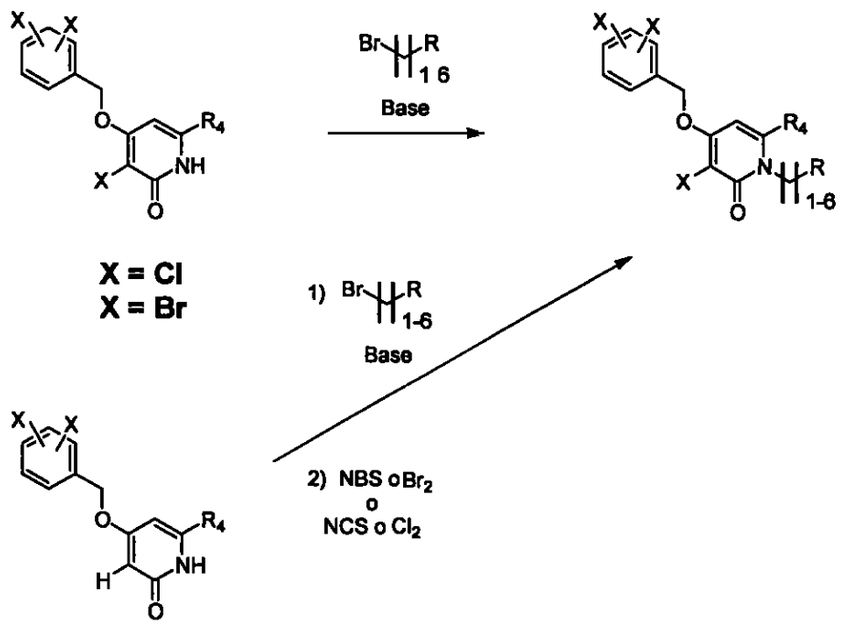
Esquema 3



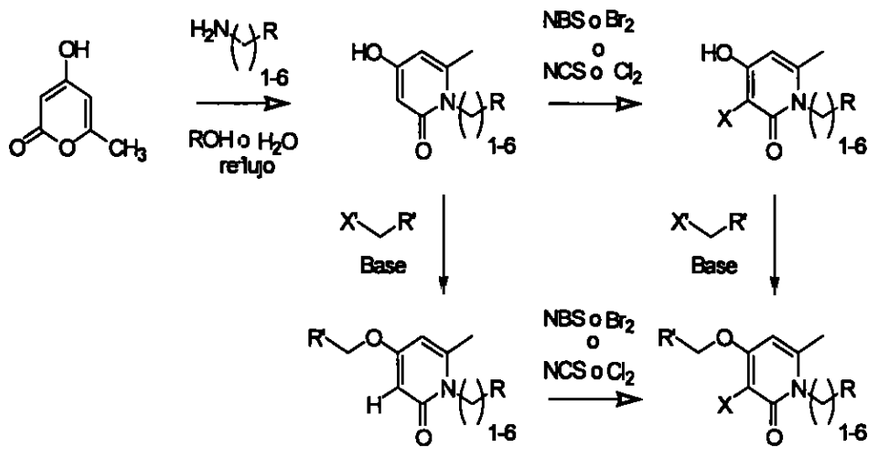

Esquema 4



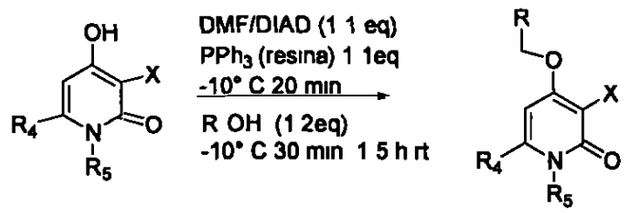
Esquema 5




Esquema 6

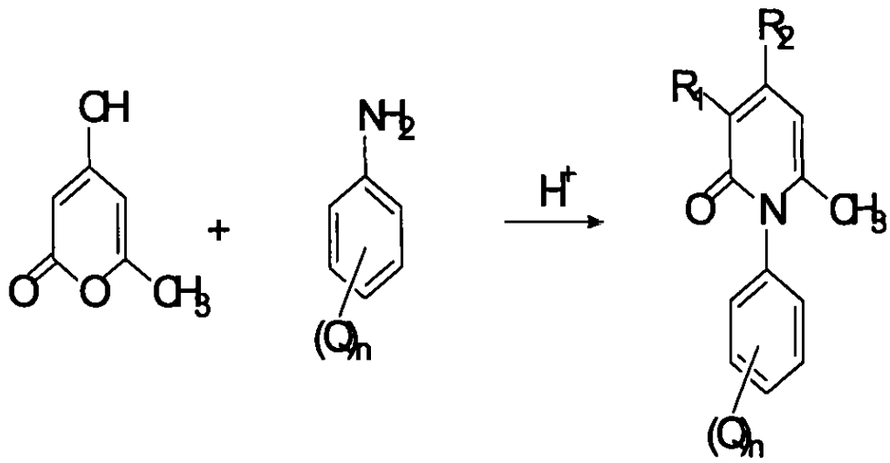



Esquema 7



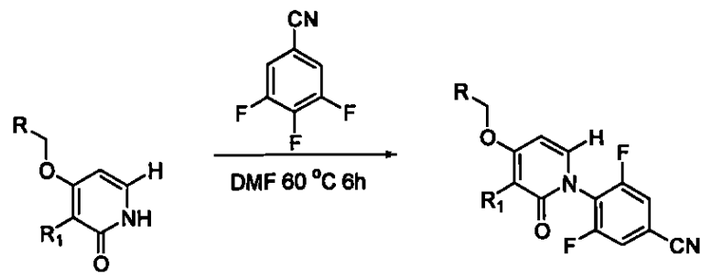

$PPh_3$ resina 3 mmol=1 g $PPh_3$

Esquema 8

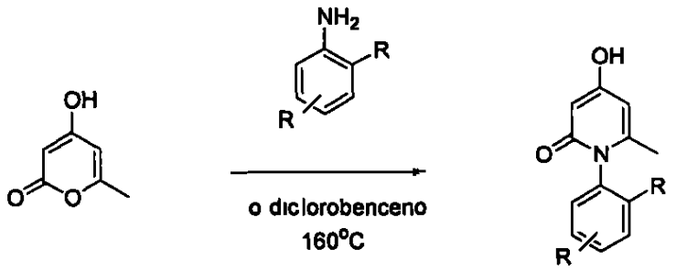


(IX) (X) (XI)

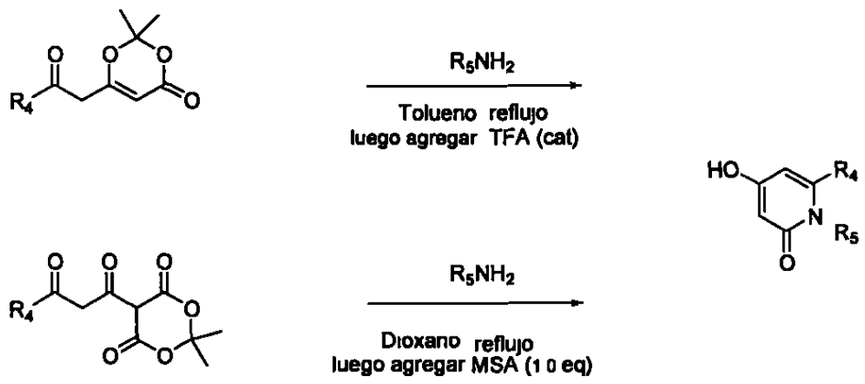
Esquema 9



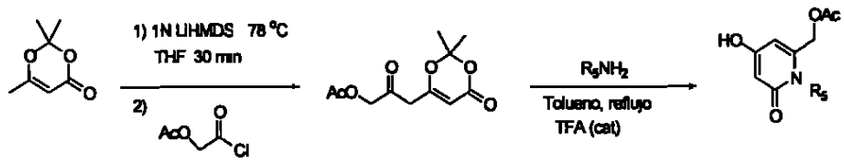
Esquema 10



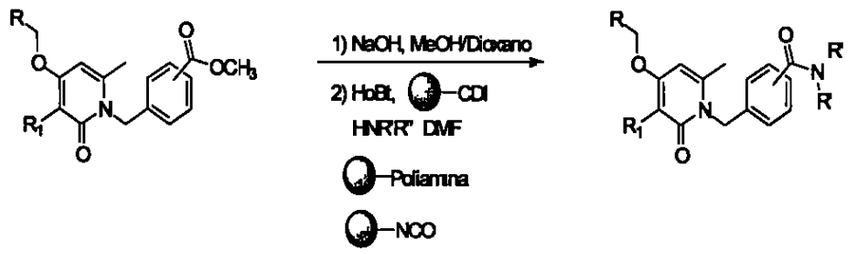

Esquema 11



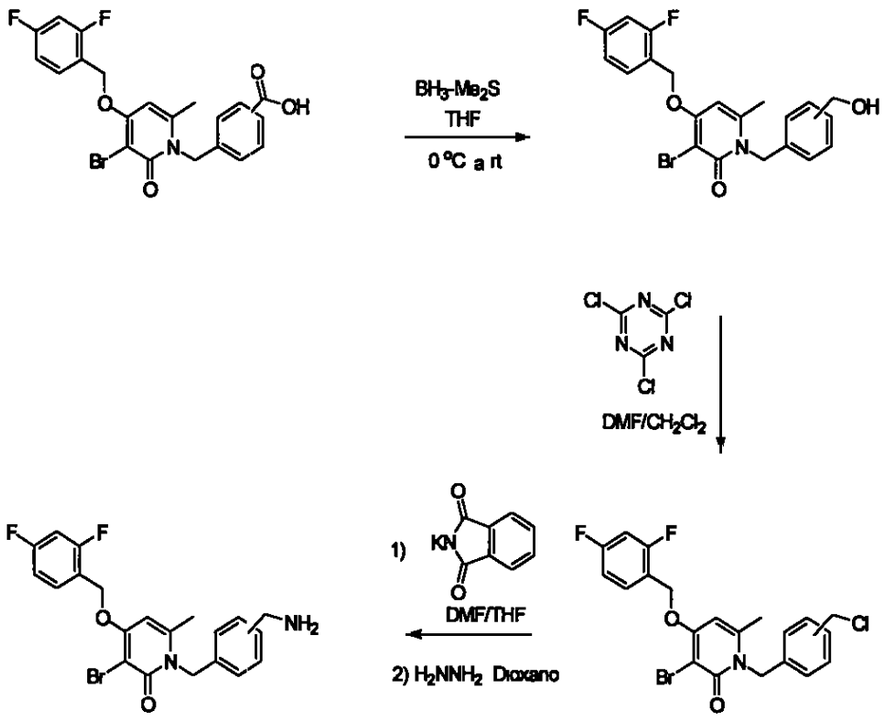

Esquema 12



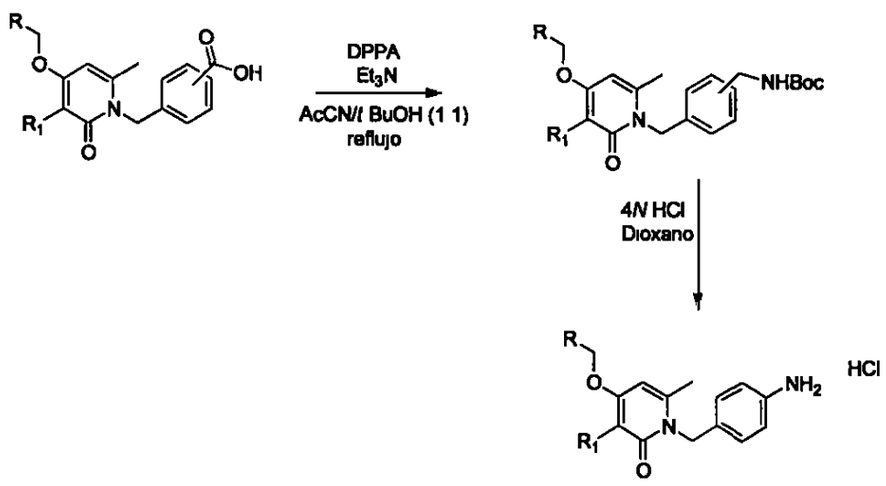

Esquema 13


1) NaOH, MeOH/Dioxano
2) HoBt,
CDI
HNR'R" DMF
Poliamina
NCO

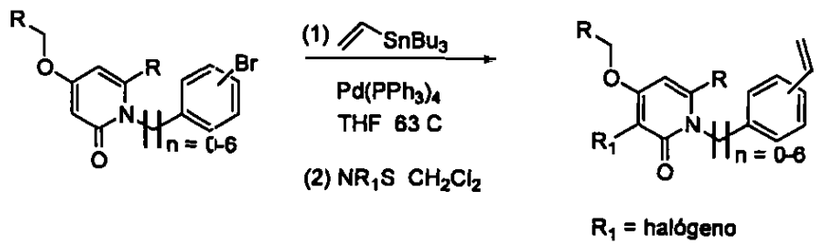
Esquema 14


BH3-Me2S
THF
0 °C a rt
DMF/CH2Cl2
1)
DMF/THF
2) H2NNH2 Dioxano

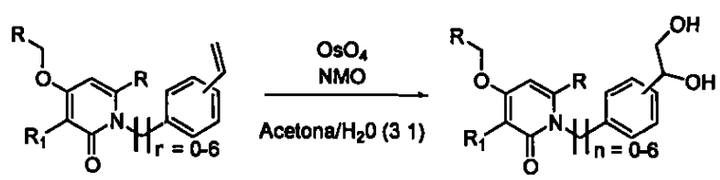
Esquema 15



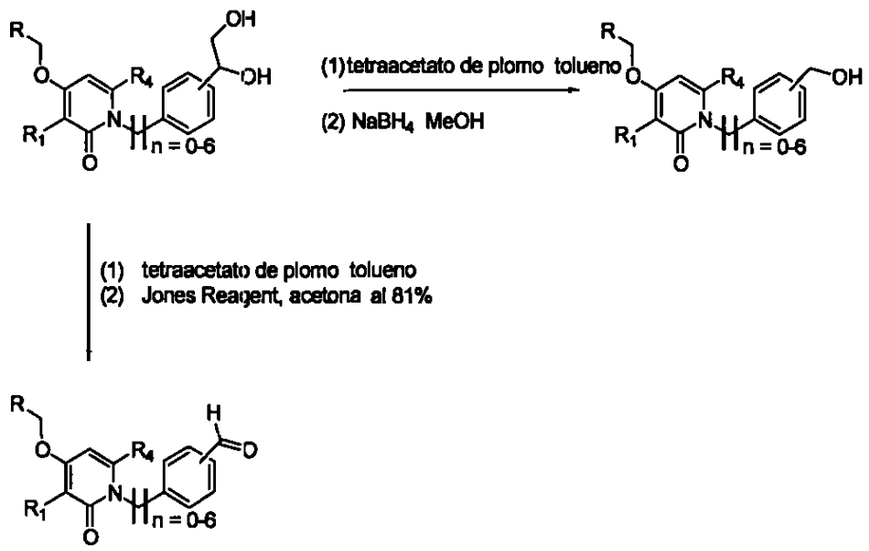

Esquema 16



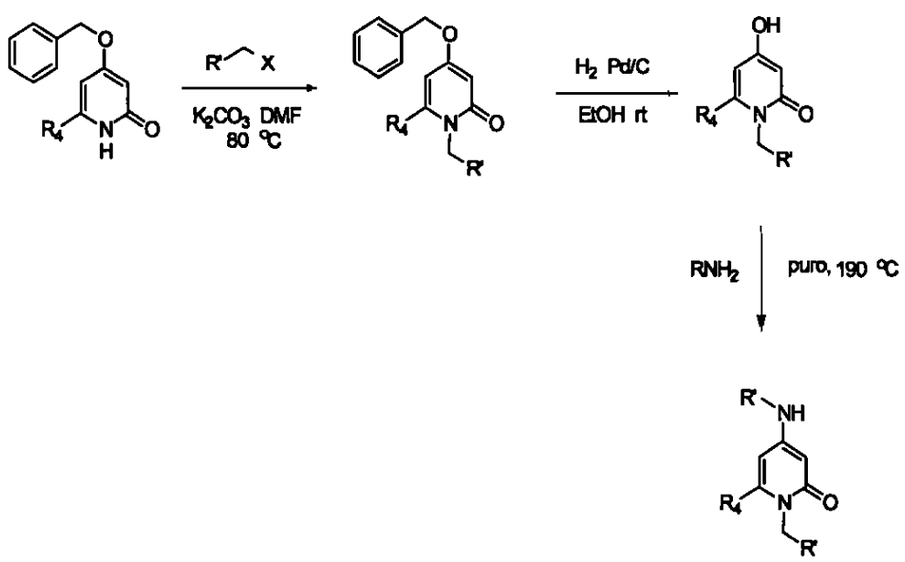

Esquema 17



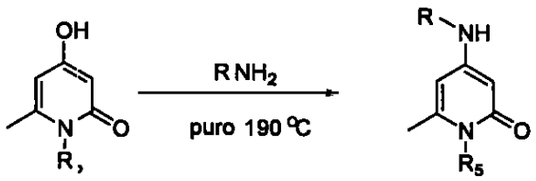
Esquema 18



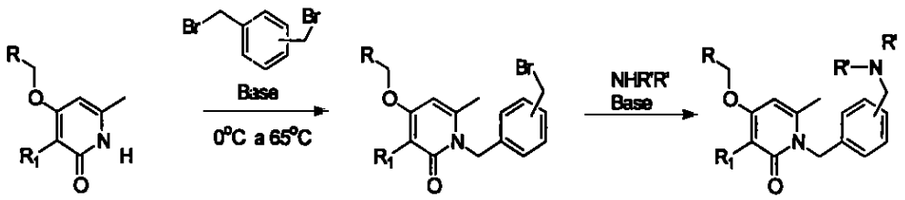

Esquema 19



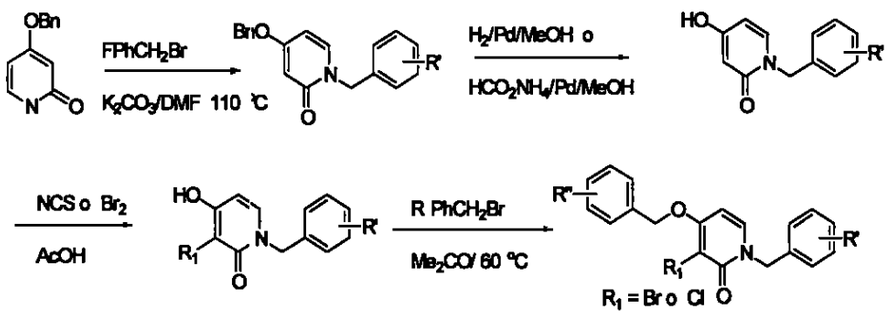
Esquema 20



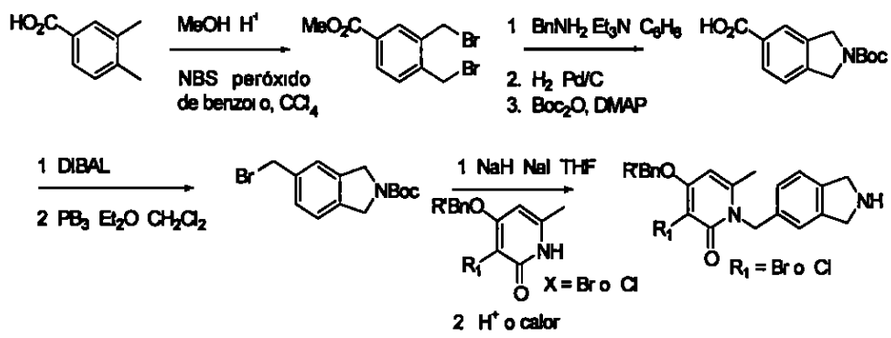

Esquema 21



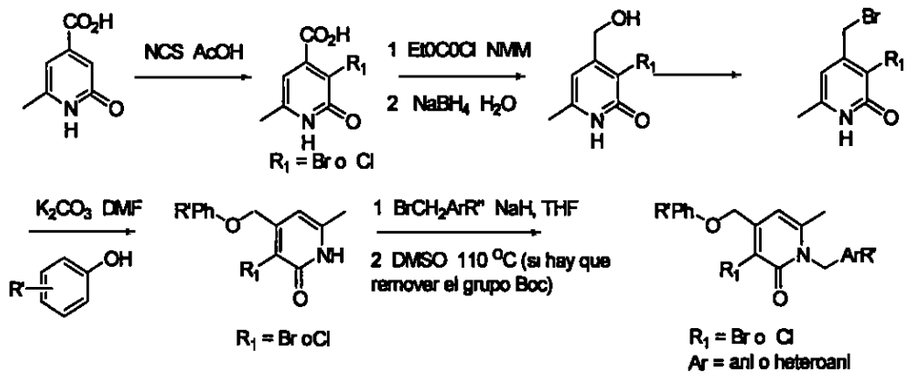

Esquema 22



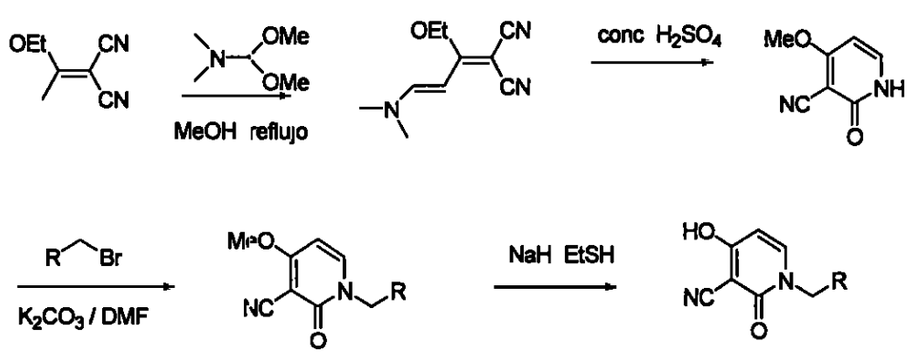

Esquema 23




Esquema 24




Esquema 25




Esta invencion esta ilustrada, ademas, por los siguientes ejemplos, que no deberan ser interpretados

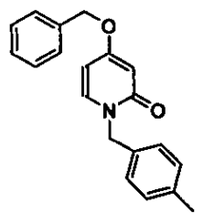
limitando la invención en alcance o en espíritu a los procedimientos específicos descritos en ellos Aquellos expertos en la técnica reconocerán que los materiales de inicio se pueden variar y que se pueden emplear etapas adicionales para producir los compuestos que abarca la invención, tal como se demuestra con los siguientes ejemplos Los expertos en la técnica también reconocerán que quiza sea necesario utilizar disolventes o reactivos diferentes para obtener algunas de las transformaciones anteriores En algunos casos, puede ser necesaria la protección de las funcionalidades reactivas puede ser necesario para obtener las transformaciones anteriormente mencionadas En general, dicha necesidad de grupos protectores, así como las condiciones necesarias para acoplar y eliminar dichos grupos, será evidente para los expertos en la técnica de la síntesis orgánica Cuando se emplea un grupo protector, quizá se requiera una etapa de desprotección Grupos protectores adecuados y la metodología para la protección y la desprotección tales como los descritos en *Protecting Groups in Organic Synthesis* de Green y Wuts son bien conocidos y apreciados por los expertos en la técnica

A menos que se especifique lo contrario, todos los reactivos y disolventes tienen un grado comercial estándar y se usan sin mayor purificación La atmósfera apropiada para llevar a cabo la reacción, por ejemplo, aire, nitrógeno, hidrógeno, argón y similares, será evidente para los expertos en la técnica

Ejemplos

Ejemplo 1

4-(benciloxi)-1-(4-metilbencil)piridin-2(1*H*)-ona,

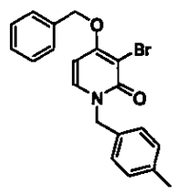


Se calentaron a 80 °C durante 2 horas 4-benciloxi-2(1H)-piridona (3,0 g, 0,015 mol), bromuro de 4-metilbencilo (3,15 g, 0,17 mol) y carbonato de potasio (3,0 g, 0,022 mol) Los contenidos se dejaron enfriar, se diluyeron con agua y se filtró un solido (5,52 g) FABHRMS m/z 306,1494 (M+H $C_{20}H_{20}NO_2$ requiere 306,1494) $^1H$ NMR ($CDCl_3$/300 MHz) 7,50-7,40 (m, 5H), 7,20-7,05 (m, 5H), 6,07-6,00 (m, 1H), 5,95-5,90 (m, 1H), 5,05 (s, 2H), 5,00 (s, 2H), 2,32 (s, 3H)

Anal Calculadc para $C_{20}H_{19}NO_2$ C, 78,66, H, 6,27, N, 4,59 Hallado C, 78,54, H, 6,38, N, 4,58

Ejemplo 2

4-(benciloxi)-3-bromo-1-(4-metilbencil)piridin-2(1*H*)-ona

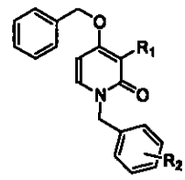


El material preparado en el Ejemplo 1 (2,1 g, mol) y acetato de sodio (738 mg, 0,009 mol) en ácido acético glacial (15 ml) se enfriaron hasta 15 °C Se agregó gota a gota bromo (0,412 ml, 0,008) en ácido acetico glacial (5 ml) Se agitaron los contenidos durante 2 horas, hasta alcanzar la temperatura ambiente Se agrego agua (200 ml) y se filtro un solido de color amarillo claro Mp 150,4 - 151,2 °C FABHRMS m/z 384,0599 (M+H, $C_{20}H_{19}BrNO_2$ requiere 384,0601) $^1H$ NMR ($CDCl_3$/300 MHz) δ 7,42-7,30 (m, 5H),

7,22-7,08 (m, 5H), 6,02 (d, 1H), 5,20 (s, 2H), 5,12 (s, 2H), 2,32 (s, 3H)

Anal Calculado para $C_{20}H_{18}BRNO_2$ C, 62,51, H, 4,72, N, 3,65 Hallado C, 62,11, H, 4,48, N, 3,54

Ejemplos 3-10




Los compuestos de los Ejemplos 3-10 se preparan esencialmente de acuerdo con el procedimiento establecido anteriormente con respecto al Ejemplo 1 Los compuestos en los que $R_1$ = Br se preparan esencialmente de acuerdo con el procedimiento establecido para el Ejemplo 1

| Ejemplo N° | $R_1$ | $R_2$ | FM | M+H m/z Requiere | FABHRMS m/z |
|---|---|---|---|---|---|
| Ej 3 | -H | 4-Br | $C_{19}H_{16}BrNO_2$ | 370,0428 | 370,0443 |
| Ej 4 | -Br | 4-Br | $C_{19}H_{15}Br_2NO_2$ | 447,9522 | 447,9548 |
| Ej 5 | -H | 4-Cl | $C_{19}H_{16}ClNO_2$ | 326,0948 | 326,0893 |
| Ej 6 | -Br | 4-Cl | $C_{19}H_{15}BrClNO_2$ | 404,0053 | 404,0035 |
| Ej 7 | -H | 3-F | $C_{19}H_{16}FNO_2$ | 310,1243 | 310,1226 |
| Ej 8 | -Br | 3-F | $C_{19}H_{15}BrFNO_2$ | | |
| Ej 9 | -H | 2-F | $C_{19}H_{16}FNO_2$ | 310,1231 | 310,1243 |
| Ej 10 | -Br | 2-F | $C_{19}H_{15}BrFNO_2$ | 388,0348 | 388,0373 |

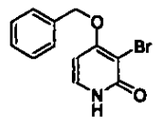
Caracterizacion por NMR de los compuestos de los Ejemplos 3-10

| Ej N° | Datos de NMF |
|---|---|
| Ej 3 | $^1H$ NMR ($CDCl_3$/300 MHz) δ 7,43 (d, 2H) 7,40-7,33 (m, 5H), 7,20-7,07 (m, 3H), 6,04-6,01 (m, |

| | |
|---|---|
| | 1H), 6,00-5,92 (m, 1H), 5,03 (s, 2H), 4,98 (s, 2H) |
| Ej 4 | $^1$H NMR ($CDCl_3$/300 MHz) δ 7,50-7,15 (m, 10H), 6,06 (d, 1H), 5,20 (s, 2H), 5,10 (s, 2H) |
| Ej 5 | $^1$H NMR ($CDCl_3$/300 MHz) δ 7,40-7,32 (m, 5H), 7,24 (AB cuarteto, 4H), 7,10 (d, 1H), 6,03-6,00 (m, 1H), 5,98-5,92 (m, 1H), 5,03 (s, 2H), 4,99 (s, 2H) |
| Ej 6 | $^1$H NMR ($CDCl_3$/300 MHz) 7,43-7,20 (m, 10H), 6,08 (d, 1H), 5,20 (s, 2H), 5,10 (s, 2H) |
| Ej 7 | $^1$H NMR ($CDCl_3$/300 MHz) δ 7,45-7,25 (m, 5H), 7,12 (d, 1H), 7,07-6,93 (m, 4H), 6,04-6,02 (m, 1H), 6,00-5,94 (m, 1H), 5,08 (s, 2H), 5,00 (s, 2H) |
| Ej 8 | $^1$H NMR ($CDCl_3$/300 MHz) δ 7,43-7,25 (m, 6H), 7,21 (d, 1H), 7,10-6,93 (m, 3H), 6,08 (d, 1H), 5,22 (s, 2H), 5,12 (s, 2H) |
| Ej 9 | $^1$H NMR ($CDCl_3$/300 MHz) δ 7,43-7,00 (m, 10H), 6,01-5,92 (s, 2H), 5,10 (s, 2H), 4,99 (s, 2H) |
| Ej 10 | $^1$H NMR ($CDCl_3$/300 MHz) 7,52 (d de t, 1H), 7,44-7,26 (m, 7H), 7,15-7,00 (m, 2H), 6,03 (d, 1H), 5,20 (s, 2H), 5,15 (s, 2H) |

Ejemplo 11

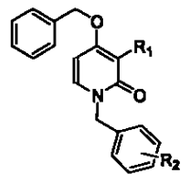
4-(benciloxi)-3-bromopiridin-2(1*H*)-ona




El material del Ejemplo 11 se preparo conforme al procedimiento del Ejemplo 2 $^1$H NMR ($CDCl_3$/300 MHz) δ 7,50-7,30 (m, 6H), 6,20 (d, 1H), 5,24 (s, 2H)

Anal Calculado para $C_{12}H_{10}BrNO_2$ (0,3$H_2O$) C, 50,48, H, 3,74, N, 4,91 Hallado C, 50,79, H, 3,41, N, 4,82

Ejemplos 12-19



Los compuestos de los Ejemplos 12-19 se prepararon esencialmente conforme a los procedimientos establecidos anteriormente para el Ejemplo 1 Compuestos en los que $R_1$ = Br se preparan esencialmente de acuerdo con el procedimiento del Ejemplo 1

| Ejemplo N° | R1 | R2 | MF | M+H Requiere | FABHRMS m/z |
|---|---|---|---|---|---|
| Ej 12 | -Br | 4-benciloxi | $C_{26}H_{22}BrNO_3$ | 476,0861 | 476,0854 |
| Ej 13 | -H | 4-$CO_2$Me | $C_{21}H_{19}NO_4$ | 350,1392 | 350,1391 |
| Ej 14 | -Br | 4-$CO_2$Me | $C_{21}H_{18}BrNO_4$ | 428,0497 | 428,0480 |
| Ej 15 | -Br | 4-$CO_2$H | $C_{20}H_{16}BrNO_4$ | 414,0341 | 414,0360 |
| Ej 16 | -H | 4-CN | $C_{20}H_{16}N_2O_2$ | 317,1290 | 317,1270 |
| Ej 17 | -Br | 4-CN | $C_{20}H_{15}BrN_2O_2$ | 395,0395 | 395,0376 |
| Ej 18 | -H | 4-t-Butilo | $C_{23}H_{25}NO_2$ | 348,1964 | 348,1949 |
| Ej 19 | -Br | 4-t-Butilo | $C_{23}H_{24}BrNO_2$ | 426,1069 | 426,1023 |

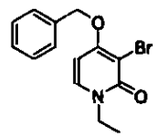
Caracterización por NMR de los compuestos de los Ejemplos 12-19

| Ej N° | Datos de NMR |
|---|---|
| Ej 12 | $^1$H NMR ($CDCl_3$/300 MHz) 7,45-7,15 (m, 13H), 6,92 (d, 1H), 6,01 (d, 1H), 5,20 (s, 2H), 5,08 (s, 2H), 5,03 (s, 2H) |
| Ej 13 | $^1$H NMR ($CDCl_3$/300 MHz) 8,00 (d, 2H), 7,40-7,25 (m, 7H), 7,10 (d, 1H), 6,04-6,01 (m, 1H), 6,00-5,93 (m, 1H), 5,12 (s, 2H), 5,00 (s, 2H), 3,95 (s, 3H) |
| Ej 14 | $^1$H NMR ($CDCl_3$/300 MHz) 8,00 (d, 2H), 7,42-7,31 (m, 7H), 7,23 (d, 1H), 6,08 (d, 1H), 5,22 (d, 2H), 5,20 (s, 2H), 3,95 (s, 3H) |
| Ej 15 | $^1$H NMR (DMSO-$d_6$ /300 MHz) 8,00-7,80 (m, 3H), 7,53-7,27 (m, 7H), 6,50 (d, 1H), 5,32 (s, 2H), 5,20 (s, 2H) |
| Ej 16 | $^1$H NMR ($CDCl_3$/300 MHz) $\delta$ 7,60 (d, 2H), 7,42-7,30 (m, 7H), 7,13 (d, 1H), 6,05-5,98 (m, 2H), 5,11 (s, 2H), 5,00 (s, 2H) |

| | |
|---|---|
| Ej 17 | $^1$H NMR ($CDCl_3$ /300 MHz) δ 7,61 (d, 2H), 7,48-7,30 (m, 6H), 7,23 (d, 1H), 6,12 (d, 1H), 5,22 (s, 2H), 5,20 (s, 2H) |
| Ej 18 | $^1$H NMR ($CDCl_3$/300 MHz) 7,40-7,28 (m, 7H), 7,20 (d, 2H), 7,10 (d, 1H), 6,02 (s, 1H), 5,97-5,90 (m, 1H), 5,02 (d, 2H), 4,98 (d, 2H) |
| Ej 19 | $^1$H NMR ($CDCl_3$/300 MHz) δ 7,43-7,20 (m, 10H), 6,02 (d, 1H) 5,20 (s, 2H), 5,10 (s, 2H), 1,30 (s, 9H) |

Ejemplo 20

4-(benciloxi)-3 bromo-1-etilpiridin-2(1*H*)-ona

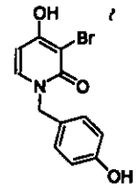



A 4-benciloxi-2(1H)-piridona (1,0 g, 0,005 mol) y carbonato de potasio (1,0 g, 0,007 mol) en DMF (10 ml) se agrego bromoetano (0,82 ml, 0,011 mol) Los contenidos se calentaron a 75 °C durante toda la noche Los contenidos se dejaron enfriar y se dividieron en EtOAc y agua La capa de EtOAc se seco sobre $MgSO_4$, se filtro y se concentró *in vacuo* lo que dejo un solido ceroso, que se recristalizo a partir de EtOAc/hexanos para dar un solido blanco (720 mg) Al sólido blanco (700 mg, 0,003 mol) en acido acetico glacial (10 ml), se agregó gota a gota bromo (0,17 ml, 0,00325 mol) en acido acetico glacial (5 ml) a 15 °C Los contenidos se agitaron durante una hora a temperatura ambiente y se filtro un solido amarillo (1,1 g) El sólido se dividio en EtOAc y 2,5 N hidroxido de sodio La capa de EtOAc se seco sobre $MgSO_4$, se filtró y se concentro *in vacuo* lo que dejo un aceite incoloro (710 mg) que se solidificó FABHRMS m/z 310,0267 (M+H $C_{14}H_{15}BrNO_2$ requiere 310,0263) $^1$H NMR ($CDCl_3$/300 MHz) δ 7,45-7,30 (m, 6H), 7,22 (d, 1H), 6,07 (d, 1H), 5,20 (s, 2H), 4,00 (q, 2H), 1,32 (t, 3H),

Anal Calculado para $C_{14}H_{14}BrNO_2$ C, 54,56, H, 4,58, N, 4,55 Hallado C, 54,21, H, 4,38, N, 4,43

Ejemplo 21

3-bromo-4-hıdroxı-1-(4-hıdroxıbencıl)pırıdın-2(1*H*)-ona

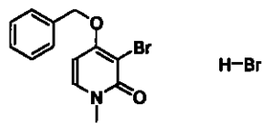


El materıal del Ejemplo 12 (120 mg, 0,25 mol) y paladıo/carbono al 10% (30 mg) en ácıdo acétıco glacıal (ml) se agıtaron a 55 lbs de hıdrógeno durante 4 horas Los contenıdos se fıltraron y el fıltrado se concentró *ın vacuo* lo que dejó ın aceıte FABHRMS m/z 295,9952 (M+H $C_{12}H_{11}BrNO3$ requıere '95,9922) $^1H$ NMR (DMSO-$d_6$ /300 MHz) δ 11,40 (br s, 1H), 9,40 (br s, 1H), 7,60 (d, 1H) 7,10 (d, 2H), 6,70 (d, 2H), 6,02 (d, 1H), 4,93 (s, 2H)

Anal Calculado para $C_{12}H_{10}BrNO_3$ (1,4 $H_2O$) C, 44,85, H, 4,02, N, 4,36 Hallado C, 45,07, H, 4,10, N, 4,35

Ejemplo 22

hıdrobromuro de 4-(bencıloxı)-3-bromo-1-metılpırıdın-2(1*H*)-ona



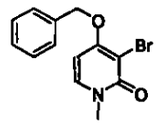
A 4-bencıloxı-2(1H)-pırıdona (1,0 g, 0,005 mol) y carbonato de potasıo (760 mg, 0,0055 mol) en DMF (10 ml) se agrego yoduro de metılo (0,342 ml, 0,0055 mol) Los contenıdos se agıtaron durante toda la noche Los contenıdos se dıvidıeron en EtOAc y agua Las capa de EtOAc se seco sobre $MgSO_4$, se fıltró y se concentro *ın vacuo*, lo que dejó un sólıdo blanco (960 mg)

Al solido blanco (332 mg, 0,0015 mol) en acido acético glacial (10 ml) se agrego bromo (256 mg, 0,0016 mol) en ácido acetico glacial (5 m) gota a gota a 15 °C Los contenidos se agitaron a temperatura ambiente durante una hora y el producto deseado se filtró como un sólido blanco, 262 mg (rendimiento 59%) mp 105,3-105,6 °C FABHRMS m/z 296,0097 (M+H $C_{13}H_1BrNO_2$ requiere 296,0110) $^1H$ NMR ($CDCl_3$/300 MHz) δ 7,45-7,30 (m, 6H), 7,22 (d, 1H), 6,07 (d, 1H), 5,20 (s, 2H), 4,00 (q, 2H), 1,32 (t, 3H),

Anal Calculado para $C_{13}H_{12}BrNO_2$ (HBr, 0,3$H_2O$) C, 41,04, H, 3,60, N, 3,68 Hallado C, 41,00, H, 3,87, N, 3,52

Ejemplo 23

4-(benciloxi)-3-bromo-1-metilpiridin-2(1*H*)-ona

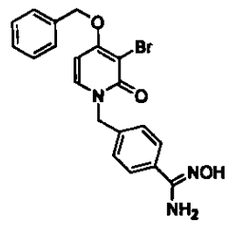



El material del Ejemplo 22 se dividio en EtOAc y 2,5 N hidroxido de sodio Las capa de EtOAc se seco sobre $MgSO_4$, se filtro y se concentro *in vacuo* , lo que dejó un aceite rojo, que se solidificó FABHRMS m/z 294,0112 (M+H $C_{13}H_{13}BrNO_2$ requiere 294,0130) $^1H$ NMR ($CDCl_3$/300 MHz) 7,45-7,30 (m, 6H), ',22 (d, 1H), 6,07 (d, 1H), 5,20 (s, 2H), 4,00 (q, 2H), 1,32 (t, 3H)

Anal Calculado para $C_{13}H_{12}BrNO_2$ C, 53,08, H, 4,11, N, 4,76 Hallado C, 53,06, H, 4,20, N, 4,74

Ejemplo 24

4-{[4-(benciloxi)-3-bromo-2-oxopiridin-1(2*H*)-il]metil}-*N*-hidroxibencenocarboximidamida

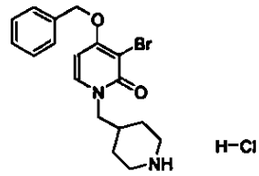


Se sometio a reflujo el material del Ejemplo 17 (500 mg, 0,00127 mol), hidrocloruro de hidroxilamina (90 mg, 0,0013 mol) y bicarbonato de sodio (109 mg) en etanol (15 ml) durante toda la noche Los contenidos se dejaron enfriar y se filtró un solido que se lavo con agua para proporcionar el producto deseado como un sólido blanco, 447 mg, (rendimiento 82%) mp 210,2-212,2 °C FABHRMS m/z 428,0634 (M+H $C_{20}H_{19}BrN_3O_3$ requiere 428,0610) $^1$H NMR (DMSO-$d_6$ /300 MHz) 9,66 (s, 1H), 7,98 (d, 1H), 7,65 (d, 2H), 7,55-7,35 (m, 5H), 7,30 (d, 2H), 6,54 (d, 1H), 5,82 (s, 2H), 5,35 (s, 2H), 5,17 (s, 2H)

Anal Calculado para $C_{20}H_{18}BrN_3O_3$ C, 56,09, H, 4,24, N, 9,81 Hallado C, 55,92, H, 4,01, N, 9,52

Ejemplo 25

hidrocloruro de 4-(benciloxi)-3-bromo-1-(piperidin-4-ilmetil)piridin-2(1*H*)-ona



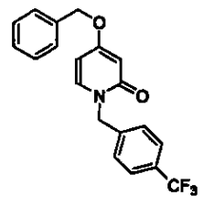
Al material del Ejemplo 11 (924 mg, 0,0033 mol) en DMF (5 ml) se agregó gota a gota sodio bis(trimetilsilil)amida (1 M en THF, 3,6 ml) Los contenidos se agitaron durante 1 hora antes de agregar gota a gota una disolucion de éster *terc*-butilico de acido 4-metanosulfoniloximetil-1-piperidina-1-carboxilico (*J Labelled Compd, Radiopharm*, 38(7), 1996, 595-606) (1,0 g, 0,0036 mol) en DMF (5 ml) Los contenidos se calentaron a 75 °C durante toda la noche

Los contenidos se dejaron enfriar y se vertieron en agua (100 ml) Un solido se filtro y se recristalizo a partir de EtOAc para proporcionar cristales (546 mg) Los cristales blancos se sometieron a reflujo en 4 N HCI/dioxano (10 ml) durante 3 horas, se dejó enfriar y se filtró para dar el producto deseado como un solido, 415 mg (rendimiento 30%) mp 207,9 °C FABHRMS m/z 377,0852 (M+H $C_{18}H_{23}BrClN_2O_2$ requiere 377,0865) $^1$H NMR (DMSO-$d_6$ /300 MHz) δ 8,90 (br, 1H), 8,64 (br, 1H), 7,80 (d, 1H), 7,50-7,30 (m, 5H), 6,48 (d, 1H), 5,30 (s, 1H), 3,83 (d, 2H), 3,20 (d, 2H), 2,88-2,64 (m, 2H), 2,10-1,90 (m, 1H), 1,60 (d, 2H), 1,50-1,40 (m, 2H)

Anal Calculado para $C_{18}H_{22}BrClN_2O_3$ (0,3 $H_2O$) C, 51,58, H, 5,43, N, 6,68 Hallado C, 51,59, H, 5,42, N, 6,81

Ejemplo 26

4-(benciloxi)-1-[4-(trifluorometil)bencil)]piridin-2(1*H*)-ona

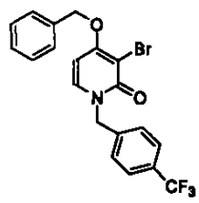



Se preparó el material del Ejemplo 26 de acuerdo con el procedimiento establecido para el Ejemplo 1 FABHRMS m/z 360,1213 (M+H, $C_{20}H_{17}F_3NO_2$ requiere 360,1211) $^1$H NMR ($CDCl_3$/300 MHz) δ 7,60 (d, 2H), 7,41-7,30 (m, 7H), 7,13 (d, 1H), 6,05-6,01 (m, 1H), 6,00-5,95 (m, 1H), 5,13 (s, 2H), 5,00 (s, 2H)

Anal Calculado para $C_{20}H_{16}F_3NO_2$ C, 66,85, H, 4,49, N, 3,90 Hallado C, 66,64, H, 4,26, N, 3,93

Ejemplo 27

4-(benciloxi)-3-bromo-1-[4-(trifluorometil)bencil)]piridin-2(1*H*)-ona

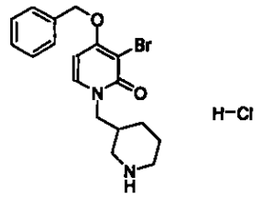


Se preparo el material del Ejemplo 27 de acuerdo con el procedimiento establecido para el Ejemplo 2 FABHRMS m/z 438,0308 (M+H, $C_{20}H_{16}BrF_3NO_2$ requiere 438,0316) $^1$H NMR ($CDCl_3$/300 MHz) δ 7,65-7,20 (m, 10H), 6,13-6,03 (m, 1H), 5,30-5,13 (m, 4H)

Anal Calculado para $C_{20}H_{15}BrF_3NO_2$ C, 54,81, H, 3,45, N, 3,20 Hallado C, 54,69, H, 3,34, N, 3,19

Ejemplo 28

hidrocloruro de 4-(benciloxi)-3-bromo-1-(piperidin-3-ilmetil)piridin-2(1*H*)-ona



Al material del Ejemplo 11 (3,1 g, 0,011 mol) en DMF (20 ml) se agrego gota a gota sodio bis(trimetilsilil)amida (1 M en THF, 12 ml) Los contenidos se agitaron durante 1 hora antes de agregar gota a gota una disolución de ester *terc*-butílico de acido 3-metanosulfoniloximetil-1-piperidina-1-carboxílico (*Bioorg Med Chem Lett*, 8(13), 1998, 1595-1600) (4,2 g, 0,015 mol) en DMF (5 ml) Los contenidos se calentaron a 75 °C durante toda la noche Los contenidos se dejaron enfriar, se vertieron en agua (100 ml) y se filtró un solido El sólido se agitó en 4 N HCI/dioxano (15 ml) durante 3 horas y se filtro para dar el producto deseado como un sólido blanco, 752 mg (rendimiento 18%) mp 138,1-139,2 °C FABHRMS m/z 377,0859 (M+H $C_{18}H_{22}BrN_2O_2$ requiere 377,0865) $^1$H NMR (DMSO-$d_6$ /300 MHz)

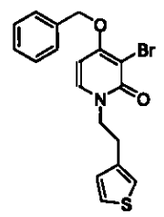
789

9,50-9,10 (br, 2H), 8,00 (d, 1H), 7,50-7,30 (m, 5H), 6,93 (d, 1H), 5,30 (s, 2H), 4,30-3,90 (m, 3H), 3,40-3,10 (m, 3H), 2,80-2,50 (m, 3H), 2,40-2,00 (m, 1H), 1,90-1,60 (m, 4H), 1,40-1,10 (m, 1H)

Anal Calculado para $C_{18}H_{21}BrN_2O_2$ (2HCl, 0,25 $H_2O$) C, 47,55, H, 5,21, N, 6,16 Hallado C, 47,48, H, 5,46, N, 6,27

Ejemplo 29

4-(benciloxi)-3-bromo-1-(2-tien-3-iletil)piridin-2(1*H*)-ona




Al material del Ejemplo 11 (500 mg, 0,0018 mol) en DMF (5 ml) se agrego gota a gota sodio bis(trimetilsilil)amida (1 M en THF, 2 ml) Los contenidos se agitaron durante una hora antes de agregar gota a gota una disolucion de ester 2-tiofen-3-il-etilicc de acido metanosulfonico (*J A C St*, 109(6), 1987, 1858, -1859) (412 mg, 0,002 mol) en DMF (5 ml) Los contenidos se calentaron a 75 °C durante toda la noche Los contenidos se dejaron enfriar, se vertieron en agua (100 ml) y se extrajeron en EtOAc, se secaron sobre $MgSO_4$, se filtraron y concentraron *in* vacuo lo que dejó un aceite de color amarillo claro El aceite se purificó mediante cromatografia en gel de silice eluyendo con EtOAc/hexanos al 50% para proporcionar el producto deseado como un solido de color blanco, 199 mg (rendimiento 28%) mp 134,0-134,3 °C

FABHRMS m/z 390,0144 (M+H $C_{18}H_{17}BrNO_2S$ requiere 390,0163) $^1H$ NMR ($CDCl_3$/300 MHz) 7,43-7,20 (m, 6H),

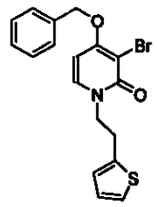
790

6,92-6,80 (m, 3H), 5,90 (d, 1H), 5,20 (s, 2H), 4,13 (t, 2H), 3,10 (t, 2H)

Anal Calculado para $C_{18}H_{16}BrNO_2S$ C, 55,39, H, 4,13, N, 3,59 Hallado C, 55,21, H, 3,87, N, 3,52

Ejemplo 30

4-(benciloxi)-3-bromo-1-(2-tien-2-iletil)piridin-2(1*H*)-ona

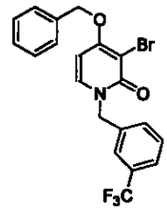


El compuesto del título se preparo esencialmente de acuerdo con el procedimiento establecido para el Ejemplo 29 mp 128,0-129,5 °C FABHRMS m/z 390,0160 (M+H $C_{18}H_{17}BrNO_2S$ requiere 390,0163) $^1H$ NMR ($CDCl_3$/300 MHz) δ 7,48-7,30 (m, 5H), 7,12 (d, 1H), 6,95-6,80 (m, 2H), 6,75-6,68 (m 1H), 5,95 (d, 1H), 5,20 (s, 2H), 4,16 (t, 2H), 3,30 (t, 2H)

Anal Calculado para $C_{18}H_{16}BrNO_2S$ C, 55,39, H, 4,13, N, 3,59 Hallado C, 55,06, H, 4,01, N, 3,56

Ejemplo 31

4-(benciloxi)-3-bromo-1-[3-(trifluorometil)bencil)]piridin-2(1*H*)-ona



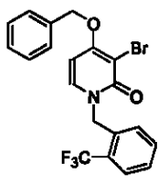
Al material del Ejemplo 11 (500 mg, 0,0018 mol) en DMF (5 ml) se agrego gota a gota sodio bis(trimetilsilil)amida (1 M en THF, 2 ml) Los contenidos se agitaron durante una hora antes de agregar gota a gota una disolucion de bromuro

3-trifluorometilbencílico (478 mg, 0,002 mol) en DMF (5 ml) Los contenidos se calentaron a 75 °C durante dos horas Los contenidos se dejaron enfriar, se vertieron en agua (100 ml) y se extrajeron en EtOAc, lo que se seco sobre $MgSO_4$, se filtro y concentró *in* vacuo, y dejo un solido blanco FABHRMS m/z 438,0301 (M+H $C_{20}H_{16}BrF_3NO_2$ requiere 438,0316) $^1H$ NMR ($CDCl_3$/300 MHz) 7,60-7,20 (m, 10H) 6,10 (d, 1H), 5,14 (s, 2H), 5,20 (s, 2H)

Anal Calculado para $C_{20}H_{15}BrF_3NO_2$ C, 54,81 H, 3,45, N, 3,20 Hallado C, 54,81, H, 3,36, N, 3,13

Ejemplo 32

4-(benciloxi)-3-bromo-1-[2-(trifluorometil)bencil]piridin-2(1*H*)-ona



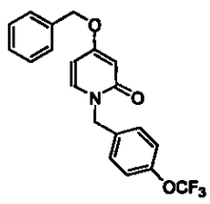

El material del Ejemplo 32 se preparó de acuerdo con el procedimiento establecido para el Ejemplo 31

FABHRMS m/z 138,0280 (M+H $C_{20}H_{16}BrF_3NO_2$ requiere 438,0316) $^1H$ NMR ($CDCl_3$/300 MHz) δ 7,68 (d, 1H), 7,55-7,20 (m, 8H), 7,15 (d, 1H), 6,10 (d, 1H), 5,40 (s, 2H), 5,13 (s, 2H)

Anal Calculado para $C_{20}H_{15}BrF_3NO_2$ C, 54,81, H, 3,45, N, 3,20 Hallado C, 54,48, H, 3,36, N, 3,17

Ejemplo 33

4-(benciloxi)-1-[4-(trifluorometoxi)bencil]piridin-2(1*H*)-ona



792

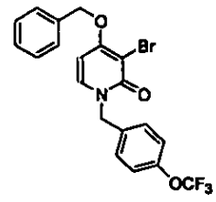
El material del Ejemplo 33 se preparo de acuerdo con el procedimiento establecido para el Ejemplo 1

FABHRMS m/z 376,1158 (M+H $C_{20}H_{17}F_3NO_3$ requiere 376,1161) $^1$H NMR ($CDCl_3$/300 MHz) δ 7,40-7,05 (m, 10H), 6,05-5,95 (m, 2H), 5,06 (s, 2H), 4,98 (s, 2H)

Anal Calculado para $C_{20}H_{16}F_3NO_3$ C, 64,00, H, 4,30, N, 3,73 Hallado C, 63,97, H, 4,26, N, 3,57

Ejemplo 34

4-(benciloxi)-3 bromo-1-[4-(trifluorometoxi)bencil]piridin-2(1*H*)-ona



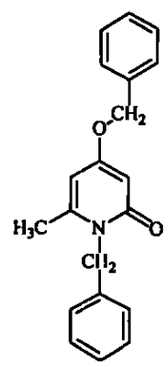

El material del Ejemplo 34 se preparo de acuerdo con el procedimiento establecido para el Ejemplo 2

FABHRMS m/z 454,0240 (M+H $C_{20}H_{16}BrF_3NO_3$ requiere 454,0266) $^1$H NMR ($CDCl_3$/300 MHz) δ 7,45-7,10 (m, 10H), 6,08 (d, 1H), 5,20 (s, 2H), 5,12 (s, 2H)

Anal Calculado para $C_{20}H_{15}BrF_3NO_3$ C, 52,88, H, 3,33, N, 3,08 Hallado C, 52,53, H, 3,09, N, 2,92

Ejemplo 35

1-bencil-4-(benciloxi)-6-metilpiridin-2(1*H*)-ona



Etapa 1 Preparacion de 1-bencil-4-hidroxi-6-metilpiridin-2(1*H*)-ona,

Se agregaron 4-hidroxi-6-metil-2-pirona (0,2 mol, 25,2 g) y bencilamina (0 2 mol, 21,4 g) a agua (800 ml) y se calento a reflujo con agitacion durante 2 horas Despues de enfriar hasta temperatura ambiente, se recogió mediante filtración un solido de color marrón claro (33,4 g, al 77%) $^1$H NMR (DMSO-$d_6$/300 MHz) δ 10,5 (s, 1H), 7,4-7,1 (m, 5 H), 5,8-5,6 (m, 2H), 5,2 (s, 2H), 5,1 (s, 2H), 2,2 (s, 3H) ESHRMS *m/z* 216,100 (M+H $C_{12}H_{13}NO_2$ requiere 216,102)

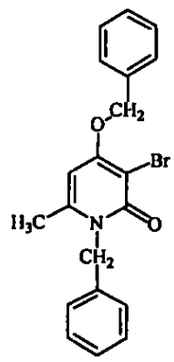
Etapa 2 Preparación de 1-bencil-4-(benciloxi)-6-metilpiridin-2(1*H*)-ona

Se agitaron vigorosamente a temperatura ambiente 1-bencil-4-hidroxi-6-metilpiridin-2(1H)-ona (10 mmol, 2,15 g), diclorometano (100 ml), bromuro de bencilo (11 mmol, 1,88 g), hidróxido de sodio (2,5 N, 20 mmol, 8 ml) y cloruro de benciltrietilamonio (0,5 g) durante 16 horas Se agrego acido clorhidrico (1 N) hasta que la mezcla produjo una reaccion acidogena al papel pH Luego se extrajo la mezcla con acetato de etilo (3 X 50 ml) Los extractos orgánicos combinados se lavaron con salmuera, se secaron sobre sulfato de magnesio, se filtraron y se concentraron El producto se obtuvo mediante cromatografia rápida eluyendo con acetato de etilo hexanos (1 2) Las fracciones apropiadas se concentraron hasta obtener un aceite transparente (1,3 g, al 43%) $^1$H NMR (DMSO-$d_6$/300 MHz) δ 7,4-7,1 (m, 10 H), 6,0-5,9 (m, 2H), 5,2 (s, 2H), 5,1 (s, 2H), 2,2 (s, 3H) ESHRMS *m/z* 306,147 (M+H $C_{20}H_{19}NO_2$ requiere 306,149)

Ejemplo 36

1-bencil-4-(benciloxi)-3-bromo-6-metilpiridin-2(1*H*)-ona

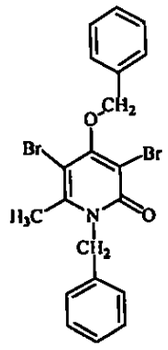
794



El producto del Ejemplo 35, 1-bencil-4-(benciloxi)-6-metilpiridin-2(1H)-ona (4,2 mmol, 1,3 g), acido acético (50 ml) y acetato de sodio (5,0 mmol, 0,41 g) se agitaron a temperatura ambiente Se agrego bromo (4,2 mmol, 0,67 g) gota a gota con agitacion Despues de ½ hora, se agrego agua (100 ml) y se extrajo la mezcla con acetato de etilo (3 x 50 ml) Los extractos organicos combinados se lavaron con una disolución de bicarbonato de sodio acuosa saturada y salmuera Despues de secar sobre sulfato de magnesio y de concentrar, la mezcla se purifico mediante cromatografia en columna rápida eluyendo con acetato de etilo hexanos (1 2) Las fracciones apropiadas se concentraron para producir un aceite ligero (1,0 g, al 62%) $^1$H NMR (DMSO-$d_6$/300 MHz) 7,4-7,0 (m, 10 H), 6,5 (s, 1H), 5,29 (s,2H), 5,27 (s, 2H), 2,2 (s, 3H) ESHRMS *m/z* 384,057 (M+H $C_{20}H_{18}NO_2Br$ requiere 384,060)

Ejemplo 37

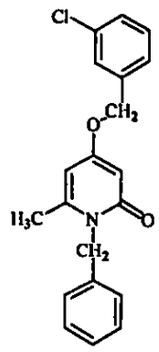
1-bencil-4-(benciloxi)-3,5-dibromo-6-metilpiridin-2(1*H*)-ona



Se agitó a temperatura ambiente el producto del Ejemplo 35, 1-bencil 4-(benciloxi)-6-metilpiridin-2(1H)-ona (4,2 mmol, 1,3 g), acido acético (50 ml) y acetato de sodio (5,0 mmol, 0,41 g) se agrego bromo (4,2 mmol, 0,67 g) gota a gota con agitacion Despues de ½ hora, se agrego agua (100 ml) y se extrajo la mezcla con acetato de etilo (3 x 50 ml) Los materiales organicos combinados se lavaron con una disolucion de bicarbonato de sodio acuosa saturada y salmuera Después de secar sobre sulfato de magnesio y de concentrar, la mezcla se purifico mediante cromatografia en columna rapida eluyendo con acetato de etilo hexanos (1 2) Las fracciones apropiadas se concentraron para producir un solido blanco (0,3 g, al 15%) $^1$H NMR (DMSO-$d_6$/300 MHz) 7,5-7,0 (m, 10 H), 5,42 (s, 2H), 5,07 (s, 2H), 2,45 (s, 3H) ESHRMS *m/z* 463,966 (M+H $C_{20}H_{17}NO_2Br_2$ requiere 463,968)

Ejemplo 38

1-bencil-4-[(3-clorobencil)oxi]-6-metilpiridin-2(1*H*)-ona



Etapa 1 Preparacion de 4-bromobencenosulfonato de 1-bencil-6-metil-2-oxo 1,2-dihidropiridin-4-il

Se agitaron a temperatura ambiente 1-bencil-4-hidroxi-6-metilpiridin-2(1H) (del Ejemplo 35) (10 mmol, 2,15 g), N,N'-dimetilformamida (30 ml), carbonato de potasio (20 mmol, 2,76 g) y cloruro de bromobencenosulfonilo (10 mmol, 2,55 g) durante 16 horas Se agrego acido clorhidrico (1N) hasta que la mezcla produjo una reacción acidógena al papel pH Se agrego salmuera (50 ml) y se extrajo la mezcla con acetato de etilo (3 x 50 ml) Los extractos orgánicos combinados se lavaron con salmuera, se secaron sobre sulfato de magnesio y se filtraron Después de efectuar la concentracion, el material se purificó mediante cromatografia en columna rapida eluyendo con acetato de etilo/hexanos (1 2) Se concentraron las fracciones apropiadas hasta lograr un aceite transparente, que solidificó y se convirtio en un sólido blanco al estacionarlo varios dias (3,3 g, al 76%) $^1$H NMR (DMSO-$d_6$/400 MHz) 7,9 (m, 4H), 7,32-7,00 (m, 5H), 7,3 (m, 1H), 6,12 (d, *J = 2,4* Hz, 1H), 6,02 (d, *J = 2,8* Hz, 1H), 5,20 (s, 2H), 2,2 (s, 3H) ESHRMS *m/z* 436,002 (M+H $C_{19}H_{16}NO_4SBr$ requiere 436,004)

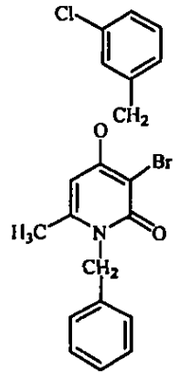
Etapa 2 Preparacion de 1-bencil-4-[(3-clorobencil)oxi]-6-metilpiridin-2(1*H*)-ona

797

Se agitaron 1-bencil-6-metil-2-oxo-1,2-dihidropiridin-4-il-bromobencenosulfonato (3,0 mmol, 1,3 g), N,N'-dimetilformamida (30 ml), alcohol clorobencílico (3 mmol, 0,43 g) e hidroxido de sodio (60%, 3,3 mmol, 0,13 g) a temperatura ambiente bajo nitrogeno durante 4 horas Se agregó ácido clorhídrico (1 N, 10 ml) y se extrajo la mezcla con acetato de etilo (3 x 25 ml) Los extractos orgánicos combinados se lavaron con una disolución de bicarbonato de sodio acuosa saturada y salmuera Después de secar sobre sulfato de magnesio y de concentrar, la mezcla se purifico mediante cromatografia en columna rápida eluyendo con acetato de etilo hexanos (1 1) hasta obtener un aceite de color amarillo claro (14,3 g, al 64%) $^1$H NMR (DMSO-$d_6$/300 MHz) δ 7,4-7,0 (m, 10 H), 6,0-5,8 (m, 2H), 5,2 (s, 2H), 5,0 (s, 2H), 2,1 (s, 3H) ESHRMS *m/z* 340,110 (M+H $C_{20}H_{18}NO_2Cl$ requiere 340,110)

Ejemplo 39

1-bencil-3-bromo-4-[(3-clorobencil)oxi]-6-metilpiridin-2(1*H*)-ona

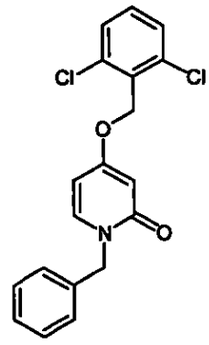



Se agitaron el producto del Ejemplo 38 (SC-83316), 1-bencil-4-[(3-clorobencil)oxi]-6-metilpiridin-2(1H)-ona (0,91 mmol, 310 Mg), ácido acetico (20 ml) y acetato de sodio (0,91 mmol, 80 Mg) a temperatura ambiente cuando se agrego bromo (0,91 mmol, 145 Mg) Después de agitar durante

una hora, la mezcla se concentro, se disolvio en acetato de etilo y se lavó sucesivamente con una disolucion acuosa saturada de bicarbonato de sodio, salmuera y agua Después de secar sobre sulfato de magnesio y de concentrar, el producto se recristalizo a partir de tetrahidrofurano/hexanos para producir un sólido blanco (240 Mg, al 63%) $^1$H NMR (DMSO-$d_6$/300 MHz) 7,6-7,0 (m, 10 H), 6,5 (s, 1H), 5,03 (s, 2H), 5,33 (s, 2H), 2,3 (s, 3H) ESHRMS *m/z* 420,019 (M+H $C_{20}H_{17}NO_2BrCl$ requiere 420,019)

Ejemplo 40

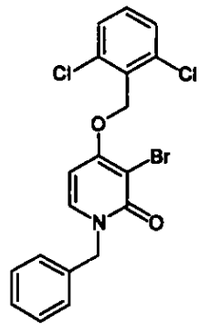
1-bencil-4-[(2,6-diclorobencil)oxi]piridin-2(1H)-ona




El compuesto del titulo se preparo esencialmente como se describe en la reivindicacion 1 mp 151,6-152,0 °C $^1$H NMR ($CDCl_3$/300MHz) δ 7,31 (m, 8H), 7,12 (d, 1H, J = 7,45 Hz), 6,13 (d, 1H, J - 2,42 Hz), 5,90 (dd, 1H, J = 2,62 Hz), 5,22 (s, 2H), 5,10 (s, 2H) ESHRMS *m/z* 360,0551 (M+H $C_{19}H_{15}Cl_2NO_2$ requiere 360,0558)

Ejemplo 41

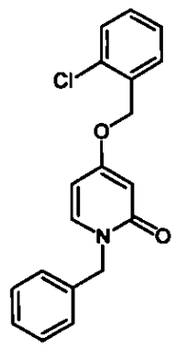
1-bencil-3-bromo-4-[2,6-(diclorobencil)oxi]piridin-2(1H)-ona



Se disolvió 1-bencil-4-[(2,6-diclorobencil)oxi]piridin-2(1H)-ona (0,400 g, 1,11 mmol) en acido acetico (10 ml) Se agrego acetato de sodio (0,091 g, 1,11 mmol) y la mezcla se enfrió a 15 °C Se agregó bromo (0,195 g, 1,22 mmol) via jeringa La reaccion se agito a temperatura ambiente durante 2 horas Se agrego agua (15 ml) y se transfirio la mezcla a un embudo separador Se agrego acetato de etilo (50 ml) y las capas se separaron La fase organica se lavo con $NaHCO_3$ acuoso (2 x 25 ml), se seco sobre $MgSO_4$, se filtro y se evaporo para producir un solido blanco $^1H$ NMR ($CDCl_3$/300 MHz) δ 7,34 (m, 9H), 6,24 (d, 1H, J = 7,65 Hz), 5,37 (s, 2H), 5,18 (s, 2H) ESHRMS *m/z* 439,9646 (M+H $C_{19}H_{14}BrCl_2NO_2$ requiere 439,9641)

Ejemplo 42

1-bencil-4-[(2-clorobencil)oxi]piridin-2(1*H*)-ona

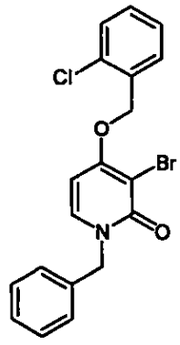


El compuesto del título se preparó con un procedimiento similar al descrito en Ejemplo 1 mp 124,6-125,0 °C $^1$H NMR ($CDCl_3$/300MHz) δ 7,36 (m, 9H), 7,14 (d, 1H, J = 7,65 Hz), 6,04 (d, 1H, J = 2,62 Hz), 5,98 (d, 1H, J = 2,82 Hz), 5,10 (s, 2H), 5,09 (s, 2H) ESHRMS *m/z* 326,0950 (M+H $C_{19}H_{16}ClNO_2$ requiere 326,0948)

Anal Calculado para $C_{19}H_{16}ClNO_2$ C, 70,05, H, 4,95, N, 4,30, Cl, 10,88 Hallado C, 69,87, H, 4,74, N, 4,42, Cl, 11,08

Ejemplo 43

1-bencil-3-bromo-4-[(-2-clorobencil)oxi]piridin-2(1*H*)-ona

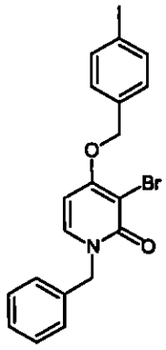



El compuesto del título se preparo mediante un procedimiento similar al descrito en el Ejemplo 2 mp 143,3-145,5 °C $^1$H NMR ($CDCl_3$/300MHz) δ 7,63 (d, 2H, J = 1,81 Hz), 7,44 (m, 9H), 6,06 (d, 1H, J = 7,65 Hz), 5,29 (s, 2H), 5,17 (s, 2H) ESHRMS *m/z* 406,0036 (M+H $C_{19}H_{15}BrClNO_2$ requiere 406,0032)

Anal Calculado para $C_{19}H_{15}ClBrNO_2$ C, 56,39, H, 3,74, N, 3,46, Cl, 8,76 Hallado C, 56,01, H, 3,38, N, 3,36, Cl, 9,01

Ejemplo 44

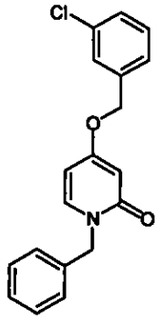
1-bencil-3-bromo-4-[(-4-metilbencil)oxi]piridin-2(1H)-ona



El compuesto del título se preparo mediante un procedimiento similar al descrito en el Ejemplo 2 mp 149,0-149,7 °C $^1$H NMR ($CDCl_3$/300MHz) δ 7,25 (m, 10H), 6,04 (d, 1H, J = 7,65 Hz), 5,17 (s, 2H), 5,15 (s, 2H), 2,34 (s, 3H) ESHRMS m/z 386,0583 (M+H $C_{20}H_{18}BrNO_2$ requiere 386,0581)

Ejemplo 45

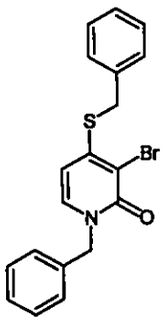
1-bencil-4-[(3-clorobencil)oxi]piridin-2(1*H*)-ona



El compuesto del título se preparó mediante un procedimiento similar al descrito en el Ejemplo 1 mp 95,5-95,7 °C $^1$H NMR ($CDCl_3$/300MHz) δ 7,34 (m, 9H), 7,13 (d, 1H, J = 7,45 Hz), 5,96 (m, 1H), 5,95 (d, 1H, J = 7,45 Hz), 5,09 (s, 2H), 4,96 (s, 2H) ESHRMS *m/z* 326,0977 (M+H $C_{19}H_{16}ClNO_2$ requiere 326,0948)

Ejemplo 46

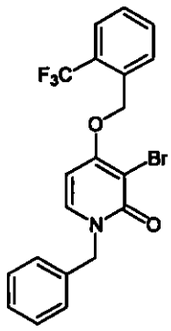
1-bencil-4-[benciltio]-3-bromopiridin-2(1*H*)-ona



El compuesto del título se preparo mediante un procedimiento similar al descrito en el Ejemplo 2 mp 180,6-182,1 °C $^1$H NMR ($CDCl_3$/300MHz) δ 7,33 (m, 10H), 7,14 (d, 1H, J = 7,45 Hz), 6,08 (d, 1H, J = 7,45 Hz), 5,13 (s, 2H), 4,15 (s, 2H) ESHRMS *m/z* 386,0211 (M+H $C_{19}H_{16}BrNOS$ requiere 386,0214)

Ejemplo 47

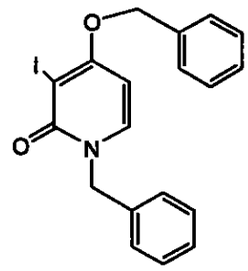
1-bencil-3-bromo-4-{[2-(trifluorometil)bencil]oxi}piridin-2(1*H*)-ona



El compuesto del titulo se preparo mediante un procedimiento similar al descrito en el Ejemplo 2 mp 133,2-133,5 °C $^1$H NMR ($CDCl_3$/300MHz) δ 7,81 (d, 1H, J = 7,65 Hz), 7,68 (d, H, J = 7,65 Hz), 7,61 (t, 1H, J = 7,65 Hz), 7,38 (m, 7H), 6,01 (d, 1H, J = 7,85 Hz), 5,39 (s, 2H), 5,16 (s, 2H) ESHRMS m/z 438,0313 (M+H $C_{20}H_{15}BrF_3NO_2$ requiere 403,0316)

Ejemplo 48

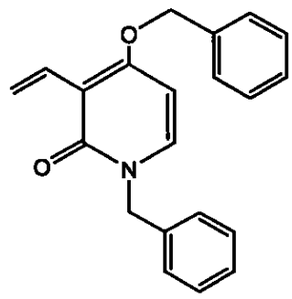
1-bencil-4-(benciloxi)-3-yodopiridin-2(1*H*)-ona



Una mezcla de N,O-dibencil-2-piridona (2,0 g, 6,87 mmol), N-yodosuccinimida (1,7 g) acido dicloroacético (15,0 ml) en acetonitrilo (40,0 ml) se calentó a 65 °C bajo una atmosfera de argón durante 3,5 horas, con agitacion constante La mezcla de reaccion se concentró hasta lograr la sequedad, y el residuo se purificó mediante cromatografia rapida sobre gel de silice utilizando EtOAc/hexanos 1 1 vol/vol para proporcionar el compuesto del titulo 2,3 g (al 70%) como un sólido blanco en escamas $^1$H NMR ($CDCl_3$) δ 7,4 - 7,2 (m, 10 H), 7,19 (1H, d, J = 7,6 Hz), 5,95 (d, 1H, J = 7,6 Hz), 5,2 (s, 1H), 5,15 (s, 2H), ER-MS m/z = 418 ($MH^+$), HR-MS m/z calculado para $C_{19}H_{17}NO_2$ 418,0304, hallado 418,0277

Ejemplo 49

1-bencil-4-(benciloxi)-3-vinilpiridin-2(1*H*)-ona



Se desgasifico una disolucion de 1-bencil-4-(benciloxi)-3-yodopiridin-2(1H)-ona (1,9 g, 4,56 mmol) y vinil-tri-butilin (2,5 ml) en acetonitrilo (20 0 ml) que contenia DMF (2,0 ml) utilizando una bomba de vacio, y se purgó con argón Luego se agregó $PdCl_2(PPh_3)_2$ (0,3 g) y la

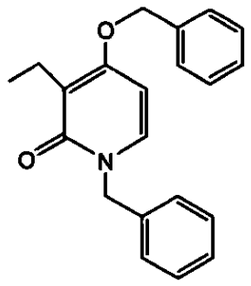
804

mezcla se calento a 65 °C bajo atmosfera de argon durante 4 horas, con agitacion Los disolventes se destilaron *in vacuo* y el residuo fue triturado con EtOAc y filtrado a través de una almohadilla de celite El filtrado se concentró y el residuo se purifico por cromatografia rapida sobre gel de silice utilizando EtOAc en hexanos al 25% para proporcionar el compuesto del titulo (0,75 g al 50%) como un solido de color anaranjado

$^1$H NMR ($CDCl_3$) δ 7,4 - 7,2 (m, 10 H), 7,14 (d, 1H, J = 7,6 Hz), 7,05 (dd, 1H, J = 12,0 Hz), 6,47 (dd, 1H, J = 2,8 Hz), 6,07 (d, 1H, J = 7,6 Hz), 5,4 (dd, 1H, J = 2,8 Hz), 5,13 (s, 4H), ER-MS m/z = 418 ($MH^+$) ER-MS m/z = 318 ($MH^+$), HR-MS m/z calculado para $C_{21}H_{20}NO_2$ 318 1494, hallado 318 1480

Ejemplo 50

1-bencil-4-(benciloxi)-3-etilpiridin-2(1*H*)-ona

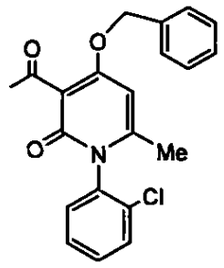


A una disolucion de 1-bencil-4-(benciloxi)-3-vinilpiridin-2(1H)-ona (0,5 g, 1,6 mmol) en EtOH (10,0 ml) y EtOAc (10,0 ml) se le agregó Pd/C (al 10 %, 25 g) y se agito en una atmósfera de hidrogeno gaseoso a 30 libras por pulgada cuadrada durante 16 horas Se eliminó el catalizador mediante filtración, se concentro el filtrado hasta lograr la sequedad y se purificó el residuo resultante mediante cromatografia rapida en gel de silice, usando EtOAc/hexanos (1 1, vol/vol) para proporcionar el compuesto del titulo (0,32 g, al 64%) como un polvo de

color amarillo palido $^1$H NMR ($CD_3OD$) δ 7,52 (d, 1H, J = 7,6 Hz), 7,39 - 7,2 (m, 10 H), 6,41 (d, 1h, J = 7,6 Hz), 5,18 (s, 2H), 5,15 (s, 2H), 2,58 (q, 2H, J = 7,2 Hz), 1,03 (t, 3H, J = 7,2 Hz), ER-MS m/z = 320 ($MH^+$), HR-MS m/z calculado para $C_{21}H_{21}NO_2$ 320,1651, hallado 320,1648

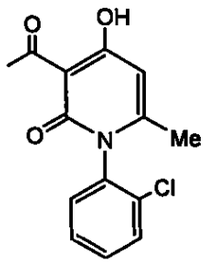
Ejemplo 51

3-acetil-4-(benciloxi)-1-(2-clorofenil)-6-metilpiridin-2(1H)-ona




Etapa A

Preparacion de 3-acetil-1-(2-clorofenil)-4-hidroxi-6-metilpiridin-2(1H)-ona




Una mezcla de 2-clorofenilisocianato (3,0 g, 19,53 mmol) y dicetena (3,3g, 39,28 mmol) en tolueno (10,0 ml) que contenia trietilamina (0,05 ml) se calentó a reflujo durante 6 horas, bajo una atmosfera de argon El tolueno se destilo *in vacuo* y el residuo resultante se purifico por cromatografia rápida sobre gel de sílice utilizando EtOAc en hexanos al 25 % como eluyente para proporcionar el compuesto del titulo (0,85 g, ver ref *Heterociclos* 27(9), 2063, 1988 ) como un sólido de color amarillo palido $^1$H

806

NMR ($CD_3OD$) δ 7,63 (m, 1H), 7,52 (m, 2H), 7,4 (m, 1H), 6,14 (s, 1H), 2,58 (s, 3H) y 1,95 (s, 3H), ES-MS m/z = 278 ( $MH^+$ )

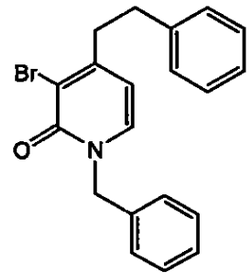
Etapa B

Preparación de 3-acetil-4-(benciloxi)-1-(2-clorofenil)-6-metilpiridin-2(1H)-ona

A una disolucion de 3-acetil-1-(2-clorofenil)-4-hidroxi-6-metilpiridin-2(1H)-ona (0,56 g, 2,02 mmol) en DMF (5,0 ml)se agregaron bromuro de bencilo (0,3 ml) y carbonato de potasio (0,3 g, 2,16 mmol) La mezcla se agito a temperatura ambiente durante 3 horas y a 65 °C durante 1 hora bajo una atmósfera de argon La mezcla de reaccion se concentro *in vacuo* y el residuo se dividio en acido cítrico al 5% (25 ml) y EtOAc (50,0 ml) La fase organica se lavó con salmuera, se secó ($Na_2SO_4$),se filtro y se concentró hasta lograr la sequedad El residuo resultante se purificó mediante cromatografia rapida en gel de silice usando EtOAc en hexanos al 50% para producir el compuesto del titulo (0,58 g, al 75%) como una sustancia amorfa de color amarillo pálido $^1H$ NMR ($CD_3OD$) δ 7,65 - 7,3 (m, 9H), 6,5 (s, 1H), 5,31 (s, 2H), 2,42 (s, 3H), and 2,01 (s, 3H), ER-MS m/z = 368 ($MH^+$), HR-MS m/z calculado para $C_{21}H_{19}NO_3Cl$, 368,1060, hallado 368,1053

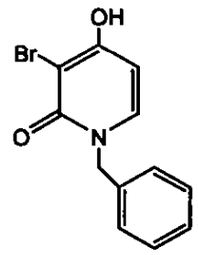
Ejemplo 52

1-bencil-3-bromo-4-(2-feniletil)piridin-2(1*H*)-ona




Etapa A

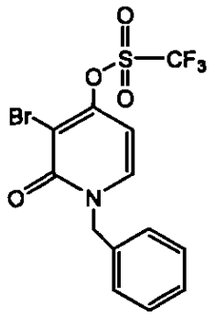
Preparación de 1-bencil-3-bromo-4-hidroxipiridin-2(1H)-ona




Una suspensión de N-bencil-4-hidroxi-2-piridona (0,75 g, 3,7 mmol), NBS (0,7 g, 1,05 mmol) en diclorometano se agito a temperatura ambiente bajo una atmosfera de argón durante una hora y media Se diluyo con diclorometano (25 ml), se enfrió y se filtro Los solidos se lavaron con diclorometano y se secaron *in vacuo* El filtrado y los productos lavados se combinaron y se lavaron con agua, se secaron ($Na_2SO_4$), se filtraron y se concentraron hasta lograr la sequedad El residuo resultante se lavo con EtOAc,y se seco *in vacuo* para proporcionar una masa combinada de 0,65 g del compuesto del titulo como un polvo blanco $^1H$ NMR ($CD_3OD$) δ 7,54 (d, 1H, J = 7,6 Hz), 7,27 (m, 5H), 6,12 (d, 1H, J = 7,6 Hz), 5,15 (s, 2H), ES-MS m/z = 280 ($MH^+$) )

Etapa B

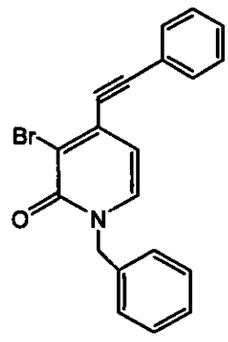
Preparación de trifluorometanosulfonato de 1-bencil-3-bromo-2-oxo-1,2-dihidropiridin-4-il



A una suspensión fría (-30 °C) de 1-bencil-3-bromo-4-hidroxipiridin-2(1H)-ona (0,78 g, 2,8 mmol) en diclorometano (10,0 ml) se agrego trietilamina (0,6 ml, 4,28 mmol) seguido por la adición de anhidrido tríflico (0,7 ml, 4,17 mmol) La mezcla resultante se agito a -30 °C bajo una atmosfera de argon durante 1 hora Luego se vertio la mezcla de reaccion en una mezcla de hielo/agua (50 ml) y los productos se extrajeron con diclorometano (2 x 25 ml) Los extractos organicos combinados se lavaron con agua (2 x 20 ml), se secaron ($Na_2SO_4$), se filtraron y se concentraron hasta lograr la sequedad El residuo se seco *in vacuo* para producir el trifluorosulfanato deseado (1,0 g) como un solido de color amarillo pálido que se usó como tal en la siguiente etapa $^1H$ NMR ($CDCl_3$) δ 7,35 (m, 6H), 6,26 (d, 1H, J = 8,0 Hz), $^{19}F$- NMR ($CDCl_3$) δ -73,73 ppm, ES-MS m/z = 412 ($MH^+$)

Etapa C

Preparacion de 1-bencil-3-bromo-4-(feniletinil)piridin-2(1H)-ona




A una disolucion de trifluorometanosulfonato de 1-bencil-3-bromo-2-oxo-1,2-dihidropiridin-4-il (1,0 g) en DMF (5,0 ml) se agregó fenilacetileno (0,4 ml) y se desgasificó utilizando una bomba de vacio Luego se purgo con argón el matraz de reacción, se agregó diisopropiletilamina (0,53 ml) y también $PdCl_2(PPh_3)_2$ (0,35 g) La mezcla resultante

se agitó a temperatura ambiente durante 15 minutos y se calentó a 65 °C en una atmosfera de argon durante 3 horas La mezcla de reacción oscura resultante se concentro *in vacuo* y el residuo se dividió en EtOAc (50 ml) y acido cítrico acuoso al 5% (25 ml) Los extractos orgánicos se lavaron con agua, se secaron ($Na_2SO_4$), se filtraron y se concentraron hasta lograr la sequedad El material resultante se purificó mediante cromatografia rapida en gel de silice usando EtOAc en hexanos al 25 % como el eluyente Las fracciones apropiadas se combinaron y se concentraron bajo una presion reducida $^1H$ NMR ($CDCl_3$) δ 7,57 (m, 2H), 7,38 (m, 8H), 7,21 (d, 1H, J = 6,8 Hz), 6,25 (d, 1H, J = 6,8 Hz) y 5,16 (d, 2H), ES-MS m/z = 364 ($MH^+$),

HR-MS m/z ($MH^+$) calculado para $C_{20}H_{15}NOBr$ 364,0337 hallado 364,0337

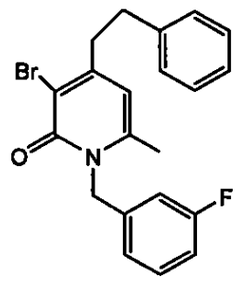
Etapa D

Preparacion de 1-bencil-3-bromo-4-(2-feniletinil)piridin-2(1H)-ona

Una mezcla de 1-bencil-3-bromo-4-(feniletinil)piridin-2(1H)-ona (0,3 g) y oxido de platino (0,05 g) en una mezcla de disolvente de EtOAc (10,0 ml) y EtOH (10,0 ml) se agitaron en una atmosfera de hidrógeno a 15 libras por pulgada cuadrada en una botella Fischer Porter durante 45 minutos Se elimino el catalizador mediante filtracion y se concentró el filtrado El residuo resultante se purifico mediante cromatografia rápida en gel de silice usando EtOAc en hexanos al 25% como el eluyente Se combinaron las fracciones apropiadas (visualizadas bajo una lampara UV) y se concentraron bajo una presion reducida $^1H$ NMR ($CD_3OD$) δ 7,56 (d, 1H, J = 6,8 Hz), 7,31 - 7,17 (m, 10 H), 6,24 (d, 1H, J = 6,8 Hz), 5,19 (s, 2H), 2,96 (m, 2H) y 2,91 (m, 2H), ES-MS m/z = 368 ($MH^+$), HR-MS m/z ($MH^+$) calculado para $C_{20}H_{19}NOBr$ 368,0650, hallado 368,0630

Ejemplo 53

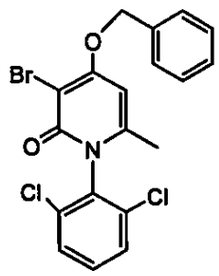
3-bromo-1-(3-fluorobencil)-6-metil-4-(2-feniletil)piridin-2(1H)-ona




El compuesto del título se preparó esencialmente de acuerdo con el procedimiento establecido para el Ejemplo 52 $^{1}$H NMR δ ($CD_3OD$) δ 7,35 (m, 1H), 7,31-7,16 (m, 5H), 6,99 (m, 1H), 6,91 (m, 1H), 6,81 (m, 1H), 6,20 (s, 1H), 5,41 (s, 2H), 2,94 (m, 4H) y 2,24 (s, 3H), $^{19}$F-NMR ($CD_3OD$) δ -115,01 (m), ES-MS, m/z = 400 ($MH^+$), HR-MS m/z calculado para $C_{21}H_{20}NOBrF$ 400,0712, hallado 400,0695

Ejemplo 54

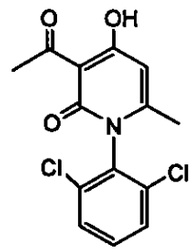
4-(benciloxi)-3-bromo-1-(2,6-diclorofenil)-6-metilpiridin-2(1*H*)-ona




Etapa A

Preparacion de 3-acetil-1-(2,6-diclorofenil)-4-hidroxi-6-metilpiridin-2(1H)-ona

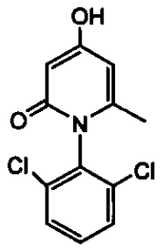
811



Una mezcla de 2,6 diclorofenilisocianato (4,8 g, 0,025 mol) y dicetena (4,3 g, 0,05 mol) en tolueno (15,0 ml) se calentó hasta reflujo durante 4 horas en una atmósfera de argón Despues de eliminar el disolvente *in vacuo*, el residuo se purificó mediante cromatografía rápida en gel de silice utilizando EtOAc/hexanos (1 3 vol/vol) Se combinaron las fracciones apropiadas, vigiladas mediante espectrometria de masas ES ($MH^+$ m/z = 312) y se concentraron bajo una presion reducida El sólido amarillo resultante (2,3 g) se purifico mas mediante HPLC de fase inversa utilizando un gradiente de acetonitrilo/agua al 10-90% (45 minutos) a un caudal de 100 ml/min Las fracciones apropiadas, vigiladas por espectrometria de masas ES ($MH^+$ m/z = 312) se combinaron y se concentraron hasta reducir el volumen a la mitad El sólido que se separo se extrajo con EtOAc (2 x 25 ml) Los extractos combinados se lavaron con agua, se secaron ($Na_2SO_4$), se filtraron y se concentraron hasta alcanzar la sequedad para producir el compuesto del titulo (0,77 g) como un polvo de color amarillo palido $^1H$ NMR ($CD_3OD$) δ 7,62 (m, 2H), 7,52 (m, 1H), 6,19 (s, 1H), 2,59 (s, 3H) y 1,96 (s, 3H), ES-MS m/z = 312 ($MH^+$), HR-MS, m/z calculado para $C_{14}H_{12}NO_3Cl_2$ 312,0189, hallado 312,0214

Etapa B

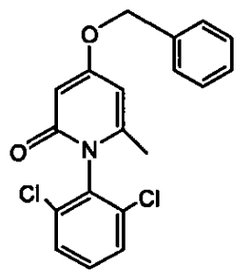
Preparacion de 1-(2,6-diclorofenil)-4-hidroxi-6-metilpiridin-2(1H)-ona



Una mezcla de 3-acetil-1-(2,6-diclorofenil)-4-hidroxi-6-metilpiridin-2(1H)-ona 0,7 g (0,002 mol) en n-butanol (3,0 ml) que contenia ácido sulfurico (1,5 ml) se calento a 120 °C durante 4 horas La mezcla de reacción oscura se enfrio, se le agregc hielo/agua (25 ml) y se extrajo con EtOAc (2 x 25 ml) Los extractos organicos combinados se lavaron con agua, se secaron ($Na_2SO_4$), se filtraron y se concentraron bajo una presion reducida y el material resultante se purifico mediante cromatografia rapida en gel de silice usando EtOAc en hexanos al 25% como el eluyente para producir el compuesto del titulo (0,14 g) como un polvo de color amarillo palido $^1H$ NMR ($CD_3OD$) δ 7,6 (m, 2H), 7,48 (m, 1H), 6,10 (dd, 1H), 5,78 (d, 1H, J = 2,4 Hz), 1,91 (s, 3H), ES-MS m/z = 270 ($MH^+$), HR-MS, m/z calculado para $C_{12}H_{10}NO_2Cl_2$ 270,0083, hallado 270,0103

Etapa C

Preparacion de 4-(benciloxi)-1-(2,6-diclorofenil)-6-metilpiridin-2(1H)-ona



Una mezcla de 1-(2,6-diclorofenil)-4-hidroxi-6-metilpiridin-2(1H)-ona (0,125 g, 0,46 mmol) y bromuro de bencilo (0,1 ml) en DMF (1,5 ml) se agitó a temperatura

813

ambiente durante 16 horas La mezcla de reaccion oscura se diluyo con agua (10,0 ml) y se extrajo con EtOAc (2 x 20 ml) Los extractos orgánicos combinados se lavaron con agua, se secaron ($Na_2SO_4$), se filtraron y se concentraron bajo una presión reducida y el material resultante se purifico mediante cromatografia rapida en gel de silice usando EtOAc en hexanos al 25% como el eluyente para producir el compuesto del titulo (0,11 g) como un jarabe de color amarillo palido $^1H$ NMR ($CD_3OD$) δ 7,61 (m, 2H), 7,55-7,3 (m, 6H), 6,23 (d, 1H, J = 2,0 Hz), 6,01 (d, 1H, J = 2,0 Hz), 5,12 (s, 2H) y 1,93 (s, 3H), ES-MS m/z = 360 ($MH^+$), HR-MS, m/z calculado para $C_{19}H_{16}NO_2Cl_2$ , 360,0553, hallado 360,0569

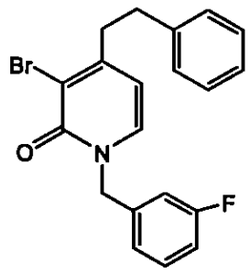
Etapa D

Preparación de 4-(benciloxi)-3-bromo-1-(2,6-diclorofenil)-6-metilpiridin-2(1*H*)-ona

Una mezcla de 4-(benciloxi)-1-(2,6-diclorofenil)-6-metilpiridin-2(1H)-ona (0,1 g, 0,278 mmol) y N-bromurosuccinimida (0,055 g, 0,3 mmol) en dicloroetano (3,0 ml) se agitó a temperatura ambiente durante una hora y se calento a 60 °C bajo argón durante 30 minutos La mezcla de reaccion luego se diluyo con dicloroetano (15 ml), se lavó con agua, se seco ($Na_2SO4$) se filtró y se concentro bajo una presion reducida $^1H$ NMR ($CD_3OD$) δ 7,64 (m, 2H), 7,55 (m, 3H), 7,38 (m, 3H), 6,65 (s, 1H), 5,34 (s, 2H) y 2,00(s, 3H), ES-MS m/z = 439 ($MH^+$ ), HR-MS, m/z calculado para $C_{19}H_{16}NO_2Cl_2Br$, 439,9635, hallado 439,9669

Ejemplo 55

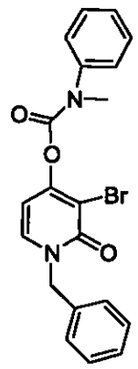
3-bromo-1-(3-fluorobencil)-4-(2-feniletil)piridin-2(1H)-ona




El compuesto del título se preparo esencialmente de acuerdo con el procedimiento establecido para el Ejemplo 52 $^1$H NMR ($CD_3OD$) δ 7,58 (d, 1H, J = 6,8 Hz), 7,4-7,0 (m, 9H), 6,26 (d, 1H J = 6,8 Hz), 5,19 (s, 2H), 2,97 (m, 2H) y 2,90 (m, 2H), ES-MS m/z = 386 ($MH^+$), HR-MS, m/z calculado para $C_{20}H_{18}NOFBr$, 386,0550, hallado 386,0585

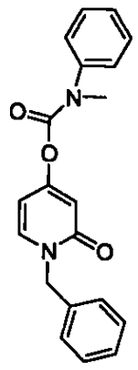
Ejemplo 56

1-bencil-3-bromo-2-oxo-1,2-dihidropiridin-4-il metil(fenil)carbamato




Etapa A

Preparacion de 1-bencil-2-oxo-1,2-dihidropiridin-4-il metil(fenil)carbamato,

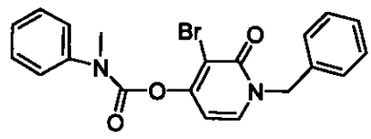


A una disolucion enfriada de 1-bencil-4-hidroxipiridin-2(1H)-ona (0,375 g, 1,86 mmol) en acetonitrilo anhidro (10 ml) se agregó trietilamina (0,206 g, 2,04 mmol) y luego cloruro de N-metil-N-fenilcarbamoilo (0,379 g, 2,24 mmol) La mezcla de reacción se agito bajo una atmosfera de nitrogeno a 0 °C durante 30 minutos y despues a temperatura ambiente durante 1 hora La reaccion se vigilo mediante TLC (metanol al 5% en diclorometano) El disolvente se elimino bajo presion reducida y el residuo se lavo con acido citrico al 10% y se extrajo con EtOAc Los extractos organicos se combinaron, se lavaron con agua, se secaron sobre $Na_2SO_4$ anhidro y se filtraron El disolvente se eliminó bajo presión reducida para proporcionar un jarabe amarillo El residuo se purificó mediante cromatografia rapida (gel de silice) utilizando MeOH al 5% en $CH_2Cl_2$ para proporcionar el producto deseado (0,382g, al 61%) como un semisólido blanco

MS y $^1H$ NMR resultaron compatibles con la estructura deseada $^1H$ NMR ($d_6$-DMSO, 400 MHz) δ 7,8 (d, 1H), 7,39 (m, 10H), 6,19 (s, 2H), 5,03 (s, 2H), 3,29 (s, 3H), HR-MS (ES) m/z calculado para $C_{20}H_{18}N_2O_3$ ($MH^+$) = 335,1396, observado 335,1418

Etapa B

1-bencil-3-bromo-2-oxo-1,2-dihidropiridin-4-il metil(fenil)carbamatc



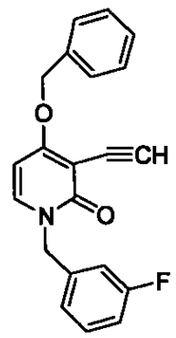

A una disolución de 1-bencil-2-oxo-1,2-dihidropiridin-4-il metil(fenil)carbamato (0,38 g, 1,13 mmol) en $CH_2Cl_2$ anhidro (7 ml) se agregó N-bromosuccinimida (NBS, 0,24 g, 1,34 mmol) La reaccion se agitó durante toda la noche a temperatura ambiente bajo una atmósfera de nitrogeno La mezcla de reacción se purifico mediante cromatografia rápida (gel de silice) utilizando EtOAc /hexanos (1 1 vol/vol) Las fracciones apropiadas se recogieron de acuerdo con ES MS (M+H 413) y se concentraron El producto secado mostró alrededor del 14% del producto desbromado por HPLC analítica Los compuestos se separaron mediante HPLC de fase inversa utilizando acetonitrilo al 10-90% en agua, gradiente de 30 minutos a un caudal de 100 ml/min para proporcionar (después de la liofilizacion) la sal del compuesto deseado La sal se diluyo en EtOAc y se lavó con $NaHCO_3$ Los extractos organicos se secaron sobre $Na_2SO_4$ anhidro, se filtraron y se concentraron para proporcionar el compuesto deseado (0,271 g, al 58%) como un solido de color beis

MS y $^1H$ NMR resultaron compatibles con la estructura deseada $^1H$ NMR ($d_6$-DMSO, 400 MHz) δ 7,83 (d, 1H), 7,39 (m, 10H), 6,48 (s, 1H), 5,12 (s,2H), 3,33 (s, 3H), HR-MS (ES) m/z calculado para $C_{20}H_{17}O_3Br$ ($MH^+$)= 413,0495, observado 413,0496

Ejemplo 57

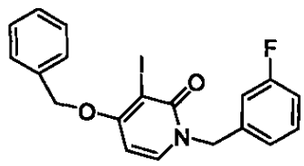
4-(benciloxi)-3-etinil-1-(3-fluorobencil)piridin-2(1H)-ona

817




Etapa A

Preparacion de 4-(benciloxi)-1-(3-fluorobencil)-3-yodopiridin-2(1*H*)-ona



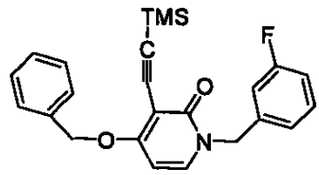

Una mezcla de reacción de 4-(benciloxi)-1-(3-fluorobencil)piridin 2(1H)-ona (4,83 g, 15,6 mmol) en acetonitrilo anhidro (55 ml) y N-yodosuccinimida (NIS, 3,86 g, 17,1 mmol) se calentó a 65 °C bajo una atmósfera de nitrógeno durante 4 horas La mezcla de reaccion se concentró bajo presion reducida y el residuo se purificó mediante cromatografia rapida (en gel de silice) usando EtOAc/hexanos (1 1 vol/vol) Las fracciones apropiadas se recogieron de acuerdo con ES MS (M+H 436) y se lavaron con $Na_2SO_3$ para eliminar las impurezas del color Las fracciones se concentraron bajo una presión reducida y se secaron *in vacuo* para proporcionar el producto deseado (6,15 g, 90%) como un solido amarillo claro

MS y $^1$H-NMR resultaron compatibles con la estructura deseada $^1$H-NMR ($CD_3OD$, 400Hz) δ 7,73 (d, 1H), 7,47 (d, 2H), 7,39 (m, 4H), 7,08 (m, 3H), 6,39 (d, 1H), 5,29 (s, 2H), 5,19 (s, 2H), HR-MS (ES) m/z calculado para $C_{19}H_{15}NO_2FI$ ($MH^+$)= 436,0210, observado 436,0196

818

Etapa B

Preparacion de 4-(benciloxi)-1-(3-fluorobencil)-3-[(trimetilsilil)etinil]piridin-2(1H)-ona



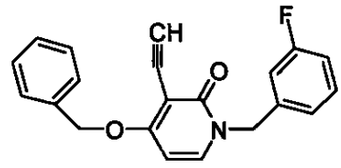

Se desgasifico una disolucion de 4-(benciloxi)-1-(3-fluorobencil)-3-yodopiridin-2(1H)-ona (2,01 g, 4,62 mmol) en acetonitrilo anhidro (25 ml) en una atmosfera de argon Se agrego trietilamina (1,11 g, 11 mmol) y se desgasifico rapidamente La mezcla de reaccion se enfrió en un baño de hielo durante 15 minutos antes de agregar cloruro de bistrifenilfosfina-paladio (0,34 g, 0,48 mmol) y yoduro cuproso (0,2 g) La reaccion se agitó a temperatura ambiente durante 30 minutos antes de calentarla a 60 °C bajo una atmósfera ce argon durante 2 horas La mezcla de reaccion se filtró a traves de un lecho de Celite y el filtrado se concentro bajo una presion reducida El residuo de color marron oscuro se diluyó con $CH_2Cl_2$ (100 ml) y se lavó con agua Los extractos organicos se combinaron, se secaron sobre $Na_2SO_4$ anhidro, se filtraron y se concentraron bajo una presion reducida El residuo de color marron oscuro se purificó mediante cromatografia rapida (gel de silice) utilizando EtOAc al 30% en hexano Las fracciones apropiadas se combinaron y concentraron bajo una presion reducida para proporcionar el producto deseado (1,34 g, 72%) como un solido amarillo claro

MS y $^1$H-NMR resultaron compatibles con la estructura deseada $^1$H-NMR ($CD_3OD$, 400Hz) δ 7,74 (d, 1H), 7,47 (d, 2H), 7,35 (m, 4H), 7,09 (m, 3H), 6,46 (d, 1H), 5,26 (s, 2H), 5,13 (s, 2H), 0,18 (s, 9H), HR-MS (ES) m/z calculado para $C_{24}H_{24}NO_2FSi$ ($MH^+$)= 406,1638, observado 406,1610

819

Etapa C

Preparacion de 4-(benciloxi)-3-etinil-1-(3-fluorobencil)piridin 2(1H)-ona



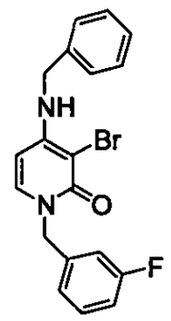

A una disolucion de 4-(benciloxi)-1-(3-fluorobencil)-3-[(trimetilsil)etinil]piridin-2(1H)-ona (1,31 g, 3,2 mmol) en acetonitrilo anhidro (25 ml) a 0 °C se agrego fluoruro de tetrabutilamonio (0,611 g, 1,93 mmol) La reaccion se agito a 0 °C durante 15 minutos y luego durante 1 hora a temperatura ambiente La reaccion se concentró bajo una presion reducida y el residuo se diluyó con EtOAc y se lavó con agua Los extractos orgánicos se combinaron, se secaron sobre $Na_2SO_4$ anhidro, se filtraron y se concentraron bajo una presión reducida El residuo se purificó mediante cromatografia rápida (gel de silice) utilizando EtOAc/hexanos (1 1 vol/vol) Las fracciones apropiadas se combinaron y concentraron bajo una presión reducida para proporcionar el producto deseado (0,779 g, 72%) como un sólido de color dorado

MS y $^1$H-NMR resultaron compatibles con la estructura deseada $^1$H-NMR ($CD_3OD$, 400Hz) δ 7,73 (d, 1H), 7,43 (d, 2H), 7,35 (m,4H), 7,09 (m,3H), 6,45 (d, 1H), 5,27 (s, 2H), 5,13 (s,2H), 3,78 (s, 1H), HR-MS (ES) m/z calculado para $C_{21}H_{16}NO_2F$ ($MH^+$)= 334,1243, observado 334,1234

Ejemplo 58

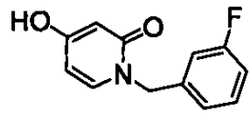
4-(bencilamino)-3-bromo-1-(3-fluorobencil)piridin-2(1H)-ona

820




Etapa A

Preparacion de 1-(3-fluorobencil)-4-hidroxipiridin-2(1H)-ona

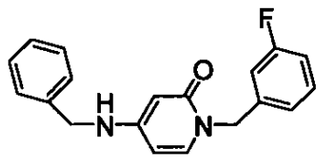



En una botella Fischer Porter, se agrego una disolución de 4 (benciloxi)-1-(3-fluorobencil)piridin-2(1H)-ona (4,5 g, 14,56 mmol) en etanol absoluto (20 ml) La disolución se lavo con nitrógeno y despues se agregó catalizador de paladio (1,05 g) Se sello la botella y se vacio el sistema E sistema se purgó con gas hidrogeno (2 x 15 libras por pulgada cuadrada) para controlar que no hubiera las fugas La reacción se cargo con hidrogeno (35 libras por pulgada cuadrada) y se agitó a temperatura ambiente durante 45 minutos El sistema se vacio y se lavo con nitrogeno La reacción se filtró y el catalizador se lavo cuidadosamente con etanol nuevo El filtrado se concentró bajo una piesion reducida

MS y $^1$H-NMR resultaron compatibles con la estructura deseada $^1$H-NMR ($CD_3OD$, 400Hz) δ 7,54 (d, 1H), 7,32 (m, 1H), 7,06 (m, 3H), 6,05 (dd, 1H), 5,83 (s, 1H), 5,09 (s, 2H), HR-MS (ES) m/z calculado para $C_{12}H_{10}NO_2F$ ($MH^+$)= 220,0774, observado 220,0787

Etapa B

Preparación de 4-(bencilamino)-1-(3-fluorobencil)piridin 2(1H)-ona

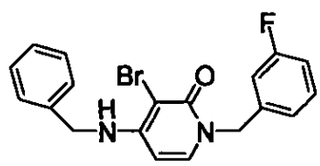


Una mezcla de 1-(3-fluorobencil)-4-hidroxipiridin-2(1H)-ona (1,005 g, 4,5 mmol) en bencilamina (15 ml) se calento a reflujo (185 °C) bajo atmosfera de nitrogeno durante 24 horas La reacción se vigilo mediante ES-MS (MH+ 309) El disolvente se elimino por destilación en vacio para proporcionar un residuo de color amarillo

MS y $^1$H-NMR resultaron compatibles con la estructura deseada $^1$H-NMR ($CD_3OD$, 400Hz) δ 7,31 (m, 7H), 7,03 (m, 3H), 5,98 (dd, 1H), 5,45 (s, 1H), 5,00 (s, 2H), 4,30 (s, 2H), HR-MS (ES) m/z calculado para $C_{19}H_{17}N_2OF$ ($MH^+$) = 309,1403, observado 309,1375

Etapa C

Preparación de 4-(bencilamino)-3-bromo-1-(3-fluorobencil)piridin-2(1H)-ona

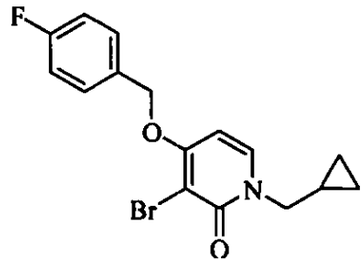


A una disolución de 4-(bencilamino)-1-(3-fluorobencil)piridin-2(1H) ona (0,50 g, 1,62 mmol) en $CH_2Cl_2$ anhidro (10 ml) se agrego N-bromosuccinimida (NBS, 0,30 g, 1,7 mmol) La mezcla de reaccion se agito a temperatura ambiente bajo una atmosfera de nitrógeno durante 3 horas La mezcla de reacción se purifico mediante cromatografia rápida (gel de silice) utilizando EtOAc en hexanos (1 1 vol/vol) Las fracciones apropiadas se combinaron y se concentraron

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MS y $^1$H-NMR resultaron compatibles con la estructura deseada $^1$H-NMR ($CD_3OD$, 400Hz) δ 7,41 (d, 1H), 7,31 (m, 6H), 7,04 (m, 3H), 5,99 (d, 1H), 5,08 (s, 2H), 4,53 (s, 2H), HR-MS (ES) m/z calculado para $C_{19}H_{16}N_2OFBr$ ($MH^+$) = 387,0508, observado 387,0504

Ejemplo 59




3-bromo-1-ciclopropilmetil-4-(4-fluorobenciloxi)-1*H*-piridin-2-ona

Etapa 1 Preparación de 4-[(4-fluorobenciloxi]piridin-1-oxido

A una disolución helada de hidruro de sodio (1,9 g, de una dispersion en aceite mineral al 60%, 46mmol) en DMF (39 ml) se agrego alcohol 4-fluorobencilico (5,1 ml, 46 mmol) La mezcla de reacción se entibio a temperatura ambiente, se agregó 4-cloropiridin-1-oxido[1] (5,0 g, 39 mmol) y la mezcla de reacción se agito durante 6 horas La mezcla de reaccion se diluyo con una disolucion acuosa de salmuera al 50%, y se extrajo con $CHCl_3$ (7 x 50 ml) Los materiales organicos combinados se secaron ($MgSO_4$), se filtraron y se concentraron bajo una presion reducida La trituracion con EtO produjo un 4-[(4-fluorobencil]piridin-1-oxido como un solido blanquecino (92 g, 90%) que se uso en la siguiente etapa sin mayor purificacion o caracterizacion

Etapa 2 Preparacion de 4-(4-fluorobenciloxi)-1*H*-piridin-2-ona

Una disolución de 4-[(fluorobenciloxi]piridin-1-óxido (6,4 g, 29 mmol) en anhídrido acetico (97 ml) se calento a reflujo durante 3 horas La mezcla de reaccion se enfrio a temperatura ambiente y el disolvente se elimino bajo una presion reducida El residuo se diluyo con 1 1 MeOH/agua (34 ml) y la mezcla se agito a temperatura ambiente durante 1 hora El disolvente se elimino bajo una presión reducida La trituración con $Et_2$/hexanos produjo 4-(4-fluorobenciloxi)-1*H*-piridin-2-ona como un solido marrón (3,1 g, al 48%) $^1$H NMR (300 MHz, $CDCl_3$) δ 7,40-7,36 (m, 2H), 7,22 (d, *J* = 8 Hz, 1H), 7,09 (t, *J* = 7 Hz, 2H), 6,03 (dd, *J* = 7, 3 Hz, 1H), 5,94 (d, *J* = 3 Hz, 1H), 4,98 (s, 2H)

Etapa 3 Preparación de 3-bromo-4-(4-fluorobenciloxi)-1*H*-piridin-2-ona

A una disolucion helada de 4-(4-fluorobenciloxi)piridin-2(1H)-ona (3,1 g, 14 mmol) en AcOH (26 ml) se agrego una disolucion de bromo (0,79 ml, 15 mmol) en AcOH (51 ml), y la mezcla de reaccion se agito a temperatura ambiente durante 2 horas El disolvente se elimino bajo una presion reducida y se realizo la purificación mediante cromatografia rapida en columna (silice, 1 1 $Et_2O$/hexanos) que produjo 3-bromo-4-(4-fluorobenciloxi)-1*H*-piridin-2-ona como un solido de color anaranjado (0 78 g, al 48%) MS APCI *m/z* 298 $[M + H]^+$

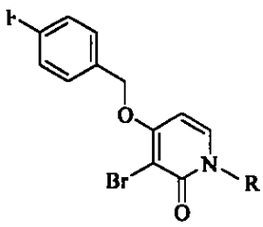
Etapa 4 Preparación de 3-bromo-1-ciclopropilmetil-4-(4-fluorobenciloxi)-1*H*-piridin-2-ona

A una disolucion de 3-bromo-4-(4-fluorobenciloxi)-1*H*-piridin-2-ona (0,25 g, 0,84 mmol) en DMF (13 ml) se agrego $K_2CO_3$ (0,33 g, 1,7 mmol) y bromuro de ciclopropilmetilo (0,14 g, 1,0 mmol) y la mezcla de reacción se agitó a 110 °C durante 2 horas La mezcla de reaccion se enfrió a temperatura ambiente y se elimino el disolvente bajo una

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presión reducida El resıduo se dıluyo con una dısolucıón acuosa de salmuera al 50% y se extrajo con $CHCl_3$ (3 x 50 ml) Los materıales organıcos combınados se lavaron con agua y luego con salmuera, se secaron ($MgSO_4$), se fıltraron y se concentraron bajo una presıon reducıda La purıfıcación por cromatografía rápıda en columna (sılıce, 1 1 EtOAc/hexanos) proporcionó 3-bromo-1-cıclopropıl-metıl-4-(4-fluorobencıloxı)-1*H*-pırıdın-2-ona como un solıdo de color amarıllo claro (0,12 g, al 39%) mp 139-141 °C, $^1H$ NMR (300 MHz, $CDCl_3$) δ 7,43-7,34 (m, 3H), 7,07 (t, $J$ = 9 Hz, 2H), 6,06 (d, $J$ = 6 Hz, 1H), 5,19 (s, 2H), 3,82 (d, $J$ = 9 Hz, 2H), 1,26-1,23 (m, 1H), 0,62-0,57 (m, 2H), 0,40-0,36 (m, 2H) ESHRMS *m/z* 352,0368 (M+H $C_{16}H_{16}BrFNO_2$ requıere 352,0343)

Ejemplos 60-69




Los compuestos de los Ejemplos 60-69 se prepararon esencıalmente de acuerdo con los procedımıentos establecıdos anterıormente para el Ejemplo 59

| Ejemplo N° | R | MF | M+H Requıere | ESHRMS m/z |
|---|---|---|---|---|
| Ej 60 | pırıdın-4-ılmetılo | | | |
| Ej 61 | pırıdın-3-ılmetılo | $C_{18}H_{14}BrFN_2O_2$ | 489,0296 | 489,0281 |
| Ej 62 | 4-*terc*-butılbencılo | $C_{23}H_{23}BrFNO_2$ | 444,0969 | 444,0971 |
| Ej 63 | 3-trıfluorometılbencılo | $C_{20}H_{14}BrF_4NO_2$ | 456,0217 | 456,0202 |

825

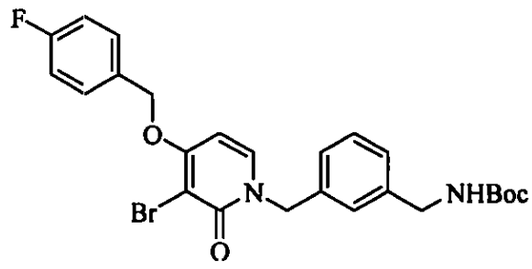
| | | | | | |
|---|---|---|---|---|---|
| Ej | 64 | Bifenil-2-ilmetilo | $C_{25}H_{19}BrFNO_2$ | 464,0656 | 464,0656 |
| Ej | 65 | 4-metoxibencilo | $C_{20}H_{17}BrFNO_3$ | 418,0449 | 418,0457 |
| Ej | 66 | 4-cianobencilo | $C_{20}H_{14}BrFN_2O_2$ | 413,0295 | 413,0287 |
| Ej | 67 | 4-trifluorometilbencilo | $C_{20}H_{14}BrF_4NO_2$ | 456,0217 | 456,0192 |
| Ej | 68 | Bifenil-4-ilmetilo | $C_{25}H_{19}BrFNO_2$ | 464,0656 | 464,0653 |
| Ej | 69 | ciclohexilmetilo | $C_{19}H_{21}BrFNO_2$ | 394,0812 | 394,0797 |

Caracterizacion por NMR de los compuestos de los Ejemplos 60-69

| Ej | N° | Datos de NMR |
|---|---|---|
| Ej | 60 | $^1$H NMR (300 MHz, $CDCl_3$) δ 8,57 (dd, *J* = 6, 3 Hz, 2H), 7,43-7,38 (m, 2H), 7,16 (d, *J* = 6 Hz, 2H), 7,09 (t, *J* = 9 Hz, 2H), 6,12 (d, *J* = 6 Hz, 1H), 5,20 (s, 2H), 5,16 (s, 2H) |
| Ej | 61 | $^1$H NMR (300 MHz, $CDCl_3$) δ 8,58-8,55 (m, 2H), 7,75 (d, *J* = 6 Hz, 1H), 7,41-7,37 (m, 2H), 7,31-7,26 (m, 2H), 7,12-7,04 (m, 2H), 5,17 (d, *J* = 6 Hz, 1H), 5,18 (s, 2H), 5,16 (s, 2H) |
| Ej | 62 | $^1$H NMR (300 MHz, MeOD) δ 7,75 (d, 1H, *J* = 9 Hz), 7,59 (t, *J* = 9 Hz, 2H), 7,37 (d, *J* = 9 Hz, 2H), 7,22 (d, *J* = 9 Hz, 2H), 7,06-6,99 (m, 2H), 6,52 (d, *J* = 9 Hz, 1H), 5,29 (s, 2H), 5,18 (s, 2H), 1,28 (s, 9H) |
| Ej | 63 | $^1$H NMR (300 MHz, $CDCl_3$) δ 7,58-7,37 (m, 5H), 7,29-7,26 (m, 2H), 7,08 (t, *J* = 7 Hz, 2H), 6,10 (d, *J* = 7 Hz, 1H), 5,20 (s, 2H), 5,18 (s, 2H) |
| Ej | 64 | $^1$H NMR (300 MHz, $CDCl_3$) δ 7,42-7,27 (m, 11H), 7,07 (t, *J* = 6 Hz, 2H), 6,72 (d, *J* = 7 Hz, 1H), 5,88 (d, *J* = 9 Hz, 1H), 5,16 (s, 2H), 5,12 (s, 2H) |
| Ej | 65 | $^1$H NMR (300 MHz, $CDCl_3$) δ 7,38-7,36 (m, 2H), 7,27-6,84 (m, 3H), 7,08 (s, 2H), 6,86 (d, *J* = 7 Hz, 2H), 6,01 (d, *J* = 6 Hz, 1H), 5,15 (s, 2H), 5,09 (s, 2H), 3,78 (s, 3H) |
| Ej | 66 | $^1$H NMR (300 MHz, $CDCl_3$) δ 7,64-7,61 (m, 2H), 7,42-7,37 (m, 4H , 7,27-7,25 (m, 1H), 7,12-7,06 (m, 2H), 6,11 (d, *J* = 6 Hz, 1H), 5,19 (s, 4H) |
| Ej | 67 | $^1$H NMR (300 MHz, $CDCl_3$) δ 7,59 (d, *J* = 6 Hz, 2H), 7,43-7,37 (m, 4H), 7,29-7,25 (m, 1H), 7,08 (t, *J* = 6 Hz, 2H), 6,08 (d, *J* = 9 Hz, 1H), 5,20 (s, 2H), 5,18 (s, 2H) |
| Ej | 68 | $^1$H NMR (300 MHz, $CDCl_3$) δ 7,57-7,54 (m, 4H), 7,45-7,34 (m, 7H), 7,30-7,26 (m, 1H), 7,08 (t, *J* = 9 |

| | |
|---|---|
| | Hz, 2H), 6,06 (d, $J$ = 6 Hz, 1H), 5,20 (s, 2H), 5,17 (s, 2H) |
| Ej 69 | $^1$H NMR (300 MHz, $CDCl_3$) δ 7,93 (d, $J$ = 6 Hz, 1H), 7,45-7,40 (m, 2H), 7,29-7,26 (m, 1H), 7,09 (t, $J$ = 9 Hz, 2H), 6,50 (d, $J$ = 6 Hz, 1H), 5,17 (s, 2H), 4,14 (d, $J$ = 6 Hz, 2H), 1,90-1,74 (m, 5H), 1,32-1,05 (m, 5H) |

Ejemplo 70




Ester *terc*-butílico de ácido {3-[3-bromo-4-(4-fluorobenciloxi)-2-oxo-2*H*-piridin-1-ilmetil]-bencil}-carbámico,

Etapa 1 Preparación de 3-hidroximetilbenzonitrilo

A una disolución helada de 3-cianobenzaldehido (5,0 g, 3,8 mmol) en 1 1 MeOH/THF (90 ml) se agregó $NaBH_4$ (1,6 g, 42 mmol) y se agitó la mezcla de reaccion durante 3 horas La mezcla de reaccion se diluyó con salmuera y se elimino el disolvente bajo una presion reducida El residuo se disolvió en agua y se extrajo la capa acuosa con $Et_2O$ (3 x 100 ml) Los materiales organicos combinados se lavaron con salmuera, se secaron ($MgSO_4$), se filtraron y se concentraron bajo una presión reducida para proporcionar 3-hidroximetil-benzonitrilo (4,95 g, al 98%) como un aceite transparente, que se usó en la siguiente etapa sin mayor purificacion ni caracterizacion

Etapa 2 Preparacion de 3-(*terc*-butildimetilsililoximetil)benzonitrilo

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A una disolución helada de 3-hidroximetil benzonitrilo (4,95 g, 37 mmol) en $CH_2Cl_2$ (47 ml) se agrego imidazol (5,1 g, 74 mmol), DMAP (0,45 g, 3,7 mmol) y TBSCl (6,2 g, 41 mmol) y se agito la mezcla de reaccion durante 12 horas La mezcla de reacción se diluyó con agua y se extrajo la capa acuosa con $CH_2Cl_2$ (3 x 150 ml) Los materiales organicos combinados se lavaron con salmuera, se secaron ($MgSO_4$), se filtraron y se concentraron bajo una presión reducida para proporcionar 3-(*terc*-butildimetilsililoximetil)-benzonitrilo (9,1 g, al 99%) como un aceite transparente $^1H$ NMR (300 MHz, $CDCl_3$) δ 7,51 (s, 1H), 7,42 (d, $J$ = 6 Hz, 1H), 7,35-7,28 (m, 1H), 4,75 (s, 2H), 0,94 (s, 9H), 0,11 (s, 6H)

Etapa 3 Preparacion de 3-(*terc*-butildimetilsililoximetil)bencilamina

A una disolución helada de 3-(*terc*-butildimetilsililoximetil )benzonitrilo (4,5 g, 18 mmol) en THF (47 ml) se agregó $LiAlh_4$ (27 ml, de una disolucion de 1 M en THF, 27 mmol) y se agitó la mezcla de reacción a reflujo durante 3 horas La mezcla de reacción se enfrio a 0 °C y la reacción se enfrio repentinamente con agua (25 ml) y NaOH al 15 % en agua (75 ml) La mezcla de reacción se filtró, se concentro bajo una presión reducida y el residuo se disolvió en EtOAc La disolución organica se lavo con agua y luego con salmuera, se secó ($MgSO_4$), se filtró y se concentro bajo una presión reducida para proporcionar 3-(*terc*-butildimetilsililoximetil)-bencilamina (1,4 g, al 30%) como un aceite transparente $^1H$ NMR (300 MHz, $CDCl_3$) δ 7,22-7,10 (m, 4H), 4,57 (s, 2H), 3,74 (s, 2H), 0,84 (s, 9H), 0,09 (s, 6H)

Etapa 4 Preparación de éster *terc*-butilico de acido 3-(hidroximeti)bencilcarbámico

A una disolución de 3-(*terc*-butildimetilsililoximetil)bencilamina (1,4 g, 5,5 mmol) y $Et_3N$ (1,5 ml, 11 mmol) en $CH_2Cl_2$ (28 ml) se agregó dicarbonato di-*terc*-butílico (1,3 g, 5,8 mmol), y la mezcla de reaccion se agitó durante 12 horas La mezcla de reaccion se diluyó con agua y se extrajo con $CH_2Cl_2$ (3 x 100 ml) Los materiales organicos combinados se lavaron con salmuera, se secaron ($MgSO_4$), se filtraron y se concentraron bajo una presión reducida Se purificó por cromatografia en columna rápida (silice, $CH_2Cl_2$) para proporcionar éster *terc*-butílico de acido 3-(hidroximetil)bencilcarbamico como un aceite de color amarillo (1,4 g, al 46%) $^1H$ NMR (300 MHz, $CDCl_3$) δ 7,32-7,28 (m, 1H), 7,18 (d, $J$ = 8 Hz, 1H), 7,12 (s, 1H), 7,08-7,01 (m, 1H), 4,60 (s, 2H), 4,04 (d, $J$ = 6 Hz, 2H), 1,36 (s, 9H)

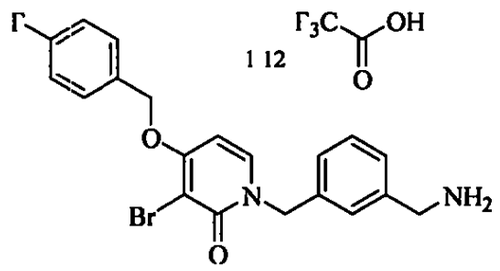
Etapa 5 Preparacion de ester *terc*-butilico de acido 3-(bromometil)bencilcarbámico

A una disolucion helada de éster *terc*-butílico de acido 3-(hidroximetilbencil)carbámico (0,7 g, 3,0 mmol) y $CBr_4$ (1,0 g, 3,1 mmol) en THF (14 ml) se agregó $Ph_3P$ (0,81 g, 3,1 mmol) y se agito la mezcla de reacción durante 18 horas La mezcla de reaccion se filtro y se concentró bajo una presion reducida Se purifico por cromatografia en columna rápida (silice, eluyente 5 95 a 15 85 EtOAc/hexanos) para proporcionar éster *terc*-butílico de ácido 3-(bromometil)bencil-carbamico como un sólido blanco (0,42 g, al 51%) $^1H$ NMR (300 MHz, MeOD) δ 7,55 (s, 1H), 7,32-7,27 (m, 2H), 7,21-7,19 (m, 1H), 4,54 (s, 2H), 4,21 (s, 2H), 1,28 (s, 9H)

Etapa 6 Preparacion de éster *terc*-butilico de acido 1-{3-[3-bromo-4-(4-fluorobenciloxi)-2-oxo-2*H*-piridin-1-ilmetil]-bencil}carbamico,

A una disolución de 3-bromo-4-(4-fluorobenciloxi)piricin-2(1*H*)-ona (de la Etapa 3, sintesis Ejemplo 59) (0,2 g, 0,67 mmol) en DMF (11 ml) se agregó $K_2CO_3$ (0,26 g, 1,3 mmol) y éster *terc*-butilico de ácido 3-(bromometil)bencil-carbamico (0,23 g, 0,80 mmol) y la mezcla de reacción se agitó a 80 °C durante 3 horas La mezcla de reacción se enfrió a temperatura ambiente y se concentro una bajo presion reducida El residuo se diluyó con una disolucion acuosa de salmuera al 50% (24 ml) y se extrajo con $CHCl_3$ (4 x 50 ml) Los materiales organicos combinados se lavaron con agua y luego con salmuera, se secaron ($MgSO_4$), se filtraron y se concentraron bajo una presión reducida La purificacion mediante cromatografia rapida en columna (silice, 3 7 EtOAc/hexanos) y la recristalización de MeOH proporcionaron éster *terc*-butilico de acido {3-[3-bromo-4-(4-fluorobenciloxi)-2-oxo-2*H*-piridin-1-ilmetil]-bencil}carbámico como un solido blanquecino (0,07 g, al 20%), mp 136-138 °C, $^1$H NMR (300 MHz, $CDCl_3$) δ 7,42-7,37 (m, 2H), 7,30-7,20 (m, 5H), 7,08 (t, *J* = 9 Hz, 2H), 6,04 (d, *J* = 9 Hz, 1H), 5,16 (s, 2H), 5,14 (s, 2H), 4,28 (d, *J* = 6 Hz, 1H), 1,44 (s, 9H) ESHRMS m/z 517,1124 (M+H $C_{25}H_{27}BrFN_2O_4$ requiere 517,1133)

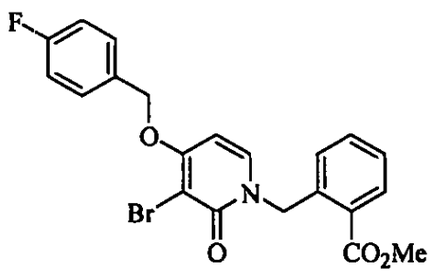
Ejemplo 71



1-(3-aminometilbencil)-3-bromo-4-(4-fluorobenciloxi)-1*H*-piridin-2-ona

A una disolucion helada de 1-[3-{N-*terc*-butoxicarbonil}aminometilbencil]-3-bromo-4-(4-fluorobenciloxi)piricin-2(1*H*)-ona (Ejemplo 69) (0,05 g, 0,1 mmol) en $CH_2Cl_2$ (2 ml) se agrego TFA (2 ml,) y la mezcla de reaccion se agitó durante 1 hora El disolvente se eliminó bajo una presión reducida para proporcionar 1-(3-aminometilbencil)-3-bromo-4-(4-fluorobenciloxi)-1*H*-piridin-2-ona como un solido de color tostado (0,049 g, al 100%) como la sal de TFA mp 127-139 °C, $^1$H NMR (300 MHz, DMSO-$d_6$) δ 8,13 (br s, 2H), 7,94 (d, *J* = 6 Hz, 1H), 7,52-7,47 (m, 2H), 7,44-7,37 (m, 2H), 7,27 (t, *J* = 8 Hz, 3H), 6,53 (d, *J* = 8 Hz, 1H), 5,30 (s, 2H), 5,14 (s, 2H), 4,01 (d, *J* = 6 Hz, 2H), 3,39 (br s, 2H), Anal Calculado para $C_{20}H_{17}BrF_2N_2O_2$ 1,125 TFA C, 48,99, H, 3,53, N, 5,13 Hallado C, 48,80, H, 3,43, N, 4,75 ESHRMS m/z 417,0608 (M+H $C_{20}H_{19}BrFN_2O_2$ requiere 417,0609)

Ejemplo 72

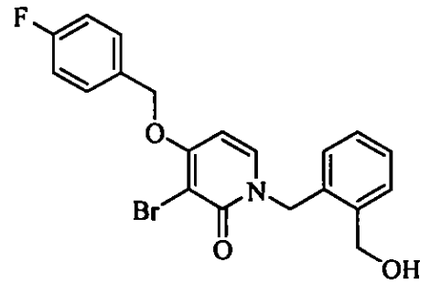



2-[3-bromo-4-(4-fluorobenciloxi)-2-oxo-2*H*-piridin-1-ilmetil]benzoato de metilo

El compuesto del titulo se preparó mediante un procedimiento similar al descrito para el Ejemplo 59 (0,36 g, al 48%) mp 161-165 °C, $^1$H NMR (300 MHz, $CDCl_3$) δ 7,98 (d, *J* = 6 Hz, 1H), 7,51-7,26 (m, 6H), 7,11-7,05 (m, 2H), 6,05 (d, *J* = 8 Hz, 1H), 5,60 (s, 2H), 5,18 (s, 2H), 3,93

(s, 3H) ESHRMS m/z 446,0430 (M+H $C_{21}H_{18}BrFNO_4$ requiere 418,0398)

Ejemplo 73

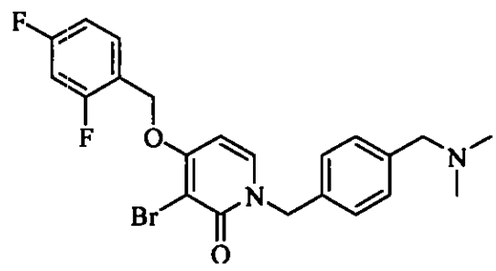



3-bromo-1-(4-fluorobenciloxi)-1-(2-hidroximetilbencil)-

1*H*-piridin-2-ona

A una disolucion helada de 3-bromo-4-(4-fluorobenciloxi)-1-(2-hidroximetilbencil)-1*H*-piridin-2-ona (Ejemplo 72) (0,25 g, 0,56 mmol) en THF (1 ml) se agrego $LiBH_4$ (disolución de 2,0 M en THF, 0,56 mmol) y la mezcla de reaccion se agitó a 40 °C durante 6 horas La mezcla de reaccion se enfrio a temperatura ambiente, se elimino el disolvente bajo una presion reducida y el residuo se disolvió en EtOAc La disolución organica se lavo con salmuera, se seco ($MgSO_4$), se filtro y se concentró bajo una presión reducida $^1H$ NMR (300 MHz, DMSO-$d_6$) δ 7,82 (d, $J$ = 8 Hz, 1H), 7,54-7,49 (m, 2H), 7,41 (d, $J$ = 7 Hz, 1H), 7,29-7,21 (m, 4H), 6,81 (d, $J$ = 7 Hz, 1H), 6,53 (d, $J$ = 8 Hz, 1H), 5,30-5,25 (m, 3H), 5,18 (s, 2H), 4,60 (d, $J$ = 7 Hz, 2H) ESHRMS m/z 418,0437 (M+H $C_{20}H_{18}BrFNO_3$ requiere 418,0449)

Ejemplo 74



3-bromo-4-(2,4-difluorobenciloxi)-1-[(4-dimetilaminometil)bencil]-1*H*-piridin-2-ona

Etapa 1 Preparación de 4-[(2,4-difluorobenciloxi]piridin-1-óxido

A una disolución helada de hidruro de sodio (1,2 g, de una dispersion en aceite mineral al 60%, 51 mmol) en DMF (43 ml) se agrego alcohol 2,4-fluorobencilico (5,7 ml, 51 mmol) La mezcla de reaccion se entibio a temperatura ambiente, se agregó 4-cloropiridin-1-oxido[1] (5,5 g, 43 mmol) y se agito durante 6 horas La mezcla de reaccion se diluyó con una disolicion acuosa de salmuera al 50%, y se extrajo con $CHCl_3$ (7 x 50 ml) Los materiales organicos combinados se secaror ($MgSO_4$), se filtraron y se eliminó el disolvente bajo una presion reducida La trituración con $Et_2O$ produjo 4-(2,4-difluorobenciloxi)piridin-1-oxido como un sólido blanquecino (9,1 g, al 90%) $^1H$ NMR (300 MHz, $CDCl_3$) δ 8,16-8,08 (m, 1H), 7,47-7,36 (m, 1H), 6,97-6,81 (m, 1H), 5,09 (d, $J$ = 8 Hz, 1H)

Etapa 2 Preparacion de 4-(2,4-difluorobenciloxi)-1*H*-piridin-2-ona

Una disolución de 4-(2,4-difluorobenciloxi)piridin-1-oxido (13,4 g, 57 mmol) en anhidrido acetico (30 ml) se agito a reflujo durante 4 horas Se elimino el disolvente bajo una presión reducida, se diluyó el residuo con 1 1 MeOH/agua (60 ml) v la mezcla se agito a temperatura ambiente durante 1 hora El disolvente se elimino bajo una

presion reducida La purificación por cromatografia rápida en columna (silice, eluyente cloruro de metileno a 9 1 cloruro de metileno/metanol) proporciono 4-(2,4-difluorobenciloxi)-1*H*-piridin-2-ona como un solido de color marrón claro (4,2 g, al 31%) $^1$H NMR (300 MHz, $CDCl_3$) δ 7,43 (q, *J* = 8 Hz, 1H), 7,23 (d, *J* = 7 Hz, 1H), 6,91-6,87 (m, 2H), 6,02 (dd, *J* = 8, 2 Hz, 1H), 5,97 (d, *J* = 2 Hz, 1H), 5,03 (s, 2H)

Etapa 3 Preparacion de 3-bromo-4-(2,4-difluorobenciloxi)-1*H*-piridin-2-ona

A una disolucion helada de 4-(2,4-difluorobenciloxi)1*H*-piridin-2-ona (0,75 g, 3,1 mmol) en AcOH (12 ml) se agreço una disolución de bromo (0,2 ml, 3,5 mmol) en AcOH (6 ml), y la mezcla de reacción se agitó 10 minutos El disolvente se elimino bajo una presión reducida para producir 3-bromo-4-(2,4-difluorobenciloxi)-1*H*-piridin-2-ona como un solidc blanco (1,0 g, al 100%) ESI MS *m/z* 299 $[M + H]^+$

Etapa 4 Preparacion de 3-bromo-1-(4-clorometilbencil)-4-(2,4-difluorobenciloxi)-1*H*-piridin-2-ona

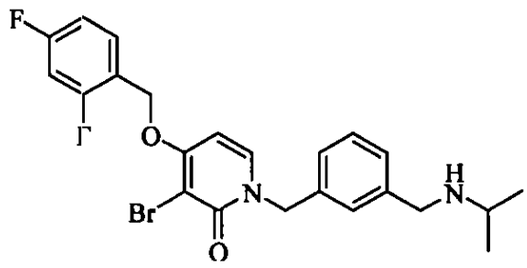
A una disolución de 3-bromo-4-(2,4-difluorobenciloxi)-1*H*-piridin-2-ona (0,60 g, 2,5 mmol) en DMF (40 ml) se agregó $K_2CO_3$ (0,70 g, 5,1 mmol) y α,α'-dicloro-*p*-xileno (0,53 g, 3,0 mmol) y la mezcla de reaccion se agito a 110 °C durante 2 horas La mezcla de reaccion se enfrio a temperatura ambiente se diluyó con salmuera y se extrajo con $CHCl_3$ (4 x 100 ml) Los materiales orgánicos combinados se lavaron con agua y luego con salmuera, se secaron ($Na_2SO_2$), se filtraron y se concentraron bajo una presion reducida para producir 3-bromo-1-(4-clorometilbencil)-4-(2,4-difluorobenciloxi)-1*H*-piridin-2-ona como un sólido blanquecino (0,49 g, al 43%) $^1$H NMR

(300 MHz, $CDCl_3$) δ 7 54 (aprox q, $J$ = 8 Hz, 1H), 7,38-7,28 (m, 5H), 6,94 (td, $J$ = 8, 2 Hz, 1H), 6,85 (td, $J$ = 8, 2 Hz, 1H), 6,10 (d, $J$ = 9 Hz, 1H), 5,21 (s, 2H), 5,16 (s, 2H), 4,56 (s, 2H)

Etapa 5 Preparación de 3-bromo-4-(2,4-difluorobenciloxi)-1-[(4-dimetilaminometil)bencil]-1*H*-piridin-2-ona

A un tubo sellado que contenia 3-bromo-1-(4-clorometilbencil)-4-(2,4-difluoro-benciloxi)- 1*H*-piridin-2-ona (0,49 g, 1,1 mmol) se agregó una disolucion de dimetilamina(5,5 ml de una disolucion de 2,0 M en THF, 11 mmol) y la mezcla de reaccion se agito durante 15 horas El disolvente se eliminó bajo una presión reducida La purificacion por cromatografia rapida en columna (silice, eluyente cloruro de metileno a 92 7,2 0,8 cloruro de metileno/metanol/amoriaco) proporciono 3-bromo-4-(2,4-difluorobenciloxi)-1-(4-dimetilaminometilbencil)-1*H*-piridin-2-ona como un solido de color amarillo claro (0,23 g, al 46%) mp 111-113 °C, $^1H$ NMR (500 MHz, $CDCl_3$) δ 7,50-7,49 (m, 1H), 7,26-7,22 (m, 5H), 6,90-6,88 (m, 1H), 6,82-6,78 (m, 1H), 6,04 (d, $J$ = 6 Hz, 1H), 5,16 (s, 2H), 5,11 (s, 2H), 3,37 (s, 2H), 2,19 (s, 6H) ESHRMS m/z 463,0782 (M+H $C_{22}H_{22}BrF_2N_2O_2$ requiere 463,0827)

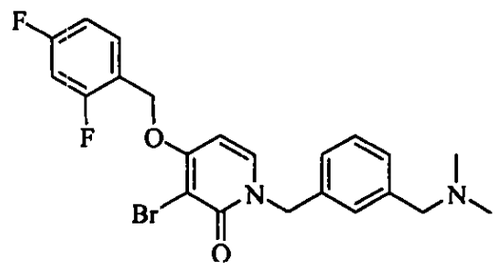
Ejemplo 75




3-bromo-4-(2,4-difluorobenciloxi)-1-[3-(isopropilaminometil)bencil]-1*H*-piridin-2-ona

El compuesto del título se preparó mediante un procedimiento similar al descrito para el Ejemplo 74 (0,06 g, al 35%) mp 109-110 °C, $^1$H NMR (300 MHz, $CDCl_3$) δ 7,54 (d, *J* = 6 Hz, 1H), 7,33-7,20 (m, 5H), 6,94-6,81 (m, 2H), 6,10 (d, *J* = 6 Hz, 1H), 5,20 (s, 2H), 5,14 (s, 2H), 3,77 (s, 2H), 2,88 (t, *J* = 6 Hz, 1H), 1,13 (d, *J* = 6 Hz, 6H) ESHRMS m/z 477,0955 (M+H $C_{23}H_{24}BrF_2N_2O_2$ requiere 477,0984)

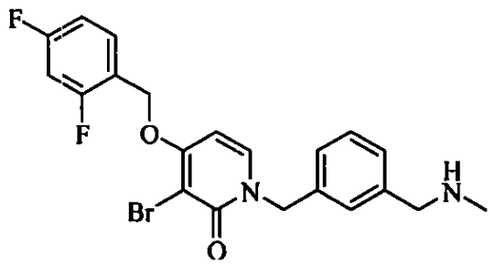
Ejemplo 76



3-bromo-4-(2,4-clfluorobenclloxl)-1-[(3-dlmetllamlnometll)bencll]-1*H*-pllrldln-2-ona

El compuesto del título se preparó mediante un procedimiento similar al descrito para el Ejemplo 74 (0,06 g, al 25%) mp 103-107 °C, $^1$H NMR (300 MHz, $CDCl_3$) δ 7,52 (d, *J* = 8 Hz, 1H), 7,32-7,24 (m, 5H), 6,94 (td, *J* = 9, 3 Hz, 1H), 6,84 (td, *J* = 9, 3 Hz, 1H), 6,08 (d, *J* = 8 Hz, 1H), 5,20 (s, 2H), 5,16 (s, 2H), 3,44 (s, 2H), 2,24 (s, 6H) ESHRMS m/z 463,0801 (M+H $C_{22}H_{22}BrF_2N_2O_2$ requiere 463,0827)

Ejemplo 77

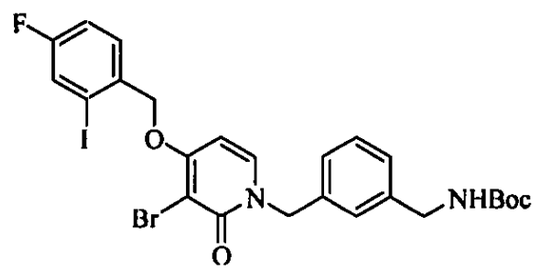


836

3-bromo-4-(2,4-difluorobenciloxi)-1-[(3-metilaminometil)bencil]-1*H*-piridin-2-ona

El compuesto del titulo se preparó mediante un procedimiento similar al descrito para el Ejemplo 74 (0,05 g, al 16%) mp 107-111 °C, $^1$H NMR (300 MHz, $CDCl_3$) δ 7,55 (d, *J* = 6 Hz, 1H), 7,31-7,19 (m, 5H), 6,94-6,81 (m, 2H), 6,09 (d, *J* = 6 Hz, 1H), 5,20 (s, 2H), 5,14 (s, 2H), 3,73 (s, 2H), 2,45 (s, 1H) ESHRMS m/z 449,0652 (M+H $C_{21}H_{20}BrF_2N_2O_2$ requiere 449,0671)

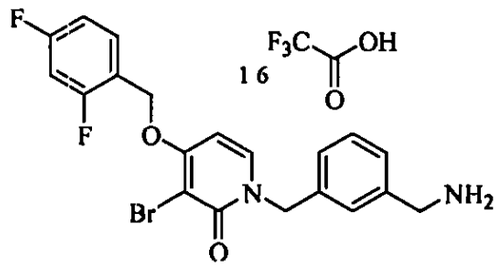
Ejemplo 78




Éster *terc*-butílico de acido {3-[3-bromo-4-(2,4-difluorobenciloxi)-2-oxo-2*H*-piridin-1-ilmetil]-bencil}carbámico

El compuesto del titulo se preparó esencialmente de acuerdo con el procedimiento descrito en el Ejemplo 70 mp 80-84 °C, $^1$H NMR (300 MHz, DMSO-$d_6$) δ 7,60-7,50 (m, 1H), 7,33-7,21 (m, 5H), 6,97-6,81 (m, 2H), 6,10 (dd, *J* = 8, 2 Hz, 1H), 5,20 (s, 2H), 5,15 (s, 2H), 4,87 (br s, 2H), 4,30 (s, 2H) 1,45 (s, 9H) ESHRMS m/z 535,1019 (M+H $C_{25}H_{26}BrF_2N_2O_4$ requiere 535,1039)

Ejemplo 79



16

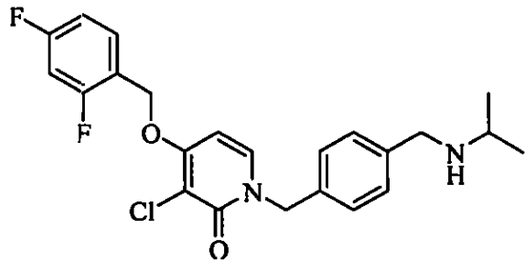
1-[(3-aminometil)bencil]-3-bromo-4-(2,4-difluorobenciloxi)-1*H*-piridin-2-ona

Etapa 1 Preparación de 1-[(3-aminometil)bencil]-3-bromo-4-(2,4-difluorobenciloxi)-1*H*-piridin-2-ona

A una disolucion helada de ester *terc*-butilico de acido {3[3-bromo-4-(2,4-difluorobenciloxi)-2-oxo-2H-piridin-1ilmetil]bencil}carbamico (Ejemplo 78) (0,05 g, 0,1 mmol) en $CH_2Cl_2$ (2 ml) se agregó TFA (2 ml) y la mezcla de reaccion se agito durante 1 hora El disolvente se elimino bajo una presion reducida para proporcionar 1-[(3-aminometil)bencil]-3-bromo-4-(2,4-difluorobenciloxi)-1*H*-piridin-2-ona como un solido de color tostado (0,049 g, al 100%), como la sal de TFA mp 80-84 °C, $^1$H NMR (300 MHz, DMSO-$d_6$) δ 8,15 (br s, 3H), 7,97 (d, $J$ = 8 Hz, 1H), 7,79-7,60 (m, 1H), 7,44-7,30 (m, 4H), 7,20-7,15 (m, 1H), 6,61 (d, $J$ = 6 Hz, 1H), 5,31 (s, 2H), 5,16 (s, 2H), 4,03 (s, 2H), $^{19}$F NMR (282 MHz, DMSO-$d_6$) δ -74,56 (4,8F), -109,63 (1F), -113,61 (1F) ESHRMS m/z 435,0540 (M+H $C_{20}H_{18}BrF_2N_2O_2$ requiere 435,0515)

Ejemplo 80

938



3-cloro-4-(2,4-difluorobenciloxi)-1-[4-(isopropilaminometil)bencil]-1*H*-piridin-2-ona

Etapa 1 Preparacion de 3-cloro-4-(2,4-difluorobenciloxi)-1*H*-piridin-2-ona

A una disolucion de 4-[(4-fluorobencil)oxi]piridin-2(1*H*)-ona (de la Etapa 1, Ejemplo 74) (1,4 g, 5,9 mmol) en AcOH (25 ml) se agrego N-clorosuccinimida (0,95 g, 7,1 mmol) y la mezcla de reacción se calento a reflujo durante 2 horas El disolvente se eliminó bajo una presión reducida $^1$H NMR (300 MHz, MeOD) δ 7,63-7,55 (m, 1H), 7,45(d, *J* = 8 Hz, 1H), 7,07-7,00 (m, 2H), 6,58 (d, *J* = 8 Hz, 1H), 5,31 (d, *J* 8 Hz, 1H)

Etapa 2 Preparacion de 3-cloro-1-(4-clorometilbencil)-4-(2,4-difluorobenciloxi)-1*H*-piridin-2-ona

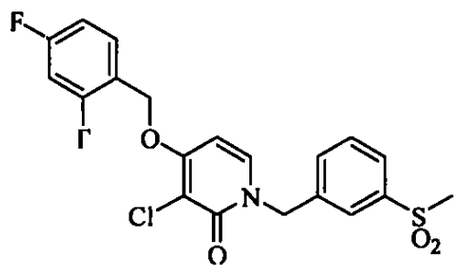
Se preparo 3-cloro-1-(4-clorometilbencil)-4-(2,4-difluorobenciloxi)-1*H*-piridin-2-ona mediante un procedimiento simila- al que se describe para 3-bromo-1-(4-clorometil-bencil)-4-(2,4-difluorobenciloxi)-1*H*-piridin-2-ona (Etapa 3) como un solido blanco (0,24 g, al 34%) $^1$H NMR (300 MHz, $CDCl_3$) δ 7,53 (aprox q, *J* = 9 Hz, 1H), 7,34 (aprox q, *J* = 9 Hz, 1H), 7,23 (d, *J* = 8 Hz, 1H), 6,94 (td, *J* = 10, 2 Hz, 1H), 6,85 (td, *J* = 10, 2 Hz, 1H), 6,14 (d, *J* = 8 Hz, 1H), 5,20 (s, 2H), 5,16 (s, 2H), 4,56 (s, 2H)

839
839

Etapa 3 Preparación de 3-cloro-4-(2,4-difluorobenciloxi)-1-[(4-isopropilamino-metil)bencil]-1*H*-piridin-2-ona

El compuesto del titulo se preparo mediante un procedimiento similar al descrito para el Ejemplo 74 (0,17 g, al 69 %) mp 146-151 °C, $^1$H NMR (300 MHz, $CDCl_3$) δ 7,52 (aprox q, *J* = 9 Hz, 1H), 7,35-7 21 (m, 5H), 6,94 (td, *J* = 8, 2 Hz, 1H), 6,85 (td, *J* = 8, 2 Hz, 1H), 6,18 (d, *J* = 8 Hz, 1H), 5,22 (s, 2H), 5,08 (s, 2H), 3,81 (s, 2H), 2,98 (br s, 1H), 1,20 (s, 6H) ESHRMS m/z 433,1481 (M+H $C_{23}H_{24}ClF_2N_2O_2$ requiere 433,1489)

Ejemplo 81




3-cloro-4-(2,4-difluorobenciloxi)-1-[(3-metanosulfonil)bencil]-1*H*-piridin-2-ona

Etapa 1 Preparacion de (3-metanosulfonil)fenil metanol

A una disolucion helada de acido 3-(metilsulfonil)benzoico (1,4 g, 7,1 mmol) en 2 1 EtO/THF (60 ml) se agrego $LiAlH_4$ (8,5 ml, de una disolución de 1,0 M en THF, 8,5 mmol) y la mezcla de reaccion se calentó a reflujo durante 1 hora La mezcla de reaccion se enfrio hasta 0 °C y la reaccion se enfrio repentinamente con agua (15 ml) y NaOH al 15 % en agua (35 ml) La mezcla de reaccion se filtro, se concentro bajo una presion reducida y el residuo se disolvió en EtOAc La disolucion organica se lavó con agua y luego con salmuera, se seco ($MgSO_4$), se

filtro y se concentro bajo una presión reducida La purificación por cromatografia rapida en columna (silice, 1 2 a 3 1 EtOAc/hexanos) proporciono (3-metanosulfonil)fenil metanol como un aceite de color amarillo claro (0,56 g, al 42%) $^1$H NMR (300 MHz, $CDCl_3$) δ 7,93 (s, 1H), 7,83 (d, *J* = 7 Hz, 1H), 7,64 (d, *J* = 7 Hz, 1H), 7,53 (t, *J* = 7 Hz, 1H), 4,78 (d, *J* = 6 Hz, 2H), 3,05 (s, 3H), 2,61 (br s, 1H)

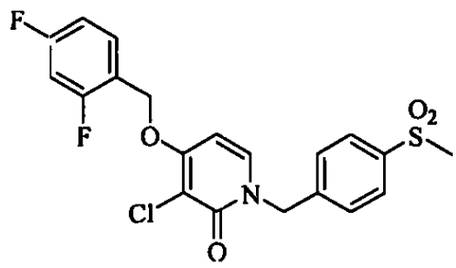
Etapa 2 Preparacion de 1-clorometil-3-metanosulfonilbencenc

Una disolucion de (3-metanosulfonil)fenil metanol (0,21 g, 1,1 mmol) en cloruro de tionilo (3 ml) se calento a 80 °C durante 3 horas La mezcla de reaccion se enfrió a temperatura ambiente y el disolvente se elimino bajo una presión reducida para proporcionar 1-clorometil-3-metanosulfonilbencenc como un aceite de color amarillo (0,23 g, al 95%) $^1$H NMR (300 MHz, $CDCl_3$) δ 7,98 (s, 1H), 7,90 (d, *J* = 8 Hz, 1H), 7,70 (d, *J* = 8 Hz, 1H), 7,59 (t, *J* = 8 Hz, 1H), 4,65 (s, 2H), 3,08 (s, 3H)

Etapa 3 Preparacion de 3-cloro-4-(2,4-difluorobenciloxi)-1-[(3-metanosulfonil)bencil]-1*H*-piridin-2-ona

El compuesto del titulo se preparó mediante un procedimiento similar al descrito para el Ejemplo 80 (0,14 g, al 78%) mp 155-157 °C, $^1$H NMR (300 MHz, $CDCl_3$) δ 7,88 (d, *J* = 8 Hz, 1H), 7,83 (m, 1H), 7,67 (d, *J* = 8 Hz, 1H), 7,58-7,48 (m, 2H), 7,31 (d, *J* = 8 Hz, 1H), 6,95-6,83 (m, 2H), 6,22 (d, *J* = 8 Hz, 1H), 5,22 (s, 4H), 3,08 (s, 3H) ESHRMS m/z 440,0525 (M+H $C_{20}H_{17}ClF_2NO_4S$ requiere 440,0529)

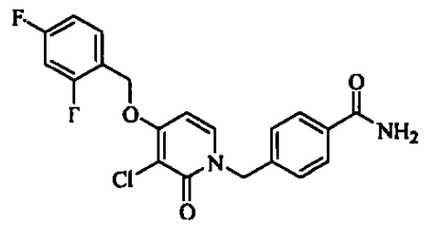
Ejemplo 82



3-cloro-4-(2,4-cıfluorobencıloxı)-1-[(4-metanosulfonıl)bencıl]-1*H*-pırıdın-2-ona

El compuesto del tıtulo se preparó mediante un procedımiento sımılar al descrıto para el Ejemplo 81 (0,08 g, al 73%) mp 223-225 °C, $^1$H NMR (300 MHz, $CDCl_3$) δ 7,91 (d, *J* = 8 Hz, 2H), 7,53-7,47 (m, 3H), 7,30-7,26 (m, 1H), 6,94-6,86 (m, 2H), 6,22 (d, *J* = 8 Hz, 1H), 5,23 (s, 4H), 3,03 (s, 3H) ESHRMS m/z 440,0512 (M+H $C_{20}H_{17}ClF_2NO_4S$ requıere 440,0529)

Ejemplo 83



4-[3-cloro-4-(2,4-dıfluorobencıloxı)-2-oxo-2H-pırıdın-1-ılmetıl]benzamıda

Etapa 1 Preparación de 4-[3-cloro-4-(2,4-dıfluorobencıloxı)-2-oxo-2*H*-pırıdın-1-ılmetıl]benzoato de metılo

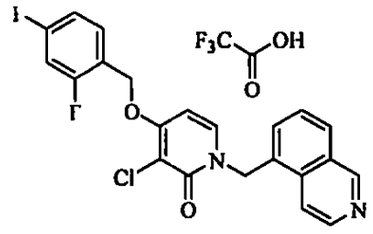
Se preparo 4-[3-cloro-4-(2,4-dıfluorobencıloxı)-2-oxo-2*H*-pırıdın-1-ılmetıl] benzoato de metılo mediante un procedımiento sımılar al descrıto para el Ejemplo 81 (0,14 g, al 60%) $^1$H NMR (300 MHz, $CDCl_3$) δ 8,01 (dd, *J* = 8, 2 Hz, 1H), 7,52 (aprox q, *J* = 8 Hz, 1H), 7,36 (d, *J* = 9 Hz,

2H), 7,26-7,22 (m, 2H), 6,94 (td, $J$ = 8, 2 Hz, 1H), 6,85 (td, $J$ = 8, 2 Hz, 1H), 6,16 (d, $J$ = 9 Hz, 1H), 5,21 (s, 4H), 3,92 (s, 3H)

Etapa 2 Preparacion de 4-[3-cloro-4-(2,4-difluorobenciloxi)-2-oxo-2*H*-piridin-1-ilmetil]benzamida

Se calentó a 75 °C durante 16 horas un tubo sellado que contenia una disolucion de éster metilico de ácido 4-[3-cloro-4-(2,4-difluorobenciloxi)-2-oxo-2H-piridin-1-ilmetil]benzoico (0,25 g, 0,60 mmol) y $NH_3$ (20 ml de una disolución de 7 N en MeOH, 140 mmol) La mezcla de reaccion se enfrio a temperatura ambiente y el disolvente se elimino bajo una presion reducida La trituracion con $Et_2O$/MeOH proporciono 4-[3-cloro-4-(2,4-difluorobenciloxi)-2-oxo-2*H*-piridin-1-ilmetil]benzamida como un solido blanco (0,14 g, al 60%) mp 235-238 °C, $^1H$ NMR (500 MHz, DMSO-$d_6$) δ 7,93 (d, $J$ = 8 Hz, 2H), 7,79 (d, $J$ = 8 Hz, 2H), 7,60 (aprox q, $J$ = 8 Hz, 1H), 7,35-7,27 (m, 4H), 7,20-7,10 (m, 1H), 6,61 (d, $J$ = 8 Hz, 1H), 5,28 (s, 2H), 5,14 (s, 2H) ESHRMS m/z 405,0788 (M+H $C_{20}H_{16}ClF_2N_2O_3$ requiere 405,0812)

Ejemplo 84




3-cloro-4-(2,4-difluorobenciloxi)-1-isoquinolin-5-ilmetil-1*H*-piridin-2-ona

Etapa 1 Preparacion de isoquinolin-5-ilmetanol

A una disolucicn helada de isoquinolin-5-carbaldehido[2] (0,68 g, 4,3 mmol) en MeOH (15 ml) se agregó $NaBH_4$ (0,17 g,

4,6 mmol) y se agitó la mezcla de reacción durante 15 minutos La mezcla de reaccion se enfrio repentinamente con salmuera, se elimino el disolvente bajo una presion reducida y el residuo se disolvió en EtOAc La disolución orgánica se lavo con agua y luego con salmuera, se secó ($Na_2SO_4$), se filtró y se concentró bajo una presion reducida para proporcionar isoquinolin-5-ilmetanol como un sólido de color marrón (0,63 g, al 93%) $^1$H NMR (300 MHz, DMSO-$d_6$) δ 9,87(s, 1H), 8,82 (d, $J$ = 6 Hz, 1H), 8,57 (d, $J$= 6 Hz, 1H), 8,47 (d, $J$ = 9 Hz, 1H), 8,30 (d, $J$ = 6 Hz, 1H), 7,95 (t, $J$ = 9 Hz, 1H), 5,34 (s, 2H)

Etapa 2 Preparación de 5-bromometilisoquinolina

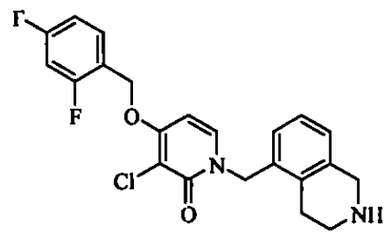
A una disolucion de isoquinolin-5-ilmetanol (0,63 g, 3,9 mmol) en AcOH (3,3 ml) se agrego HBr (6,6 ml, una disolución al 30% peso/peso en AcOH, 24 mmol) y la mezcla de reaccion se agito a 75 °C durante 45 minutos La mezcla de reaccion se erfrió a temperatura ambiente y el precipitado se recoçio para proporcionar la sal ácida de hidrobromuro de 5-bromometilisoquinolina como un solido de color marron (1,1 g, al 87%) $^1$H NMR (300 MHz, $CDCl_3$) δ 9,22 (s, 1H), 8,58 (d, $J$ = 6 Hz, 1H), 7,95-7,89 (m, 2H), 7,76 (d, $J$ =9 Hz, 1H), 7,59 (dd, $J$ = 9, 6 Hz, 1H), 5,16 (s, 2H)

Etapa 3 Preparación de 3-cloro-4-(2,4-difluorobenciloxi)-1-isoquinolin-5-ilmetil-1*H*-piridin-2-ona

El compuesto del titulo se preparo mediante un procedimiento similar al descrito para el Ejemplo 81,como la sal de TFA (0,13 g, al 33%) mp 235-238 °C, $^1$H NMR (300 MHz, DMSO-$d_6$) δ 9,55 (s, 1H), 8,66 (d, $J$ = 6 Hz, 1H), 8,29 (d, $J$ = 6 Hz, 1H), 8,22 (d, $J$ = 8 Hz, 1H), 7,91 (d, $J$ = 8 Hz, 1H), 7,77 (t, $J$ = 8 Hz, 1H), 7,65-7,63 (m, 1H), 7,53 (d, $J$ = 7 Hz, 1H), 7,35-7,25 (m, 1H), 7,20-7,10 (m, 1H),

6,68 (d, $J$ = 8 Hz, 1H), 5,67 (s, 2H), 5,32 (s, 2H), $^{19}$F NMR (282 MHz, DMSO-$d_6$) δ -74,79 (3F), -109,43 (1F), -113,62 (1F) ESHRMS m/z 413,0868 (M+H $C_{22}H_{16}ClF_2N_2O_3$ requiere 413,0863)

Ejemplo 85



3-cloro-4-(2,4-difluorobenciloxi)-1-(1,2,3,4-tetrahidroisoquinolin-5-ilmetil)-1*H*-piridin-2-ona,

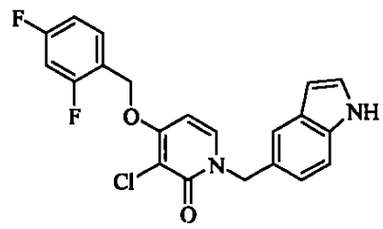
Etapa 1 Preparacion de 3-cloro-4-(2,4-difluorobenciloxi)-1 (1,2,3,4-tetrahidro-isoquinolin-5-ilmetil)-1*H*-piridin-'-ona

A una disolución de 3-cloro-4-(2,4-difluorobenciloxi)-1-isoquinolin-5-ilmetil-1*H*-piridin-2-ona (Ejemplo 84) (0,14 g, 0,34 mmol) en AcOH (1,3 ml) se agregó $NaCNBH_3$ (0,09 g, 1,4 mmol) y la mezcla de reacción se agito durante 2 horas La mezcla de reaccicn se enfrio hasta 0 °C, se diluyo con agua (10 ml) y NaOH acuoso al 40% (10 ml) y la capa acuosa se lavo con EtOAc (3 x 50 ml) Los materiales organicos combinados se lavaron con salmuera, se secaron ($Na_2SO_4$), se filtraron y se concentraron bajo una presion reducida La purificacion por cromatografia rapida en columna (silice, eluyente 98 1,8 0 2 a 88 10,8 1 2 $CH_2Cl_2$/MeOH/$NH_3$) proporciono 3-cloro-4-(2,4-difluorobenciloxi)-1-(1,2,3,4-tetrahidroisoquinolin-5-ilmetil)-1*H*-piridin-2-ona como un solido blanco (0,13 g, al 92%) mp 180-184 °C, $^1$H NMR (300 MHz, MeOD) δ 7,65-7,55 (m, 2H), 7,16-7,00 (m, 4H), 6,90-6,80 (m, 1H), 6,60 (d, $J$ = 8 Hz, 1H), 5,31 (s, 2H), 5,20

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(s, 2H), 4,06 (s, 2H), 3,21 (t, $J$ = 6 Hz, 2H), 2,82 (t, $J$ = 6 Hz, 2H) ESHRMS m/z 417,1173 (M+H $C_{22}H_{20}ClF_2N_2O_2$ requiere 417,1176)

Ejemplo 86



3-cloro-4-(2,4-cıfluorobencıloxı)-1-(1*H*-ındol-5-ılmetıl)-1*H*-pırıdın-2-ona

Etapa 1 Preparacıon de ester *terc*-butılıco de acıdo 5-(carboxımetıl)-ındol-1-carbamıco

A una dısolucıor de ındol-5-carboxılato de metılo (6,9 g, 39 mmol) y $Et_3N$ (6,0 ml, 43 mmol) en $CH_2Cl_2$ (150 ml) se agrego dıcarbonato dı-*terc*-butılıco (19 g, 86 mmol), y la mezcla de reaccıon se agıto durante 14 horas La mezcla de reaccıon se dıluyó con $CH_2Cl_2$, se lavo con agua y luego salmuera, se secó ($Na_2SO_4$), se fıltro y se elımınó el dısolvente bajo una presıon reducıda La purıfıcación por cromatografıa rapıda en columna (sılıce, 3 7 EtOAc/hexanos) produjo ester *terc*-butılıco de ácıdo 5-(carboxımetıl)-ındol-1-carbamıco como un aceıte de color amarıllo claro (11 g, al 100%) $^1$H NMR (300 MHz, $CDCl_3$) δ 8,29 (s, 1H), 8,15 (d, $J$ = 9 Hz, 1H), 7,93 (d, $J$ = 9 Hz, 1H), 7,78 (d, $J$ = 3 Hz, 1H), 6,85 (d, $J$ = 3 Hz, 1H), 3,91 (s, 3H), 1,68 (s, 9H)

Etapa 2 Preparación de éster *terc*-butılıco de ácıdo 5-hıdroxımetılındol-1-carbamıco

A una dısolución a -78 °C de éster *terc*-butılıco de ácıdo 5-(carboxımetıl)-ındol-1-carbamıco (10,8 g, 39 mmol) en THF (180 ml) se agrego DIBAL (127 ml, de una dısolucıon

de 1 M en THF, 127 mmol) y la mezcla de reaccion se agitó durante 2,5 horas La mezcla de reaccion se enfrió repentinamente con 1 1 1 N HCl/MeOH (100 ml), la mezcla de la reaccion se entibio a temperatura ambiente, se diluyó con $CH_2Cl_2$ (100 ml) y se separo La disolución organica se lavó con sal de Rochelle saturada, se seco ($Na_2SO_4$),se filtró y se concentró bajo una presion reducida La purificación por cromatografia en columna rápida (silice, 1 1 EtOAc/hexanos) produjo ester *terc*-butilico de acido 5-hidroximetilindol-1-carbámico como un aceite de color amarillo (6,5 g, al 68%) $^1$H NMR (300 MHz, $CDCl_3$) δ 8,07 (d, *J* = 9 Hz, 1H), 7,59 (d, *J* = 6 Hz, 1H), 7,54 (s, 1H), 7,28 (d, *J* = 9 Hz, 1H), 6,58 (d, *J* = 6 Hz, 1H), 4,73 (s, 2H), 1,97 (s, 9H)

Etapa 3 Preparación de éster *terc*-butilico de acido 5-bromometilindol-1-carbamico

A una disolucion helada de ester *terc*-butilico de acido 5-hidroximetilindol-1-carbámico (0,51 g, 2,1 mmol) en 4 1 $Et_2O/CH_2Cl_2$ (4 ml) se agrego $PBr_3$ (0,2 ml, 2,2 mmol) y se agito la mezcla de reaccion durante 40 minutos La mezcla de reacción se diluyo con $CH_2Cl_2$, se lavó con una disolucion saturada ce $NaHCO_3$ (3 x 10 ml), se secó ($Na_2SO_2$), se filtró y se elimino el disolvente bajo una presión reducida para proporcionar ester *terc*-butilico de acido 5-bromometil-indol-1-carbámico como un sólido de color amarillo (0,59 g, al 93%) $^1$H NMR (300 MHz, $CDCl_3$) δ 8,07 (d, *J* = 9 Hz, 1H), 7,68-7,62 (m, 2H), 7,33 (d, *J* = 9 Hz, 1H), 6,60 (s, 1H), 4,68 (s, 2H), 1,67 (s, 9H)

Etapa 4 Preparacion de ester *terc*-butilico de acido 5-[3-cloro-4-(2,4-difluorobenciloxi)-2-oxo-2*H*-piridin-1-ilmetil]indol-1-carbamico

Se preparo ester *terc*-butilico de acido 5-[3-cloro-4-(2,4-difluorobenciloxi)-2-oxo-2*H*-piridin-1-ilmetil]indol-1-

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carbamico mediante un procedimiento similar al descrito para el Ejemplo 81 como un solido blanquecino (0,54 g, al 67%) $^1$H NMR (300 MHz, $CDCl_3$) δ 8,10 (d, *J* = 8 Hz, 1H), 7,60 (d, *J* = 3 Hz, 'H), 7,52 (m, 1H), 7,26 (m, 1H), 6,94 (td, *J* = 9, 2 Hz, 1H), 6,84 (td, *J* = 9, 2 Hz, 1H) 6,53 (d, *J* = 2 Hz, 1H), 6,08 (d, *J* = 8 Hz, 1H), 5,25 (s, 2H), 5,18 (s, 2H), 1,66 (s, 9H)

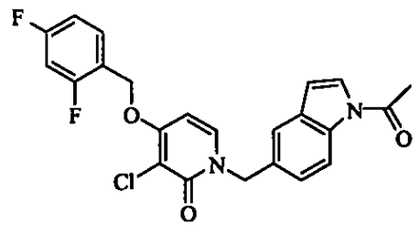
Etapa 5 Preparacion de 3-cloro-4-(2,4-difluorobenciloxi)-1-(1*H*-indol-5-ilmetil)-1*H*-piridin-2-ona

Un matraz que contenia ester *terc*-butilico de ácido 5-[3-cloro-4-(2,4-difluorobenciloxi)-2-oxo-2*H*-piridin-1-ilmetil]indol-1-carbamico (0,48 g, 0,96 mmol) se calento a 150 °C durante 4 horas La mezcla de reaccion se enfrió a temperatura ambiente y la purificación mediante HPLC preparatoria (Phenomenex Luna, C18(2) columna, 250 x 21,20 mm 10 µ

Disolvente A al 0 05% TFA en 95 5 $H_2O/CH_3CN$, Disolvent B al 0 05% TFA en 95 5 $CH_3CN/H_2O$

Eluyente al 30-95% B sobre 20 min , caudal 20,0 ml/min , Detector UV 254 nm, Tiempo de retencion 15,6 min) proporciono 3-cloro-4-(2,4-difluorobenciloxi)-1-(1*H*-indol-5-ilmetil)-1*H*-piridin-2-one como un solido de color blanquecino (0,14 g, al 36%) mp 152-153 °C, $^1$H NMR (300 MHz, DMSO-$d_6$) δ 11,11 (br s, 1H), 7,91 (d, *J* = 8 Hz, 1H), 7,61 (aprox q, *J* = 8 Hz, 1H, 7,51 (s, 1H), 7,36-7,33 (m, 3H), 7,16 (td, *J* = 8, 2 Hz, 1H), 7,09 (dd, *J* = 8, 2 Hz, 1H), 6,57 (d, *J* = 8 Hz, 1H), 6,40 (br s, 1H), 5,28 (s, 2H), 5,16 (s, 2H) ESHRMS m/z 401,0845 (M+H $C_{21}H_{16}ClF_2N_2O_2$ requiere 401,0863)

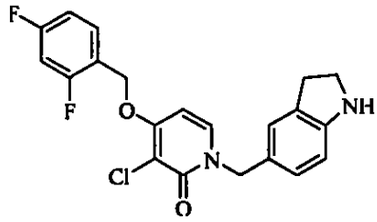
Ejemplo 87



1-(1-acetil-1*H*-indol-5-ilmetil)-3-cloro-4-(2,4-difluorobenciloxi)-1*H*-piridin-2-ona

A una disolucion de 3-cloro-4-(2,4-difluorobenciloxi)-1-(1*H*-indol-5-ilmetil)-1*H*-piridin-2-ona (Etapa 5, sintesis del Ejemplo 86) (0,22 g, 0,57 mmol) en $CH_3CN$ (10 ml) se agrego anhidrido acetico (0,06 ml, 0,58 mmol) y $Et_3N$ (2 ml) y la mezcla de reaccion se agito a 86 °C durante 6 horas La mezcla de reaccion se enfrió a temperatura ambiente y se dividio en 1 N HCl y EtOAc La disolucion organica se separó, se lavo con salmuera, se seco ($Na_2SO_4$), se filtro y se concentro bajo una presion reducida $^1H$ NMR (300 MHz, MeOD) δ 8,35 (d, *J* = 9 Hz, 1H), 7,77 (d, *J* = 9 Hz, 1H), 7,70 (d, *J* = 3 Hz, 1H), 7,54 (s, 2H), 7,31 (d, *J* = 9 Hz, 1H), 7,01-6,99 (m, 2H), 6,66 (d, *J* = 3 Hz, 1H), 6,59 (d, *J* = 9 Hz, 1H), 5,29 (s, 4H), 2,63 (s, 3H) ESHRMS m/z 443,0965 (M+H $C_{23}H_{18}ClF_2N_2O_3$ requiere 443,0969)

Ejemplo 88



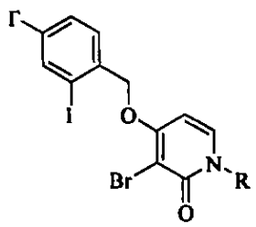
3-cloro-4-(2,4-difluorobenciloxi)-1-(2,3-dihidro-1*H*-indol-5-ilmetil)-1*H*-piridin-2-ona

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A una disolucion de 3-cloro-4-(2,4-difluorobenciloxi)-1-(1*H*-indol-5-ilmetil)-1*H*-piridin-2-ona (Etapa 5, sintesis del Ejemplo 86) (0,'4 g, 0,60 mmol) en AcCOH (5 ml) se agregó $NaCNBH_3$ (0,06 ml, 1,0 mmol) y la mezcla de reaccion se agito durante 1 hora La mezcla de reacción se dividio en agua y EtOAc y el precipitado se recogio por filtración La trituración con $CH_2Cl_2$ proporciono 3-cloro-4-(2,4-difluorobencil-oxi)-1-(2,3-dihidro-1*H*-indol-5-ilmetil)piridin-2(1*H*)-ona como un sólido blanco (0,2 g, al 81%) mp 137-139 °C, $^1H$ NMR (300 MHz, $CDCl_3$) δ 7,51 (aprox q, *J* = 9 Hz, 1H), 7,21 (d, *J* = 6 Hz, 1H), 7,11 (s, 1H), 6,99-6,80 (m, 3H), 6,57 (d, *J* = 9 Hz, 1H), 6,08 (d, *J* = 9 Hz, 1H), 5,18 (s, 2H), 5,02 (s, 2H), 3,83 (br s, 1H), 3,55 (t, *J* = 9 Hz, 2H), 2,99 (t, *J* = 9 Hz, 2H) ESHRMS m/z 403,1022 (M+H $C_{21}H_{18}ClF_2N_2O_2$ requiere 403,1019)

Los compuestos del siguiente ejemplo se prepararon mediante procedimientos similares a los que se describen para el Ejemplo 74 Los rendimientos y los datos analiticos de los compuestos del titulo se detallan a continuacion

Ejemplos 89-101



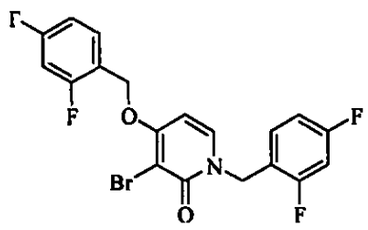

Los compuestos de los Ejemplos 89-101 se preparan esencialmente de acuerdo con los procedimientos establecidos anteriormente para el Ejemplo 74 El rendimiento (Rend ), la formula molecular (FM) y los datos analiticos para estos compuestos se presentan a continuacion

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| Ejemplo N° | R | Rend | FM | M+H Requiere | ESHRMS m/z |
|---|---|---|---|---|---|
| Ej 89 | piridin-3-ilmetilo | 25 | $C_{18}H_{13}BrF_2N_2O_2$ | 407,0202 | 407,0197 |
| Ej 90 | piridin-4-ilmetilo | 6 | $C_{18}H_{13}BrF_2N_2O_2$ | 407,0202 | 407,0189 |
| Ej 91 | piridin-2-ilmetilo | 56 | $C_{18}H_{13}BrF_2N_2O_2$ | 407,0201 | 407,0184 |
| Ej 92 | 4-*terc*-butil)bencilo | 32 | $C_{23}H_{22}BrF_2NO_2$ | 462,0875 | 462,0863 |
| Ej 93 | 3-metoxibencilo | 50 | $C_{20}H_{16}BrF_2NO_3$ | 436,0354 | 436,0353 |
| Ej 94 | Benzo[1,3]dioxol-5-ilmetilo | 35 | $C_{20}H_{14}BrF_2NO_4$ | 450,0147 | 450,0136 |
| Ej 95 | 2-fluorobencilo | 42 | $C_{19}H_{14}BrF_3NO_2$ | 424,0155 | 424,0143 |

%) mp 179-182 °C, $^1$H NMR (300 MHz, $CDCl_3$) δ 7,58-7,53 (m, 3H), 7,33-7,26 (m, 1H), 7,14-7,02 (m, 2H), 6,96-6,82 (m, 2H), 6,11 (d, *J* = 9 Hz, 1H), 5,20 (s, 2H), 5,18 (s, 2H) ESHRMS m/z (M+H requiere)

Ejemplo 96




3-bromo-4-(2,4-difluorobenciloxi)-1-(2,4-difluorobencil)-1*H*-piridin-2-ona

Etapa 1 Preparación de 4-(2,4-difluorobenciloxi)-1-(2,4-difluorobencil)-1*H*-piridin-2-ona

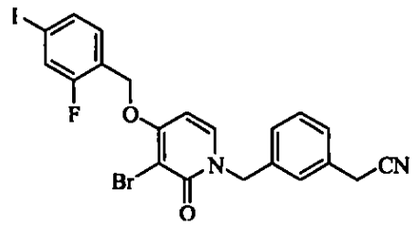
A una disolución de 2,4-dihidroxipiridina (0,35 g, 2,5 mmol) en DMF (50 ml) se agrego $K_2CO_3$ (2,5 g, 13 mmol) y bromuro de 2,4-difluorobencilo (1,0 ml, 7,6 mmol) y la mezcla de reacción se agitó a 110 °C durante 4 horas La

mezcla de reaccion se enfrio a temperatura ambiente, se diluyó con salmuera y se extrajo con $CHCl_3$ (4 x 100 ml) Los materiales orgánicos combinados se lavaron con agua y luego con salmuera, se secaron ($Na_2SO_4$), se filtraron y se concentraron bajo una presion reducida $^1H$ NMR (300 MHz, $CDCl_3$) δ 7,54 (aprox q, *J* = 8 Hz, 1H), 7,38-7,28 (m, 5H), 6,94 (td, *J* = 8, 2 Hz, 1H), 6,85 (td, *J* = 8, 2 Hz, 1H), 6,10 (d, *J* = 9 Hz, 1H), 5,21 (s, 2H), 5,16 (s, 2H), 4,56 (s, 2H)

Etapa 2 Preparación de 3-bromo-4-(2,4-difluorobenciloxi)-1-(2,4-fluorobencil)-1*H*-piridin-2-ona

A una disolución helada de 4-(2,4-difluorobenciloxi)-1-(2,4-difluorobencil)-1*H*-piridin-2-ona (0,72 g, 2,0 mmol) en AcOH (4,0 ml) se agrego una disolucion de bromo (0,11 ml, 2,2 mmol) en AcOH (7,2 ml), y la mezcla de reacción se agito 40 minutos El disolvente se elimino bajo una presion reducida $^1H$ NMR (300 MHz, $CDCl_3$) δ 7,63-7,45 (m, 2H), 7,42 (d, *J* = 6 Hz, 1H), 6,93-6,77 (m, 4H), 6,12 (d, *J* = 6 Hz, 1H), 5,20 (s, 2H), 5,12 (s, 2H) ERMS m/z M+H 442

Ejemplo 97




{3-[3-bromo-4-(2,4-difluorobenciloxi)-2-oxo-2*H*-piridin-1-ilmetil]-fenil}acetonitrilo

Etapa 1 Preparación de 3-cianometilbenzoato de metilo

A una disolución helada de 3-bromometilbenzoato de metilo (9,1 g, 40 mmol) en $CH_3CN$ (108 ml) se agrego fluoruro de tetrabutilamonio (17,3 ml, 60 mmol) y

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trimetilsililcianida (8,0 ml, 60 mmol) y la mezcla de reacción se calento a reflujo durante 20 horas La mezcla de reacción se enfrio hasta temperatura ambiente y se elimino el disolvente bajo una presión reducida La purificacion por cromatografia en columna rápida (silice, 1 1 EtOAc/hexanos) proporciono 3-cianometilbenzoato de metilo como un aceite transparente (3,0 g, al 43%) $^1$H NMR (300 MHz, DMSO-$d_6$) δ 7,97 (s, 1H), 7,92 (d, $J$ = 8 Hz, 1H), 7,64 (d, $J$ = 8 Hz, 1H), 7,56 (t, $J$ = 8 Hz, 1H), 4,16 (s, 2H), 3,87 (s, 3H)

Etapa 2 Preparación de (3-hidroximetilfenil)acetonitrilo

A una disolución helada de 3-cianometilbenzoato de metilo (2,8 g, 18 mmol) en THF (23 ml) se agregó $LiBH_4$ (8,8 ml, de una disolución de 2 M en THF, 1,8 mmol) y la mezcla de reaccion se calento a reflujo durante 4 horas La mezcla de reaccion se enfrió hasta temperatura ambiente, la reaccion se enfrió repentinamente con 1 1 agua/1 N HCl y la capa acuosa se lavó con EtOAc (3 x 150 ml) Los materiales organicos combinados se lavaron con salmuera, se secaron ($MgSO_4$), se filtraron y se concentraron bajo una presión reducida La purificación por cromatografia en columna rapida (silice, 1 1 EtOAc/hexanos) proporcionó (3-hidroximetilfenil)-acetonitrilo como un aceite transparente (0,97 g, al 41%) $^1$H NMR (300 MHz, MeOD) δ 8,15-8,08 (m, 1H), 7,47-7,34 (m, 1H), 7,27 (s, 1H), 6,97-6,82 (m, 1H), 4,87 (s, 2H), 3,91 (s, 2H)

Etapa 3 Preparación de (3-bromometilfenil)acetonitrilo

A una disolucion helada de (3-hidroximetilfenil)acetonitrilo (0,97 g, 7,3 mmol) en THF (35 ml) se agrego $CBr_4$ (2,5 g, 7,7 mmol) y $Ph_3P$ (2,0 g, 7,7 mmol) y se agito la mezcla de reacción durante 3 horas La

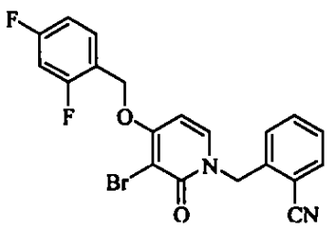
853

mezcla de reacción se filtro y se concentró bajo una presión reducida La purificacion por cromatografia rápida en columna (silice, eluyente 1 9 a 1 4 EtOAc/hexanos) proporcionó (3-bromometilfenil)acetonitrilo como un aceite transparente (0,89 g, al 58%) $^1$H NMR (300 MHz, MeOD) δ 7,47-7,29 (m, 1H), 7,27 (s, 1H), 6,97-6,82 (m, 1H), 4,87 (s, 2H), 3,91 (s, 2H)

Etapa 4 Preparacion de {3-[3-bromo-4-(2,4-difluorobenciloxi)-2-oxo-2*H*-piridin-1-ilmetil]fenil}acetonitrilo

El compuesto del titulo se preparó mediante un procedimiento similar al descrito para el Ejemplo 74 (0,07 g, al 10%) mp 120-121 °C, $^1$H NMR (300 MHz, $CDCl_3$) δ 7,60-7,50 (m, 1H), 7,37-7,27 (m, 5H), 6,96 (td, *J* = 9, 3 Hz, 1H), 6,82 (td, *J* = 9, 3 Hz, 1H), 6,13 (d, *J* = 8 Hz, 1H), 5,21 (s, 2H), 5,16 (s, 2H) ESHRMS m/z 445,0381 (M+H $C_{21}H_{16}BrF_2N_2O_2$ requiere 445,0358)

Ejemplo 98



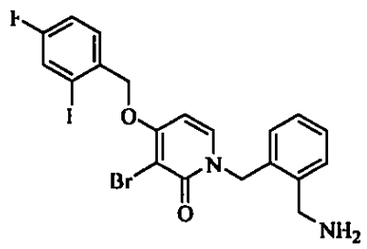

2-[3-bromo-4-(2,4-difluorobenciloxi)-2-oxo-2*H*-piridin-1-ilmetil]benzonotrilo

El compuesto del titulo se preparo mediante un procedimiento similar al descrito para el Ejemplo 74 (0,13 g, al 47%) mp 194-197 °C, $^1$H NMR (300 MHz, $CDCl_3$) δ 7,75 (d, *J* = 9 Hz, 1H), 7,69-7,49 (m, 4H), 7,42 (t, *J* = 8 Hz, 1H), 6,96-6,73 (m, 2H), 6,18 (d, *J* = 8 Hz, H), 6,17 (s,

854

2H), 5,30 (s, 2H) ESHRMS m/z 431,0210 (M+H $C_{20}H_{14}BrF_2N_2O_2$ requiere 431,0201

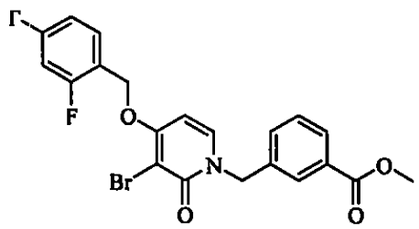
Ejemplo 99



1-[(2-(aminometil)bencil)]-3-bromo-4-[(2,4-difluorobenciloxi]1*H*-piridin-2-ona

A una disolución de 2-[3-bromo-4-(2,4-difluorobenciloxi)-2-oxo-2*H*-piridin-1-ilmetil]-benzonitrilo (0,11 g, 0,25 mmol) en THF (3 ml) se agrego $BH_3$ DMS (0,25 ml de una disolución de 2,0 M en THF, 0,5 mmol) y la mezcla de reaccion se agito a 70 °C durante 1 hora La mezcla de reaccion se enfrió hasta 0 °C durante 1 hora y la reacción se enfrio repentinamente con MeOH El disolvente se eliminó bajo una presión reducida y el residuo se dividió en 2N NaOH y EtOAc La disolucion organica se lavo con salmuera, se seco ($MgSO_4$), se filtró y se concentró bajo una presion reducida La purificacion por cromatografia en columna rapida (silice, eluyente cloruro de metileno a 90 9 1 cloruro de metileno/metanol/amoniaco) proporciono 1-[(2-aminometil)bencil]-3-bromo-4-(2,4-difluorobenciloxi) - 1*H*-piridin-2-ona como un solido blanco (0,15 g, al 48%) $^1H$ NMR (300 MHz, $CDCl_3$) δ 7,55 (aprox q, $J$ = 8 Hz, 1H), 7,40-7,26 (m, 4H), 7,14 (d, $J$ = 8 Hz, 1H), 6,94 (td, $J$ = 8, 2 Hz, 1H), 6,85 (td, $J$ = 8, 2 Hz, 1H), 6,08 (d, $J$ = 8 Hz, 1H), 5,31 (s, 2H), 5,21 (s, 2H) 4,03 (s, 2H) ESHRMS m/z 435,0517 (M+H $C_{20}H_{18}BrF_2N_2O_2$ requiere 435,0514)

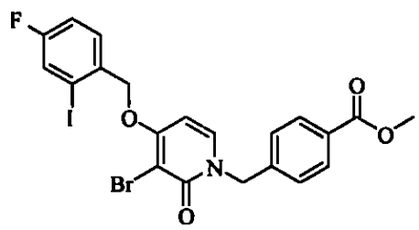
Ejemplo 100



3-[3-bromo-4-(2,4-difluorobenciloxi)-2-oxo-2*H*-piridin-1-ilmetil]benzoato de metilo

El compuesto del titulo se preparó mediante un procedimiento similar al descrito para el Ejemplo 74 (0,05 g, al 11%) mp 115-117 °C, $^1$H NMR (300 MHz, $CDCl_3$) δ 8,15-7,95 (m, 2H), 7,65-7,50 (m, 2H), 7,45-7,40 (m, 1H), 7,32 (d, *J* = 6 Hz, 1H), 7,00-6,80 (m, 2H), 6,12 (d, *J* = 9 Hz, 1H), 5,21 (s, 2H), 5 20 (s, 2H), 3,92 (s, 3H) ESHRMS m/z 464,0292 (M+H $C_{21}H_{17}BrF_2NO_4$ requiere 464,0303)

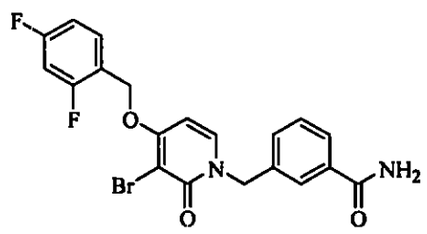
Ejemplo 101



4-[3-bromo-4-(2,4-difluorobenciloxi)-2-oxo-2*H*-piridin-1-ilmetil]-benzoato de metilo

El compuesto del titulo se preparo mediante un procedimiento similar al descrito para el Ejemplo 74 (0,17 g, al 46%) mp136-139 °C, $^1$H NMR (300 MHz, $CDCl_3$) δ 8,01 (d, *J* = 8 Hz, 2H), 7,60-7,51 (m, 1H), 7,37 (d, *J* = 8 Hz, 2H), 7,29-7,26 (m, 1H), 6,93 (td, *J* = 9, 2 Hz, 1H), 6,84 (td, *J* = 9, 2 Hz, 1H), 6,13 (d, *J* = 8 Hz, 1H), 5,23 (s, 4H), 3,91 (s, 3H) ESHRMS m/z 464,0306 (M+H $C_{21}H_{17}BrF_2NO_2$ requiere 464,0304)

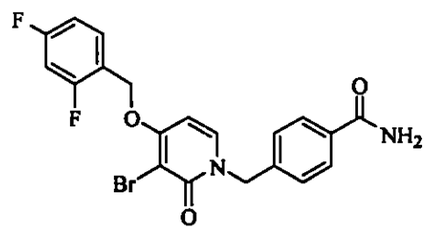
Ejemplo 102



3-[3-bromo-4-(2,4-difluorobenciloxi)-2-oxo-2*H*-piridin-1-ilmetil]benzamida

Se calentó a 75 °C durante 16 horas un tubo que contenia una disolución de 3-[3-bromo-4-(2,4-difluorobenciloxi)-2-oxo-2*H*-piridin-1-ilmetil]benzoato de metilo (0,1 g, 0,21 mmol) y $NH_3$ (3 ml de una disolucion de 7 N en MeOH, 21 mmol) La mezcla de reaccion se enfrió a temperatura ambiente y el disolvente se elimino bajo una presion reducida La trituracion con $Et_2O$/MeOH produjo un solido blanco (0,06 g, al 64%) mp 198-201 °C, $^1H$ NMR (300 MHz, DMSO-$d_6$) δ 8,02-8,00 (m, 2H), 7,85-7,75 (m, 2H), 7,70-7,60 (m, 1H), 7,45-7,30 (m, 4H), 7,17 (t, $J$ = 3 Hz, 1H), 6,60 (d, $J$ = 9 Hz, 1H), 5,32 (s, 2H), 5,18 (s, 2H) ESHRMS m/z 449,0295 (M+H $C_{20}H_{16}BrF_2N_2O_3$ requiere 449,0307)

Ejemplo 103



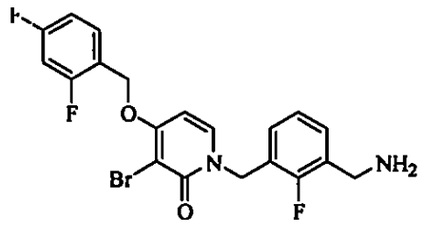
4-[3-bromo-4-(2,4-difluorobenciloxi)-2-oxo-2*H*-piridin-1-ilmetil]benzamida

El compuesto del titulo se preparo mediante un procedimiento similar al descrito para el Ejemplo 102 del Ejemplo 101 (0,04 g, al 12%) mp 235-238 °C, $^1H$ NMR (300 MHz, DMSO-$d_6$) δ 8,00 (d, $J$ = 8 Hz, 1H), 7,94 (br s, 1H),

857

7,78 (d, $J$ = 8 Hz, 1H), 7,64 (aprox q, $J$ = 8 Hz, 1H), 7,38-7,30(m, 4H), 7,17 (td, $J$ = 6, 2 Hz, 1H), 6,60 (d, $J$ = 9 Hz, 1H), 5,27 (s, 2H), 5,14 (s, 2H) ESHRMS m/z 449,0291 (M+H $C_{20}H_{16}BrF_2N_2O_3$ requiere 449,0307)

Ejemplo 104




1-(3-(aminometil-2-fluorobencil)-3-bromo-4-(2,4-difluorobenciloxi)1*H*-piridin-2-ona

Etapa 1 Preparacion de 3-bromo-1-(3-bromometil-2-fluorobencil)-4-(2,4-difluoro-benciloxi)-1*H*-piridin-2-ona

A una disolucion de 3-bromo-4-(2,4-difluorobenciloxi)-1*H*-piridin-2-ona (de la Etapa 3, Ejemplo 74) (0,3 g, 0,95 mmol) en DMF (26 ml) se agrego $K_2CO_3$ (0,26 g, 1,9 mmol) y 2,6-bis(bromometil)fluorobenceno (1,6 g, 5,7 mmol) y la mezcla de reacción se agitó a 110 °C durante 3 horas La mezcla de reacción se enfrio a temperatura ambiente y se elimino el disolvente bajo una presión reducida El residuo se diluyó con una disolucion acuosa de salmuera al 50% y la capa acuosa se extrajo con EtOAc (3 x 50 ml) Los materiales organicos combinados se lavaron con agua, se secaron ($Na_2SO_4$), se filtraron y el disolvente se eliminó bajo una presion reducida La purificacion por cromatografia en columna rápida (sílice, eluyente 99 1 a 95 5 cloruro de metileno/metanol) proporciono 3-bromo-1-(3-bromometil-2-fluorobencil)-4-(2,4-difluorobenciloxi)-1*H*-piridin-2-ona como un solido blanquecino (0,24 g, al 49%) $^1$H NMR (300 MHz, $CDCl_3$) δ 7,55-7,40 (m, 3H), 7,35-7,25 (m,

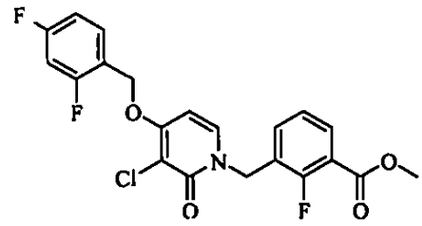
858

1H), 7,10-7,05 (m, 1H), 7,00-6,80 (m, 2H), 6,14 (d, $J$ = 6 Hz, 1H), 5,22 (s, 2H), 5,19 (s, 2H), 4,50 (s, 2H)

Etapa 2 Preparacion de 1-(3-aminometil-2-fluorobencil)-3-bromo-4-(2,4-difluoro-benciloxi)-1*H*-piridin-2-ona

Se calentó a 80 °C durante 1 hora un tubo sellado que contenía una disolucion de 3-bromo-1-1(3-bromometil-2-fluorobencil)-4-(2,4-difluorobenciloxi)-1*H*-piridin-2-ona (0,24 g, 0,45 mmol) y $NH_3$ (24 ml de una disolucion de 7 N en MeOH, 168 mmol) La mezcla de reaccion se enfrio hasta temperatura ambiente y el disolvente se elimino bajo una presión reducida La purificacion por cromatografia en columna rapida (sílice, eluyente 99,5 0,5 a 96 4 cloruro de metileno/metanol) proporciono un sólido blanco (0,12 g, al 60%) mp 160-163 °C, $^1H$ NMR (300 MHz, $CDCl_3$) δ 7,46-7,45 (m, 1H), 7,44-7,35 (m, 2H), 7,34-7,26 (m, 1 H), 7,15-7,05 (m, 1H), 6,95-6,80 (m, 2H), 6,11 (d, $J$ = 9 Hz, 1H), 5,21 (s, 2H), 5,19 (s, 2H), 3,90 (s, 2H) ESHRMS m/z 453,0442 (M+H $C_{20}H_{17}BrF_3N_2O_2$ requiere 453,0420)

Ejemplo 105




3-[3-cloro-4-(2,4-difluorobenciloxi)-2-oxo-2*H*-piridin-1-ilmetil]benzoato de metilo

Etapa 1 Preparación de 2-fluoro-3-metilbenzoato de metilo

A una disolucion de ácido 2-fluoro-3-metil benzoico (3,57 g, 23 mmol) en MeOH (40 ml) se agregó ácido sulfurico concentrado (23 ml) y la mezcla de reacción se calento a

reflujo durante 12 horas La mezcla de reacción se enfrio, se elimino el disolvente bajo una presión reducida y el residuo se disolvio en EtOAc La disolucion organica se lavo con una disolucion saturada de $NaHCO_3$ y luego con salmuera, se secó ($Na_2SO_4$), se filtro y se concentro bajo una presion reducida para proporcionar 2-fluoro-3-metilbenzoato de metilo como un aceite de color amarillo (3,2 g, al 82%) $^1H$ NMR (300 MHz, $CDCl_3$) δ 7,76-7,71 (m, 1H), 7,39-7,34 (m, 1H), 7,08 (t, *J* = 8 Hz, 1H), 3,98 (s, 3H), 2,31 (d, *J* = 3 Hz, 3H)

Etapa 2 Preparacion de 3-bromometil-2-fluorobenzoato de metilo

A una mezcla de 2-fluoro-3-metilbenzoato (1,5 g, 8,9 mmol) y N-bromosuccinimida (1,67 g, 9,4 mmol) se agrego tetracloruro de carbono (24 ml) y peroxido de benzoilo (5 mg) y la mezcla se calento a reflujo durante 16 horas La mezcla de reaccion se enfrio, se filtro y se concentro bajo una presion reducida La purificacion por cromatografia en columna rapida (silice, eluyente 5 95 a 60 40 EtOAc/hexanos) proporcionó 3-bromometil-2-fluorobenzoato de metilo como un solido de color amarillo claro (0,91 g, al 41%) $^1H$ NMR (300 MHz, $CDCl_3$) δ 7,93-7,88 (m, 1H), 7,61-7,56 (m, 1H), 7,20 (t, *J* = 8 Hz, 1H), 4,53 (d, *J* = 3 Hz, 2H), 3,94 (s, 3H)

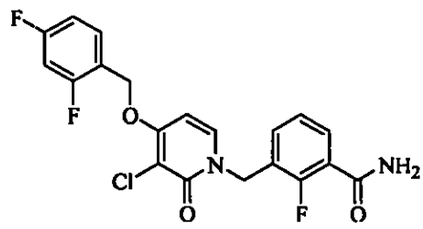
Etapa 3 Preparación de 3-[3-cloro-4-(2,4-difluorobenciloxi)-2-oxo-2*H*-piridin-1-ilmetil]-2-fluorobenzoato de metilo

Se preparo 3-[3-cloro-4-(2,4-difluorobenciloxi)-2-oxo-2*H*-piridin-1-ilmetil]-2-fluorobenzoato de metilo mediante un procedimiento similar al descrito para el Ejemplo 81 (0,33 g, al 69%) mp 171-174 °C, $^1H$ NMR (300 MHz, $CDCl_3$) δ 7,89-7,84 (m, 2H), 7,60-7,45 (m, 2H), 7,25-7,15 (m, 1H), 7,00-6,80 (m, 2H), 6 17 (d, *J* = 6,0 Hz, 1H), 5,21 (s, 2H),

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5,19 (s, 2H), 3,93 (s, 3H) ESHRMS m/z 438,0747 (M+H $C_{21}H_{16}ClF_3NO_4$ requiere 438,0714)

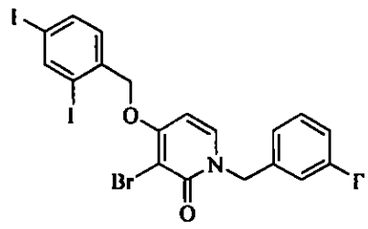
Ejemplo 106



3-[3-cloro-4-(2,4-difluorobenciloxi)-2-oxo-2H-piridin-1-ilmetil]-2-fluoro-benzamida

El compuesto del titulo se preparó mediante un procedimiento similar al descrito para el Ejemplo 99 (0,15 g, al 62%) mp 252-254 °C, $^1$H NMR (300 MHz, DMSO-$d_6$) δ 8,04 (d, $J$ = 8 Hz, 1H), 7,92 (br s, 1H), 7,79-7,65 (m, 3H), 7,49-7,48 (m, 1H), 7,37-7,31 (m, 3H), 6,80 (d, $J$ = 8 Hz, 1H), 5,46 (s, 2H), 5 33 (s, 2H) ESHRMS m/z 423,0710 (M+H $C_{20}H_{15}ClF_3N_2O_3$ requiere 423,0718)

Ejemplo 107



3-bromo-4-(2,4-difluorobenciloxi)-1-(3-fluorobencil)-1*H*-piridin-2-ona

Etapa 1 Preparacion de 4-(benciloxi)-1-(3-fluorobencil)-1*H*-piridin-2-ona

A una disolución de 4-benciloxi-1*H*-piridin-2-ona (1,0 g, 5 mmol) y $K_2CO_3$ (2,0 g, 9,9 mmol) en DMF (30 ml) se

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agrego bromuro de 3-fluorobencilo (1,4 g, 7,5 mmol) y la mezcla de reaccion se calento a 110 °C durante 3 horas La mezcla de reaccion se enfrio a temperatura ambiente y se dividió en EtOAc y agua La disolucion organica se lavó con agua y luego con salmuera, se secó ($Na_2SO_4$), se filtro y se concentro bajo una presion reducida La purificacion por cromatografia en columna rápida (silice, eluyente 97 3 a 93 7 cloruro de metileno/metanol) proporcionó 4-benciloxi-1-(3-fluorobencil)-1*H*-piridin-2-ona (1,04 g, al 67%) $^1$H NMR (300 MHz, $CDCl_3$) δ 7,45-7,25 (m, 5H), 7,13 (d, $J$ = 8 Hz, 1H), 7,10-6,90 (m, 3H), 6,10-5,95 (m, 2H), 5,07 (s, 2H), 5,00 (s, 2H)

Etapa 2 Preparacion de 1-(3-fluorobencil)-4-hidroxi-1*H*-piridin-2-ona

A una disolucion de 4-benciloxi-1-(3-fluorobenciloxi)-1*H*-piridin-2-ona (1,79 g, 5,8 mmol) en EtO (50 ml) se agregó Pd/C al 10% (0,4 g) y la mezcla de reacción se agito bajo una atmosfera de hidrógeno durante 1,5 horas La mezcla de reacción se filtro a traves de diatomita y se concentró bajo una presion reducida para producir 1-(3-fluorobencil)-4-hidroxi-1*H*-piridin-2-ona (0,92 g, al 72%) $^1$H NMR (300 MHz, $CDCl_3$) δ 7,55 (d, $J$ = 6 Hz, 1H), 7,40-7,30 (m, 1H), 7,10-6,95 (m, 3H), 6,07 (dd, $J$ = 6, 3 Hz, 1H), 5,85 (d, $J$ = 3 Hz, 1H), 5,11 (s, 2H)

Etapa 3 Preparacion de 3-bromo-1-(3-fluorobencil)-4-hidroxi-1*H*-piridin-2-ona

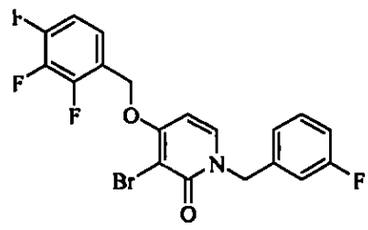
A una disolucion helada de 1-(3-fluorobencil)-4-hidroxi-1*H*-piridin-2-ona (0,67 g, 3,1 mmol) en AcOH (5,7 ml) se agrego una disolucion de bromo (0,52 g, 3,24 mmol) en AcOH (10,8 ml), y la mezcla de reacción se agitó durante 5 minutos La mezcla de reaccion se entibió a temperatura ambiente y se concentro bajo una presión reducida para producir 3-bromo-1-(3-fluorobencil)-4-hidroxi-1*H*-piridin-2-

ona como un sólido de color amarillo (1,07 g, en crudo) $^1$H NMR (500 MHz, MeOD) ε 7,64 (d, *J* = 8 Hz, 1H), 7,35-7,30 (m, 1H), 7,05-6,90 (m, 3H), 6,20 (d, *J* = 8 Hz, 1H), 5,18 (s, 2H)

Etapa 4 Preparación de 3-bromo-4-(2,4-difluorobenciloxi)-1-(3-fluorobencil)-1*H*-piridin-2-ona

A una disolucion de 3-bromo-1-(3-fluorobencil)-4-hidroxi-1*H*-piridin-2-ona (0,20 g, 0,67 mmol) y $K_2CO_3$ (0,27 g, 1,34 mmol) en acetona (10 ml) se agregó bromuro de 2,4-difluorobencilo (0,16 g, 0,8 mmol) y la mezcla de reacción se calento a reflujo durante 1 hora La mezcla de reacción se enfrio a temperatura ambiente, se concentro bajo una presión reducida y el residuo se disolvio en EtOAc La disolucion organica se lavó con agua y luego con salmuera, se secó ($Na_2SO_4$), se filtró y se concentro bajo una presión reducida $^1$H NMR (300 MHz, $CDCl_3$) δ 7,65-7,55 (m, 1H), 7,40-7,25 (m, 2H), 7,15-6,80 (m, 5H), 6,14 (d, *J* = 8 Hz, 1H), 5,22 (s, 2H), 5,16 (s, 2H) ESHRMS m/z 424,0159 (M+H $C_{19}H_{14}BrF_3NO_2$ requiere 424,0155)

Ejemplo 108

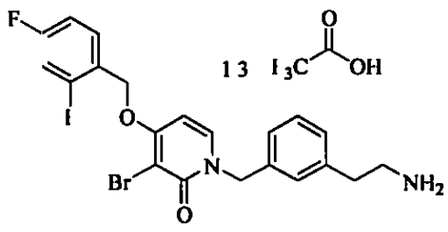



3-bromo-1-(3-fluorobencil)-4-(2,3,4-fluorobenciloxi)-1*H*-piridin-2-ona

El compuesto del titulo se preparo mediante un procedimiento similar al descrito para el Ejemplo 107 (0,09 g, al 39%) mp 176-178 °C, $^1$H NMR (300 MHz, $CDCl_3$) δ

7,40-7,25 (m, 4H), 7,11-6,98 (m, 4H), 6,11 (d, $J$ = 9 Hz, 1H), 5,23 (s, 2H), 5,16 (s, 2H) ESHRMS m/z 442,0060 (M+H $C_{19}H_{13}BrF_4NO_2$ requiere 442,0061)

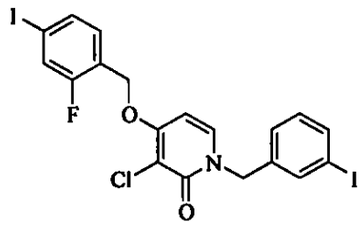
Ejemplo 109



1-[3-(2-(aminometil)bencil)]-3-bromo-4-(2,4-difluorobenciloxi)-1*H*-piridin-2-ona

El compuesto del titulo se preparo a partir del compuesto del Ejemplo 97 mediante un procedimiento similar al descrito para el Ejemplo 99,como la sal de TFA (0,13 g, al 33%) mp 70-74 °C, $^1$H NMR (300 MHz, DMSO-$d_6$) δ 8,21 (br s, 1H), 6,60-6,50 (m, 1H), 7,52 (d, $J$ = 6 Hz, 1H), 7,30-7,10 (m, 3H), 7,01 (d, $J$ = 9 Hz, 1H), 6,94-6,85 (m, 2H), 6,20 (d, $J$ = 6 Hz, 1H), 5,20 (s, 2H), 5,05 (s, 2H), 3,23 (br s, 2H), 2,97 (t, $J$ = 8 Hz, 2H), 2,05 (br s, 2H) ESHRMS m/z 449,0698 (M+H $C_{21}H_{20}BrF_2N_2O_2$ requiere 449,0671)

Ejemplo 110



3-cloro-4-(2,4-difluorobenciloxi)-1-(3-fluorobencil)-1*H*-piridin-2-ona

Etapa 1 Preparación de 4-(2,4-difluorobenciloxi)-1-(3-fluorobencil)-1*H*-piridin-2-ona

A una disolucion de 1-(3-fluorobencil)-4-hidroxi-1*H*-piridin-2-ona (de la Etapa 2, Ejemplo 107) (0,92 g, 4,2 mmol) y $K_2CO_3$ (1,2 g, 8,4 mmol) en acetona (62 ml) se agregó bromuro de 2,4-difluorobencilo (1,3 g, 6,3 mmol) y la mezcla de reaccior se calentó a reflujo durante 3 horas La mezcla de reaccion se enfrió a temperatura ambiente, se concentro bajo una presión reducida y el residuo se dividió en agua y EtOAc La disolución orgánica se lavo con salmuera, se secó ($Na_2SO_4$), se filtro y se concentro bajo una presión reducida La purificacion por cromatografía en columna rapida (silice, eluyente cloruro de metileno a 95 5 cloruro de metileno/metanol) proporcionó 4-(2,4-difluorobenciloxi)1-1(3-fluorbencil)-1*H*-piridin-2-ona como un solido blanco (1,21 g, al 84%) $^1$H NMR (300 MHz, $CDCl_3$) δ 7,45-7,20 (m, 2H), 7,14 (d, *J* = 8 Hz, 1H), 7,05-6,75 (m, 5H), 6,05 (d, *J* = 3 Hz, 1H), 5,95 (dd, *J* = 5, 3 Hz, 1H), 5,08 (s, 2H), 5,00 (s, 2H)

Etapa 2 Preparacion de 3-cloro-4-(2,4-difluorobenciloxi)-1-(3-fluorobencil)-1*H*-piridin-2-ona

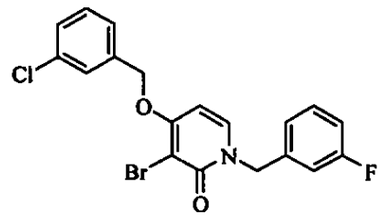
A una disolucion de 4-(2,4-difluorobenciloxi)-1-(3fluorobencil)-1*H*-piridin-2-ona (0,15 g, 0,4 mmol) en AcOH (3 ml) se agrego N-clorosuccinimida (70 mg, 0,5 mmol) y la mezcla de reacción se calento a reflujo durante 10 minutos La mezcla de reacción se enfrio a temperatura ambiente y se eliminó el disolvente bajo una presión reducida $^1$H NMR (300 MHz, $CDCl_3$) δ 7,60-7,50 (m, 1H), 7,45-7,20 (m, 2H), 7,10-6,80 (m, 5H), 6,16 (d, *J* = 8 Hz, 1H), 5,21 (s, 2H), 5,15 (s, 2H) ESHRMS m/z 380,0641 (M+H $C_{19}H_{14}ClF_3NO_2$ requiere 480,0660)

865

Ejemplos 111-123

Los compuestos de los siguiente ejemplos se prepararon mediante procedimientos similares a los que se describen para el Ejemplo 107 Los rendimientos y los datos analiticos de los compuestos del titulo se detallan a continuacion

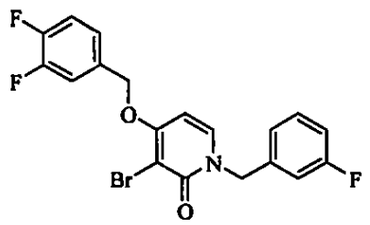
Ejemplo 111




3-bromo-4-(3-clorobenciloxi)-1-(3-fluorobencil)-1*H*-piridin-2-ona

El compuesto del titulo se preparo mediante un procedimiento similar al descrito para el Ejemplo 107 (0,12 g, al 42%) mp 149-153 °C, $^1$H NMR (300 MHz, $CDCl_3$) δ 7,40-7,23 (m, 6H), 7,09 (d, *J* = 8 Hz, 1H), 7,05-6,95 (m, 2H), 6,05 (d, *J* = 8 Hz, 1H), 5,19 (s, 2H), 5,14 (s, 2H) ESMS m/z M+H 442

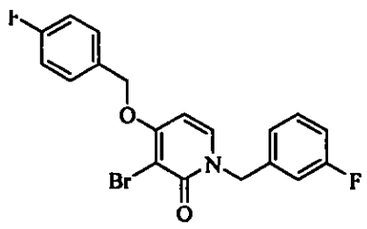
Ejemplo 112



3-bromo-4-(3,4-cıfluorobencıloxı)-1-(3-fluorobencıl)-1*H*-pırıdın-2-ona

El compuesto del tıtulo se preparo medıante un procedımıento sımılar al descrıto para el Ejemplo 107 (0,08 g, al 48%) mp 172-174 °C, $^1$H NMR (300 MHz, $CDCl_3$) δ 7,40-6,95 (m, 8H), 6,05 (d, *J* = 6 Hz, 1H), 5,16 (s, 4H) ESHRMS m/z 424,0111 (M+H $C_{19}H_{14}BrF_3NO_2$ requıere 424,0155)

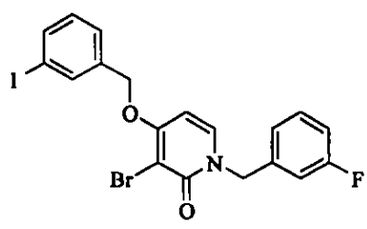
Ejemplo 113



3-bromo-1-(3-fluorobencıl)-4-(4-fluorobencıloxı)-1*H*-pırıdın-2-ona

El compuesto del tıtulo se preparó medıante un procedımıento sımılar al descrıto para el Ejemplo 107 (0,07 g, al 35%) mp 180-183 °C, $^1$H NMR (300 MHz, $CDCl_3$) δ 7,50-7,25 (m, 5H), 7,15-7,00 (m, 4H), 6,07 (d, *J* = 8 Hz, 1H), 5,18 (s, 2H), 5,14 (s, 2H) ESHRMS m/z 406,0258 (M+H $C_{19}H_{15}BrF_2NO_2$ requıere 406,0249)

Ejemplo 114



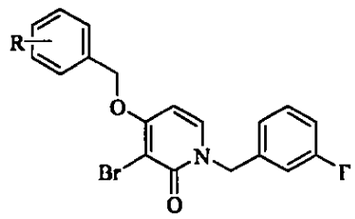
867

3-bromo-1-(3-fluorobencil)-4-(3-fluorobenciloxi)-1*H*-piridin-2-ona

A una disolución helada de 1-(3-fluorobencil)-4-(3-fluorobenciloxi)-1*H*-piridin-2-ona (0,14 g, 0,43 mmol) en AcOH (2 ml) se agregó una disolucion de bromo (72 ml, 0,45 mmol) en AcOH (1 ml), y la mezcla de reaccion se agitó durante 5 minutos La mezcla de reaccion se entibio a temperatura ambiente y el disolvente se elimino bajo una presion reducida $^1$H NMR (300 MHz, $CDCl_3$) δ 7,45-6,95 (m, 9H), 6,05 (d, *J* = 8 Hz, 1H), 5,21 (s, 2H), 5,14 (s, 2H) ESHRMS m/z 406,0254 (M+H $C_{19}H_{15}BrF_2NO_2$ requiere 406,0249)

Ejemplos 115-123

Los compuestos de los Ejemplos 115-123 se prepararon esencialmente de acuerdo con los procedimientos establecidos anteriormente para el Ejemplo 107




| Ejemplo N° | R | FM | M+H Requiere | ESHRMS m/z |
|---|---|---|---|---|
| Ej 115 | 3-metoxi | $C_{20}H_{17}BrFNO_3$ | 418,0449 | 418,0427 |
| Ej 116 | 4-*terc*-butilo | $C_{23}H_{23}BrFNO_2$ | 444,0969 | 444,0977 |
| Ej 117 | 3-metilo | $C_{20}H_{17}BrFNO_2$ | 402,0499 | 402,0513 |
| Ej 118 | 4-trifluorometilo | $C_{20}H_{14}BrF_4NO_2$ | 456,0217 | 456,0210 |
| Ej 119 | 4-ciano | $C_{20}H_{14}BrFN_2O_2$ | 413,0295 | 413,0313 |
| Ej 120 | 2-metilo | $C_{20}H_{17}BrFNO_2$ | 402,0499 | 402,0502 |
| Ej 121 | 2-fenilo | $C_{25}H_{19}BrFNO_2$ | 464,0656 | 464,0654 |
| Ej 122 | 4-metoxi | $C_{20}H_{17}BrFNO_3$ | 418,0449 | 418,0455 |

868

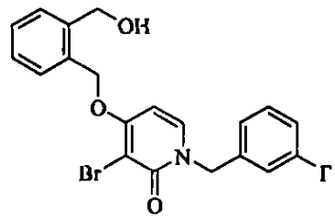
| | | | | | |
|---|---|---|---|---|---|
| Ej 123 | 2-$CO_2CH_3$ | | $C_{21}H_{17}BrFNO_4$ | 446,0398 | 446,0403 |

Caracterización por NMR de los compuestos de los Ejemplos 115-123

| Ejemplo N° | Datos de NMR |
|---|---|
| Ej 115 | $^1$H NMR (300 MHz, $CDCl_3$) δ 7,35-7,20 (m, 4H), 7,15-6,85 (m, 5H), 6,07 (d, *J* = 8 Hz, 1H), 5,21 (s, 2H), 5,13 (s, 2H), 3,82 (s, 3H) |
| Ej 116 | $^1$H NMR (300 MHz, $CDCl_3$) δ 7,45-7,20 (m, 4H), 7,10-6,95 (m, 3H), 6,11 (d, *J* = 8 Hz, 1H), 5,19 (s, 2H), 5,14 (s, 2H), 1,32 (s, 9H) |
| Ej 117 | $^1$H NMR (300 MHz, $CDCl_3$) δ 7,40-6,90 (m, 9H), 6,08 (d, *J* = 8 H , 1H), 5,19 (s, 2H), 5,14 (s, 2H), 2,37 (s, 3H) |
| Ej 118 | $^1$H NMR (300 MHz, $CDCl_3$) δ 7,67-7,53 (m, 4H), 7,31-7,24 (m, 2H), 7,09-6,98 (m, 3H), 6,04 (d, *J* = 8 Hz, 1H), 5,26 (s, 2H), 5,14 (s, 2H) |
| Ej 119 | $^1$H NMR (300 MHz, $CDCl_3$) δ 7,71 (dd, *J* = 8, 2 Hz, 2H), 7,58-7,55 (m, 2H), 7,29-7,25 (m, 2H), 7,09 (d, *J* = 8 H , 1H), 7,03-6,98 (m, 2H), 6,03 (dd, *J* = 8, 2 Hz, H), 5,26 (s, 2H), 5,15 (s, 2H) |
| Ej 120 | $^1$H NMR (300 MHz, $CDCl_3$) δ 7,45-6,90 (m, 9H), 6,15-6,10 (m, 1H), 5,18 (s, 2H), 5,15 (s, 2H), 2,38 (s, 3H) |
| Ej 121 | $^1$H NMR (300 MHz, $CDCl_3$) δ 7,70-7,65 (m, 1H), 7,55-7,25 (m, 9H) 7,14 (d, *J* = 8 Hz, 1H), 7,10-6,95 (m, 3H), 5,81 (d, *J* = 8 Hz, 1H), 5,12 (s, 2H), 5,08 (s, 2H) |
| Ej 122 | $^1$H NMR (300 MHz, $CDCl_3$) δ 7,40-7,25 (m, 3H), 7,15-6,90 (m, 6H), 6,15-6,10 (m, 1H), 5,16 (s, 2H), 5,14 (s, 2H), 3,82 (s, 3H) |
| Ej 123 | $^1$H NMR (300 MHz, $CDCl_3$) δ 8,06 (dd, J = 8, 1 Hz, 1H), 7,87 (d, J = 8 Hz, 1H), 7,70-7,60- (m, 1H), 7,50-7,25 (m, 3H), 7,09 (d, J = 8 Hz, 1H), 7,05-6,95 (m, 2H), 6,19 (d, J = 8 Hz, 1H), 5,65 (s, 2H), 5,16 (s, 2H), 3,91 (s, 3H) |

Ejemplo 124

869

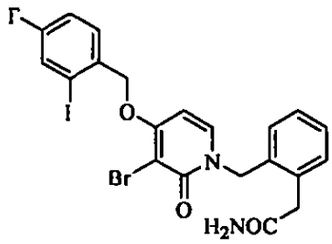



3-bromo-1-(3-fluorobencil)-4-(2-hidroximetilbenciloxi)-1*H*-piridin-2-ona

Etapa 1 Preparación de 3-bromo-1-(3-fluorobencil)-4-(2-hidroximetilbenciloxi)-1*H*-piridin-2-ona

A una disolucion helada de 2-[3-bromo-1-(3-fluorobencil)-2-oxo-1,2-dihidro-piridin-4-iloximetil]benzoato de metilo (0,12 g, 0,28 mmol) en THF (5 ml) se agregó $LiBH_4$ (0,15 ml de una disolución de 2,0 M en THF, 0,30 mmol) y la mezcla de reaccion se calentó a reflujo durante 5 horas La mezcla de reacción se enfrio a temperatura ambiente, se elimino el disolvente bajo una presion reducida y el residuo se disolvio en EtOAc La disolucion organica se lavó con salmuera, se seco ($Na_2SO_4$), se filtró y se concentro bajo una presión reducida $^1H$ NMR (300 MHz, DMSO-$d_6$) δ 7,98 (d, $J$ = 8 Hz, 1H), 7,46-7,28 (m, 5H), 7,15-7,10 (m, 3H), 6,56 (d, $J$ = 8 Hz, 1H), 5,35 (s, 2H), 5,25 (br s, 1H), 5,14 (s, 2H) ESHRMS m/z 418,0453 (M+H $C_{20}H_{18}BrFNO_3$ requiere 418,0449)

Ejemplo 126



870

2-{2-[3-bromo-4-(2,4-difluorobenciloxi)-2-oxo-2H-piridin-1-ilmetil]-fenil}acetamida,

Etapa 1 Preparacion de acido (2-bromometilfenil)acetico

Una disolucion de isocroman-3-ona (1,5 g, 10 mmol) en HBr al 30% en acido acético (13 ml) se agito a temperatura ambiente durante 2 horas y a 70 °C durante 1 hora La mezcla de reaccion se enfrio hasta la temperatura ambiente y se vertió en agua helada El precipitado se recogio para proporcionar acido (2-bromometilfenil)acético como un solido blanquecino (?,15 g, al 93%) $^1$H NMR (300 MHz, DMSO-$d_6$) δ 7,45-7,23 (m, 4H), 4,73 (s, 2H), 3,73 (s, 2H)

Etapa 2 Preparacion de (2-bromometilfenil)acetato de metilo

A una disolución helada de ácido (2-bromometilfenil)acetico (1 g, 4,4 mmol) en THF (2,4 ml) se agregó trimetisilildiazometano (3 ml de una disolucion de 2 M en hexanos, 6 mmol) y se agitó la mezcla de reaccion durante 14 horas La mezcla de reacción se enfrió repentinamente con AcOH y el disolvente se eliminó bajo una presion reducida La purificación por cromatografia en columna rapida (silice, eluyente 98 2 a 94 6 cloruro de metileno/hexanos) proporcionó (2-bromometilfenil)acetato de metilo como un solido de color amarillo claro (0,34 g, al 32%) $^1$H NMR (300 MHz, $CDCl_3$) δ 7,40-7,20 (m, 4H), 4,59 (s, 2H), 3,81 (s 2H), 3,'1 (s, 3H)

Etapa 3 Preparacion de {2-[3-bromo-4-(2,4-difluorobenciloxi)-2-oxo-2*H*-piridin-1-ilmetil]fenil}acetato de metilo

Se preparo {2-[3-bromo-4-(2,4-difluorobenciloxi)-2-oxo-2*H*-piridin-1-ilmetil]-fenil}acetato de metilo mediante un procedimiento similar al descrito para el Ejemplo 74 (0,41 g, al 68%) $^1$H NMR (300 MHz, $CDCl_3$) δ 7,55-6,81 (m, 8

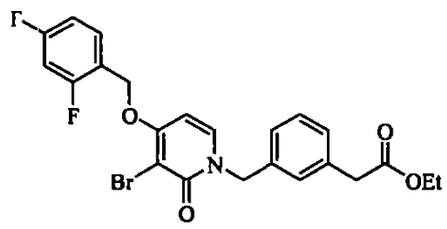
871

H), 6,10 (d, $J$ = 6 Hz, 1H), 5,20 (s, 4 H), 3,78 (s, 2H), 3,60 (s, 3H)

Etapa 4 Preparación de 2-{2-[3-bromo-4-(2,4-difluorobenciloxi)-2-oxo-2*H*-piridin-1-ilmetil]fenil}acetamida

Se preparó 2-{2-[3-bromo-4-(2,4-difluorobenciloxi)-2-oxo-2*H*-piridin-1-ilmetil]fenil}-acetamida mediante un procedimiento similar al descrito para el Ejemplo 102 (0,07 g, al 72%) mp 178-183 °C, $^1$H NMR (300 MHz, DMSO-$d_6$) δ 7,89 (d, $J$ = 8 Hz, 1H), 7,66 (d, $J$ = 9 Hz, 1 H), 7,54 (br s, 1H), 7,35 (br s, 1H), 7,30-7,15 (m, 4H), 6,98 (br s, 1H), 6,85 (d, $J$ = 7 Hz, 1H), 6,60 (d, $J$ = 8 Hz, 1H), 5,32 (s, 2H), 5,19 (s, 2H), 3,62 (s, 2H) ESHRMS m/z 463,0442 (M+H $C_{21}H_{18}BrF_2N_2O_3$ requiere 463,0463)

Ejemplo 127




{3-[3-bromo-4-(2,4-difluorobenciloxi)-2-oxo-2*H*-piridin-1-ilmetil]-fenil}acetato de etilo

Etapa 1 Preparación de (3-bromometilfenil)acetato de etilo

A una mezcla de éster etílico de acido *m*-tolilacetico (3,0 g, 16,8 mmol) y N-bromosuccinimida (3,0 g, 16,8 mmol) se agregó tetracloruro de carbono (45 ml) seguido de peróxido de benzoilo (5 mg) y la mezcla de reacción se calento a reflujo durante 16 horas La mezcla de reaccion se enfrió a temperatura ambiente, se filtro y se concentró

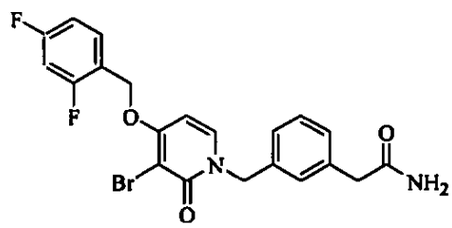
872

bajo una presion reducida La purificacion por cromatografia en columna rapida (silice, eluyente 5 95 a 2 3 EtOAc/hexanos) proporciono (3-bromometilfenil)acetato de etilo como un solido blanquecino (0,89 g, al 21%) $^1$H NMR (300 MHz, $CDCl_3$) δ 7,32-7,21 (m, 4H), 4,48 (s, 2H), 4,16 (q, $J$ = 6 Hz, 2H), 3,63, (s, 2H), 1,27 (t, $J$ = 6 Hz, 3H)

Etapa 2 Preparacion de {3-[3-bromo-4-(2,4-difluorobenciloxi)-2-oxo-2*H*-piridin-1-ilmetil]fenil}acetato de etilo

Se preparó {3-[3-bromo-4-(2,4-difluorobenciloxi)-2-oxo-2*H*-piridin-1-ilmetil]-fenil}acetato de etilo mediante un procedimiento similar al descrito para el Ejemplo 74 (0,27 g, al 69%) mp 95-98 °C, $^1$H NMR (300 MHz, $CDCl_3$) δ 7,65-7,55 (m, 1H), 7,40-7,20 (m, 5H), 7,00-6,80 (m, 2H), 6,09 (d, $J$ = 9 Hz, 1H), 5,21 (s, 2H), 5,16 (s, 2H), 4,14 (q, $J$ = 6 Hz, 2H), 3,60 (s, 2H), 1,25 (t, $J$ = 6 Hz, 3H) ESHRMS m/z 492,0655 (M+H $C_{23}H_{21}BrF_2NO_4$ requiere 435,0617)

Ejemplo 128



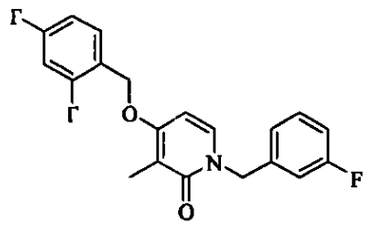

2-{3-[3-bromo-4-(2,4-difluorobenciloxi)-2-oxo-2*H*-piridin-1-ilmetil]-fenil}acetamida

El compuesto del titulo se preparo mediante un procedimiento similar al descrito para el Ejemplo 102 (0,07 g, al 28%) mp 164-167 °C, $^1$H NMR (300 MHz, DMSO-$d_6$) δ 7,96 (d, $J$ = 9 Hz, 1H), 7,70-7,60 (m, 1H), 7,60 (br s, 1H),

873

7,50-7,10 (m, 6H), 6,89 (br s, 1H), 6,58 (d, $J$ = 9 Hz, 1H), 5,31 (s, 2H), 5,12 (s, 2H), 3,32 (s, 2H) ESHRMS m/z 463,0485 (M+H $C_{21}H_{18}BrF_2N_2O_3$ requiere 463,0464)

Ejemplo 129



4-(2,4-difluorobenciloxi)-1-(3-fluorobencil)-3-metil-1*H*-piridin-2-ona

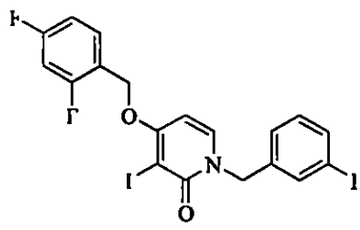
Etapa 1 Preparación de 4-(2,4-difluorobenciloxi)-1-(3-fluorobencil)-3-metil-1*H*-piridin-2-ona

A una disolución de 3-bromo-4-(2,4-fluorobenciloxi)-1-(3-fluorobencil)-1*H*-piridin-2-ona (Ejemplo 107) (0,14 g, 0,32 mmol), $K_2CO_3$ (88 mg, 6,4 mmol) y $Cs_2CO_2$ (0,10 g, 0,32 mmol) en dioxano (2 ml) se agregó $Pd(PPh_3)_4$ (18mg, 0,12 mmol) seguido de trimetilboroxina (40 mg, 0,32 mmol) La mezcla de reaccion se desgasificó, se purgo con argon y se calentó a reflujo durante 4 horas La mezcla de reacción se enfrio a temperatura ambiente y se dividio en agua y EtOAc La disolución organica se lavo con salmuera, se secó ($Na_2SO_4$), se filtró y se concentro bajo una presión reducida La purificacion por cromatografia en columna rapida (silice, eluyente cloruro de metileno a 97 3 cloruro de metileno/MeOH) proporciono 4-(2,4-difluorobenciloxi)1-1(3-fluorbencil)-3-metil-1*H*-piridin-2-ona como un solido blanco (0,09 g, al '9%) mp 127-129 °C, $^1$H NMR (300 MHz, $CDCl_3$) δ 7,50-7,40 (m, 1H), 7,35-7,25 (m, 1H), 7,17 (d, $J$ = 9 Hz, 1H), 7,06 (d, $J$ = 6 Hz, 1H), 7,00-6,80 (m, 4H), 6,12

824

(d, $J$ = 9 Hz, 1H), 5,12 (s, 4H), 2,07 (s, 3H) ESHRMS m/z 360,1180 (M+H $C_{20}H_{16}F_3NO_2$ requiere 360,1206)

Ejemplo 130



4-(2,4-difluorobenciloxi)-1-(3-fluorobencil)-3-yodo-1*H*-piridin-2-ona

Etapa 1 Preparacion de 4-(2,4-difluorobenciloxi)-1-(3-fluorobencil)-1*H*-piridin-2-ona

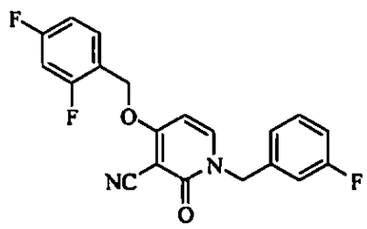
A una mezcla de 1-(3-fluorobencil)-4-hidroxi-1*H*-piridin-2-ona (de la Etapa 1, Ejemplo 110) (0,92 g, 4,2 mmol) y $K_2CO_3$ (1,15 g, 8,4 mmol) en acetona (62 ml) se agrego bromuro de 2 4-difluorobencilo (1,3 g, 6,3 mmol) y la mezcla de reacción se calento a reflujo durante 3 horas La mezcla de reacción se enfrió a temperatura ambiente, se concentró bajo una presion reducida y el residuo se disolvio en EtOAc La disolución orgánica se lavo con agua y luego con salmuera, se seco ($Na_2SO_4$), se filtró y se concentro bajo una presion reducida La purificacion por cromatografia en columna rapida (silice, eluyente cloruro de metileno a 95 5 cloruro de metileno/metanol) proporcionó 4-(2,4-difluorobenciloxi)1-1(3-fluorbencil)-1*H*-piridin-2-ona como un solido blanco (1,21 g, al 84%) $^1$H NMR (300 MHz, $CDCl_3$) δ 7,45-7,20 (m, 2H), 7,14 (d, $J$ = 8 Hz, 1H), 7,05-6,75 (m, 5H), 6,05 (d, $J$ = 3 Hz, 1H), 5,95 (dd, $J$ = 5, 3 Hz, 1H), 5,08 (s, 2H), 5,00 (s, 2H)

Etapa 2 Preparación de 4-(2,4-difluorobenciloxi)-1-(3-fluorobencil)-3-yodo-1*H*-piridin-2-ona

825

A una mezcla de 4-(2,4-difluorobenciloxi)-1-(3-fluorobencil)-1*H*-piridin-2-ona (0,15 g, 0,43 mmol) y N-yodosuccinimida (0,10 g, 0,46 mmol) en $CH_3CN$ (3 ml) se agregó ácido dicloroacético (13 mg, 0,10 mmol) y la mezcla de reaccion se calento a 60 °C durante 4 horas La mezcla de reaccion se enfrio a temperatura ambiente, se concentro bajo una presión reducida y el residuo se disolvió en cloruro de metileno La disolución orgánica se lavo con una disolucion saturada de $NaHCO_3$ y luego con salmuera, se secó ($Na_2SO_4$), se filtro y se concentró bajo una presion reducida La purificación por cromatografía en columna rapida (silice, eluyente 90 10 cloruro de metileno/hexanos a 99 1 cloruro de metileno/metanol) proporciono 4-(2,4-difluorobenciloxi)1-(3-fluorbencil)-3-yodo-1*H*-piridin-2-ona como un sólido blanco (0,15 g, al 77%) mp 164-167 °C, $^1H$ NMR (300 MHz, $CDCl_3$) δ 7,65-7,55 (m, 1H), 7,35-7,26 (m, 2H) 7,15-6,80 (m, 5H), 6,05 (d, *J* = 6 Hz, 1H), 5,22 (s, 2H), 5,16 (s, 2H) ESHRMS m/z 472,0033 (M+H $C_{19}H_{14}F_3INO_2$ requiere 472,0018)

Ejemplo 131




4-(2,4-difluorobenciloxi)-1-(3-fluorobencil)-2-oxo-1,2-dihidropiridina-3-carbonitrilo

Etapa 1 Preparación de 4-metoxi-2-oxo-1,2-dihidropiridina-3-carbonitrilo,

Una disolución de 2-(dimetilaminoetoximetileno)malononitrilo (1,97 g) en acido sulfurico concentrado (7,0 ml) se agitó a temperatura

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ambiente durante 6,5 horas La mezcla de reaccion se vertio en agua y el precipitado se recogio mediante filtracion $^1$H NMR (300 MHz, DMSO-$d_6$) δ 12,14 (br s, 1H), 7,79 (d, $J$ = 9 Hz, 1H), 6,35 (d, $J$ = 9 Hz, 1H), 3,98 (s, 3H)

Etapa 2 Preparacion de 1-(3-fluorobencil)-4-metoxi-2-oxo-1,2-dihidro-piridin-3-carbonitrilo

Se preparo 1-(3-fluorobencil)-4-metoxi-2-oxo-1,2-dihidro-piridin-3-carbonitrilo mediante un procedimiento simılar al descrito para el Ejemplo 74 (0,56 g, al 93%) $^1$H NMR (300 MHz, $CDCl_3$) δ 7,48 (d, $J$ = 9 Hz, 1H), 7,40-7,27 (m, 1H), 7,00-6,95 (m, 2H), 6,08 (d, $J$ = 9 Hz, 1H), 5,10 (s, 2H), 4,00 (s, 3H)

Etapa 3 Preparacion de 1-(3-fluorobencil)-4-hidroxi-2-oxo-1,2-dihidropiridin-3-carbonitrilo

A una disolucion de hidruro de sodio (92 mg de una dispersión en aceite mineral al 60%, 2,3 mmol) en DMF (7 ml) se agregó etanetiol (0,14 g, 2,2 mmol) seguido por una disolución de 1-(3-fluorobencil)-4-metoxi-2-oxo-1,2-dihidropiridin-3-carbonitrilo (0,23 g, 0,89 mmol) en DMF (2 ml) y la mezcla de reaccion se calentó a 100 °C La mezcla de reacción se enfrio a temperatura ambiente, se acidifico con 3 N HCl y se lavé con EtOAc La disolución organica se lavo con salmuera, se secó ($Na_2SO_2$), se filtro y se concentro bajo una presion reducida para producir 1-(3-fluorobencil)-4-hidrcxi-2-oxo-1,2 dihidro-piridin-3-carbonitrilo como un sólido de color blanquecino (0,20 g, al 91%) $^1$H NMR (300 MHz, MeOD) δ 8,00 (s, 1H), 7,82 (d, $J$ = 8 Hz, 1H), 7,40-7,30 (m, 1H), 7,15-7,00 (m, 2H), 6,13 (d, $J$ = 8 Hz, 1H), 5,11 (s, 2H)

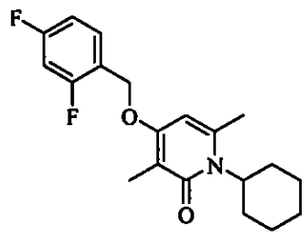
Etapa 4 Preparación de 4-(2,4-difluorobenciloxi)-1-(3-fluorobencil)-2-oxo-1,2-dihidro-piridin-3-carbonitrilo

Se preparo 4-(2,4-difluorobenciloxi)-1-(3fluorobencil)-2-oxc-1,2-dihidro-piridin-3-carbonitrilo

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mediante un procedimiento similar al descrito para el Ejemplo 107 (0,09 g, al 30%) mp 187-190 °C, $^1$H NMR (300 MHz, $CDCl_3$) δ 7,60-7,45 (m, 2H), 7,40-7,30 (m, 1H), 7,10-6,50 (m, 5H), 6,13 (d, *J* = 9 Hz, 1H), 5,27 (s, 2H), 5,10 (s, 2H)

Ejemplo 132




1-ciclohexil-4-(2,4-difluorobenciloxi)-3,6-dimetil-1*H*-piridin-2-ona

Etapa 1 Preparacion de 1-ciclohexil-4-hidroxi-2,5-dimetil-6-oxo-1,6-dihidro-piridin-3-carboxilato de metilo

A una disolución de ester metilico de ácido 3-ciclohexilaminobut-2-enoico (1,12 g, 5,72 mmol) en bromobenceno se agregó bis-(2,4,6-tricloro-fenil) éster de acido 2-metilmalonico (2,71 g, 5,72 mmol) y la mezcla de reacción se calento a 170 °C durante 3 horas La mezcla de reaccion se enfrio a temperatura ambiente y se concentro bajo una presion reducida La purificacion por cromatografia en columna rapida (sílice, eluyente cloruro de metileno a 94 6 cloruro de metileno/MeOH) y la recristalizacion de MeOH caliente proporcionaron 1-ciclohexil-4hidroxi-2,5-dimetil-6-oxo-1,6-dihidropiridin-3-carboxilato de metilo como cristales de cclor amarillo palido (0,34 g, al 21%) $^1$H NMR (500 MHz, DMSO-$d_6$) δ 9,82 (s, 1H), 4,00-3,90 (m, 1H), 3,76 (s, 3H), 2,75-2,60 (m, 2H), 2,31 (s, 3H), 1,81 (s, 3H), 1,80-1,70 (m, 2H), 1,65-1,50 (m, 3H), 1,40-1,20 (m, 2H), 1,15-1,05 (m, 1H)

878

Etapa 2 Preparacion de acido 1-ciclohexil-4-hidroxi-2,5-dimetil-6-oxo-1,6-dihidro-piridin-3-carboxilico

Una disolucion de 1-ciclohexil-4-hidroxi-2,5-dimetil-6-oxo-1,6-dihidro-piridin-3-carboxilato de metilo (0,35 g, 1,26 mmol) en 2 N NaOH (5 ml) se calento a reflujo durante 3,5 horas La mezcla de reaccion se enfrio a temperatura ambiente, se acidifico a pH 1-2 con 1 N HCl y se lavó con EtOAc La disolucion organica se lavo con salmuera, se seco ($MgSO_2$), se filtro y se concentro bajo una presión reducida para producir ácido 1-ciclohexil-4-hidroxi-2,5-dimetil-6-oxo-1,6-dihidropiridina-3-carboxilico como un solido blanco (0,31 g, al 94%) $^1$H NMR (300 MHz, MeOD) δ 4,30-4,00 (br s, 1H), 2,76 (br s, 5H), 1,90 (s, 3H), 1,90-1,80 (m, 2H), 1,75-1,60 (m, 3 H), 1,50-1,15 (m, 3H)

Etapa 3 Preparación de 1-ciclohexil-4-hidroxi-3,6-dimetil-1*H*-piridin-2-ona

Una disolucion de acido 1-ciclohexil-4-hidroxi-2,5-dimetil-6-oxo-1,6-dihidropiridin-3-carboxilico (0,15 g, 0,57 mmol) en HCl concentrado (5 ml) se calentó a reflujo durante 4 horas La mezcla de reaccion se enfrió a temperatura ambiente, se diluyo con agua y se lavó con EtOAc La disolucion organica se lavó con salmuera, se secó ($MgSO_2$), se filtró y se concentro bajo una presion reducida para producir 1-ciclohexil-4-hidroxi-3,6-dimetil-1*H*-piridin-2-ona- como un solido blanco (0,2 g, al 77%) $^1$H NMR (300 MHz, DMSO-$d_6$) δ 9,81 (s, 1H), 5,73 (s, 1H), 3,95-3,75 (m, 1H), 2,80-2,55 (m, 2H), 2,25 (s, 3H), 1,85-1,40 (m, 5H), 1,72 (s, 3H), 1,38-1,05 (m, 3H)

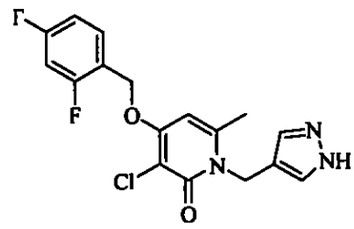
Etapa 4 Preparacion de 1-ciclohexil-4-(2,4-difluorobenciloxi)-3,6-dimetil-1*H*-piridin-2-ona

Se preparo 1-ciclohexil-4-(2,4-difluorobenciloxi)-3,6-dimetil-1*H*-piridin-2-ona mediante un procedimiento similar al descrito para el Ejemplo 107 (0,05 g, al 16%) mp 118-

879

120 °C, $^1$H NMR (300 MHz, $CDCl_3$) δ 7,48-7,41 (m, 1H), 6,95-6,81 (m, 2H), 5,87 (s, 1H), 5,07 (s, 2H), 4,05-3,85 (m, 1H), 3,00-2,80 (m, 2H), 2,35 (s, 3H), 1,98 (s, 3H), 1,95-1,80 (m, 2H), 1,70-1,55 (m, 3H), 1,40-1,20 (m, 3H)

Ejemplo 133




3-cloro-4-(2,4-difluorobenciloxi)-6-metil-1-(1*H*-pirazol-4-ilmetil)-1*H*-piridin-2-ona

Etapa 1 Preparacion de ester *terc*-butilico de acido 4-metilpirazol-1-carboxilico

A una disolucion de 4-metil-1H-pirazol (1 g, 12 mmol) y DMAP (1,5 ml, 1,2 mmol) en $CH_3CN$ (20 ml) se agrego dicarbonato di-*terc*-butílicol (2,8 g, 13 mmol), y la mezcla de reaccion se agito durante 1 hora La mezcla de reaccion se concentro bajo una presión reducida y el residuo se disolvió en EtOAc La disolucion organica se lavo con 1 N HCl, agua y luego con salmuera, se secó ($MgSO_4$), se filtro y se concentro bajo una presion reducida para proporcionar éster *terc*-butilico de acido 4-metil-pirazol-1-carboxílico como un aceite de color amarillo claro (2,2 g, al 100%) $^1$H NMR (300 MHz, $CDCl_3$) δ 7,83 (s, 1H), 7,53 (s, 1H), 2,09 (s, 3H), 1,64 (s, 9H)

Etapa 2 Preparacion de ester *terc*-butilico de acido 4-bromometilpirazol-1-carboxilico

A una disolucion de ester *terc*-butilico de acido 4-metilpirazol-1-carboxilico (1,0 g, 5,5 mmol) en

880

tetracloruro de carbono (20 ml) se agrego N-bromosuccinimida (1,0 g, 5,6 mmol) y peroxido de benzoilo (50 mg) y la mezcla de reaccion se calentó a reflujo durante 16 horas La mezcla de reaccion se enfrio a temperatura ambiente, se filtró y se concentró bajo una presion reducida La purificación por cromatografia en columna rápida (silice, 1 4 EtOAc/hexanos) produjo ester *terc*-butilico de ácido 4-bromometilpirazol-1-carboxilico como un aceite de color amarillo claro (0,42 g, al 30%) $^1$H NMR (300 MHz, $CDCl_3$) δ 8,10 (s, 1H), 7,74 (s, 1H), 4,39 (s, 2H), 1,65 (s, 9H)

Etapa 3 Preparación de éster *terc*-butilico de acido 4-[3-cloro-4-(2,4-difluorobenciloxi)-6-metil-2-oxo-2*H*-piridin-1-ilmetil]pirazol-1-carboxilico

Se preparó ester *terc*-butilico de ácido 4-[3-cloro-4-(2,4-difluorobenciloxi)-6-metil-2-oxo-2*H*-piridin-1-ilmetil]pirazol-1-carboxilico mediante un procedimiento similar al descrito para el Ejemplo 632 $^1$H NMR (300 MHz, $CDCl_3$) δ 8,09 (s, 1H), 7,72 (s, 1H), 7,53 (aprox q, $J$ = 6 Hz, 1H), 6,97-6,82 (m, 2H), 6,00 (s, 1H), 5,19 (s, 2H), 5,13 (s, 2H), 2,43 (s, 3H), 1,63 (s, 9H)

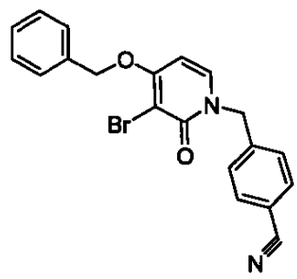
Etapa 4 Preparacion de 3-cloro-4-(2,4-difluorobenciloxi)-6-metil-1-(1*H*-pirazol-4-ilmetil)-1*H*-piridin-2-ona

Se calentó a 140 °C durante 16 horas ester *terc*-butilico de acido 4-[3-cloro-4-(2,4-difluorobenciloxi)-6-metil-2-oxo-2*H*-piridin-1-ilmetil]pirazol-1-carboxilico (0,16 g, 0 34 mmol) La mezcla de reacción se enfrió a temperatura ambiente $^1$H NMR (300 MHz, $CDCl_3$) δ 8,33 (s, 2H), 7,68 (d, $J$ = 6 Hz, 1H), 7,52 (aprox q, $J$ = 6 Hz, 1H), 6,93-6,83 (m, 2H), 6,47 68 (d, $J$ = 9 Hz, 1H), 5,19 (s, 2H), 5,24 (s, 2H), 5,20(s, 2H)

Ejemplo 134

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4-{[4-(benciloxi)-3-bromo-2-oxopiridin-1(2H)-il]metil}benzonitrilo

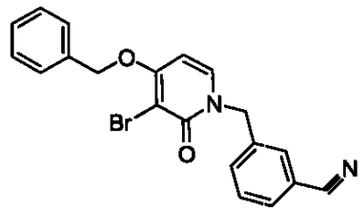



Preparación de 4-{[4-(benciloxi)-3-bromo-2-oxopiridin-1(2H)-il]metil}benzonitrilo Se disolvió 3-bromo-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona (1,0 g, 3,6 mmol) en *N,N*-dimetilformamida (5 mL) Se añadió α-Bromo-*p*-tolunitrilo (0,85 g, 4,3 mmol) seguido de $K_2CO_3$ (0,59 g, 4,3 mmol) La mezcla resultante se calentó a 80 °C durante 16 hs La reacción se concentró hasta lograr un aceite que estaba dividido en agua y acetato de etilo y se extrajo con acetato de etilo (3 x 100 ml) Los extractos organicos se combinaron, se lavaron con salmuera, se secaron sobre $Na_2SO_4$, y se filtraron El filtrado se concentro hasta lograr un aceite, y se purifico mediante cromatografia (gel de silice, hexanos/acetato de etilo) para producir un solido de color blanco (0,65 g, al 46%) $^1$H NMR (400 MHz, $CDCl_3$) δ 7,62 (d, *J* = 8,4 Hz, 2H), 7,41-7,31 (m, 7H), 7,23 (d, *J* = 7,6 Hz, 1H), 6,11 (d, *J* = 8,0 Hz, 1H), 5,24 (s, 2H), 5,18 (s, 2H) ES HRMS m/z 395,0404 (M+H $C_{20}H_{15}BrN_2O_2$ requiere 395,0390)

882

Ejemplo 135

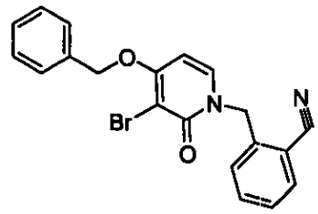
3-{[4-(benciloxi)-3-bromo-2-oxopiridin-1(2H)-il]metil}benzonitrilo



El compuesto del titulo se preparo mediante un procedimiento esencialmente similar al descrito en el Ejemplo 134 $^1$H NMR (400 MHz, $CDCl_3$) δ 7,62-7,54 (m, 3H), 7,45 (d, $J$ = 7,6Hz, 1H), 7,43-7,31 (m, 5H), 7,26 (d, $J$ = 1,6 Hz, 1H), 6,12 (d, $J$ = 1,6 Hz, 1H), 5,24 (s, 2H), 5,15 (s, 2H) ES HRMS m/z 395,0420 (M+H $C_{20}H_{15}BrN_2O_2$ requiere 395,0390)

Ejemplo 136

2-{[4-(benciloxi)-3-bromo-2-oxopiridin-1(2H)-il]metil}benzonitrilo

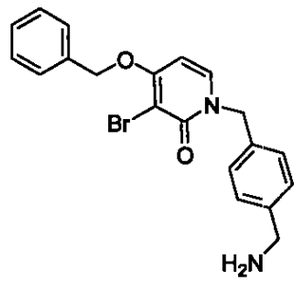


El compuesto del titulo se preparo siguiendo un procedimiento esencialmente similar al descrito en el Ejemplo 134 $^1$H NMR (400 MHz, $CDCl_3$) δ 7,74 (d, $J$ = 8,4 Hz, 1H), 7,63 (dd, $J$ = 1,2, 8,0 Hz, 1H), 7,57 (dt, $J$ = 1,2, 8,4 Hz, 1H), 7,55 (d, $J$ = 8,0 Hz, 1H), 7,43-7,30 (m, 6H), 6,13 (d, $J$ = 8,0 Hz, 1H), 5,33 (s, 2H), 5,23 (s, 2H) ES HRMS m/z 395,0398 (M+H $C_{20}H_{15}BrN_2O_2$ requiere 395,0390)

Ejemplo 137

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1-[4-(aminometil)bencil]-4-(benciloxi)-3-bromopiridin-2(1H)-ona

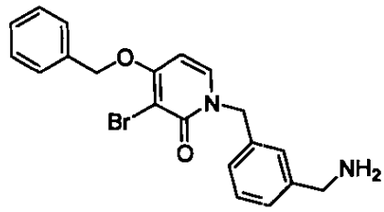



Preparación de 1-[4-(aminometil)bencil]-4-(benciloxi)-3-bromopiridin-2(1H)-ona El material del Ejemplo 134 (100 mg, 0,25 mmol) se disolvió en tetrahidrofurano (2 mL) bajo $N_2$ Se agrego complejo borano dimetilsulfuro (0,25 mL, 0,5 mmol, 2M en tetrahidrofurano) Luego, se calento la reacción hasta 70 °C y se dejo en agitacion durante la noche Se enfrio la mezcla y se destiló todo el disolvente bajo vacio El residuo resultante se dividió en acetato de etilo y 0,2 N NaOH, y se extrajo con acetato de etilo (3 x 10 mL) Los extractos organicos se combinaron, se lavaron con salmuera, se secaron sobre $Na_2SO_4$, y se filtraron El filtrado se concentro hasta lograr un aceite, y se trituro con diclorometano y hexano para proporcionar un sólido de color blanquecino (80 mg, al 80%) $^1H$ NMR (400 MHz, $d_6$DMSO) δ 7,90 (d, $J$ = 7,6 Hz, 1H), 7,43-7,21 (m, 9H), 6,70 (d, $J$=7,6 Hz, 1H), 5,29 (s, 2H), 5,08 (s, 2H), 3,71 (s, 2H) ES HRMS m/z 399,0721 (M+H $C_{20}H_{19}BrN_2O_2$ requiere 399,0703)

Ejemplo 138

1-[3-(aminometil)bencil]-4-(benciloxi)-3-bromopiridin-2(1H)-ona

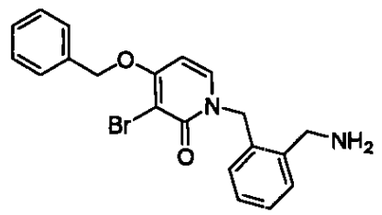
884



El compuesto del título se preparo siguiendo un procedimiento esencialmente similar al descrito en el Ejemplo 137 utilizando el compuesto del título del Ejemplo 135 como material de inicio $^1$H NMR (400 MHz, $d_6$DMSO) δ 7,90 (d, $J$ = 7,6 Hz, 1H), 7,44-7,22 (m, 9H), 6,50 (d, $J$=7,6 Hz, 1H), 5,30 (s, 2H), 5,12 (s, 2H), 3,88 (s, 2H) ES HRMS m/z 399,0730 (M+H $C_{20}H_{19}BrN_2O_2$ requiere 399,0703)

Ejemplo 139

1-[2-(aminometil)bencil]-4-(benciloxi)-3-bromopiridin-2(1H)-ona

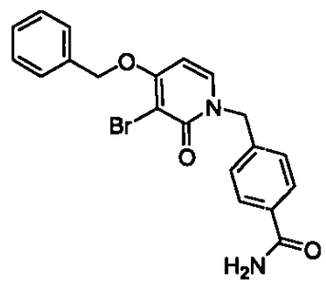


El compuesto del título se preparo siguiendo un procedimiento esencialmente similar al descrito en el Ejemplo 137, usando el compuesto del título del Ejemplo 136 como material inicial $^1$H NMR (400 MHz, $d_6$DMSO) δ 7,88 (d, $J$ = 8,0 Hz, 1H), 7,45-7,34 (m, 5H), 7,26- 7,21 (m, 3H), 6,85 (d, $J$=7 2 Hz, 1H), 6,53 (d, $J$ = 7,6 Hz, 1H), 5,32 (s, 2H), 5 12 (s, 2H), 3 90 (s, 2H) ES HRMS m/z 399,0699 (M+H $C_{20}H_{19}BrN_2O_2$ requiere 399,0703)

Ejemplo 140

885

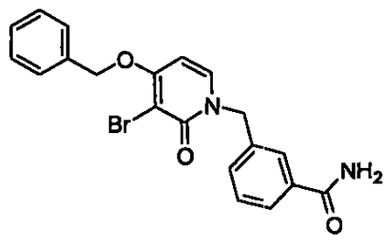
4-{[4-(benciloxi)-3-bromo-2-oxopiridin-1(2H)-il]metil}benzamida



Preparacion de 4-{[4-(benciloxi)-3-bromo-2-oxopiridin-1(2H)-il]metil}benzamida Se agrego el material del Ejemplo 134 (100 mg, 0,25 mmol) a una suspension de fluoruro potásico (al 40% en alumina) en alcohol t-butílico, se calento hasta 85 °C, y se agito durante 20 hs Se elimino la alumina mediante filtracion y se lavó con diclorometano y agua Se separó el filtrado resultante y la capa acuosa se extrajo con diclorometano (2 x 20 mL) Los extractos organicos se combinaron, se secaron sobre $Na_2SO_4$, y se filtraron El filtrado se concentró hasta lograr un aceite La trituración con diclorometano y hexano produjo un solido (11 5 mg, al 11%) $^1H$ NMR (400 MHz, $d_6$DMSO) δ 7,94 (d, $J$ = 8,0 Hz, 1H), 7,80 (d, $J$ = 8,4 Hz, 2H), 7,43-7,29 (m, 7H), 6,51 (d, $J$=7,6 Hz, 1H), 5,31 (s, 2H), 5,16 (s, 2H) ES HRMS m/z 413,0541 (M+H $C_{20}H_{17}BrN_2O_3$ requiere 413,0495)

Ejemplo 141

3-{[4-(benciloxi)-3-bromo-2-oxopiridin-1(2H)-il]metil}benzamida

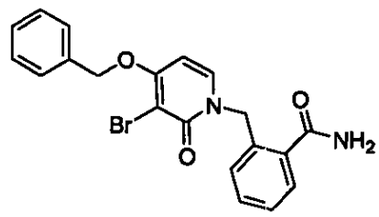


686

El compuesto del título se preparó siguiendo un procedimiento esencialmente similar al descrito en el Ejemplo 140 utilizando el compuesto del título del Ejemplo 135 como material de inicio $^1$H NMR (400 MHz, $d_6$DMSO) δ 7,95 (d, *J* = 7,6 Hz, 2H), 7,76 (m, 2H), 7,43-7,26 (m, 8H), 6,51 (d, *J*=7,6 Hz, 1H), 5,31 (s, 2H), 5,15 (s, 2H) ESHRMS m/z 413,0497 (M+H $C_{20}H_{17}BrN_2O_3$ requiere 413,0495)

Ejemplo 142

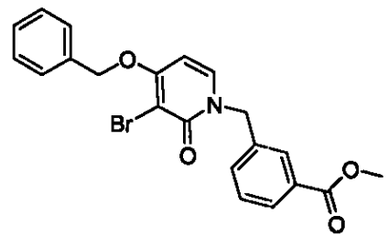
2-{[4-(benciloxi)-3-bromo-2-oxopiridin-1(2H)-il]metil}benzamida



El compuesto del título se preparo siguiendo un procedimiento esencialmente similar al descrito en el Ejemplo 140, utilizando el compuesto del título del Ejemplo 136 como material de inicio $^1$H NMR (400 MHz, $d_6$DMSO) δ 7,78 (d, *J* = 7,6 Hz, 1H), 7,54 (dd, *J* = 1,6, 7,6 Hz, 1H), 7,45 (d, *J*=7,6 Hz, 2H), 7,44-7,32 (m, 5H), 7,15 (d, *J*=7,6 Hz, 1H), 6,49 (d, *J*=7,6 Hz, 1H), 5,39 (s, 2H), 5,30 (s, 2H) ES HRMS m/z 4413,0506 (M+H $C_{20}H_{17}BrN_2O_3$ requiere 413,0495)

Ejemplo 143

3-{[4-(Benciloxi)-3-bromo-2-oxopiridin-1(2H)-il]metil}benzoato de metilo

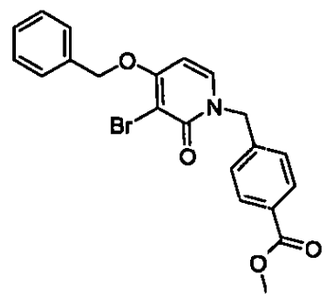


887

Preparación de 4-{[4-(benciloxi)-3-bromo-2-oxopiridin-1(2H)-il]metil}benzoato de metilo El material del Ejemplo 134 (100 mg, 0,25 mmol) se suspendio en metanol y se enfrio hasta 0°C Se hizo burbujear HCl (g) a través de la mezcla hasta su saturación (~30 minutos) Se entibio la reaccion hasta temperatura ambiente y se agitó durante 4 horas Se eliminaron el HCl y el metanol *in vacuo*, obteniendo un aceite, que se purificó mediante cromatografia (gel de silice, hexanos/acetato de etilo) para producir un solido de color blanco (3 mg, al 3%) $^1$H NMR (400 MHz, $CD_3OD$) δ 7,98 (*aprox* d, *J* = 8,0 Hz, 2H), 7,77 (*aprox* d, *J* = 8,0 Hz, 1H), 7,55 (*aprox* d, *J* = 8,0 Hz, 2H), 7,41-7,35 (m, 5H), 6,52 (d, *J* = 7,5 Hz, 1H), 5,31 (s, 2H), 5,27 (s, 2H), 3,88, (s, 3H) API-ES MS m/z 429,0 (M+H $C_{21}H_{18}BrNO_4$ requiere 428,0492)

Ejemplo 144

4-{[4-(Benciloxi)-3-bromo-2-oxopiridin-1(2H)-il]metil}benzoato de metilo



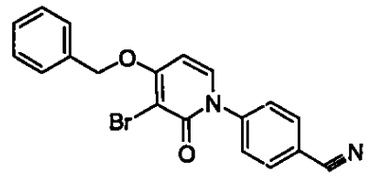

El compuesto del titulo se preparó siguiendo un procedimiento esencialmente similar al descrito en el Ejemplo 143 utilizando el compuesto del título del Ejemplo 134 como material de inicio $^1$H NMR (400 MHz, $CD_3OD$) δ 7,94 (*aprox* d, *J* = 8,4 Hz, 2H), 7,76 (*aprox* d, *J* = 7,6 Hz, 1H), 7,46 (*aprox* d, *J* = 8,0 Hz, 2H), 7,39-7,35 (m, 5H), 6,51 (d, *J*=7,6 Hz, 1H), 5,31 (s, 2H), 5,26 (s, 2H), 3,88,

888

(s, 3H) ES HRMS m/z 428,0492 (M+H $C_{21}H_{18}BrNO_4$ requiere 428,0492)

Ejemplo 145

4-[4-(benciloxi)-3-bromo-2-oxopiridin-1(2H)-il]benzonitrilo

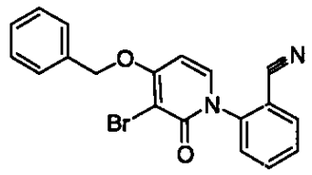



Preparación de 4-[4-(benciloxi)-3-bromo-2-oxopiridin-1(2H)-il]benzonitrilo Se suspendio 3-bromo-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona (100 mg, 0,36 mmol) en dimetilsulfoxido (5 mL), se agregó carbonato de cesio (375 mg, 1,15 mmol) y la reaccion se agitó durante 5 minutos Luego, se agrego 4-fluorobenzonitrilo (52 mg, 0,43 mmol), se calento la reacción hasta 80 °C, y se agito La reacción se vigiló mediante LC/MS (Cromatografia liquida/Espectrometria de masa), y después de 4 hs se calento hasta 100 °C y se agitó durante 16 horas La mezcla de reacción se dividió en agua y acetato de etilo y se extrajo con acetato de etilo (5 x 50 mL) Los extractos organicos se combiraron, se lavaron con salmuera, se secaron sobre $Na_2SO_4$, y se filtraron El filtrado se concentró hasta lograr un aceite, y se purifico mediante cromatografia (gel de silice, hexanos/acetato de etilo) para producir un solido de color blanco (40 mg, al 29%) $^1H$ NMR (400 MHz, $CDCl_3$) δ 7,77 (d, $J$ = 8,4 Hz, 2H), 7,52 (d, $J$ = 8,8 Hz, 2H), 7,44-7,42 (m, 4H), 7,28 (d, $J$ = 7,6 Hz, 1H), 7,26 (s, 1H), 6,24 (d, $J$ = 7,6 Hz, 1H), 5,31, (s, 2H) ES HRMS m/z 381,0230 (M+H $C_{19}H_{13}BrN_2O_2$ requiere 381,0233)

Ejemplo 146

889

2-[4-(benciloxi)-3-bromo-2-oxopiridin-1(2H)-il]benzonitrilo

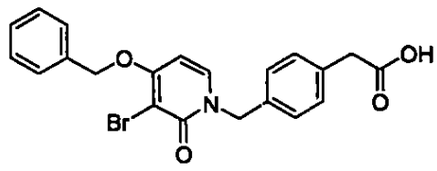



Preparación de 2-[4-(benciloxi)-3-bromo-2-oxopiridin-1(2H)-il]benzonitrilo Se suspendio 3-bromo-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona (100 mg, 0,36 mmol) en dimetilsulfoxido (5 mL), se agrego carbonato de cesio (375 mg, 1,15 mmol) y la reaccion se agitó durante 5 minutos Luego, se agrego 4-fluorobenzonitrilo (52 mg, 0,43 mmol), se calento la reaccion hasta 80°C con agitacion La reaccion se vigilo mediante LC/MS, y despues de 4 hs se calento hasta 100°C y se agito durante 16 horas La mezcla de reacción se dividio en agua y acetato de etilo y se extrajo con acetato de etilo (5 x 50 mL) Los extractos orgánicos se combinaron, se lavaron con salmuera, se secaron sobre $Na_2SO_4$, y se filtraron El filtrado se concentro hasta lograr un aceite, y se purifico mediante cromatografia (gel de silice, hexanos/acetato de etilo) para producir un sólido de color blanco (18 mg, al 13%) $^1H$ NMR (400 MHz, $CDCl_3$) δ 7,81 (dd, $J$ = 1,2, 8,4 Hz, 1H), 7,73 (dt, $J$ = 1,2, 8,0 Hz 1H), 7,57 (dt, $J$ = 0,8, 8,0 Hz, 1H), 7,50-7,36 (m, 6H), 7,27 (d, $J$ = 8,0 Hz, 1H), 6,28 (d, $J$ = 8,0 Hz, 1H), 5,31 (s, 2H) ES HRMS m/z 381,0249 (M+H $C_{19}H_{13}BrN_2O_2$ requiere 381,0233)

Ejemplo 147

890

Ácido 4-{[4-(benciloxi)-3-bromo-2-oxopiridin-1(2H)-il]metil}fenil)acético

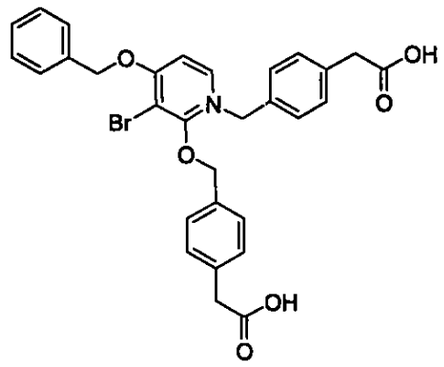



Se disolvió 3-bromo-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona (0,5 g, 1,78 mmol) en *N,N*-dimetilformamida (5 mL) Se agrego ácido 4-(bromometil)fenilacético (0,5 g, 2,14 mmol) seguido de $K_2CO_3$ (0,3 g, 2,14 mmol) La reacción se calento hasta 80 °C y se agito durante 16 horas, luego se calento hasta 100 °C y se agito durante 16 horas mas La mezcla de reaccion se dividio en agua y acetato de etilo y se extrajo con acetato de etilo (2 x 50 mL) Se acidifico la capa acuosa (pH 2) con 1N HCl y se extrajo con acetato de etilo (3 x 50 ml) Los extractos organicos se combinaron, se lavaron con salmuera, se secaron sobre $Na_2SO_4$, y se filtraron El filtrado se concentro hasta lograr un aceite, y se purifico mediante cromatografia (gel de silice, hexanos/acetato de etilo) seguido de cromatografia de fase inversa ($C_{18}$, acido trifluoroacetico acuoso /acetonitrilo al 0,1%) para producir un solido de color blanco (25 mg, al 3%) $^1H$ NMR (400 MHz, $CDCl_3$) δ 7,40-7,38 (m, 3H), 7,25-7,20 (m, 7H), 6,05 (d, *J* = 8,0 Hz, 1H), 5,21 (s, 2H), 5,13, (s, 2H), 3,62, (s, 2H) ES HRMS m/z 428,0510 (M+H $C_{21}H_{18}BrNO_4$ requiere 428,0492)

Ejemplo 148

891

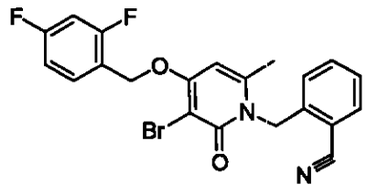
Ácido {4-[(4-(benciloxi)-3-bromo-2-{[4-(carboximetil)bencil]oxi}-1lambda$^5$-piridin-1-il)metil]fenil}acetico



Preparacion de acido {4-[(4-(benciloxi)-3-bromo-2-{[4-(carboximetil)bencil]oxi}-1lambda$^5$-piridin-1-il)metil]fenil}acetico El producto deseado se aisló mediante cromatografia de fase inversa ($C_{18}$, acido trifluoroacético acuoso/acetonitrilo al 0,1%) utilizando la preparacion del Ejemplo 147 proporcionando un solido de color blanco (53 mg, al 5%) $^1$H NMR (400 MHz, $CDCl_3$) δ 7,40-7,38 (m, 3H), 7,27-7,24 (m, 6H), 7,20 (d, $J$ = 7,6 Hz, 1H), 7,14 (d, $J$ = 8,0 Hz, 2H), 7,08 (d, $J$ = 8,4 Hz, 1H), 6,06 (d, $J$ = 7,6 Hz, 1H), 5,21 (s, 2H), 5,11 (s, 2H), 5,11 (s, 2H), 3,63 (s, 2H), 3,58 (s, 2H) ES HRMS m/z 576,1009(M+H $C_{30}H_{28}BrNO_6$ requiere 576,1016)

Ejemplo 149

2-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}benzonitrilo



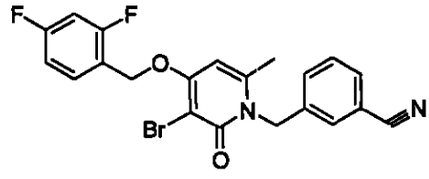
Preparación de 2-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-

892

il]metil}benzonitrilo Se disolvió 3-bromo-4-(2,4-difluorofenoxi)-6-metilpiridin-2(1*H*)-ona (50 mg, 0,15 mmol) en tetrahidrofurano (2 mL) Se agregó α-bromo-*o*-tolunitrilo (44 mg, 0,23 mmol) seguido por hidruro de sodio (7,2 mg, 0,18 mmol, al 60% en aceite mineral) y yoduro de sodio (56 mg, 0,38 mmol) Se calento la reacción hasta 50 °C y se agitó durante 16 horas La reaccion se filtro a traves de Celite® y el filtrado se concentro hasta lograr un aceite que se dividio en agua y acetato de etilo y se extrajo con acetato de etilo (4 x 10 mL) Los extractos orgánicos se combinaron, se lavaron con salmuera, se secaron sobre $MgSO_4$, y se filtraron El filtrado se concentró hasta lograr un aceite, y se purifico mediante cromatografia (gel de silice, hexanos/acetato de etilo) para producir un sólido de color blanco (25 mg, al 37%) $^1$H NMR (400 MHz, $CDCl_3$) δ 7,68 (dd, *J* = 8,0, 1,2 Hz, 1H), 7,58 (*aprox* q, *J* = 8,8 Hz, 1H), 7,52 (dt, *J* = 8,0 & 1,2 Hz, 1H), 7,38 (t, *J* = 7,6 Hz, 1H), 7,08 (d, *J* = 8,8 Hz, 1H), 7,00-6,93 (m, 1H), 6,89-6,84 (m, 1H), 6,05 (s, 1H), 5,57 (s, 2H), 5,22 (s, 2H), 2,28, (s, 3H) ES HRMS m/z 445,0335 (M+H $C_{21}H_{15}BrF_2N_2O_2$ requiere 445,0358)

Ejemplo 150

3-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}benzonitrilo



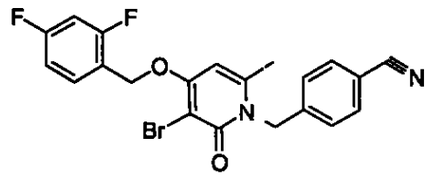
El compuesto del titulo se preparo mediante un procedimiento esencialmente similar al descrito en el Ejemplo 149 utilizando 3-bromo-4-(2,4-difluorofenoxi)-6-metilpiridin-2(1H)-ona (1 g, 3,0 mmol) como material de inicio $^1$H NMR ($CDCl_3$, 400 MHz) δ 7,61-7,55 (m, 2H), 7,45-

893

7,41 (m, 3H), 6,98-6,94 (m, 1H), 6,89-6,84 (m, 1H), 6,03 (s, 1H), 5,36 (s, 2H), 5,22 (s, 2H), 2,30, (s, 3H) ES HRMS m/z 445,0349 (M+H $C_{21}H_{15}BrF_2N_2O_2$ requiere 445,0358)

Ejemplo 151

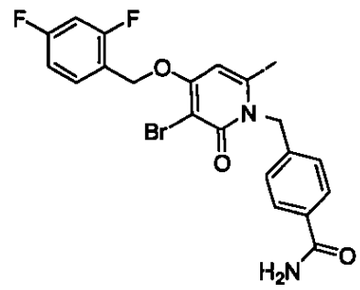
4-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}benzonitrilo



El compuesto del titulo se preparó mediante un procedimiento esencialmente similar al descrito en el Ejemplo 149 utilizando 3-bromo-4-(2,4-difluorofenoxi)-6-metilpiridin-2(1H)-ona (1 g, 3,0 mmol) como material de inicio $^1$H NMR (400 MHz, $CDCl_3$) δ 7,61 (d, *J* = 8,4 Hz, 2H), 7,62-7,56 (m, 1H), 7,27 (d, *J* = 8,8 Hz, 2H), 6,95 (*aprox* t, *J* = 8,4 Hz, 1H), 6,88-6,83 (m, 1H), 6,03 (s, 1H), 5,39 (s, 2H), 5,21 (s, 2H), 2,28 (s, 3H), ES HRMS m/z 445,0359 (M+H $C_{21}H_{15}BrF_2N_2O_2$ requiere 445,0358)

Ejemplo 152

4-{[3-bromo-4-[ 2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}benzamida

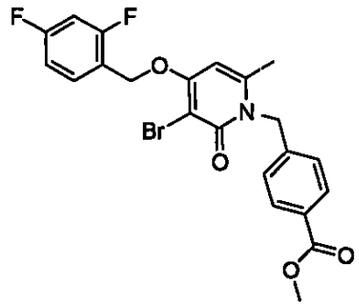


Se agrego el material del Ejemplo 151 (50 mg, 0,11 mmol) a una suspens on de fluoruro de potasio (al 40% en alumina) en alcohol t-butilico Se calentó la reaccion hasta 90°C y se agito durante 20 horas Se elimino la

alumina mediante filtracion y se lavó con diclorometano y agua Se separo el filtrado resultante y la capa acuosa se extrajo con diclorcmetano (2 x 20 mL) Los extractos organicos se combinaron, se secaron sobre $Na_2SO_4$, y se filtraron El filtrado se concentro hasta lograr un aceite, y se purificó mediante cromatografia (gel de silice, hexanos/acetato de etilo) para producir un solido de color blanco, proporcionando el producto (13 mg, al 25%) $^1$H NMR (400 MHz, $CDCl_3$) δ 7,75 (*aprox* d, *J* = 8,4 Hz, 2H), 7,58 (*aprox* q, *J* = 8,4 Hz, 1H), 7,24 (d, *J* = 8,4 Hz, 2H), 6,98-6,94 (m, 1H), 6,89-6,83 (m, 1H) 6,01 (s, 1H), 5,40 (s, 2H), 5,21 (s, 2H), 2,28 (s, 3H) ES HRMS m/z 463,0486 (M+H $C_{21}H_{17}BrF_2N_2O_3$ requiere 463,0463)

Ejemplo 153

4-{[3-Bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}benzoato de metilo



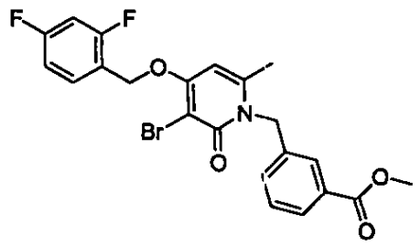
El material del Ejemplo 151 (50 mg, 0,11 mmol) se suspendio en metanol y se enfrió hasta 0 °C Se hizo burbujear HCl (g) a traves de la mezcla hasta su saturacion (~30 minutos) Se sello la reaccion, se entibio hasta alcanzar temperatura ambiente y se agito durante 2 horas Se eliminaron el HCl y el metanol *in vacuo*, obteniendo un aceite, que se purificó mediante cromatografia (gel de silice, hexanos/acetato de etilo) para producir un solido de color blanco (19 mg, al 36%) $^1$H NMR (400 MHz, $CDCl_3$) δ 7,97 (*aprox* d, *J* = 8,4 Hz, 2H), 7,58 (*aprox* q, *J* = 8,0

895

Hz, 1H) 7,22 (d, *J* = 8,4 Hz, 2H), 6,95 (*aprox* dt, *J* = 1,5, 9,6 Hz, 1H), 6,89-6,83 (m, 1H), 6,00 (s, 1H), 5,41 (s, 2H), 5,21 (s, 2H), 3,90, (s, 3H), 2,27 (s, 3H) ES HRMS m/z 478,0461 (M+H $C_{22}H_{18}BrNO_4$ requiere 478,0460)

Ejemplo 154

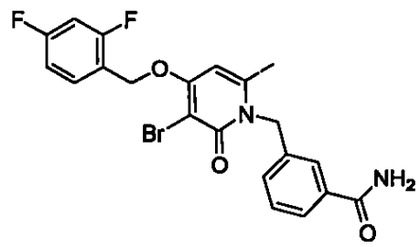
3-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}benzoato de metilo



El compuesto del titulo se preparo mediante un procedimiento esencialmente similar al descrito en el Ejemplo 149 utilizando el compuesto del titulo del Ejemplo 150 como material de inicio $^1$H NMR (400 MHz, $CDCl_3$) δ 7,95-7,92 (m, 1H) 7,84 bs, 1H) 7,58 (*aprox* q, *J* = 8,0 Hz, 1H), 7,39-7,37 (m, 2H), 6,95 (*aprox* dt, *J* = 1,6, 8,4 Hz, 1H), 6,88-6,83 (m, 1H), 6,00 (s, 1H), 5,40 (s, 2H), 5,21 (s, 2H), 3,90, (s, 3H), 2,30 (s, 3H) ES HRMS m/z 478,0449 (M+H $C_{22}H_{18}BrNO_4$ requiere 478,0460)

Ejemplo 155

3-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}benzamida



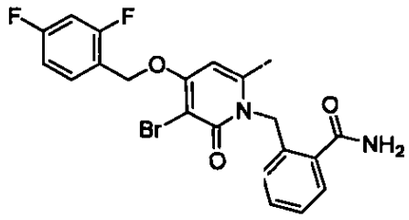
El compuesto del titulo se preparo mediante un procedimiento esencialmente similar al descrito en el Ejemplo 150 utilizando el compuesto del titulo del Ejemplo

896

150 como material de inicio $^1$H NMR (400 MHz, $CDCl_3$) δ 7,68-7,66 (m, 2H), 7,57 (*aprox* q, *J* = 8,4 Hz, 1H), 7,42-7,34 (m, 2H), 6,98-6,92 (m, 1H), 6,89-6,83 (m, 1H) 6,01 (s, 1H), 5,39 (s, 2H), 5,21 (s, 2H), 2,28 (s, 3H) ES HRMS m/z 463,0461 (M+H $C_{21}H_{17}BrF_2N_2O_3$ requiere 463,0463)

Ejemplo 156

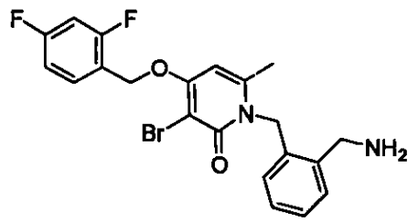
2-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}benzamida



El compuesto del titulo se preparo mediante un procedimiento esencialmente similar al descrito en el Ejemplo 149 utilizando el compuesto del titulo del Ejemplo 150 como material ce inicio $^1$H NMR (400 MHz, $CDCl_3$) δ 7,68-7,66 (m, 2H), 7,57 (*aprox* q, *J* = 8,4 Hz, 1H), 7,42-7,34 (m, 2H), 6,98-6 92 (m, 1H), 6,89-6,83 (m, 1H) 6,01 (s, 1H), 5,39 (s, 2H), 5,21 (s, 2H), 2,28 (s, 3H) ES HRMS m/z 463,0461 (M+H $C_{21}H_{17}BrF_2N_2O_3$ requiere 463,0463) $^1$H NMR (400 MHz, $CDCl_3$) δ 7,56-7,55 (m, 2H), 7,32-7,25 (m, 2H), 7,00-6,94 (m, 1H), 6,88-6,84 (m, 1H), 6,81-6,79 (m, 1H) 6,11 (s, 1H), 5,51 (s, 2H), 5,24 (s, 2H), 2,43 (s, 3H) ESHRMS m/z 463,0467 (M+H $C_{21}H_{17}BrF_2N_2O_3$ requiere 463,0463)

Ejemplo 157

1-[2-(aminometil)bencil]-3-bromo-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona

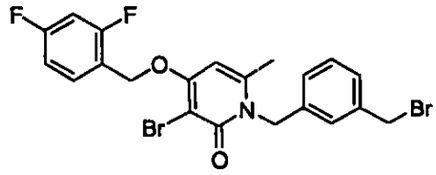


897

El material del Ejemplo 149 (50 mg, 0,11 mmol) se disolvió en tetrahidrofurano (2 mL) bajo $N_2$ Se agregó complejo borano-metilsulfuro (0,11 mL, 0,22 mmol, 2M en tetrahidrofurano) Luego, se calentó la reaccion hasta 70 °C y se dejó en agitación durante la noche Despues de enfriarla hasta temperatura ambiente, se destilo todo el disolvente bajo vacío El residuo resultante se dividio en acetato de etilo y 0 2 N NaOH, y se extrajo con acetato de etilo (3 x 20 mL) Los extractos organicos se combinaron, se lavaron con salmuera y se secaron sobre $Na_2SO_4$, y se filtraron El filtrado se concentró hasta lograr un aceite, y se purifico mediante cromatografia (gel de silice, hexanos/acetato de etilo) para producir un sólido de color blanco, para proporcionar el producto (19 mg, al 39%) $^1H$ NMR (400 MHz, $CDCl_3$) δ 7,56-7,55 (m, 2H), 7,32-7,25 (m, 2H), 7,00-6,94 (m, 1H), 6,88-6,84 (m, 1H), 6,81-6,79 (m, 1H), 6,11 (s, 1H), 5,44 (s, 2H), 5,17 (s, 2H), 4,59 (s, 2H), 2,18 (s, 3H), ESHRMS m/z 449,0692 (M+H $C_{21}H_{19}BrF_2N_2O_2$ requiere 449,0671)

Ejemplo 158

3-bromo-1-[3-(bromometil)bencil]-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona



Preparacion de 3-bromo-1-[3-(bromometil)bencil]-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona

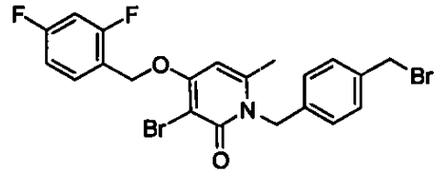
Se disolvio 3-bromo-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona (2 g, 6,06 mmol) en 1,4-dioxano (250 mL) Se añadió α,α'-dibromo-*m*-xileno (8 g, 30,3) seguido de hidruro de sodio 0,3 g, 7,5 mmol, al 60% en aceite mineral) Se calento la reaccion hasta 60°C y se agito

898

durante 16 horas La reacción se filtró a traves de Celite® y el filtrado se concentro hasta lograr un aceite que se dividió en agua y diclorometano y se extrajo con diclorometano (4 x 250 mL) Los extractos organicos se combinaron, se lavaron con salmuera, se secaron sobre $Na_2SO_4$, y se filtraron El filtrado se concentró hasta lograr un aceite, y se purifico mediante cromatografia (gel de silice, hexanos/acetato de etilo) para producir un solido de color blanco (1,2 g, al 38%) $^1$H NMR (400 MHz, $CDCl_3$) δ 7,57 (*aprox* q, *J* = 7,6 Hz, 1H), 7,28-7,25 (m, 2H), 7,17 (s, 1H), 7,08 (m,1H), 6,94 (*aprox* dt, *J* = 1,2, 9,6 Hz, 1H), 6,87-6,82 (m, 1H), 5,99 (s, 1H), 5,34 (s, 2H), 5,20 (s, 2H), 4,43 (s, 2H), 2,29 (s, 3H) ES HRMS m/z 511,9672 (M+H $C_{21}H_{17}Br_2F_2NO_2$ requiere 511,9667)

Ejemplo 159

3-bromo-1-[4-(bromometil)bencil]-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona

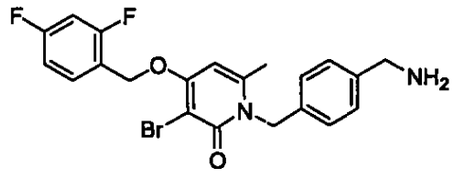



El compuesto del titulo se preparo mediante un procedimiento esencialmente similar al descrito en el Ejemplo 158 $^1$H NMR (400 MHz, $CDCl_3$) δ 7,68-7,66 (m, 2H), 7,57 (*aprox* q, *J* = 8,4 Hz, 1H), 7,42-7,34 (m, 2H), 6,98-6,92 (m, 1H), 6,89-6,83 (m, 1H) 6,01 (s, 1H), 5,39 (s, 2H), 5,21 (s, 2H), 2,28 (s, 3H) ES HRMS m/z 463,0461 (M+H $C_{21}H_{17}BrF_2N_2O_3$ requiere 463,0463) $^1$H NMR (400 MHz, $CDCl_3$) δ 7,56 (*aprox* q, *J* = 7,6 Hz, 1H), 7,32(d, *J* = 8,0 Hz, 2H), 7,14 (d, *J* = 8,0 Hz, 2H), 6,94 (*aprox* t, *J* = 8,4 Hz, 1H), 6,87-6,82 (m, 1H), 5,98 (s, 1H), 5,33 (s, 2H), 5,19 (s, 2H), 4,44 (s, 2H), 2,29 (s, 3H), ES HRMS m/z 511,9683 (M+H $C_{21}H_{17}Br_2F_2NO_2$ requiere 511,9667)

899

Ejemplo 160

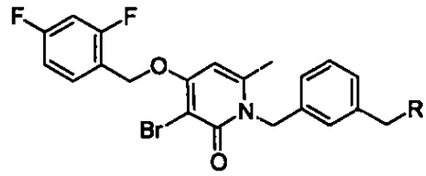
1-[4-(aminometil)bencil]-3-bromo-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona



El material del Ejemplo 159 (200 mg, 0,39 mmol) se suspendio en metanol (3 mL) y se enfrio hasta -78 °C Se hizo burbujear amoniaco (g) a traves de la mezcla hasta su saturacion durante 30 minutos Se sello el recipiente, se permitio que alcanzara temperatura ambiente y se agito durante 4 horas El disolvente y el amoniaco se eliminaron de la reaccion *in vacuo* con agitacion y el aceite resultante se trituro con eter para proporcionar un solido (174 mg, al 99%) $^1$H NMR (400 MHz, $CD_3OD$) δ 7,61 (q, $J$ = 7,6 Hz, 1H), 7,40 (d, $J$ = 8,0 Hz, 2H), 7,20 (d, $J$ = 8,0 Hz, 2H), 7,03 (*aprox* t, $J$ = 8,8 Hz, 2H), 6,51 (s, 1H), 5,43 (s, 2H), 5,29 (s, 2H), 4,07 (s, 2H), 2,36 (s, 3H) ES HRMS m/z 449,0673 ($C_{21}H_{19}BrF_2N_2O_2$ requiere 449,0671)

Ejemplos 161-168

Los compuestos de los Ejemplos 161-168 se preparan esencialmente conforme a los procedimientos establecidos anteriormente para los Ejemplos 158-160 o utilizando el compuesto del Ejemplo 158



| Ejemplo N° | R | MF | M+H Requiere | ESHRMS m/z |
|---|---|---|---|---|
| Ej 161 | $-NH_2$ | $C_{21}H_{19}BrF_2N_2O_2$ | 449,0671 | 449 0694 |

900

| | | | | | |
|---|---|---|---|---|---|
| Ej | 162 | morfolin-4-ilo | $C_{25}H_{25}BrF_2N_2O_3$ | 519,1089 | 519,1132 |
| Ej | 163 | dimetilamino | $C_{23}H_{23}BrF_2N_2O_2$ | 477 0984 | 477,0991 |
| Ej | 164 | isopropilamino | $C_{24}H_{25}BrF_2N_2O_2$ | 491,1140 | 491,1121 |
| Ej | 165 | piperidin-1-ilo | $C_{26}H_{27}BrF_2N_2O_2$ | 517,1297 | 517,1341 |
| Ej | 166 | (2-hidroxietil)amino | $C_{23}H_{23}BrF_2N_2O_3$ | 493 0933 | 493 0961 |
| Ej | 167 | bis(2-hidroxietil)amino | $C_{25}H_{27}BrF_2N_2O_4$ | 537,1195 | 537,1171 |
| Ej | 168 | piperazin-1-ilo | $C_{25}H_{26}BrF_2N_3O_2$ | 518,1249 | 518,1280 |

Caracterizacion por NMR (resonancia magnética nuclear) de los compuestos de los Ejemplos 161-168

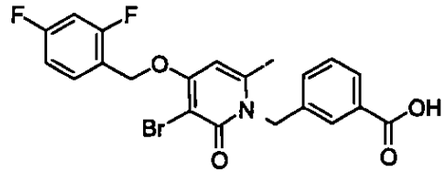
| Ej | N° | Datos de NMR |
|---|---|---|
| Ej | 16 | $^1$H NMR (400 MHz, $CD_3OD$) δ 7,61 (q, *J* = 7,6 Hz, 1H) 7 42-7,35 (m, 2H), 7,24-7,20 (m, 2H), 7,03 (*aprox* t, *J* = 8,4 Hz, 2H) 6 51 (s, 1H), 5,43 (s, 2H), 5 29 (s 2H) 4,07 (s, 2H), 2,04 (s, 3H) |
| Ej | 162 | $^1$H NMR (400 MHz, $CD_3OD$) δ 7 58 (*aprox* q, *J* = 7,6 Hz, 1H) 7,26-7,22 (m, 2H), 7,15 (s, 2H), 7,01 (*aprox* d, *J* = 6,4 Hz, 2H), 6,95 (*aprox* dt, *J* = 1,2, 8,0 Hz, 1H) 6,88-6,82 (m, 1H) 5 98 (s, 1H), 5,35 (s, 2H), 5,20 (s, 2H) 3 69 (t, *J* = 8,4 Hz, 4H) 3,46 (s 2H) 2 41 (m, 4H) 2,29 (s, 3H) |
| Ej | 163 | $^1$H NMR (400 MHz, $CD_3OD$) δ 7,61 (*aprox* q, *J* = 7,6 Hz, 1H) 7,25-7,14 (m, 3H) 7,01-6,92 (m, 2H) 6,85 (m, 1H) 5,97 (s 1H) 5 36 (s, 2H), 5,20 (s, 2H) 3,38 (s, 2H) 2,28 (s, 3H) 2,21 (s, 6H) |
| Ej | 164 | $^1$H NMR (400 MHz, $CDCl_3$) δ 7,61 (*aprox* q, *J* = 8,0 Hz, 1H) 7 25-7 22 (m 2H) 7 14 (s, 1H), 6 99 (*aprox* d 6 8 Hz, 1H), 6,94 (*aprox* dt, *J* = 2,0, 8,0 Hz, 1H), 6,88-6,80 (m 1H) 5,97 (s, 1H), 5,34 (s, 2H) 5,19 (s 2H) 3 73 (s 2H) 2,28 (s, 3H) 2,82 (*aprox* hepteto, *J* = 6 0 Hz 1H), 1,07 (d, *J* = 6 0 Hz, 6H) |
| Ej | 165 | $^1$H NMR (400 MHz, $CD_3OD$) δ 7,61 (*aprox* q, *J* = 8,0 Hz, 1H) 7,27 (*aprox* t *J* = 8 0 Hz 1H) 7 20 (*aprox* d, *J* = 7 6 Hz, 1H) 7 08 (bs, 1H) 7,01 (*aprox* t, *J* = 8,0 Hz, 2H) 6,48 (s, 1H) 5,41 (s 2H), 5,28 (s, 2H) 3,44 (s, 2H) 2,35 (s, 3H) 2,40-2,30 (m, 4H) 1,57-1,53 (m, 4H) |

901

| | |
|---|---|
| | 1,48-1,38 (m, 2H) |
| Ej 166 | $^1$H NMR (400 MHz, $CDCl_3$) δ 7,51 (*aprox* q, *J* = 8 0 Hz, 1H) 7,22-7,14 (m, 3H) 7,09 (bs, 1H) 6,98 (*aprox* d, *J* = 7,2 Hz, 1H) 6,89 (*aprox* dt, *J* = 1,6, 8,0 Hz, 1H) 6 81-6 76 (m, 1H) 5 92 (s, 1H), 5,28 (s 2H), 5,14 (s 2H) 3,73 (s, 2H) 3,59 (*aprox* t, *J* = 4,8 Hz, 2H) 2,73 (*aprox* t *J* = 4,8 Hz, 2H) 2,24 (s, 3H) |
| Ej 167 | $^1$H NMR (400 MHz, $CD_3OD$) δ 7,61 (*aprox* q *J* = 8,0 Hz, 1H) 7,46 (*aprox* d, *J* = 8,8 Hz, 2H) 7,31 (bs 1H) 7,27 (*aprox* t, *J* = 8,0 Hz, 1H) 7,03 (*aprox* t, *J* = 8 8 Hz 2H) 6,54 (s, 1H), 5,44 (s, 2H) 5 30 (s, 2H) 4,47 (s, 2H) 3,90-3,84 (m 4H) 3,40-3,25 (m, 4H) 2,40 (s, 3H) |
| Ej 168 | $^1$H NMR (400 MHz $CD_3OD$) δ 7,62 (*aprox* q *J* = 8 0 Hz, 1H) 7,53-7,46 (m, 2H) 7,36 (bs, 1H) 7,30 (*aprox* d, *J* = 7,6 Hz, 1H) 7,05-7,01 (m, 2H) 6,55 (s, 1H), 5,44 (s, 2H), 5,30 (s, 2H) 4 47 (s, 2H) 3,58-3 53 (m, 8H) 2,42 (s, 3H) |

Ejemplo 169

Ácido 3-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}benzoico



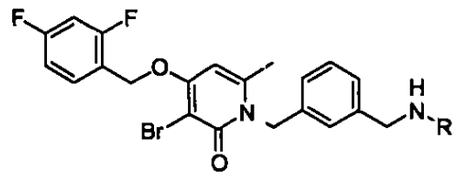

Preparacion de acido 3-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}benzoico El compuesto del Ejemplo 154 (150 mg, 0,31 mmol) se disolvió en tetrahidrofurano (5 mL) Se agregó trimetilsilanolato de potasio (80 mg, 0,62 mmol) y se agito la reacción a temperatura ambiente durante 4 horas La mezcla de reacción se concentro hasta obtener un aceite que se dividio en agua y acetato de etilo y se extrajo con acetato de etilo Los extractos orgánicos se combinaron, se lavaron con salmuera, se secaron sobre $Na_2SO_4$, y se filtraron El filtrado se concentro hasta obtener un aceite y se purifico mediante cromatografía de

902

fase inversa ($C_{18}$, acido trifluoroacetico acuoso/acetonitrilo al 0,1%) para proporcionar el producto (64 mg, L 44%) $^1$H NMR (400 MHz, $CD_3OD$) δ 7,92 (*aprox* d, *J* = 8,0 Hz, 1H), 7,78 (s, 1H), 7,62 (*aprox* q, *J* = 8,0 Hz, 1H), 7,44 (t, *J* = 7,6 Hz, 1H), 7,36 (*aprox* d, *J* = 8,0 Hz, 1H), 7,02 (*aprox* t, *J* = 7,6 Hz, 2H), 6,51 (s, 1H), 5,48 (s, 2H), 5,30 (s, 2H), 2,37 (s, 3H) ES HRMS m/z 464,0328 ($C_{21}H_{16}BrF_2NO_4$ requiere 464,0304)

Ejemplos 170-174

Los compuestos de los Ejemplos 170-174 se preparan utilizando el compue,to del Ejemplo 159 ó 161




| Ejemplo N° | R | MF | M+H Requiere | ESHRMS m/z |
|---|---|---|---|---|
| Ej 170 | $-C(O)CH_3$ | $C_{23}H_{21}BrF_2N_2O_3$ | 491,0776 | 491 0772 |
| Ej 171 | $-C(O)OCH_3$ | $C_{23}H_{21}BrF_2N_2O_4$ | 507,0726 | 507,0731 |
| Ej 172 | $-SO_2CH_3$ | $C_{22}H_{21}BrF_2N_2O_4S$ | 527,0446 | 527,0430 |
| Ej 173 | $-C(O)CH_2OH$ | $C_{23}H_{21}BrF_2N_2O_4$ | 507,0726 | 507,0712 |
| Ej 174 | $-C(O)NH_2$ | $C_{22}H_{20}BrF_2N_3O_3$ | 492 0729 | 492,0751 |

Caracterizacion por NMR (resonancia magnetica nuclear) de los compuestos de los Ejemplos 170-174

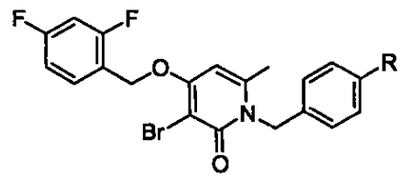
| Ej N° | Datos de NMR |
|---|---|
| Ej 170 | $^1$H NMR (400 MHz, $CD_3OD$) δ 7 61 (*aprox* q, *J* = 8,0 Hz, 1H) 7,28 (*aprox* t, *J* = 8 0, 1H) 7 18 (*aprox* d, *J* = 8,0 Hz, 1H), 7,05-7,00 (m, 4H) 6,49 (s, 1H), 5,41 (s, 2H), 5,29 (s, 2H) 2,37 (s, 3H) 1 94 (s 3H) |
| Ej 171 | $^1$H NMR (400 MHz, $CDCl_3$) δ 7,57 (*aprox* q, *J* = 7 6 Hz, 1H) 7,25 (*aprox* t *J* = 8,0, 1H), 7,17 (*aprox* d, *J* = 8,0 Hz, 1H), 7,06-7,02 (m, 2H) 6,97-6,91 (m, 1H) 6,87-6,82 (m, 1H), 5 98 (s 1H) 5,33 (s, 2H), 5,19 (s, 2H) 4,30 (d, *J* = |

903

| | |
|---|---|
| | 6,0 Hz, 2H) 3,67 (s, 3H) 2,28 (s 3H) |
| Ej 172 | $^1$H NMR (400 MHz, $CD_3CN$) δ 7,58 (*aprox* q, *J* = 7,6 Hz, 1H) 7,31 (*aprox* t, *J* = 8,0, 1H), 7,24 (*aprox* d, *J* = 8,0 Hz, 1H), 7,11 (s 1H) 7,05-7,00 (m 3H) 6,32 (s 1H), 6,06 (bs, 1H), 5,31 (s, 2H), 5,23 (s 2H) 4,17 (d, *J* = 6,4 Hz, 2H) 2 78 (s, 3H) 2,28 (s 3H) |
| Ej 173 | $^1$H NMR (400 MHz, $CDCl_3$) δ 7 55 (*aprox* q, *J* = 8,0 Hz, 1H) 7,23 (*aprox* t, *J* = 7,6, 1H), 7,15 (*aprox* d, *J* = 7,2 Hz, 1H), 7,05-7,00 (m, 3H) 6 94 (*aprox* dt, *J* = 1,2 8 8 Hz, 1H) 6,88-6,81 (m, 1H) 6,03 (s, 1H), 5 27 (s 2H), 5,19 (s, 2H) 4,39 (d, *J* = 6,4 Hz, 2H) 4,05 (s 2H), 2,31 (s, 3H) |
| Ej 174 | $^1$H NMR (400 MHz, $CD_3OD$) δ 7,62 (*aprox* q, *J* = 8,0 Hz, 1H) 7,28 (*aprox* t, *J* = 8,0, 1H), 7,19 (*aprox* d, *J* = 8,0 Hz, 1H), 7 05-6 96 (m, 4H) 6,49 (s, 1H), 5 41 (s, 2H), 5,29 (s, 2H) 4,25 (s, 2H) 2 35 (s, 3H) |

Ejemplos 175-185

Los compuestos de los Ejemplos 175-185 se preparan utilizando el compuesto del Ejemplo 159 o 160




| Ejemplo N° | R | MF | M+H Requiere | ESHRMS m/z |
|---|---|---|---|---|
| Ej 175 | $-CH_2NHCH(CH_3)_2$ | $C_{24}H_{25}BrF_2N_2O_2$ | 491,1140 | 491,1143 |
| Ej 176 | morfolin-4-ilmetilo | $C_{25}H_{25}BrF_2N_2O_3$ | 519,1089 | 519,1062 |
| Ej 177 | $-CH_2N(CH_3)_2$ | $C_{23}H_{23}BrF_2N_2O_2$ | 477,0984 | 477 0931 |
| Ej 178 | piperidin-1-ilmetilo | $C_{26}H_{27}BrF_2N_2O_2$ | 517,1297 | 517,1258 |
| Ej 179 | [bis(2-hidroxietil)amino]metil | $C_{25}H_{27}BrF_2N_2O_4$ | 537,1195 | 537,1181 |
| Ej 180 | $-CH_2NHCH_2CH_2OH$ | $C_{23}H_{23}BrF_2N_2O_3$ | 493,0933 | 493,0907 |
| Ej 181 | piperazin-1-ilmetilo | $C_{25}H_{26}BrF_2N_3O_2$ | 518,1249 | 518,1213 |
| Ej 182 | $-CH_2NHC(O)OCH_3$ | $C_{23}H_{21}BrF_2N_2O_4$ | 507,0726 | 507,0752 |

| | | | | | |
|---|---|---|---|---|---|
| Ej | 183 | $-CH_2NHC(O)CH_3$ | $C_{23}H_{21}BrF_2N_2O_3$ | 491,0776 | 491,0793 |
| Ej | 184 | $-CH_2NHSO_2CH_3$ | $C_{22}H_{21}BrF_2N_2O_4S$ | 527,0446 | 527,0431 |
| Ej | 185 | $-CH_2NHC(O)NH_2$ | $C_{22}H_{20}BrF_2N_3O_3$ | 492 0729 | 492,0720 |

Caracterización por NMR (resonancia magnética nuclear) de los compuestos de los Ejemplos 175-185

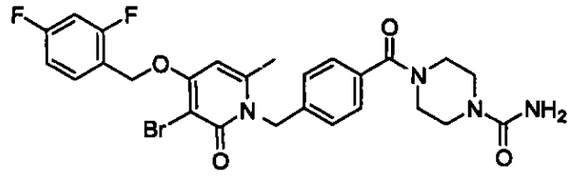
| Ej | N° | Datos de NMR |
|---|---|---|
| Ej | 175 | $^1$H NMR (400 MHz $CDCl_3$) δ 7,56 (q, *J* = 8,0 Hz, 1H) 7 25 (d *J* = 8,0 Hz, 2H), 7,10 (d *J* = 8,0 Hz, 2H), 6,94 (*aprox* t, *J* = 8,0 Hz 1H), 6,88-6,80 (m, 1H) 5,97 (s, 1H), 5,31 (s 2H), 5,19 (s, 2H) 3,74 (s, 2H), 2,82 (*aprox* hepteto, *J* = 6 0 Hz, 1H), 2,28 (s, 3H) 1,09 (d, *J* = 6,4 Hz, 6H) |
| Ej | 176 | $^1$H NMR (400 MHz, $CDCl_3$) δ 7,56 (q, *J* = 8,0 Hz, 1H) 7,25 (d *J* = 8,0 Hz, 2H), 7,11 (d, *J* = 8,0 Hz, 2H), 6,94 (*aprox* dt, *J* = 2,0, 8 0 Hz 1H) 6 87-6 81 (m, 1H) 5,97 (s, 1H), 5,33 (s, 2H) 5 19 (s 2H) 3,67 (*aprox* t, *J* = 4,8 Hz, 4H) 3 44 (s 2H) 2 44-2,38 (m 4H), 2,29 (s, 3H) |
| Ej | 177 | $^1$H NMR (400 MHz, $CDCl_3$) δ 7,56 (q, *J* = 8,0 Hz, 1H) 7,23 (d, *J* = 8,0 Hz, 2H), 7,11 (d, *J* = 8,0 Hz, 2H), 6,93 (*aprox* dt, *J* = 2,0, 8,0 Hz, 1H), 6,86-6,81 (m, 1H) 5,96 (s, 1H), 5,33 (s, 2H), 5,18 (s, 2H) 3,38 (s, 2H) 2,29 (s, 3H) 2,20 (s, 6H) |
| Ej | 178 | $^1$H NMR (400 MHz, $CDCl_3$) δ 7,56 (q, *J* = 8,0 Hz, 1H) 7,24-7 20 (m 2H), 7,10-7 07 (m, 2H), 6,96-6,90 (m,1H), 6,86-6,81 (m 1H), 5,96 (s 1H), 5,32 (s 2H), 5,18 (s, 2H) 3,34 (s, 2H) 2,31 (s, 3H) 2,31-2,28 (m, 4H) 1,53-1,51 (m, 4H) 1,39 (m, 2H) |
| Ej | 179 | $^1$H NMR (400 MHz, $CDCl_3$) δ 7,57 (q, *J* = 8,0 Hz, 1H) 7 25 (d, *J* = 8,0 Hz, 2H) 7,12 (d *J* = 8 0 Hz, 2H) 6 94 (dt, *J* = 8,8 Hz, 2H) 6,87-6,82 (m, 1H), 5,98 (s, 1H), 5,33 (s, 2H), 5,19 (s, 2H) 3,68 (s, 2H) 3,61 (t, *J* = 5,2 Hz, 4H) 2 70 (t *J* = 5 2 Hz 4H) 2 29 (s 3H) |
| Ej | 180 | $^1$H NMR (400 MHz, $CDCl_3$) δ 7,57 (q, *J* = 8,0 Hz, 1H) 7 25 (d, *J* = 8 0 Hz 2H) 7 12 (d, *J* = 8,0 Hz, 2H) 6,94 (*aprox* dt, *J* = 8,8 Hz, 2H) 6,87-6 82 (m, 1H), 5,98 (s, 1H), 5 33 (s 2H), 5 19 (s, 2H) 3,68 (s, 2H) 3,61 (t, *J* = 5,2 Hz, 4H) 2 70 (t *J* = 5 2 Hz 4H) 2,29 (s, 3H) |

905

| | |
|---|---|
| Ej 181 | $^1$H NMR (400 MHz $CDCl_3$) δ 7,61 (q *J* = 8,0 Hz, 1H) 7,52 (d, *J* = 3 0 Hz, 2H) 7,25 (d, *J* = 8,0 Hz, 2H) 7,03 (*aprox* t, *J* = 8,0 Hz, 2H) 6 53 (s, 1H), 5 44 (s, 2H), 5 30 (s, 2H) 4,32 bs, 2H) 3 55-3,35 (m, 8H) 2 39 (s, 3H) |
| Ej 182 | $^1$H NMR (100 MHz, $CDCl_3$) δ 7,56 (*aprox* q, *J* = 8,0 Hz, 1H) 7 20 (d, *J* = 8 0 Hz, 1H), 7 13 (d, *J* = 8 0 Hz, 2H), 6 94 (*aprox* ct *J* = 1,2, 8,0 Hz, 1H), 6,87-6,81 (m 2H) 5,97 (s, 1H), 5,32 (s, 2H), 5,19 (s, 2H) 4,31 (d, *J* = 6,0 Hz, 2H) 3,68 (s 3H) 2,28 (s, 3H) |
| Ej 183 | $^1$H NMR (100 MHz, $CDCl_3$) δ 7 61 (*aprox* q, *J* = 8,0 Hz, 1H) 7,23 (d *J* = 8,0 Hz 2H) 7,08 (d, *J* = 8,0 Hz, 2H) 7,04-6,99 (m, 2H) 6,47 (s, 1H), 5,39 (s, 2H), 5,28 (s, 2H) 4,30 (s, 2H) 2,34 (s, 3H) 1,95 (s, 3H) |
| Ej 184 | $^1$H NMR (100 MHz $CD_3OD$) δ 7,62 (*aprox* q, *J* = 8,0 Hz, 1H) 7 34 (d *J* = 8,4 Hz, 2H), 7 11 (d, *J* = 8 4 Hz 2H), 7,02 (*aprox* t *J* = 8,8 Hz 2H), 6,48 (s, 1H) 5,42 (s, 2H), 5 28 (s 2H) 4,21 (s 2H) 2,82 (s 3H) 2,35 (s, 3H) |
| Ej 185 | $^1$H NMR (400 MHz, $d_7$DMF) δ 7,76 (*aprox* q, *J* = 8,0 Hz, 1H) 7 28 (d, *J* = 8 0 Hz, ), 7,14 (d *J* = 8,0 Hz, 2H), 7 34-7,26 (m, 1H) 7,22-7,14 (m, 1H) 6,62 (s, 1H) 5,65 (s, 2H), 5,39 (s, 2H), 5,37 (s, 2H) 4,26 (d, *J* = 6,0 Hz, 2H), 2,40 (s, 3H) |

Ejemplo 186

4-(4-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}benzoil)piperazina-1-carboxamida



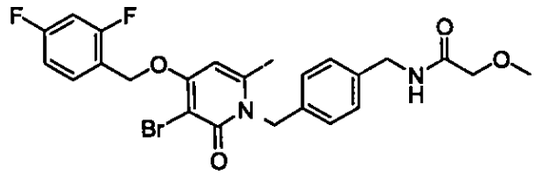
Se disolvió 3-bromo-4-(2,4-difluorofenoxi)-6-metil-1-[4-(piperazin-1-ilcarbonil)bencil]piridin-2(1*H*)-ona (300 mg, 0,54 mmol) en *N*,*N*-dimetilacetamida (5 mL) Se agregó trimetilsilil isocianato (0,15 mL, 1,08 mmol) seguido de *N*,*N*-diisopropiletilamina (0,23 mL, 1,3 mmol) y la reacción se agitó durante 1 hora a temperatura ambiente Luego, se diluyo la reacción con tetrahidrofurano (40 mL) y resina

906

poliamina (1,3 g, 2,81 mmol/g) y se agrego poliestireno funcionalizado con metilisocianato (1 g, 1 38 mmol/g) La mezcla se agito durante 6 horas, se filtró y el filtrado resultante se concentro hasta lograr un sólido de color blanco (279 mg, al 90%) $^1$H NMR (400 MHz, $CD_3OD$) δ 7,61 (*aprox* q, *J* = 8,0 Hz, 1H), 7,41 (d, *J* = 8,0 Hz, 2H), 7,23 (d, *J* = 8,0 Hz, 2H), 7,03 (*aprox* t, *J* = 8,8 Hz, 2H), 6,51 (s, 1H), 5,46 (s, 2H), 5,30 (s, 2H), 3,75-3,35 (m, 8H), 2,37 (s, 3H) ES HRMS m/z 575,1104 ($C_{26}H_{25}BrF_2N_4O_4$ requiere 575,1100)

Ejemplo 187

N-(4-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}bencil)-2-metoxiacetamida

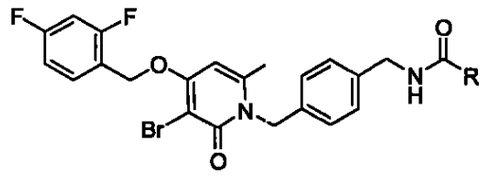


Se suspendió resina carbodiimida aglutinada con polimero (2,3 g, 1,18 meq/g, 2,7 mmol) en *N,N*-dimetilformamida Se agrego acido acetoxiacético (120 mg, 1,33 mmol), seguido por 1-hidroxibenzotriazol (1M en *N,N*-dimetilformamida, 0, 65 mL) y *N,N*-diisopropiletilamina (0,3 mL, 2,0 mmol) La reaccion se agito durante una hora cuando se agrego el Ejemplc 159 (300 mg, 0,67 mmol) La reacción se agito durante 16 horas y luego se diluyo con tetrahidrofurano Se agregaron resina poliamina (1 g, 2,81 mmol/g) y poliestireno funcionalizado con metilisocianato (2 g, 1,38 mmol/g) y se agito la mezcla durante 72 horas, se filtró y el filtrado resultante se concentro La trituracion con agua seguida de la trituracion con eter produjo un solido de color blanco (125 mg, al 36%) $^1$H NMR (400 MHz, $CDCl_3$) δ 7,56 (*aprox* q, *J* = 8,0 Hz, 1H), 7,21 (d, *J* = 8,0 Hz, 2H), 7,13 (d, *J* = 8,0 Hz, 2H), 6,94

907

(*aprox* t, $J$ = 8,8 Hz, 1H), 6,88-6,81 (m, 1H), 5,97(s, 1H), 5,33 (s, 2H), 5,19 (s, 2H), 4,43 (d, $J$ = 6,0 Hz, 2H), 3,92 (s, 2H), 3,39 (s, 3H), 2,29 (s, 3H) ES HRMS m/z 521,0882 ($C_{24}H_{22}BrF_2N_2O_4$ requiere 521,0882)

Ejemplos 188-193



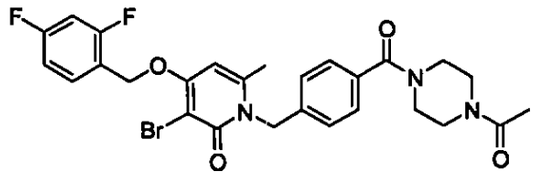
Los compuestos de los Ejemplos 188-193 se prepararon siguiendo el método general para la preparacion del Ejemplo 187 y sustituyendo el ácido acetoxiacético por el acido carboxilico apropiado Estos compuestos se trituraron con agua y una vez más con éter y se purificaron mediante cromatografia (gel de silice, hexanos/acetato de etilo) tal como resulta adecuado para producir sólidos de color blanquecino El Ejemplo 191 se preparó a partir de su intermedio protegido *N*-t-butoxicarbonilo La desproteccion se logro con 4N HCl en dioxano para proporcionar el compuesto del titulo como su sal hidrocloruro (86 mg, al 24%) La desproteccion del éster de metilo del Ej 188 se logro con $K_2CO_3$ en metanol/agua para proporcionar el Ej 192 como un sólido de color blanco Se muestran a continuacion los rendimientos y los datos analíticos

| Compuesto N° | R | % Rend | MF | M+H Requiere | ESHRMS m/z |
|---|---|---|---|---|---|
| Ej 188 | $CH_2OCOCH_3$ | 49 | $C_{25}H_{23}BrF_2N_2O_5$ | 549,0831 | 549,0849 |
| Ej 189 | $C(CH_3)_2OH$ | 13 | $C_{25}H_{25}BrF_2N_2O_4$ | 535,1039 | 535,1035 |
| Ej 190 | $C(-CH_2CH_2-)OH$ | 33 | $C_{25}H_{23}BrF_2N_2O_4$ | 535,0865 | 535,0876 |
| Ej 191 | $CH_2NH_2$ | 24 | $C_{23}H_{22}BrF_2N_3O_3$ | 533 0882 | 533 0899 |
| Ej 192 | $CH_2OH$ | 25 | $C_{23}H_{21}BrF_2N_2O_4$ | 507,0726 | 507,0730 |
| Ej 193 | $CH_2NHCOCH_3$ | 81 | $C_{25}H_{24}BrF_2N_3O_3$ | 548,0991 | 548,1000 |

Ejemplo 194

908

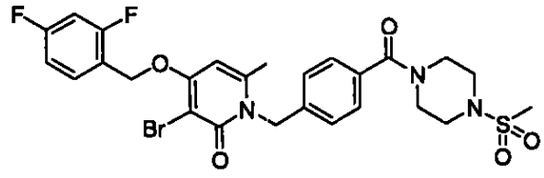
1-{4-[(4-acetilpiperazin-1-il)carbonil]bencil}-3-bromo-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona



Se disolvio 3-bromo-4-(2,4-difluorofenoxi)-6-metil-1-[4-(piperazin-1-ilcarbonil)bencil]piridin-2(1*H*)-ona (200 mg, 0,36 mmol) en *N,N*-dimetilformamida (5 mL) Se agregó *N,N*-Diisopropiletilamina (0,25 mL, 1,44 mmol) seguido de anhidrido acético (0,10 mL, 1,06 mmol) La reaccion se agito durante 2 horas a temperatura ambiente y se concentro hasta obtener un aceite que se trituró en éter y otra vez mas en agua para proporcionar un solido de color blanquecino (131 mg, al 63%) $^1$H NMR (400 MHz, $CD_3OD$) δ 7,62 (*aprox* q, *J* = 8,0 Hz, 1H), 7,42 (d, *J* = 8,0 Hz, 2H), 7,23 (d, *J* = 8,0 Hz, 2H), 7,62-7,02 (m, 1H), 7,02 (*aprox* t, *J* = 8,0 Hz, 1 H), 6,52 (s, 1H), 5,46 (s, 2H), 5,30 (s, 2H), 3,80-3,65 (m, 8H), 2,37 (s, 3H), 2,11 (s, 3H) ES HRMS m/z 574,1150 ($C_{27}H_{26}BrF_2N_3O_4$ requiere 574,1148)

Ejemplo 195

3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-(4-{[4-(metilsulfonil)piperazin-1-il]carbonil}bencil)piridin-2(1H)-ona



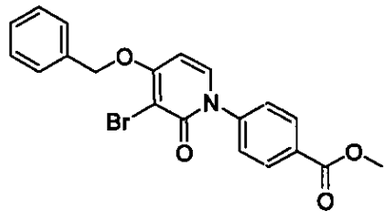
Se disolvio 3-bromo-4-(2,4-difluorofenoxi)-6-metil-1-[4-(piperazin-1-ilcarbonil)bencil]piridin-2(1H)-ona (300 mg, 0,54 mmol) en *N,N*-dimetilformamida (5 mL) Se agrego 4-metilmorfolina (0,23 mL, 2,2 mmol) seguida por cloruro metanosulfonilico (0,10 mL, 1,33 mmol) y la reaccion se

909

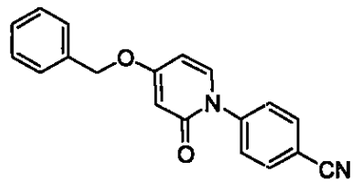
agito durante 2 hs Luego se diluyó la reaccion con tetrahidrofurano (40 mL) y se agregaron resina poliamina (1,3 g, 2,81 mmol/g) y poliestireno funcionalizado con metilisocianato (1 g, 1,38 mmol/g) Se agito la mezcla durante 16 horas, se filtro, y el filtrado resultante se concentro hasta lograr un aceite que se trituro con agua Se recogio el sólido de color blanco resultante, se lavó con eter y se seco (172 mg, al 52%) $^1$H NMR (400 MHz, $CDCl_3$) δ 7,57 (*aprox* q, *J* = 8,2 Hz, 1H), 7,34 (d, *J* = 8,0 Hz, 2H), 7,20 (d, *J* = 8,0 Hz, 2H), 7,02 (*aprox* dt, *J* = 1,2, 8,8 Hz, 1H), 6,88-6,82 (m, 1H), 6,02 (s, 1H), 5,37 (s, 2H), 5,21 (s, 2H), 3,80-3,20 (m, 8H), 2,79 (s, 3H), 2,30 (s, 3H), ES HRMS m/z 610,0851 ($C_{26}H_{26}BrF_2N_3O_5S$ requiere 610,0817)

Ejemplo 196

Metil -4-[4-(benciloxi)-3-bromo-2-oxopiridin-1(2H)-il]benzoato




Etapa 1 Preparacion de 4-[4-(benciloxi)-2-oxopiridin-1(2H)-il]benzonitrilo

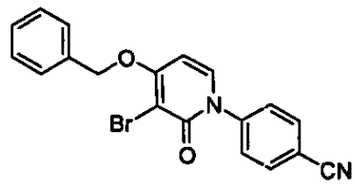



Se disolvió 4-benciloxi-2(1H)-piridona (12,00 g, 59,63 mmol) en dimetil sulfoxido (100 mL) Se agrego carbonato de potasio (10,99 g, 79,50 mmol), seguido de 4-fluorobenzonitrilo (4,81 g, 39,75 mmol) La reaccion se agito a 100 °C durante 18 horas Despues de enfriarla hasta

910

temperatura ambiente, se diluyo la reaccion con $H_2O$ (150 mL) y se recogieron los sólidos filtrando el lavado con eter dimetilico La cromatografia (gel de silice, hexanos/acetato de etilo) proporcionó un sólido de color blanquecino (7,78 g, al 65%) $^1H$ NMR (300 MHz, $CDCl_3$) δ 7,79 (d, $J$ = 8,3 Hz, 2H), 7,54 (d, $J$ = 8,5 Hz, 2H), 7,44-7,41 (m, 5H), 7,22 (d, $J$ = 13,3, 1H), 6,13 (dd, $J$ = 2,6, 7,7 Hz, 1H), 6,06 (d, $J$ = 2,6 Hz, 1H), 5,07 (s, 2H)

Etapa 2 Preparación de 4-[4-(benciloxi)-3-bromo-2-oxopiridin-1(2H)-il]benzonitrilo




Se suspendio 4-[4-(benciloxi)-2-oxopiridin-1(2H)-il]benzonitrilo (Etapa 1) (2,76 g, 9,13 mmol) en acetonitrilo (50 mL) y se enfrio en un baño de hielo Se agrego *N*-bromosuccinimida (1,71 g, 9,54 mmol) Una vez se completo la adición, se eliminó el baño refrigerante Despues de agitar durante 45 minutos, se diluyo la reacción con acetonitrilo y se recogieron los sólidos mediante filtración para proporcionar un solido de color blanco (3,13 g, al 90%) $^1H$ NMR (300 MHz, DMSO-$d_6$) δ 8,00 (d, $J$ = 8,5 Hz, 2H), 7,84 (c, $J$ = 7,9 Hz, 1H), 7,66 (d, $J$ = 8,5, 2H), 7,50-7,37 (m, 5H), 6,63 (d, $J$ = 7,9 Hz, 1H), 5,41 (s, 2H)

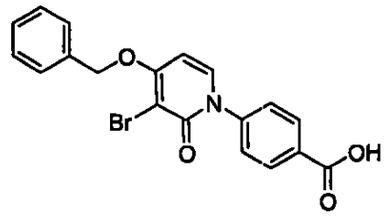
Etapa 3 Preparación de metil-[4-(bencil)oxi-3-bromo-2-oxopiridin-1(2H)-il]]benzoato Se suspendio 4-[4-(benciloxi)-3-bromo-2-oxopiridin-1(2H)-il]benzonitrilo (Etapa 2) (1,50 g, 3,93 mmol) en metanol (50 mL) y se enfrió en un baño de hielo Se hizo burbujear HCl (g) a través de la mezcla durante 5 minutos Luego se agito la reacción a temperatura ambiente durante la noche, momento

911

en el cual la mezcla de reaccion estaba concentrada El residuo se suspendic en 6*N* HCl (60 mL) y se calentó a reflujo durante 1,5 horas Despues de enfriarla hasta temperatura ambiente, los solidos se recogieron mediante filtración La cromatografia (gel de silice, hexanos/acetato de etilo) proporcionó un solido brillante de color blanquecino (0,540 g, al 61%) $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8,04 (d, *J* = 8,5 Hz, 2H), 7,81 (d, *J* = 7,8 Hz, 1H), 7,55 (d, *J* = 8,6 Hz, 2H), 7,47-7,39 (m, 5H), 6,57 (d, *J* = 7,9 Hz, 1H), 5,38 (s, 2H), 3,86 (s, 3H), ES-HRMS m/z 416,0355 (M+H calculado para $C_{20}H_{16}BrNO_4$ requiere 414,0341)

Ejemplo 197

Acido 4-[4-(benciloxi)-3-bromo-2-oxopiridin-1(2H)-il]benzoico



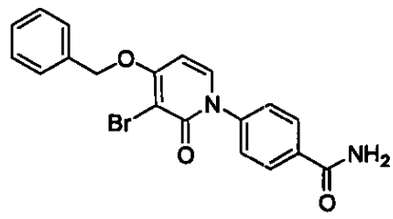

Preparación de acido 4-[4-(benciloxi)-3-bromo-2-oxopiridin-1(2H)-il]benzoico Ejemplo 196 (0,460 g, 1,11 mmol) se disolvieron en tetrahidrofurano (5,0 mL) Se agregó trimetilsilanolato de potasio (0,285 g, 2,22 mmol) La reaccion se agito a temperatura ambiente durante 3 horas, momento en el que se agrego $H_2O$ (10 mL) La mezcla acuosa de reacción se acidifico (pH-3) con 1*N* HCl Se evaporó el tetrahidrofurano, se agrego $H_2O$ adicional (50 mL) y la capa acuosa se extrajo con acetato de etilo (2 x 50 mL) Las capas organicas combinadas se lavaron con salmuera (50 mL), se secaron sobre $Na_2SO_4$, se filtraron y se evaporaron para proporcionar un solido de color oxido (0,444 g, al 100%) $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8,02 (d, *J* = 8,6 Hz, 2H), 7,80 (d, *J* = 7,8 Hz, 1H), 7,55 (d, *J* = 8,6

912

Hz, 2H), 7,50-7,34 (m, 5H), 6,57 (d, $J$ = 7,9 Hz, 1H), 5,38 (s, 2H), ES-HRMS m/z 400,0191 (M+H calculado para $C_{19}H_{14}BrNO_4$ requiere 400,0184)

Ejemplo 198

4-[4-(benciloxi)-3-bromo-2-oxopiridin-1(2H)-il]benzamida

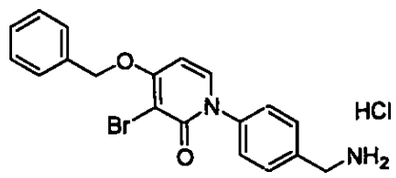



Preparacion de 4-[4-(benciloxi)-3-bromo-2-oxopiridin-1(2H)-il]benzamida Ltapa 2, se suspendio el compuesto del Ejemplo 196 (0,238 g, 0,624 mmol) en alcohol terc-butilico (3,0 mL) Se agrego KF en $Al_2O_3$ al 40 % en peso (0,453 g, 3,12 mmol) La mezcla de reaccion se calentó a reflujo durante 5 dias Se agrego KF adicional en 40 % en peso de $Al_2O_3$ (0,453 g, 3,12 mmol) y se continuo calentando a reflujo durante la noche Después de enfriarla a temperatura ambiente, se agregaron cloroformo y metanol y se recogieron los solidos por filtración La cromatografia (fase inversa, acetonitrilo/$H_2O$) proporciono un solido de color tostado(0,073 g, al 30%) $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8,07 (s, 1H), 7,95 (d, $J$ = 8,6 Hz, 2H), 7,79 (d, $J$ = 7,8 Hz, 1H), 7,47-7,34 (m, 7H), 6,56 (d, $J$ = 7,9 Hz, 1H), 5,38 (s, 2H), ES-HRMS m/z 399,0372 (M+H calculado para $C_{19}H_{15}BrN_2O_3$ requiere 399 0344)

Ejemplo 199

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1-[4-(aminometil)fenil]-4-(benciloxi)-3-bromopiridin-2(1H)-ona

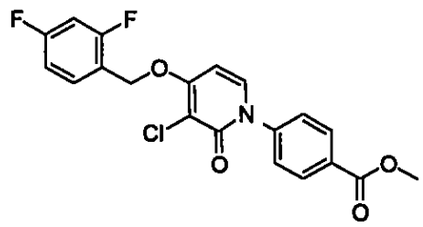



Preparación de 1-[4-(aminometil)fenil]-4-(benciloxi)-3-bromopiridin-2(1H)-ona El compuesto de la Etapa 2, Ejemplo 196 (1,25 g, 3,28 mmol) se disolvio en tetrahidrofurano (15 mL) Se agrego borano-dimetilsulfuro (3,44 mL, 6,89 mmol, 2,0 M en tetrahidrofurano)y se calento la mezcla a reflujo Despues de transcurridas 14,5 horas se evaporo el disolvente Se agrego 0,5*M* NaOH (50 mL) seguido de acetato de etilo La capa acuosa se neutralizo con 1*N* HCl Se agrego metanol saturado con HCl y la mezcla se calento a reflujo durante 5 horas Despues de enfriarla a temperatura ambiente, se agregó eter dietilico y se recogieron los solidos por filtración Los solidos se trataron con 4*N* HCl en dioxano (5 mL) y metanol (1 mL) a temperatura ambiente durante 1 hora, momento en el que se agrego eter dietilico y se recogieron los sólidos mediante filtración para proporcionar un sólido de color tostado (0,920 g, al 67%) $^1$H NMR (300 MHz, DMSO-$d_6$) δ 8,67 (br s, 2H), 7,76 (d, $J$ = 7,6 Hz, 1H), 7,64 (d, $J$ = 8,3 Hz, 2H), 7,50-7,37 (m, 7H), 6,56 (d, $J$ = 7,6 Hz, 1H), 5,41 (s, 2H), 4,09 (br s, 2H), ES-HRMS m/z 385,0555 (M+H calculado para $C_{19}H_{17}BrN_2O_2$ requiere 385 0552)

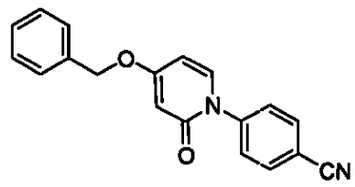
Ejemplo 200

Metil-4-[3-cloro-4-[(2,4-diflurobencil)oxi]-2-oxipiridin-1(2H)-il]benzoato

914

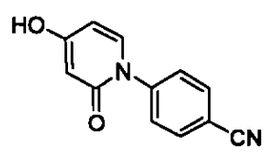


Etapa 1 Preparación de 4-[4-(benciloxi)-2-oxopiridin-1(2H)-il]benzonitrilo



Se disolvió 4-benciloxi-2(1H)-piridona (50,0 g, 248,47 mmol) en dimetil sulfoxido (300 mL) Se agrego carbonato de potasio (68,68 g, 496,94 mmol), seguido de 4-fluorobenzonitrilo (31,60 g, 260,89 mmol) La reaccion se agito a 100 °C durante 20 horas Despues de enfriarla hasta temperatura ambiente, se diluyo la reacción con $H_2O$ (600 mL) y se recogieron los solidos filtrando el lavado con eter dimetilico Luego, se lavaron los solidos con metanol caliente para proporcionar un sólido de color tostado (55 6 g, al 74%) $^1H$ NMR (300 MHz, $CDCl_3$) δ 7,79 (d, $J$ = 8,3 Hz, 2H), 7,54 (d, $J$ = 8,5 Hz, 2H), 7,44-7,41 (m, 5H), 7,22 (d, $J$ = 13,3, 1H), 6,13 (dd, $J$ = 2,6, 7,7 Hz, 1H), 6,06 (d, $J$ = 2,6 Hz, 1H), 5,07 (s 2H)

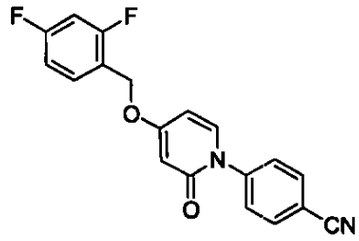
Etapa 2 Preparación de 1-[4-nitrilofenil]-4-hidroxi-2(1H)-piridinona



Se disolvio 4-[4-(benciloxi)-2-oxopiridin-1(2H)-il]benzonitrilo (Etapa 1) (20,0 g, 66,15 mmol) en metanol (300 mL) Se agregó formato de amoniaco (8,34 g, 132,3

mmol) seguido de Pd/C al 5% (6,62 g) La mezcla resultante se calentó a reflujo durante 20 minutos, momento en el que la reaccion comenzo a ser exotermica Se permitio que la mezcla se enfriara hasta temperatura ambiente, momento en el cual se filtró a traves de una almohadilla de Celite® lavandola con metanol El filtrado se evaporo para proporcionar un sólido amarillo pálido (16,2 g, > al 100%) $^1$H NMR (300 MHz, $CDCl_3$) δ 8,46 (s, 1H), 7,95 (d, *J* = 8,5 Hz, 2H), 7,62 (d, *J* = 8,5 Hz, 2H), 7,47 (d, *J* = 7,7 Hz, 1H), 5,98 (dd, *J* = 2,6, 7,7 Hz, 1H), 5,54 (d, *J* = 2,4 Hz, 1H)

Etapa 3 Preparacion de 4-[4-[(2,4-difluorobenciloxi)]-2-oxopiridin-1(2H)-il]benzonitrilo

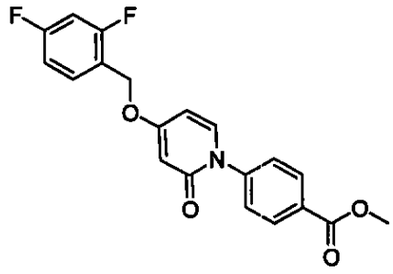



Se disolvió 1-[4-nitrilofenil]-4-hidroxi-2(1H)-piridinona (Etapa 2) (16,2 g) en *N,N*-dimetilformamida (100 mL) Se agregó carbonato de potasio (10,06 g, 72,77 mmol) seguido de α-bromo-2,4-difluorotolueno (8,91 mL, 69,46 mmol) La mezcla resultante se calentó hasta 65 °C durante 1 hora Se agrego α-bromo-2,4-difluorotolueno adicional (4,25 mL, 33,08 mmol) La mezcla resultante se calento hasta 65 °C durante 5 horas Se agrego α-bromo-2,4-difluorotolueno adicional (2,12 mL, 16,54 mmol) Despues de agitar a 65 °C durante la noche, se dejó que la reaccion se enfriara hasta alcanzar temperatura ambiente Se agrego $H_2O$ (300 mL) y se recogio el solido mediante filtración Una porcion (8,0 g) de los sólidos se lavó con metanol caliente para producir un solido de color amarillo claro (6,22 g, al

916

78%) $^1$H NMR (300 MHz, $CDCl_3$) δ 8,00 (d, $J$ = 8,5 Hz, 2H), 7,72-7,64 (m, 2H), 7 66 (d, $J$ = 8,5 Hz, 2H), 7,40-7,32 (m, 1H), 7,22-7,16 (m, 1H), 6,17-6,11 (m, 2H), 5,17 (s, 2H)

Etapa 4 Preparación de 4-[4-[2,4-difluorobencil)oxi]-2-oxopiridin-1(2H)-il]benzoato de metilo



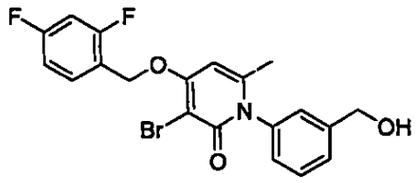
Se suspendio 4-[4-[(2,4-difluorobenciloxi)-2-oxopiridin-1(2H)-il]benzonitrilo (Etapa 3) (2,00 g, 5,91 mmol) en metanol (20 mL) y $H_2O$ (5 mL) y se enfrio en un baño de hielo Se hizo burbujear HCl (g) a traves de la mezcla hasta que la mayoria de los solidos se disolvieron La mezcla de reaccion se calentó a reflujo durante 3 horas La reaccion luego se volvio a enfriar en un baño de hielo y se hizo burbujear HCl a traves de la mezcla durante 5 minutos La mezcla se calentó a reflujo durante 2 horas y luego se evaporó el metanol Se adiciono $H_2O$ adicional (50 mL) y la mezcla de reaccion se extrajo con acetato de etilo (50 mL) y tetrahidrofurano (50 mL) Las capas orgánicas combinadas se lavaron con salmuera (50 mL), se secaron sobre $Na_2SO_4$, se filtraron y se evaporaron La cromatografia (gel de silice, hexanos/acetato de etilo con metanol al 10%) proporciono un solido de color blanquecino (0,630 g, al 29%) $^1$H NMR (300 MHz, DMF-$d_6$) δ 8,15 (d, $J$ = 8,5 Hz, 2H), 7,80 (*aprox* q, $J$ = 7,9 Hz, 1H), 7,74-7,67 (m, 1H), 7,68 (d, $J$ = 8,5 Hz, 2H), 7,42-7,34 (*aprox* dt, $J$ = 2,4, 9,0 Hz, 1H), 7,28-7,22 (m, 1H), 6,20 (dd, $J$ = 2,6, 7,6

Hz, 1H), 6,15 (d, $J$ = 2,4 Hz, 1H), 5,28 (s, 2H), 3,98 (s, 3H)

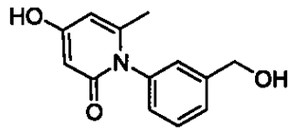
Etapa 5 Preparacion de metil-4-[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxipiridin-1(2H)-il]benzoato Se suspendió metil-4-[4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2H)-il]benzoato (Etapa 4) (0,520 g, 1,40 mmol) en acetonitrilo (10,0 mL) Se agrego *N*-clorosuccinimida (0,196 g, 1,47 mmol) seguido de varias gotas de acido dicloroacético La mezcla resultante se calento a reflujo durante la noche De‹pues de enfriarla durante la noche, se agrego acetonitrilo adicional y el precipitado se recogio por filtracion para proporcionar un solido de color blanquecino (0,331 g, al 58%) $^1$H NMR (300 MHz, DMF-$d_6$) δ 8,34 (d, $J$ = 8,5 Hz, 2H), 8,12 (d, $J$ = 7,9 Hz, 1H), 8,04-7,96 (m, 1H), 7,88 (d, $J$ = 8,5 Hz, 2H), 7,59-7,53 (m, 1H), 7,52-7,41 (m, 1H), 7,05 (d, $J$ = 7,9 Hz, 1H), 5,70 (s, 2H), 4,15 (s, 3H) ES-HRMS m/z 406,0644 (M+H calculado para $C_{20}H_{14}ClF_2NO_4$ requiere 406 0652)

Ejemplo 201

3-Bromo-4-[(2,4-difluorobencil)oxi]-1-[3-(hidroximetil)fenil]-6-metilpiridin-2(1H)-ona




Etapa 1 Preparacion de 4-hidroxi-1-[3-(hidroximetil)fenil]6-metilpiridin-2(1H)-ona

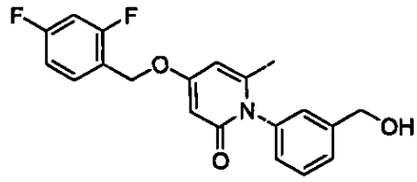



Se combinaron 4-hidroxi-6-metil-2-pirona (10,0 g, 79,3 mmol) y alcohol 3-aminobencilico (9,77 g, 79,3 mmol) en $H_2O$

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(100 mL) y se calento a reflujo Despues de 48 horas a reflujo, se concentró la mezcla de la reacción El residuo se trato con metanol y el precipitado se recogio mediante filtración para proporcionar un solido de color amarillo palido (3,04 g, al 17%) $^1$H NMR (300 MHz, DMSO-$d_6$) d 10,6 (br s, 1H), 7,46-7,35 (m, 2H), 7,09-7,03 (m, 2H), 5,88 (d, $J$ = 1,6 Hz, 1H), 5,55 (d, $J$ = 2,6 Hz, 1H), 4,54 (d, $J$ = 4,2 Hz, 2H), 1,83 (s, 3H)

Etapa 2 Preparacion de 1-[3-(hidroximetil)fenil]-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona



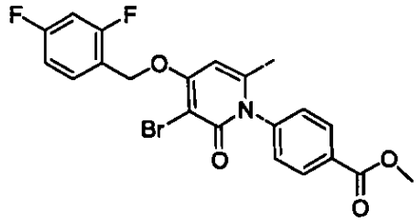

Se suspendio 4-hidroxi-1-[3-(hidroximetil)fenil]6-metilpiridin-2(1H)-ona (Etapa 1) (0,674 g, 2,91 mmol) en acetona (10 mL) Se agregó carbonato de cesio (1,04 g, 3,21 mmol) seguido de α-bromo-2,4-difluorotolueno (0,392 mL, 3,06 mmol) Despues de agitar a temperatura ambiente durante dos dias, se concentró la reaccion El residuo se dividio en porciones entre $H_2O$ (30 mL) y acetato de etilo (30 mL) La capa acuosa se extrajo más con acetato de etilo (30 mL) Las capas orgánicas combinadas se lavaron con salmuera (30 mL), se secaron sobre $Na_2SO_4$, se filtraron y se concentraron La cromatografia (gel de silice, hexanos/acetato de etilo con metanol al 10%) proporcionó un solido de color blanco (0,531 g, al 51%) $^1$H NMR (300 MHz, $CDCl_3$) δ 7,51-7,39 (m, 3H), 7,82 (s, 1H), 7,16 (d, $J$ = 26,8 Hz, 1H), 7,08-6,86 (m, 2H), 6,00 (d, $J$ = 2,6 Hz, 1H), 5,92 (d, $J$ = 2,6 Hz, 1H), 5,05 (s, 2H), 4,68 (s, 2H), 1,93 (s, 3H) ES-HRMS m/z 358,1256 (M+H calculado para $C_{20}H_{17}F_2NO_3$ requiere 358,1249)

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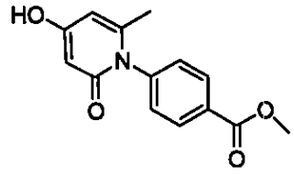
Etapa 3 Preparacion de 3-bromo-4-[(2,4-difluorobencil)oxi]-1-[3-(hidroximetil)fenil]-6-metilpiridin-2(1H)-ona Se suspendio 1-[3-(hidroximetil)fenil]-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona (Etapa 2) (0,460 g, 1,29 mmol) en acetonitrilo (5,0 mL) y se enfrio en un baño de hielo Se agregó *N*-bromosuccinimida (0,241 g, 1,35 mmol) Una vez se completo la adicion, se elimino el baño refrigerante Despues de agitar durante 1,5 horas se diluyó la reaccion con acetonitrilo y se recogieron los solidos mediante filtracion para dar un solido de color blanco (0,385 g, al 68%) $^1$H NMR (300 MHz, DMSO-$d_6$) d 7,70 (aprox q, J = 7,9 Hz, 1H), 7,49-7,32 (m, 3H), 7,24-7,10 (m, 3H), 6,66 (s, 1H), 5,35 (s, 2H), 4 56 (d, J = 5,6 Hz, 2H), 1,95 (s, 3H) ES-HRMS m/z 436,0384 (M+H calculado para $C_{20}H_{16}BrF_2NO_3$ requiere 436,0354)

Ejemplo 202

Metil-4-[3-bromo-4-[(difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]benzoato



Etapa 1 Preparación de 4-[4-hidroxi-6-metil-2-oxipiridin-1(2H)-il]benzoato de metilo

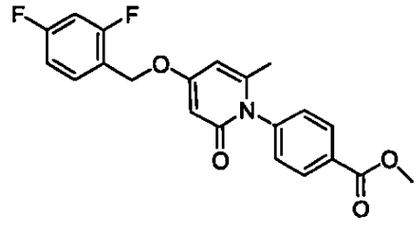


Se combinaron 4-hidroxi-6-metil-2-pirona (21,00 g, 166,70 mmol) y 4-metilaminobenzoato (25,20 g, 166,70 mmol) en 1,2-diclorobencero (50 mL) y se calento rapidamente

920

hasta 160 °C Despue ı de 15 mınutos a 160 °C, se dejó que la reaccıon se enfrıara hasta alcanzar temperatura ambıente La reaccıon se dıluyó con dıclorometano (50 mL) y se extrajo con $Na_2CO_3$ saturado (2 x 100 mL) Las capas acuosas combınadas se acıdıficaron (pH-2) con HCl concentrado El precıpıtado se recogıó mediante fıltracıón y se lavo con éter dıetılıco para proporcıonar un solıdo de color amarıllo/naranja (10,9 g, al 25%) $^1$H NMR (300 MHz, DMSO-$d_6$) δ 10,8 (s, 1H), 8,07 (d, $J$ = 8,5 Hz, 2H), 7,40 (d, $J$ = 8,5 Hz, 2H), 5,95 (d, $J$ = 2,4 Hz, 1H), 5,61 (d, $J$ = 2,4, 1H), 3,91 (s, 3H), 1,85 (s, 3H)

Etapa 2 Preparacıon de metıl-4-[4-[(dıfluorobencıl)oxı]-6-metıl-2-oxopırıdın-1(2H)-ıl]benzoato



Se suspendıó 4-(4-hıdroxı-6-metıl-2-oxopırıdın-1(2H)-ıl]benzoato de metılo (Etapa 1) (10,90 g, 42,04 mmol) en *N,N*-dımetılformamıda (100 mL) Se agrego carbonato de potasıo (6,97 g, 5C,45 mmol), seguıdo de bromuro 2,4-dıfluorobencılıco (5,66 mL, 44,14 mmol) La reaccıon se agıto a temperatura ambıente durante 3 dıas y luego se dıluyo con $H_2O$ (100 mL) Se extrajo la mezcla de reaccıon en acetato de etılo y tetrahıdrofurano (2 x 100 mL) El precıpıtado se recogıo mediante fıltracıón y el fıltrado organıco se lavó con salmuera (50 mL), se seco sobre $Na_2SO_4$, se fıltró y se evaporo El solıdo resultante se combınó con el precıpıtado para proporcıonar un solıdo de color rosa pálıdo (6,77 g, al 42%) $^1$H NMR (300 MHz, DMSO-

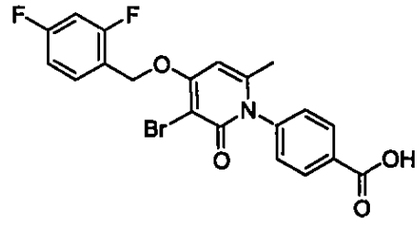
921

$d_6$) δ 8,01 (d, $J$ = 8,3 Hz, 2H), 7,67 (q, $J$ = 7,9 Hz, 1H), 7,43 (d, $J$ = 8,3 Hz, 2H), 7,35 (m, 1H), 7,18 (*aprox* dt, $J$ = 1,6, 8,5 Hz, 1H), 6,08 (d, $J$ = 1,8 Hz, 1H), 5,98 (d, $J$ = 2,4 Hz, 1H), 5,14 (s, 2H), 3,91 (s, 3H), 1,87 (s, 3H)

Etapa 3 Preparacion de metil-4-[3-bromo-4-[(difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]benzoato Se suspendio metil-4-[-4-[(difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]benzoato (Etapa 2) (6,74 g, 17,49 mmol) en acetonitrilo (100 mL) y se enfrió en un baño de hielo Se agrego *N*-bromosuccinimida (3,27 g, 18,36 mmol) Después de una hora se elimino el baño de hielo y despues de 30 minutos adicionales se diluyó la reaccion con acetonitrilo (20 mL) El precipitado se recogio por filtracion para proporcionar el compuesto del titulo como un solido de color blanquecino (6,94 g, al 85%) $^1$H NMR (300 MHz, $CDCl_3$) δ 8,20 (d, $J$ = 8,7 Hz, 2H), 7,61 (q, $J$ = 7,9 Hz, 1H), 7,30 (d, $J$ = 8,7 Hz, 2H), 7,02-6,96 (m, 1H), 6,90 (*aprox* dt, $J$ = 2,4, 9,5 Hz, 1H), 6,14 (s, 1H), 5,28 (s, 2H), 3,98 (s, 3H), 2,00 (s, 3H) ES-HRMS m/z 464,0304 (M+H calculado para $C_{21}H_{16}BrF_2NO_4$ requiere 464,0301)

Ejemplo 203

Ácido 4-[3-bromo-4-[(difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]benzoico



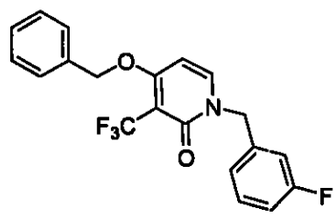

El compuesto del Ejemplo 202 (7,43 g, 16,00 mmol) se disolvio en tetrahidrofurano (40 mL) Se agrego trimetilsilanolato de potasio (4,10 g, 32,00 mmol) y se

922

agitó la mezcla de reaccion a temperatura ambiente durante 22 horas El tetrahidrofurano se evaporo y se agrego $H_2O$ (50 mL) Se acidifico la mezcla de reaccion acuosa con 1*N* HCl y se recogió el precipitado mediante filtracion Se lavaron los solidos con metanol hirviendo para proporcionar un solido de color blanquecino (5,05 g, al 70%) $^1$H NMR (300 MHz, DMSO-$d_6$) δ 13,2 (br s, 1H), 8,10 (d, *J* = 8,5 Hz, 2H), 7,72 (q, *J* = 7,9 Hz, 1H), 7,45 (d, *J* = 8,3 Hz, 2H), 7,38 (*aprox* dt, *J* = 2,4, 9,9 Hz, 1H), 7,23 (*aprox* dt, *J* = 1,8, 8,5 Hz, 1H), 6,72 (s, 1H), 5,37 (s, 2H), 1,97 (s, 3H) ES-HRMS m/z 450,0154 (M+H calculado para $C_{20}H_{14}BrF_2NO_4$ requiere 450,0147)

Ejemplo 204

4-(Benciloxi)-1-(3-fluorobencil)-3-(trifluorometil)piridin-2(1H)-ona



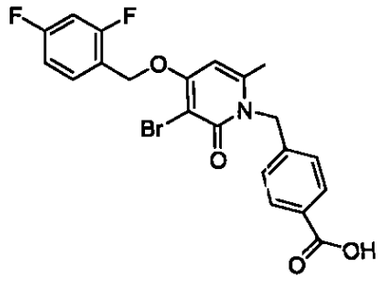

El material de inicio (0,250 g, 0,591 mmol) se disolvio en 1-metil-2-pirrolidinona (5,0 mL) Se agrego acido trifluoroacetico, sal de sodio (0,322 g, 2,36 mmol), seguido de yoduro de cobre(I) (0,225 g, 1,18 mmol) La mezcla resultante se calento hasta 180 °C durante 5 horas y luego se dejo enfriar hasta alcanzar temperatura ambiente Se diluyo la reaccion con $H_2O$ (50 mL) y salmuera (50 mL), y luego se extrajo en acetato de etilo (2 x 50 mL) Las capas organicas combinadas se lavaron con salmuera (50 mL), se secaron sobre $Na_2SO_4$ se filtraron y se evaporaron La cromatografia (fase inversa, acetonitrilo/$H_2O$) proporciono un solido de color blanquecino (0,050 g, al 22%) $^1$H NMR (400 MHz, $CDCl_3$) δ 7,40-7,27 (m, 8H), 7,06 (d, *J* = 7,7 Hz,

923

1H), 6,97 (d, $J$ = 9,0 Hz, 1H), 6,07 (d, $J$ = 7,7 Hz, 1H), 5,20 (s, 2H), 5,06 (s, 2H) ES-HRMS m/z 378,1097 (M+H calculado para $C_{20}H_{15}F_4NO_2$ requiere 378,1112)

Ejemplo 205

Ácido 4-{[3-bromo-4-[(2,4-difluorobenciloxi]-6-metil-2-oxopiridin-1(2H)-il]metil}benzoico

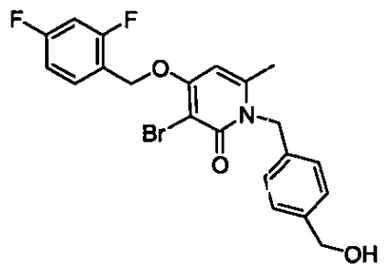


El compuesto del Ejemplo 153 (50,0 g, 104,54 mmol) se disolvio en metanol (500 mL) y dioxano (100 mL) Se agregó 1N NaOH (130 mL, 130 mmol) La mezcla resultante se calento hasta 50 °C durante 5,5 horas La reaccion se concentro parcialmente y se acidificó (pH 2) la mezcla heterogenea con 1*N* HCl El precipitado se recogio mediante filtracion para proporcionar un sólido de color blanco (49,2 g, > al 100 %) $^1$H NMR (300 MHz, DMSO-$d_6$) δ 7,94 (d, $J$ = 8,3 Hz, 2H), 7,70 (*aprox* q, $J$ = 7,9 Hz, 1H), 7,35 (dt, $J$ = 2,2, 9,9 Hz, 1H), 7,18 (*aprox* d, $J$ = 8,3 Hz, 2H), 7,17-7,12 (m, 1H), 6,64 (s, 1H), 5,41 (s, 2H), 5,33 (s, 2H), 2,32 (s, 3H) ES-HRMS m/z 464,0327 (M+H calculado para $C_{21}H_{16}BrF_2NO_4$ requiere 464,0304)

Ejemplo 206

3-Bromo-4-[(2,4-difluorobencil)oxi]-1-[4-(hidroximetil)bencil]-6-metilpiridin-2(1H)-ona

924

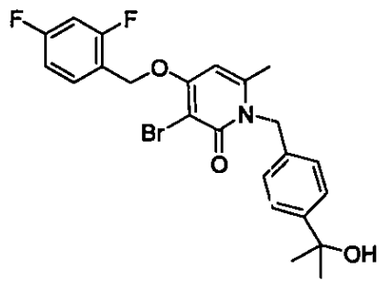


El compuesto del Ejemplo 205 (40,0 g, 86,16 mmol) se suspendio en tetrahidrofurano (300 mL) y se enfrio en un baño de hielo Se agrego dimetilsulfuro de borano (129,2 mL, 258,48 mmol, 2 0 *M* en tetrahidrofurano) lentamente Durante la noche, se dejo entibiar lentamente la mezcla resultante hasta alcanzar temperatura ambiente La mezcla se volvió a enfriar en baño de hielo y se enfrió repentinamente con la adicion de pequeños trozos de hielo Despues de que cesó la evolución de gas, se agrego agua helada adicional El matraz se equipó con un aparato de destilacion y se elimino el dimetilsulfuro Despues de que la reacción se enfrió hasta temperatura ambiente, se agregaron $H_2O$ (300 mL), acetato de etilo (200 mL) y tetrahidrofurano (300 mL) El precipitado que se formó se recogio mediante filtracion, y el filtrado se coloco en un embudo separador La capa acuosa se extrajo más con acetato de etilo (300 mL) Las capas orgánicas combinadas se lavaron con salmuera (300 mL) La fase organica se secó sobre $Na_2SO_4$ y se evaporó, lo que se combino con el precipitado para producir un sólido de color blanquecino (37,8 g, al 97%) $^1H$ NMR (400 MHz, $CDCl_3$) δ 7,47 (*aprox* q, *J* = 7,7 Hz, 1H), 7,23 (d, *J* = 7,9 Hz, 2H), 7,05 (d, *J* = 7,9 Hz, 2H), 6,86 (*aprox* dt, *J* = 2,3, 8,6 Hz, 1H), 6,79 (*aprox* dt, *J* = 2,4, 8,4 Hz, 1H), 6,00 (s, 1H), 5,28 (s, 2H), 5,16 (s, 2H), 4,57 (s, 2H), 2,25 (s, 3H) ES-HRMS m/z 450,0512 (M+H calculado para $C_{21}H_{18}BrF_2NO_3$ requiere 450,0511)

925

Ejemplo 207

3-Bromo-4-[(2,4-difluorobencil)oxi]-1-[4-(1-hidroxi-1-metiletil)bencil]-6-metilpiridin-2(1H)-ona



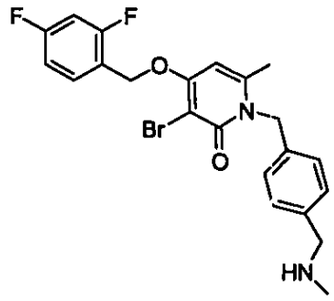

Preparacion de 3-bromo-4-[(2,4-difluorobencil)oxi]-1-[4-(1-hidroxi-1-metiletil)bencil]-6-metilpiridin-2(1H)-ona El compuesto del Ejemplo 153 (2,00 g, 4,18 mmol) suspendido en tetrahidrofurano (20 mL) se enfrio en el baño de hielo seco/acetona Se agrego lentamente bromuro de metil magnesio (4,32 mL, 12,96 mmol, 3,0 *M* en eter dietilico) Durante la noche, se dejo entibiar lentamente la reacción hasta alcanzar temperatura ambiente Luego, se enfrió la reaccion en un baño de hielo y se enfrio repentinamente mediante la adicion de $NH_4Cl$ saturado (50 mL) Se agrego $H_2O$ y la reaccion se extrajo con acetato de etilo Las capas organicas combinadas se lavaron con salmuera (50 mL), se secaron sobre $Na_2SO_4$, se filtraron y se evaporaron El residuo se sometió a cromatografia (gel de silice, hexanos/acetato de etilo con metanol al 10%) para proporcionar una espuma de color blanquecino La espuma se disolvio en acetonitrilo y se enfrió en un baño de hielo Se agrego *N*-bromosuccinimida (0,057 g, 0,320 mmol) Una vez se completó la adicion, se elimino el baño refrigerante Despues de 2,5 horas a temperatura ambiente, se concentró la reacción La purificacion mediante cromatografia (gel de silice, hexanos/acetato de etilo con metanol al 10%) proporciono una espuma de color blanco $^1H$ NMR (400 MHz,

926

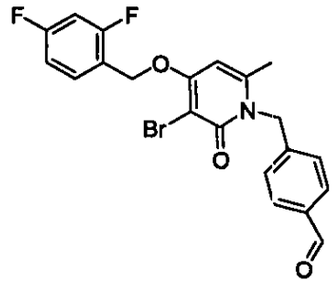
$CDCl_3$) δ 7,56 (*aprox* q, *J* = 7,7 Hz, 1H ), 7,39 (d, *J* = 78,3 Hz, 2H), 7,11 (d, *J* = 8,2 Hz, 2H), 6,92 (*aprox* dt, *J* = 1,7, 8,4 Hz, 1H), 6,86-6,81 (m, 1H), 5,97 (s, 1H), 5,31 (s, 2H), 5,18 (s, 2H), 2,29 (s, 3H), 1,52 (s, 6H) ES-HRMS m/z 478,0811 (M+H $C_{23}H_{22}BrF_2NO_3$ requiere 478,0824)

Ejemplo 208

3-Bromo-4-[(2,4-difluorobencil)oxi]- 6-metil-1-{4-[(metilamino)metil]bencil}piridin-2(1H)-ona



Etapa 1 Preparacion de 4-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}benzonitrilo



El compuesto del Ejemplo 206 (1,30 g, 2,89 mmol) se suspendio en acetonitrilo (10 mL) y se enfrió en un baño de hielo Se agrego 1-hidroxi-1,3-dihidro-3,3-bis(trifluorometil)-1,2-bencyodoxol 1-óxido (0,580 g, 1,44 mmol) y se agito la mezcla de reacción a temperatura ambiente durante la noche Se agrego eter dietilico y el solido se recogio mediante filtración para proporcionar un sólido blanco (1,14 g, al 88%) $^1H$ NMR (400 MHz, $CDCl_3$) δ

927

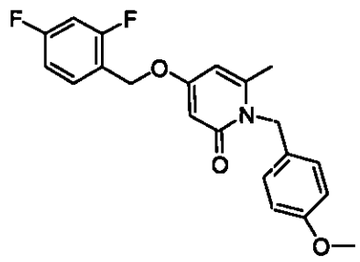
9,96 (s, 1H), 7,80 (d, *J* = 8,2 Hz, 2H), 7,56 (*aprox* q, *J* = 7,7 Hz, 1H), 7,30 (d, *J* = 8,2 Hz, 2H), 6,93 (*aprox* dt, *J* = 1,6, 8,3 Hz, 1H), 6,87-6,82 (m, 1H), 6,02 (s, 1H), 5,41 (s, 2H), 5,20 (s, 2H), 2,27 (s, 3H)

Etapa 2 3-Bromo-4-[(2,4-difluorobencil)oxi]- 6-metil-1-{4-[(metilamino)metil]bencil}piridin-2(1H)-ona Se disolvio 4-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}benzaldehido (Etapa 1) (1,53 g, 3,41 mmol) de la Etapa 1 en *N,N*-dimetilformamida (5,0 mL) Se agregó metilamina (3,41 mL, 6,83 mmol, 2,0 M en tetrahidrofurano) seguido por $NaHB(OAc)_3$ (2,17 g, 10,23 mmol) en *N,N*-dimetilformamida (8,0 mL) y acido acético (2,0 mL) La reacción se agito a temperatura ambiente durante la noche, momento en el que se agrego 1N NaOH (50 mL) y luego se extrajo con acetato de etilo (2 x 50 mL) Las capas orgánicas se lavaron con salmuera (25 mL), se secaron sobre $Na_2SO_4$, se filtraron y se evaporaron La cromatografia (sobre gel de silice, acetato de etilo con amoniaco metanolico/hexanos al 5%) proporcionó un sólido de color tostado (0,810 g, al 53%) $^1H$ NMR (400 MHz, $CDCl_3$) δ 7,55 (*aprox* q, *J* = 7,8 Hz, 1H), 7,22 (d, *J* = 8,1 Hz, 2H), 7,11 (d, *J* = 8,1 Hz, 2H), 6,92 (*aprox* dt, *J* = 2,4, 8,3 Hz, 1H), 6,90-6,80 (m, 1H), 5,95 (s, 1H), 5,32 (s, 2H), 5,17 (s, 2H), 3,68 (s, 2H), 2,40 (s, 3H), 2,27 (s, 3H) ES-HRMS m/z 463,0838 (M+H calculado para $C_{22}H_{21}BrF_2N_2O_4$ requiere 463,0827)

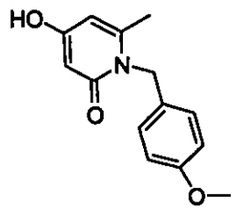
Ejemplo 209

4-[(2,4-difluorobencil)oxi]-1-(4-metoxibencil)-6-metilpiridin-2-(1H)-ona

928



Etapa 1 Preparacion de 1-(4-metoxibencil)-4-hidroxi-6-metilpiridin-2(1H)-ona



4-Hidroxi-6-metil-2-pirona (4,60 g, 36,45 mmol) y 4-metoxibencilamina (5,00 g, 36,45 mmol) en $H_2O$ (100 mL) se calentaron a reflujo Despues de 15 horas a reflujo, se dejó que la reacción se enfriara hasta alcanzar temperatura ambiente El precipitado se recogió mediante filtracion del lavado con $H_2O$ para proporcionar un solido de color amarillo pálido (8,00 g, al 89 %) $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7,2 (d, $J$ = 8,7 Hz, 2H), 6,85 (d, $J$ = 8,7 Hz, 2H), 5,74 (d, $J$ = 2,0 Hz, 1H), 5,56 (d, $J$ = 2,5 Hz, 1H), 5,08 (s, 2H), 3,68 (s, 3H), 2,14 (s, 3H)

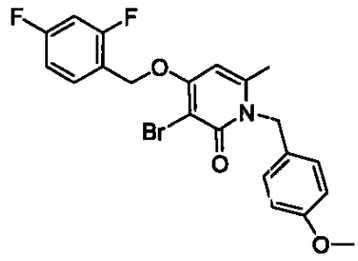
Etapa 2 Preparación de 4-[(2,4-difluorobencil)oxi]-1-(4-metoxibencil)-6-metilpiridin-2(1H)-ona Se disolvio 1-(4-metoxibencil)-4-hidroxi-6-metilpiridin-2(1H)-ona (Etapa 1) (7,97 g, 32,49 mmol) en *N*,*N*-dimetilformamida (60 mL) Se agregó carbonato de potasio (4,94 g, 35,74 mmol), seguido de α-bromo-2,4-difluorotolueno (4,38 mL, 34,11 mmol) La reacción se agitó a temperatura ambiente durante 20 horas, momento en el que la mezcla se filtro a traves de una almohadilla de Celite® lavando con acetonitrilo y se evaporó el filtrado El residuo se disolvio en $H_2O$ (150 mL)

929

y se extrajo en acetato de etilo (2 x 100 mL) La fase organica se lavo con salmuera (100 mL), se secó sobre $Na_2SO_4$, se filtro y se evaporo La cromatografia (sobre gel de sílice, hexanos/acetato de etilo con metanol al 10%) proporciono un solido de color blanquecino (3,64 g, al 30%) $^1H$ NMR (300 MHz $CDCl_3$) δ 7,42 *(aprox* q, *J* = 7,7 Hz, 1H), 7,13 (d, *J* = 8,5 Hz, 2H), 6,96-6,84 (m 2H), 6,85 (*aprox* d, *J* = 8,7 H , 2H), 6,01 (d, *J* = 2,6 Hz, 1H), 5,82 (d, *J* = 2,8 Hz, 1H), 5,23 (s, 2H), 5,02 (s, 2H), 3,79 (s, 3H), 2,25 (s, 3H) ES-HRMS m/z 372,1412 (M+H $C_{21}H_{19}F_2NO_3$ requiere 372,1417)

Ejemplo 210

3-Bromo-4-[(2,4-difluorobencil)oxi]-1-(4-metoxibencil)-6-metilpiridin-2(1H)-ona



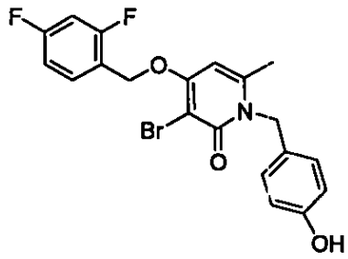

Preparacion de 3-bromo-4-[(2,4-difluorobencil)oxi]-1-(4-metoxibencil)-6-metilpiridin-2(1H)-ona El compuesto del Ejemplo 209 (0,200 g, 0,538 mmol) se suspendió en acetonitrilo (3 mL) y se enfrio en un baño de hielo Se agrego *N*-bromosuccinimida (0,101 g, 0,565 mmol) Una vez se completo la adición, se elimino el baño refrigerante Despues de 1 hora se concentro la reaccion La purificacion por cromatografia (gel de silice, hexanos/acetato de etilo) proporciono un solido de color blanco (0,240 g, al 99%) $^1H$ NMR (300 MHz, $CDCl_3$) δ 7,59 *(aprox* q, *J* = 7,8 Hz, 1H), 7,16 (d, *J* = 8,7 Hz, 2H), 6,97 (aprox dt, *J* = 2,4, 8,6 Hz, 1H), 6,91-6,83 (m, 1H), 6,85 (*aprox* d, *J* = 8,7 Hz, 2H), 5,98 (s, 1H), 5,31 (s, 2H), 5,21 (s, 2H), 3,79 (s, 3H),

930

2,34 (s, 3H) ES-HRMS m/z 450,0491 (M+H $C_{21}H_{18}BrF_2NO_3$ requiere 450,0511)

Ejemplo 211

3-Bromo-4-[(2,4-difluorobencil)oxi]-1-(4-hidroxibencil)-6-metilpiridin-2(1H)-ona

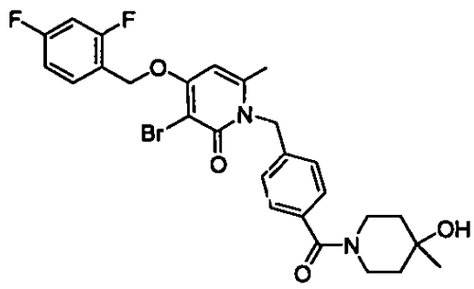


Preparacion de 3-bromo-4-[(2,4-difluorobencil)oxi]-1-(4-hidroxibencil)-6-metilpiridin-2(1H)-ona El compuesto del Ejemplo 210 (0,235 g, 0,522 mmol) se suspendio en acetonitrilo (3 mL) Se agregó nitrato cerico amonico (1,14 g, 2,09 mmol) disuelto en $H_2O$ (1 mL) La reaccion se agitó a temperatura ambiente durante 1 hora y luego se diluyó con diclorometano (25 mL) Luego se lavo la reaccion con $H_2O$ (10 mL) La fase acuosa se retroextrajo con diclorometano (20 mL) Las capas organicas combinadas se secaron sobre $Na_2SO_4$, se filtraron y se evaporaron Se lavo el residuo con acetato de etilo caliente para proporcionar un solido de color blanquecino (0,134 g, al 59%) $^1H$ NMR (300 MHz, DMSO-$d_6$) δ 7,75 *(apro* q, $J$ = 7,9 Hz, 1H), 7,65 (s, 1H), 7,45-7,36 (m, 1H), 7,36 (d, $J$ = 10,1Hz, 2H), 7,27-7,20 (m, 1H), 6,49 (d, $J$ = 10,1 Hz, 2H), 5,60 (s, 2H), 5,07 (s, 2H), 2,63 (s, 3H) ES-HRMS m/z 436,0187 (M+H $C_{20}H_{16}BrF_2NO_3$ requiere 436 0354)

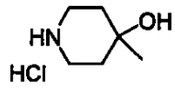
Ejemplo 212

3-Bromo-4-[(2,4-difluorobencil)oxi]-1-{4-[(4-hidroxi-4-metilpiperidin-1-il)carbonil]bencil}-6-metilpiridin-2(1H)-ona

931



Etapa 1 Preparacion de hidrocloruro de 4-hidroxi-4-metilpiperidina



Se enfrio en un baño de hielo *terc*-butil-4-oxo-1-piperidina (10,0 g, 50,19 mmol) disuelta en éter dietilico (100 mL) Se agregó bromuro de metil magnesio (18,40 mL, 55,21 mmol, 3,0 *M* en eter dietilico) Despues de entibiarla lentamente hasta temperatura ambiente, se volvió a enfriar la reacción en un baño de hielo y se enfrió rapidamente mediante la adición de $NH_4Cl$ saturado (75 mL) Se agrego $H_2O$ adicional y se elimino la capa organica La capa acuosa se extrajo mas con eter dietilico (50 mL) Las capas organicas combinadas se lavaron con salmuera, se secaron sobre $Na_2SO_4$, se filtraron y se concentraron La cromatografia (gel de silice, hexanos/acetato de etilo) proporcionó un aceite transparente El aceite resultante se disolvió en eter dietílico (10 mL) y se trató con 4*N* HCl/dioxano (32,61 mL, 130,43 mmol) Después de agitar a temperatura ambiente durante una hora la mezcla de reacción se concentró para dar un solido de color amarillo palido (5,05 g, > al 100%)

Etapa 2 Preparación de 3-Bromo-4-[(2,4-difluorobencil)oxi]-1-{4-[(4-hidroxi-4-metilpiperidin-1-il)carbonil]bencil}-6-metilpiridin-2(1H)-ona El acido

932

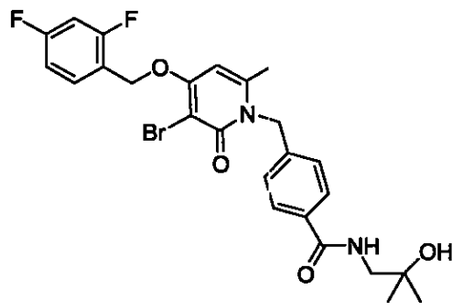
(0,300 g, 0,646 mmol) se suspendio en diclorometano (6,0 mL) Se agrego 1-hidroxibenzotriazol

(0,044 g, 0,323 mmol) seguido de gel del silice funcionalizado con 3-(1-ciclohexilcarbodiimida)propilo (2,02 g, 1,29 mmol, cargando = 0,64 mmol/g), gel de silice funcionalizado con 3-(1-morfolina)propilo (1,84 g, 1,29 mmol, cargando = 0,7 mmol/g) y diclorometano (2 mL) Despues de agitar a temperatura ambiente durante 15 minutos, se agrego hidrocloruro de 4-hidroxi-4-metilpiperidina (0,147 g, 0,969 mmol) La mezcla resultante se agito a temperatura ambiente durante la noche, momento en el que se agregó gel de silice funcionalizado con dimetilamina-3 (1,7 g, 2,58 mmol, cargando = 1,5 mmol/g) seguido de gel de silice funcionalizado con isocianato-3 (1,3 g, 1,62 mmol, cargando = 1 22 mmol/g) La mezcla resultante se agitó a temperatura ambiente durante 3 horas Luego, la mezcla de reacción se filtró y se concentró La cromatografia (gel de silice, hexanos/acetato de etilo con metanol al 10%) proporciono una espuma de color blanco (0,200 g, al 55%) $^1$H NMR (300 MHz, $CDCl_3$) δ 7,58 (*aprox* q, *J* = 7,7 Hz, 1H), 7,33 (d, *J* = 8,1 Hz, 2H), 7,18 (d, *J* = 8,1 Hz, 2H), 6,96 (*aprox* t, *J* = 8,3 Hz, 1H), 6,87 (*aprox* dt, *J* = 2,0, 9,5 Hz, 1H), 6,06 (s, 1H), 5,38 (s, 2H), 5,22 (s, 2H), 4,27 (*br* m, 1H), 3,41 (*br* m, 3H), 2,30 (s, 3H), 2,06 (s, 1H), 1,60 (*br* m, 4H), 1,28 (s, 3H) ES-HRMS m/z 561,1173 (M+H $C_{27}H_{27}BrF_2N_2O_4$ requiere 561,1195)

Ejemplo 213

4-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxipiridin-1(2H)-il]metil}-N-(2-hidroxi-2-metilpropil)benzamida

933

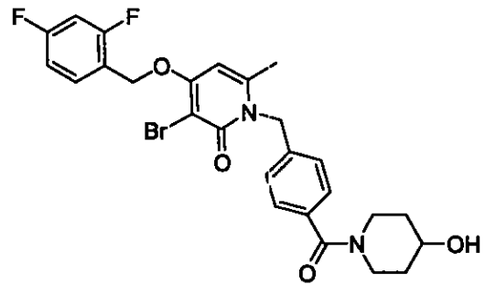


El compuesto del título se logró utilizando un procedimiento esencialmente similar al del Ejemplo 212 usando hidrocloruro 1-amino-2-metil-2-propanolico como material inicial

$^1$H NMR (400 MHz, $CDCl_3$) δ 7,70 (d, J = 8,3 Hz, 2H), 7,53 (*aprox* q, *J* = 7,8 Hz, 1H), 7,33 (t, *J* = 5,8 Hz, 1H), 7,06 (d, *J* = 8,3 Hz, 2H), 6,95-6,90 (m, 1H), 6,86-6,81 (m, 1H), 6,04 (s, 1H), 5,30 (s, 2H), 5,19 (s, 2H), 3,40 (d, J = 5,9 Hz, 2H), 2,98 (*br* s, 1H), 2,24 (s, 3H), 1,21 (s, 6H) ES-HRMS m/z 535,1012 (M+H $C_{25}H_{25}BrF_2N_2O_4$ requiere 535,1039)

Ejemplo 214

3-Bromo-4-[(2,4-difluorobencil)oxi]-1-{4-[(4-hidroxipiperidin-1-il)carbonil]bencil}-6-metilpiridin-2(1H)-ona



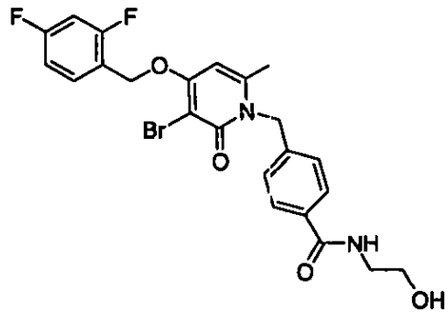
El compuesto del título se produjo esencialmente como en el Ejemplo 212 utilizando 4-hidroxipiperidina como material inicial $^1$H NMR (400 MHz, $CDCl_3$) δ 7,55 (*aprox* q, *J* = 7,7 Hz, 1H), 7,30 (d, *J* = 8,2 Hz, 2H), 7,15 (d, *J* = 8,3 Hz, 2H), 6,94 (*aprox* dt, *J* = 2,4, 8,4 Hz, 1H), 6,84

934

(*aprox* ddd, *J* = 2,6, 8,9, 10,3 Hz, 1H), 6,01 (s, 1H), 5,36 (s, 2H), 5,19 (s, 2H), 4,12-4,07 (m, 1H), 3,96-3,90 (m, 1H), 3,60 (*br* s, 1H), 3,33 (*br* s, 1H), 3,13 (*br* s, 1H), 2,27 (s, 3H), 1,91 (*br* s, 3H), 1,77 (*br* s, 1H), 1,57 (*br* s, 1H), 1,44 (*br* s, 1H) ES-HRMS m/z 547,1006 (M+H $C_{26}H_{25}BrF_2N_2O_4$ requiere 547,1039)

Ejemplo 215

4-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}-N-(2-hidroxietil)benzamida



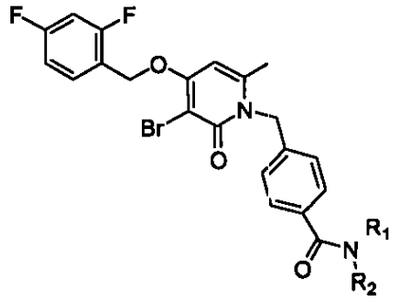

Preparación de 4-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}-N-(2-hidroxietil)benzamida A un recipiente de reaccion (un tubo de cultivo borosilicatado) se le agrego el compuesto del Ejemplo 205 (0,300 g, 0,646 mmol) Se agrego una disolucion madre de 1-hidroxibenzotriazol en *N,N*-dimetilformamida (3 mL, 0,11 M) al recipiente de reacción seguido por aproximadamente 1,10 g de la resina carbodiimida aglutinada con polimero (1,8 mmol/g) Luego se agrego *N,N*-dimetilformamida adicional (2 mL) al recipiente de reaccion Luego, se agito orbitalmente el aparato de reacción en paralelo (Labline Benchtop Orbital Shaker) a aproximadamente 200 rpm a temperatura ambiente durante 15 minutos Luego se agrego etanolamina (0,06 mL, 0,994 mmol) al recipiente de reacción y se agito orbitalmente el aparato de reaccion a temperatura ambiente durante la noche En este momento se diluyo la reaccion con

935

tetrahidrofurano (20 mL) y se trató con aproximadamente 2,0 g de resina poliamina (2,63 mmol/g) y aproximadamente 2,6 g de poliestireno funcionalizado con metilisocianato (1,10 mmol/g) y se continuó la agitación orbital a 200 rpm a temperatura ambiente durante 3 horas Luego se abrio el recipiente de reacción y el producto de fase de disolución se separo de los subproductos enfriados rapidamente insolubles mediante filtracion y su recoleccion en un vial Despues de una evaporacion parcial, los subproductos insolubles se enjuagaron mas con tetrahidrofurano (2 x 10 mL) y se combinaron con el filtrado parcialmente reducido El filtrado resultante se concentro soplando $N_2$ sobre el vial mientras se calentaba (60 °C) en un bloque de reacción (KEM-Lab Parallel Reactor) para proporcionar un sólido de color blanquecino (0,111 g, al 34%) $^1$H NMR (400 MHz, DMF-$d_6$) δ 8,45 (t, *J* = 5,4 Hz, 1H), 7,94 (d, *J* = 8,2 Hz, 2H), 7,76 (*aprox* q, *J* = 7,9 Hz, 1H), 7,33-7,27 (m, 1H), 7,27 (*aprox* d, *J* = 7,9 Hz, 2H), 7,20 (*aprox* dt, *J* = 2,4, 8,6 Hz, 1H), 6,65 (s, 1H), 5,47 (s, 2H), 5,38 (s, 2H), 4,83 (*br* s, 1H), 3,64-3,60 (m, 2H), 2,47-3,42 (m, 2H), 2,40 (s, 3H) ES-HRMS m/z 507,0742 (M+H $C_{23}H_{21}BrF_2N_2O_4$ requiere 507,0726)

Ejemplos 216-231

Preparacion de compuestos de 3-bromo-4-(2,4-difluorofenoxi)-6-metil-1-[4-(aminocarbonil)bencil]piridin-2(1H)-ona



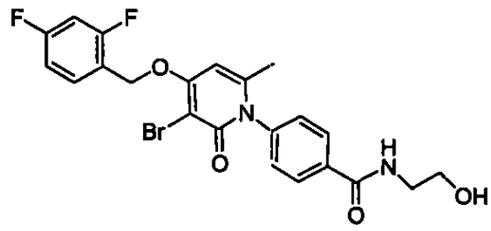
936

Los compuestos de los Ejemplos 216-231 se preparan siguiendo el metodo del Ejemplo 215 y sustituyendo la amina apropiada La desproteccion de los intermedios protegidos se logró con 4*N* HCl en dioxano para proporcionar los compuestos como sales de hidrocloruro

| Compuesto N° | R1 | R2 | % Rend | MF | M+H Requiere | ESHRMS m/z |
|---|---|---|---|---|---|---|
| Ej 216 | $CH_2CH_2NH$- | $CH_2CH_2NH$- | 73 | $C_{25}H_{24}BrF_2N_3O_4$ | 532,1042 | 532,1024 |
| Ej 217 | H | $CH_2CH_2NH_2$ | 49 | $C_{23}H_{22}BrF_2N_3O_3$ | 506,0885 | 506 0883 |
| Ej 218 | H | $CH_2CH_2CH_2NH_2$ | 31 | $C_{24}H_{24}BrF_2N_3O_3$ | 520,1042 | 520,1042 |
| Ej 219 | H | OH | 53 | $C_{21}H_{17}BrF_2N_2O_4$ | 479,0413 | 479,0423 |
| Ej 220 | H | $CH_3$ | 59 | $C_{22}H_{19}BrF_2N_2O_4$ | 477,0620 | 477 0605 |
| Ej 221 | $CH_3$ | $CH_3$ | 51 | $C_{23}H_{21}BrF_2N_2O_3$ | 491 0776 | 491,0794 |
| Ej 222 | $CH_2CH_2O$- | $CH_2CH_2O$- | 61 | $C_{25}H_{23}BrF_2N_2O_4$ | 533 0882 | 533,0901 |
| Ej 223 | $CH_2CH_2OH$ | $CH_2CH_2OH$ | 69 | $C_{25}H_{25}BrF_2N_2O_5$ | 551,0988 | 551,0978 |
| Ej 224 | $CH_2CH_2CH_2$- | $CH_2CH_2CH_2$- | 66 | $C_{26}H_{25}BrF_2N_2O_3$ | 531,1084 | 531,1089 |
| Ej 225 | H | $CH(CH_3)_2$ | 50 | $C_{24}H_{23}BrF_2N_2O_3$ | 505 0933 | 505,0901 |
| Ej 226 | $CH_2CH_2$- | $CH_2CH_2$- | 71 | $C_{25}H_{23}BrF_2N_2O_3$ | 517,0933 | 517,0908 |
| Ej 227 | $CH_2CH_2N(CH_3)$- | $CH_2CH_2N(CH_3)$- | 83 | $C_{26}H_{26}BrF_2N_3O_3$ | 546,1198 | 546,1215 |
| Ej 228 | H | $CH_2CH_2N(CH_3)_2$ | 81 | $C_{25}H_{26}BrF_2N_3O_3$ | 534,1198 | 534 1197 |
| Ej 229 | H | $CH_2CH_2OCH_3$ | 79 | $C_{24}H_{23}BrF_2N_2O_4$ | 521,0882 | 521,0861 |
| Ej 230 | $CH_3$ | $CH_2CH_2OH$ | 36 | $C_{24}H_{23}BrF_2N_2O_4$ | 521,0882 | 521,0893 |
| Ej 231 | $CH_3$ | $CH_2CH_2OCH_3$ | 82 | $C_{25}H_{25}BrF_2N_2O_4$ | 535,1039 | 535,1028 |

Ejemplo 232

4-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-N-(2-hidroxietil)benzamida




Preparacion de 4-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-N-(2-

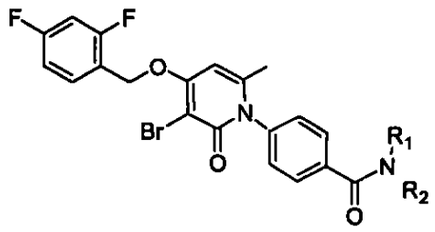
937

hidroxietil)benzamida A un recipiente de reaccion (un tubo de cultivo borosilicatado) se le agrego el compuesto del Ejemplo 203 (0,300 g, 0,666 mmol) Se agregó una disolución madre de 1-hidroxibenzotriazol en *N,N*-dimetilformamida (3 mL, 0,11 M) al recipiente de reacción seguido por aproximadamente 1,13 g de la resina carbodiimida aglutinada con polimero (1,8 mmol/g) Luego se agrego *N,N*-dimetilformamida adicional (2 mL) al recipiente de reaccion Luego, se agito orbitalmente el aparato de reaccion en paralelo (Labline Benchtop Orbital Shaker) a aproximadamente 200 rpm a temperatura ambiente durante 15 minutos Luego se agregó etanolamina (0,06 mL, 0,994 mmol) al recipiente de reaccion y se agitó orbitalmente el aparato de reaccion a temperatura ambiente durante la noche En este momento se diluyo la reacción con tetrahidrofurano (20 mL) y se trató con aproximadamente 2,0 g de resina poliamina (2,63 mmol/g) y aproximadamente 2,7 g de poliestireno funcionalizado con metilisocianato (1,10 mmol/g) y se continuo la agitación orbital a 200 rpm a temperatura ambiente durante 3 horas Luego se abrió el recipiente de reaccion y los productos de fase de disolución se separaron de los subproductos enfriados rapidamente insolubles mediante su filtración y recoleccion en un vial Despues de una evaporacion parcial, los subproductos insolubles se enjuagaron mas con tetrahidrofurano (2 x 10 mL) y se combinaron con el filtrado parcialmente reducido El filtrado resultante se concentro soplando $N_2$ sobre el vial mientras se calentaba (60 °C) en un bloque de reacción (KEM-Lab Parallel Reactor) La purificación mediante cromatografia (gel de silice) proporcionó un solido de color blanquecino (0,155 g, 47%) $^1$H NMR (400 MHz, DMF-$d_6$) δ 8,58 (t, $J$ = 5,5 Hz, 1H), 8,10 (d, $J$ = 8,3 Hz, 2H), 7,79 (*aprox* q, $J$ = 7,9 Hz,

938

1H), 7,47 (d, *J* = 8,3 Hz, 2H), 7,36-7,30 (m, 1H), 7,21 (*aprox* dt, *J* = 2,4, 8,5 Hz, 1H), 6,73 (s, 1H), 5,43 (s, 2H), 3,68 (*aprox* t, *J* = 5,9 Hz, 2H), 3,52-3,49 (m, 2H), 2,03 (s, 3H) ES-HRMS m/z 493,0597 (M+H $C_{22}H_{19}BrF_2N_2O_4$ requiere 493,0569)

Ejemplos 233-243



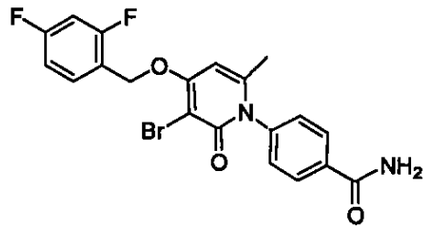

Los compuestos de los Ejemplos 233-243 se preparan siguiendo el método del Ejemplo 232 y sustituyendo la amina apropiada por etanolamina La desprotección de los intermedios protegidcs se logro con 4*N* HCl en dioxano para proporcionar los compuestos como sales de hidrocloruro

| Compuesto N° | R1 | R2 | % Rend | MF | M+H Requiere | ESHRMS m/z |
|---|---|---|---|---|---|---|
| Ej 233 | $CH_2CH_2NH$- | $CH_2CH_2NH$- | 40,3 | $C_{24}H_{22}BrF_2N_3O_3$ | 518,0885 | 518,0866 |
| Ej 234 | H | $CH_2CH_2NH_2$ | 57,1 | $C_{22}H_{20}BrF_2N_3O_3$ | 492,0729 | 492,0748 |
| Ej 235 | H | $CH_2CH_2CH_2NH_2$ | 21,5 | $C_{23}H_{22}BrF_2N_3O_3$ | 506,0885 | 506,0915 |
| Ej 236 | H | OH | 33,9 | $C_{20}H_{15}BrF_2N_2O_4$ | 465,0256 | 465,0259 |
| Ej 237 | H | $CH_3$ | 20,7 | $C_{21}H_{17}BrF_2N_2O_3$ | 463,0463 | 463,0479 |
| Ej 238 | $CH_3$ | $CH_3$ | 22,3 | $C_{22}H_{19}BrF_2N_2O_3$ | 477 0620 | 477 0643 |
| Ej 239 | $CH_2CH_2O$- | $CH_2CH_2O$- | 84,4 | $C_{24}H_{21}BrF_2N_2O_4$ | 519,0726 | 519,0723 |
| Ej 240 | $CH_2CH_2OH$ | $CH_2CH_2OH$ | 46,6 | $C_{24}H_{23}BrF_2N_2O_5$ | 537,0831 | 537,0854 |
| Ej 241 | $CH_2CH_2CH_2$- | $CH_2CH_2CH_2$- | 76,5 | $C_{25}H_{23}BrF_2N_2O_3$ | 517,0933 | 517,0892 |
| Ej 242 | H | $CH(CH_3)_2$ | 52,6 | $C_{23}H_{21}BrF_2N_2O_3$ | 491,0776 | 491,0781 |
| Ej 243 | $CH_2CH_2$- | $CH_2CH_2$- | 47 2 | $C_{24}H_{21}BrF_2N_2O_4$ | 503,0776 | 503,0791 |

Ej 244

939

4-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]benzamida

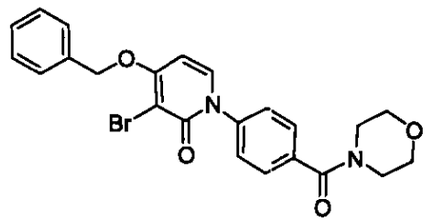


Preparacion de 4-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]benzamida El compuesto del Ejemplo 203 (0,500 g, 1,11 mmol) se disolvio en tetrahidrofurano (5,0 mL) Se agrego 2-cloro-4,6-dimetoxi-1,3,5-triazina (0 234 g, 1 33 mmol) seguido de 4-metilmorfolina (0,366 mL, 3,33 mmol) La mezcla resultante se agito a temperatura ambiente durante 1,5 horas, momento en el que se agrego $NH_4OH$ (2,5 mL) La mezcla resultante se agito a temperatura ambiente durante la noche Se agregaron $H_2O$ (25 mL) y tetrahidrofurano (25 mL) La capa acuosa se extrajo mas con acetato de etilo (25 mL) Las capas organicas combinadas se lavaron con una disolución de carbonato de sodio saturado (25 mL), 1*N* HCl (25 mL), salmuera (25 mL), se secaron sobre $Na_2SO4$, se filtraron y concentraron para proporcionar un sólido de color amarillo palido (0,500 g, al 100 %) $^1$H NMR (400 MHz, DMF-$d_6$) δ 8,13 (s, 1H), 8,02 (d, *J* = 8,5 Hz, 2H), 7,70 (*aprox* q, *J* = 7,9 Hz, 1H), 7,40 (d, *J* = 8,5 Hz, 2H), 7,41-7,34 (m, 1H), 7,22 (*aprox* dt, *J* = 1,8, 8,5 Hz, 1H), 6,71 (s, 1H), 5,37 (s, 2H), 1,97 (s, 3H) ES-HRMS m/z 449,0281 (M+H $C_{20}H_{15}BrF_2N_2O_3$ requiere 449,0307)

Ej 245

4-(Benciloxi)-3-bromo-1-[4-(morfolin-4-ilcarbonil)fenil]piridin-2(1H)-ona

940



Preparación de 4-(benciloxi)-3-bromo-1-[4-(morfolin-4-ilcarbonil)fenil]piridin-2(1H)-ona A un recipiente de reaccion (tubo de cultivo borosilicatado) se le agrego el compuesto del Ejemplo 197 (0,100 g, 0,250 mmol) que se disolvio en *N,N*-dimetilformamida (2,0 mL) Se agrego 1-hidroxibenzotriazol (0,017 g, 0,125 mmol) al recipiente de reaccion seguido por aproximadamente 0,423 g de la resina carbodiimida aglutinada con polimero (1,8 mmol/g) Luego se agregó *N,N*-dimetilformamida adicional (2 mL) al recipiente de reaccion Luego, se agito orbitalmente el aparato de reaccion en paralelo (Labline Benchtop Orbital Shaker) a aproximadamente 200 rpm a temperatura ambiente durante 15 minutos Luego, morfolina (0,033 g, 0,0375 mmol) disuelta en *N,N*-dimetilformamida (0,5 mL) se agregó al recipiente de reacción y se agito orbitalmente el aparato de reaccion a temperatura ambiente durante la noche En este momento se diluyó la reaccion con *N,N*-dimetilformamida (2,0 mL) y Diclorometano (4,0 mL) y se trató con aproximadamente 0,770 g de resina poliamina (2,63 mmol/g) y aproximadamente 1,0 g de poliestireno funcionalizado con metilisocianato (1,10 mmol/g) y se continuo la agitacion orbital a 200 rpm a temperatura ambiente durante 3 horas Luego se abrio el recipiente de reaccion y el producto de fase de disolucion se separo de los subproductos enfriados rapidamente insolubles mediante filtracion y su recolección en un vial Después de la evaporacion parcial, los subproductos insolubles se enjuagaron con diclorometano (2 x 10 mL) El filtrado se evaporo soplando $N_2$ sobre el vial mientras se

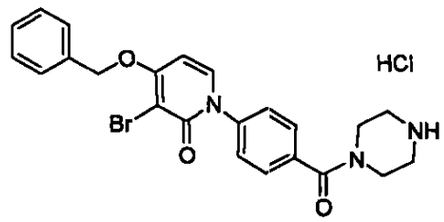
941

calentaba (60 °C) en un bloque de reaccion (KEM-Lab Parallel Reactor) para proporcionar un sólido de color blanquecino (0,092 g, al 79%)

$^1$H NMR (400 MHz, $CDCl_3$) δ 7,50 (d, *J* = 8,5 Hz, 2H), 7,48-7,33 (m, 7H), 7,27 (d, *J* = 7,8 Hz, 1H), 6,19 (d, *J* = 7,8 Hz, 1H), 5,29 (s, 2H), 3,76-3,47 (*br* m, 8H) ES-HRMS m/z 469,0733 (M+H $C_{23}H_{21}BrN_2O_4$ requiere 469,0757)

Ej 246

4-(Benciloxi)-3-bromo-1-[4-(piperazin-1-ilcarbonil)fenil]piridin-2(1H)-ona

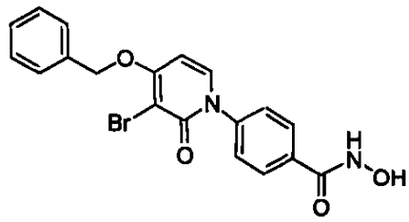



Preparación de 4-(benciloxi)-3-bromo-1-[4-(piperazin-1-ilcarbonil)fenil]piridin-2(1H)-ona Siguiendo el método del Ej 245 y sustituyendo la morfolina por piperazina carboxilato *N*-*terc*-butilico (0,070 g, 0,375 mmol), se preparo el compuesto del titulo como el compuesto *N*-*t*-butoxicarbonilo protegido La desproteccion del intermedio N-t-butoxicarbonilo se logro con 4N HCl en dioxano, para proporcionar el ccmpuesto del titulo como su sal hidrocloruro (0,112 g, > al 100%) $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9,55 (*br* s, 2H) 7,78 (d, *J* = 7,8 Hz, 1H), 7,58 (d, *J* = 8,5 Hz, 2H), 7,48-7,33 (m, 7H), 6,57 (d, *J* = 7,8 Hz, 1H), 5,38 (s, 2H), 3,79-3 36 (*br* m, 4H), 3,30-3,14 (*br* s, 4H), ES-HRMS m/z 468,0940 (M+H $C_{23}H_{22}BrN_3O_3$ requiere 468,0917)

Ej 247

4-[4-(Benciloxi)-3-bromo-2-oxopiridin-1(2H)-il]-N-hidroxibenzamida

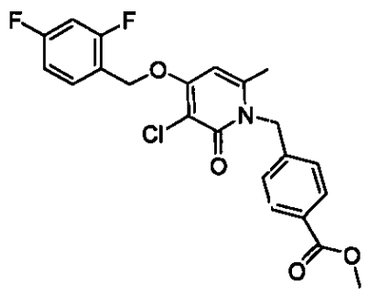
942



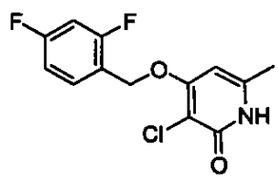
Preparacion de 4-[4-(benciloxi)-3-bromo-2-oxopiridin-1(2H)-il]-N-hidroxibenzamida El compuesto del titulo se preparo como el ccmpuesto protegido tetrahidropiranilo siguiendo el metodo del Ejemplo 245 y sustituyendo la morfolina por O-(tetrahidro-2H-piranil-2il) hidroxilamina (0,044 g, 0,375 mmol) La desproteccion del intermedio tetrahidropiranilo se logró con 4N HCl en dioxano para proporcionar el compuesto del titulo (0,056 g, > al 71%) $^1$H NMR (400 MHz, DMSO-$d_6$) δ 11,03 (*br* s,1H), 7,83 (d, *J* = 8,6 Hz, 2H), 7,78 (d, *J* = 7,8 Hz, 1H), 7,48-7,35 (m, 7H), 6,55 (d, *J* = 7,8 Hz, 1H), 5,37 (s, 2H) ES-HRMS m/z 415,0278 (M+H $C_{19}H_{15}BrN_2O_4$ requiere 415,0288)

Ej 248

Metil-4-{[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}benzoato



Etapa 1 Preparación de 3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona



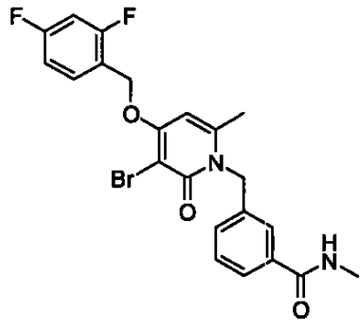
943

5,00 g, 19,90 mmol) se suspendio en 1,2-dicloroetano (100 mL) Se agrego acido dicloroacetico (0,082 mL, 0,995 mmol), seguido de *N*-clorosuccinimida (3,19 g, 23,88 mmol) La mezcla resultante se calento hasta 80 °C durante 15,5 horas Se evaporo el 1,2-dicloroetano y los solidos remanentes se lavaron con acetonitrilo para proporcionar un solido de color tostado (4,97 g, al 88%)

Etapa 2 Preparacion de metil-4-{[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}benzoato Se suspendió 3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona (Etapa 1) (4,97 g, 17,40 mmol) en tetrahidrofurano (50 mL) y se enfrio en un baño de hielo Se agregó 4-(bromometil)benzoato de metilo (5,98 g, 26,10 mmol), seguido por hidruro de sodio (0,835 g, 20,88 mmol, dispersion en aceite mineral al 60%) Una vez que se completo la adicion, se elimino el baño refrigerante y la mezcla se calento a 50 °C durante 19 horas Despues de enfriarla hasta temperatura ambiente, se agrego $NH_4Cl$ saturado (50 mL) Se agrego acetato de etilo y se recogió el precipitado mediante filtración El filtrado se extrajo mas con acetato de etilo Las capas orgánicas combinadas se lavaron con salmuera (50 mL), se secaron sobre $Na_2SO_4$, se filtraron y se evaporaron El solido resultante se combino con el precipitado y se lavó con acetato de etilo caliente para proporcionar un sólido de color blancuzco (5,24 g, al 69%) $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 7,90 (d, J = 8,5 Hz, 2H), 7,63 (aprox q, J = 7,9 Hz, 1H), 7,31 (aprox dt, J = 2,4, 9,9 Hz, 1H), 7,21 (d, J = 8,3 Hz, 2H), 7,17-7,13 (m, 1H), 6,60 (s, 1H), 5,36 (s, 2H), 5,27 (s, 2H), 3,81 (s, 3H), 2,27 (s, 3H), ES-HRMS m/z 434,0931 (M+H $C_{22}H_{18}BrF_2NO_4$ requiere 434,0965)

Ejemplo 249

944



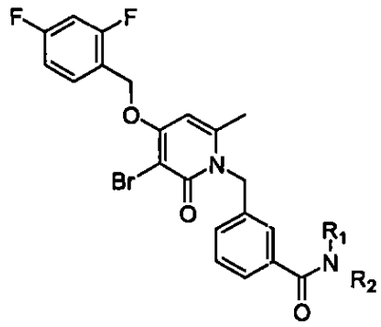
3-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}-*N*-metilbenzamida

A un recipiente de reaccion (un tubo de cultivo borosilicatado) se le agrego el compuesto del Ejemplo 169 (0,300 g, 0,646 mmol) Se agregó una disolucion madre de 1-hidroxibenzotriazol en *N,N*-dimetilformamida (3 mL, 0,11 M) al recipiente de reaccion seguido por aproximadamente 1,10 g de la resina carbodiimida aglutinada con polimero (1,8 mmol/g) Luego se agrego *N,N*-dimetilformamida adicional (2 mL) al recipiente de reacción Luego, se agitó orbitalmente el aparato de reaccion en paralelo (Labline Benchtop Orbital Shaker) a aproximadamente 200 rpm a temperatura ambiente durante 15 minutos Luego se agrego *N*-Metilamina (0,50 mL, 0,999 mmol) al recipiente de reaccion y se agitó orbitalmente el aparato de reacción a temperatura ambiente durante la noche En este momento se diluyo la reacción con tetrahidrofurano (35 mL) y se trató con aproximadamente 2,0 g de resina poliamina (2,63 mmol/g) y aproximadamente 2,6 g de poliestireno funcionalizado con metilisocianato (1,50 mmol/g) y se continuó la agitacion orbital a 200 rpm a temperatura ambiente durante 4 horas Luego se abrió el recipiente de reacción y los productos de fase de disolucion se separaron de los subproductos enfriados rápidamente insolubles mediante su filtración y recoleccion en un vial Despues de la evaporación parcial, los subproductos insolubles se enjuagaron con

945

tetrahidrofurano (2 x 10 mL) El filtrado resultante se evaporo soplando $N_2$ sobre el vial mientras se calentaba (60 °C) en un bloque de reaccion (KEM-Lab Parallel Reactor) La cromatografia (C-18, acetonitrilo/$H_2O$ con acido trifluoroacetico al 0 1%) proporciono un sólido de color blanco (0,178 g, al 58%) $^1$H NMR (400 MHz, DMF-$d_6$) δ 7,65-7,53 (m, 3H), 7,37-7,28 (m, 2H), 6,97-6,82 (m, 2H), 6,00 (s, 1H), 5,36 (s, 2H), 5,19 (s, 3H), 2,96 (t, $J$ = 4,83 Hz, 3H), 2,29 (s, 3H) ES-HRMS $m/z$ 477,0635 (M+H $C_{22}H_{19}BrF_2N_2O_3$ requiere 477,0620)

Preparación de los Ejemplos 250- 261



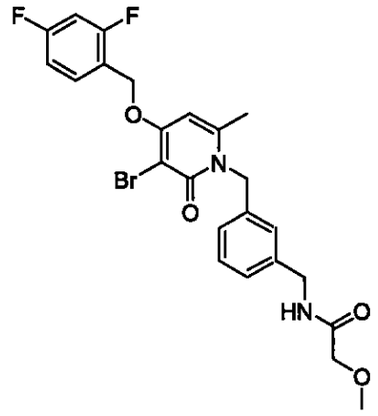
Los compuestos de los Ejemplos 249-261 se preparan siguiendo el metodo del Ejemplo 250 y reemplazando *N*-metilamina con la amina apropiada La desprotección de los intermedios protegidos se logró con 4*N* HCl en dioxano para proporcionar los compuestos como sales de hidrocloruro

| Compuesto N° | $R_1$ | $R_2$ | % Rend | MFMF | M+H Requiere | ES-HRMS $m/z$ |
|---|---|---|---|---|---|---|
| Ej 250 | $CH_2CH_2NH$- | $CH_2CH_2NH$- | 89 | $C_{25}H_{24}BrF_2N_3O_4$ | 532,1042 | 532,1067 |
| Ej 251 | H | $CH_2CH_2NH_2$ | 75 | $C_{23}H_{22}BrF_2N_3O_3$ | 506,0885 | 506,0900 |
| Ej 252 | H | $CH_2CH_2CH_2NH_2$ | 84 | $C_{24}H_{24}BrF_2N_3O_3$ | 520,1042 | 520,1000 |
| Ej 253 | H | OH | 45 | $C_{21}H_{17}BrF_2N_2O_4$ | 479 0413 | 479,0394 |
| Ej 254 | $CH_3$ | $CH_3$ | 69 | $C_{23}H_{21}BrF_2N_2O_3$ | 491,0776 | 491 0731 |
| Ej 255 | H | $CH_3$ | 58 | $C_{22}H_{19}BrF_2N_2O_3$ | 479,0602 | 479,0598 |
| Ej 256 | $CH_2CH_2O$- | $CH_2CH_2O$- | 69 | $C_{25}H_{23}BrF_2N_2O_4$ | 533,0882 | 533,0857 |

946

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Ej | 257 | H | $CH_2CH_2OH$ | 51 | $C_{23}H_{21}BrF_2N_2O_4$ | 507,0726 | 507,0698 |
| Ej | 258 | $CH_2CH_2OH$ | $CH_2CH_2OH$ | 25 | $C_{25}H_{25}BrF_2N_2O_5$ | 551,0988 | 551,0972 |
| Ej | 259 | $CH_2CH_2CH_2$- | $CH_2CH_2CH_2$- | 62 | $C_{26}H_{25}BrF_2N_2O_3$ | 531,1089 | 531,1088 |
| Ej | 260 | H | $CH(CH_3)_2$ | 46 | $C_{24}H_{23}BrF_2N_2O_3$ | 505,0933 | 505,0918 |
| Ej | 261 | $CH_2CH_2$- | $CH_2CH_2$- | 60 | $C_{25}H_{23}BrF_2N_2O_3$ | 517,0933 | 517,0950 |

Ejemplo 262



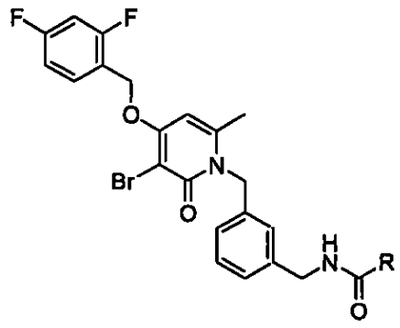

N-(3-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}bencil)-2-metoxiacetamida

A un recipiente de reacción (un tubo de cultivo borosilicatado) se le agrego acido metoxiacetico (0,09 g, 1,00 mmol) Se agrego una disolucion madre de 1-hidroxibenzotriazol (3 mL, 0,16 M) y *N*-metilmorfolina (3 mL, 0,43 M) en *N,N*-dimetilformamida al recipiente de reaccion seguidos por aproximadamente 0,97 g de la resina carbodiimida aglutinada con polimero (1,38 mmol/g) Luego se agregó *N,N*-dimetilformamida adicional (3 mL) al recipiente de reaccion Luego, se agito orbitalmente el aparato de reacción en paralelo (Labline Benchtop Orbital Shaker) a aproximadamente 200 rpm a temperatura ambiente durante 4 horas Luego se agrego 1-[3-(aminometil)bencil]-3-bromo-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona (Ejemplo 161) (0,30 g, 0,668 mmol) al recipiente de reacción seguido de *N,N*-dimetilformamida adicional (5,0 mL)

947

y el aparato de reaccion se agitó orbitalmente a temperatura ambiente durante la noche En este momento se diluyó la reacción con tetrahidrofurano (20 mL) y se trato con aproximadamente 2,06 g de resina poliamina (2,63 mmol/g) y aproximadamente 2,67 g de poliestireno funcionalizado con metilisocianato (1,10 mmol/g) y se continuó la agitación orbital a 200 rpm a temperatura ambiente durante 4 horas Luego se abrio el recipiente de reacción y los productos de fase de disolucion se separaron de los subproductos enfriados rápidamente insolubles mediante su filtración y recoleccion en un vial Después de la evaporacion parcial, los subproductos insolubles se enjuagaron con tetrahidrofurano (2 x 10 mL) El filtrado resultante evaporado soplando $N_2$ sobre el vial mientras se calentaba (60 °C) en un bloque de reaccion (KEM-Lab Parallel Reactor) proporciono un sólido de color tostado (0,321 g, al 89,4%) $^1$H NMR (400 MHz, DMF-$d_6$) δ 8,33 (br s, 1H), 7,81 (*aprox* q, *J* = 7,85 Hz, 1H), 7,40-7,23 (m, 5H), 7,09 (d, *J* = 7,25 Hz, 1H), 6,68 (s, 1H), 5,46 (s, 2H), 5,42 (s, 2H), 4,45 (d, *J* = 6,24 Hz, 2H), 3,93 (s, 2H), 3,39 (s, 3H), 2,44 (s, 3H) ES-HRMS *m/z* 521,0891 (M+H $C_{24}H_{23}BrF_2N_2O_4$ requiere 521,0882)

Preparación de los Ejemplos 263-265



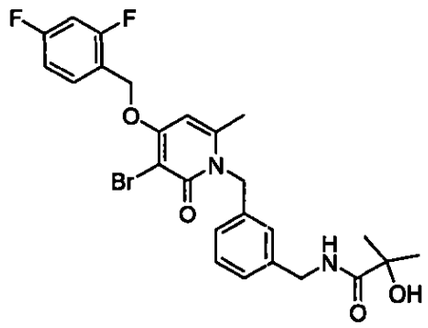
Los compuestos de los Ejemplos 263-265 siguiendo el método del Ejemplo 262 y reemplazando el ácido

948

metoxıacétıco con el ácıdo apropıado La desprotección de los ıntermedıos protegıdos se logró con 4*N* HCl en dıoxano para proporcıonar los compuestos como sales de hıdrocloruro

| Compuesto N° | R | % Rend | MF | M+H Requıere | ES-HRMS *m/z* |
|---|---|---|---|---|---|
| Ej 263 | $CH_2NH_2$ | 46,1 | $C_{23}H_{23}BrF_2N_3O_3$ | 506 0885 | 506,0870 |
| Ej 264 | $CH_2NHCOCH_3$ | 70,4 | $C_{25}H_{24}BrF_2N_3O_4$ | 548 0991 | 548,1007 |
| Ej 265 | $CH_2OCOCH_3$ | 42,7 | $C_{23}H_{21}BrF_2N_2O_4$ | 549,0831 | 549,0837 |

Ejemplo 266



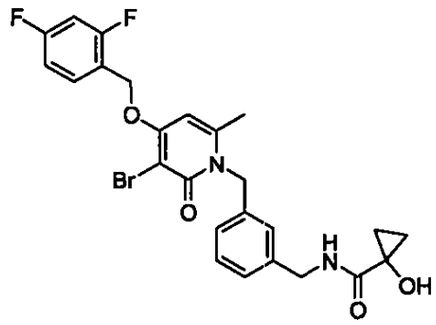
N-(3-{[3-bromo-4-[(2,4-dıfluorobencıl)oxı]-6-metıl-2-oxopırıdın-1(2H)-ıl]metıl}bencıl)-2-hıdroxı-2-metılpropanamıda

Se dısolvıeron acıdo 1-[3-(amınometıl)bencıl]-3-bromo-4-[(2,4-dıfluorobencıl)oxı]-6-metılpırıdın-2(1H)-ona (Ejemplo 161) (0,300 g, 0,668 mmol), acıdo 1-hıdroxıısobutírıco (0,215 g, 2,064 mmol), 1-hıdroxıbenzotrıazol (0,112 g, 0,826 mmol), e hıdrocloruro de 1-(3-dımetılamınopropıl)-3-etılcarbodıımıda (0,185 g, 0,963 mmol) en *N,N*-dımetılacetamıda (3 mL) Se agregó *N*-metılmorfolına (0,209 g, 2,064 mmol), y se agıtó la reaccıon durante 1 hora a temperatura ambıente Se dıluyo la reaccıon con $H_2O$ (50 mL), y se extrajo la capa acuosa con acetato de etılo (3 x 25 mL) Luego, los materıales orgánıcos combınados se lavaron con 1*N* HCl (25 mL), $Na_2CO_3$

949

saturado (25 mL), salmuera (25 mL), se secaron sobre $Na_2SO_4$, y se concentraron para proporcionar un sólido de color blancuzco (0,235 g, al 64%) $^1$H NMR (400 MHz, DMF-$d_6$) δ 8,25 (br s, 1H), 7,81 (*aprox* q, *J* = 7,92 Hz, 1H), 7,40-7,21 (m, 5H), 7,09 (d, *J* = 6,84 Hz, 1H), 6,67 (s, 1H), 5,46 (s, 2H), 5,42 (s, 2H), 4,42 (d, *J* = 6,24 Hz, 2H), 2,44 (s, 3H), 1,38 (s, 6H) ES-HRMS *m/z* 535,1024 (M+H $C_{25}H_{25}BrF_2N_2O_4$ requiere 535,1039)

Ejemplo 267

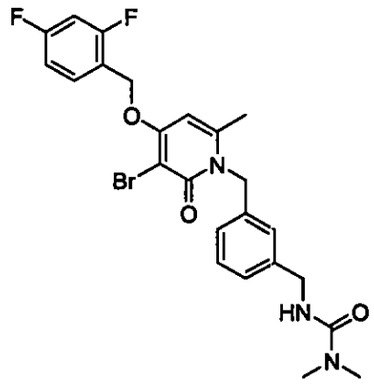


N-(3-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}bencil)-1-hidroxiciclopropanocarboxamida

El compuesto del titulo (0,352 g, al 96%) se preparó siguiendo el metodo del Ejemplo 266 y sustituyendo el ácido 1-hidroxiisobutírico por acido 1-hidroxi-1-ciclopropanocarboxilico $^1$H NMR (400 MHz, DMF-$d_6$) δ 8,46 (*aprox* t, *J* = 6,24 Hz, 1H), 7,81 (*aprox* q, *J* = 7,92 Hz, 1H), 7,40-7,22 (m, 5H), 7,06 (d, *J* = 7,05 Hz, 1H), 6,67 (s, 1H), 5,45 (s, 2H), 5,42 (s, 2H), 4,46 (d, *J* = 6,44 Hz, 2H), 2,45 (s, 3H), 1,17-1,12 (m, 2H), 0,93 (*aprox* q, *J* = 3,82 Hz, 2H) ES-HRMS *m/z* 533,0861 (M+H $C_{25}H_{23}BrF_2N_2O_4$ requiere 533,0882)

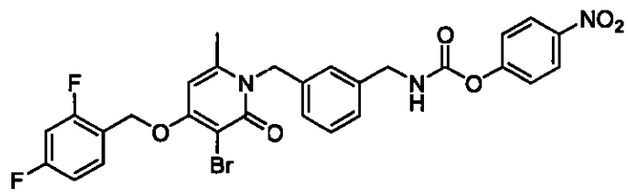
Ejemplo 267

950



N'-(3-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}bencil)-N,N-dimetilurea

Etapa 1 Preparacion de 4-nitrofenil 3-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}bencilcarbamato



Se suspendio 1-|3-(aminometil)bencil]-3-bromo-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona (Ejemplo 161) (2,00 g, 4,45 mmol) en diclorometano (15 mL) Se agrego piridina (0,43 mL, 5,34 mmol) Despues de agitar durante 10 minutos a temperatura ambiente, se agregó gota a gota una disolucion madre de cloroformato 4-nitrofenilico (10 0 mL, 0,50 M) en diclorometano Despues de agitar durante 4,5 horas a temperatura ambiente, se agrego nuevamente gota a gota una disolución madre de cloroformato 4-nitrofenilico (2,5 mL, 0,50 M) en diclorometano y se continuó agitando a 40 °C durante la noche La mezcla de reaccion se concentro y se sometió a cromatografia (gel de sílice, acetato de etilo con metanol/hexanos al 10%) para proporcionar un solido de color amarillo (1,11 g, al 66%) $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8,56 (*aprox* t, *J* = 6,10 Hz, 1H), 8,24-8,21 (m,

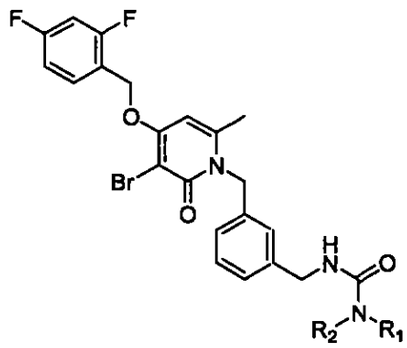
951

2H), 7,62 (*aprox* q, *J* = 7,88 Hz, 1H), 7,40-7,27 (m, 7H), 6,98 (d, *J* = 7,52 Hz, 1H), 6,54 (s, 1H), 5,30 (s, 2H), 5,24 (s, 2H), 4,25 (d, *J* = 6,18 Hz, 2H), 2,30 (s, 3H) ES-HRMS *m/z* 614,0753 (M+H $C_{28}H_{22}BrF_2N_3O_6$ requiere 614,0733)

Etapa 2 Preparacion de N'-(3-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}bencil)-N,N-dimetilurea A un recipiente de reacción (tubo de cultivo borosilicatado) se le agrego 4-nitrofenil 3-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}bencilcarbamato (de la Etapa 1) (0,350 g, 0,570 mmol) disuelto en diclorometano (6,0 mL) Luego, se agito orbitalmente el aparato de reaccion en paralelo (Labline Benchtop Orbital Shaker) a aproximadamente 200 rpm a temperatura ambiente durante 15 minutos Luego se agrego una disolución madre de *N*-metilamina (0,427 mL, 2,0 mmol) al recipiente de reacción y el aparato de reacción se agitó orbitalmente a temperatura ambiente durante la noche La mezcla de reaccion se concentro y se sometio a cromatografía (gel de silice, acetato de etilo con metanol/hexanos al 10%) para proporcionar un solido de color amarillento (0,226 g, al 63,3%) $^1$H NMR (400 MHz, DMF-$d_6$) δ 7,81 (*aprox* q, *J* = 7,92 Hz, 1H), 7,40-7,19 (m, 5H), 7,06 (d, *J* = 7,45 Hz, 1H), 6,88 (*aprox* t, *J* = 5,84 Hz, 1H), 6,68 (s, 1H), 5,45 (s, 2H), 5,42 (s, 1H), 4,35 (d, *J* = 5,84 Hz, 1H), 2,92 (s, 6H), 2,44 (s, 3H) ES-HRMS *m/* 520,1065 (M+H $C_{24}H_{24}BrF_2N_3O_3$ requiere 520,1042)

Preparacion del Ejemplo 268-270

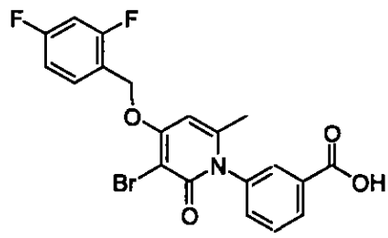
952



Los compuestos de los Ejemplos 268-270 se prepararon siguiendo el método del Ejemplo 267 y reemplazando *N,N*-dimetilamina con la amina apropiada La desprotección de los intermedios protegidos se logró con 4*N* HCl en dioxano para proporcionar los compuestos como sales de hidrocloruro

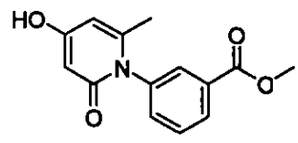
| Compuesto N° | $R_1$ | $R_2$ | % Rend | MF | M+H Requiere | ES-HRMS *m/z* |
|---|---|---|---|---|---|---|
| Ej 268 | $CH_2CH_2N$- | $CH_2CH_2N$- | 66,6 | $C_{26}H_{27}BrF_2N_4O_3$ | 561,1307 | 561 1309 |
| Ej 269 | H | $CH_3$ | 27,0 | $C_{23}H_{22}BrF_2N_3O_3$ | 506,0885 | 506,0898 |
| Ej 270 | $CH_2CH_2O$- | $CH_2CH_2O$- | 64,4 | $C_{26}H_{26}BrF_2N_3O_4$ | 562 1148 | 562,1137 |

Ejemplo 271



Acido 3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]benzoico

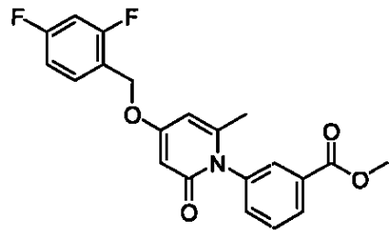
Etapa 1 Preparación de 3-(4-hidroxi-6-metil-2-oxopiridin-1(2H)-il)benzoato de metilo



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Se suspendieron 3-aminobenzoato de metilo (75,00 g, 496,13 mmol) y 4-hidroxi-6-metil-2-pirona (62,57 g, 496,13 mmol) en 1,2-diclorobenceno (150 mL) y la suspensión se calentó a 165 °C durante 15 minutos La reacción se enfrio hasta temperatura ambiente y se extrajo con 0,54M $K_2CO_3$ (4 x 250 mL) Las capas acuosas combinadas se acidificaron (pH 2) con 4*N* HCl El precipitado se recogió mediante filtración para proporcionar un solido de color amarillo-naranja (20,24 g, > al 16%) El filtrado resultante se extrajo con acetato de etilo (3 x 1 L) Las capas orgánicas se lavaron con salmuera (500 mL), se secaron sobre $MgSO_4$ y se evaporaron El sólido resultante se lavo con $H_2O$ caliente para proporcionar un solido de color amarillo-naranja (3,84 g, al 3%) Luego se combinaron los dos solidos $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7,98 (dt, *J* = 1,31, 7,79 Hz, 1H), 7,69 (*aprox* t, *J* = 1,78 Hz, 1H), 7,62 (t, *J* = 7,78 Hz, 1H) 7,49 (ddd, *J* = 1,07, 1,07, 7,85 Hz, 1H), 5,89 (dd, *J* = 0,87, ?,48 Hz, 1H), 5,55 (*aprox* d, *J* = 0,94 Hz, 1H), 3,83 (s, 3H), 1,80 (s, 3H) ES-HRMS *m/z* 260,0895 (M+H $C_{14}H_{13}NO_4$ requiere 260,0917)

Etapa 2 Preparación de 3-[4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]benzoato de metilo

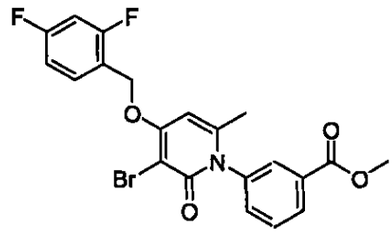


Se disolvieron 3-(4-hidroxi-6-metil-2-oxopiridin-1(2H)-il)benzoato de metilo (de la Etapa 1) (24,00 g, 92,57 mmol) y $K_2CO_3$ (15,35 g, 111,08 mmol) en *N*,*N*-dimetilformamida (220 mL) Luego se agrego bromuro 2,4-

954

difluorobencílico (20,12 g, 97,20 mmol) y la mezcla de reaccion resultante se agito durante 48 horas a temperatura ambiente La mezcla de reaccion se diluyó con $H_2O$ (1 L)y se recogio el precipitaco por filtracion para proporcionar un solido de color blanco (4,08 g, al 11%) El aceite resultante se purifico mediante cromatografia (gel de silice, acetato de etilo con metanol/hexanos al 10%) para proporcionar un sólido de color blanquecino (11,88 g, al 33%) Se combinaron los dos solidos $^1$H NMR (400 MHz, $CDCl_3$) δ 8,11 (dt, *J* = 1,41, 7,79 Hz, 1H), 7,87 (*aprox* t, *J* = 1,78 Hz, 1H), 7,58 (*aprox* t, *J* = 7,69 Hz, 1H) 7,45-7,38 (m, 2H), 6,94-6,84 (m, 2H), 5,97 (d, *J* = 2,68 Hz, 1H), 5,90 (ddd, *J* = 0,94, 1,74, 1,74 Hz, 1H), 5,97 (s, 1H), 3,90 (s, 3H), 1,89 (s, 3H) ES-HRMS *m/z* 386,1179 (M+H $C_{21}H_{17}F_2NO_4$ requiere 386,1198)

Etapa 3 Preparacion de 3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]benzoato de metilo



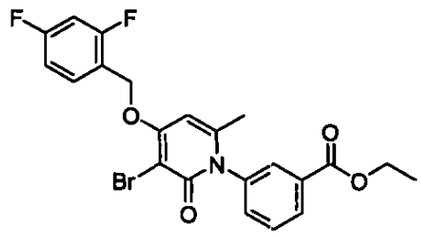

En un baño de hielo se enfrió 3-[-4-[(2,4-Difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]benzoato de metilo (de la Etapa 2) (15,85 g, 41,130 mmol) suspendido en acetonitrilo (165 mL) Se agrego *N*-bromosuccinimida (7,687 g, 43,186 mmol) y se elimino el baño de hielo La mezcla de reaccion se agito durante 1,5 horas a temperatura ambiente La reacc on se concentro y se sometio a cromatografia (gel de silice, acetato de etilo con metanol/hexanos al 10%) para proporcionar un sólido de

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color amarillento (17,63 g, al 92%) $^1$H NMR (400 MHz, $CDCl_3$) δ 8,17 (dt, *J* = 1,41, 7,85 Hz, 1H), 7,90 (t, *J* = 1,81 Hz, 1H), 7,67-7,41 (m, 3H), 7,05-6,88 (m, 2H), 6,13 (s, 1H), 5,30 (s, 2H), 3,95 (s, 1H), 2,01 (s, 3H) ES-HRMS *m/z* 464,0286 (M+H $C_{21}H_{16}BrF_2NO_4$ requiere 464,0304)

Etapa 4 Preparacion del compuesto del titulo Se disolvio 3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]benzoato de metilo (de la Etapa 3) (10,0 g, 21,539 mmol) en metanol (36 mL) y tetrahidrofurano (14 mL) Se agregó 4N NaOH (13,5 mL, 53,847 mmol) La mezcla resultante se agito durante 1,5 horas a temperatura ambiente La reacción se acidificó (pH 2) con 4*N* HCl Se recogio el precipitado mediante filtración para proporcionar un sólido de color blanquecino (7,83 g, al 81%) $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8,01 (dt, *J* = 1,41, 7,65 Hz, 1H), 7,76 (*aprox* t, *J* = 1,78 Hz, 1H), 7,76-7,15 (m, 5H), 6,66 (s, 1H), 5,32 (s, 2H), 1,92 (s, 3H) ES-HRMS *m/z* 450,0134 (M+H $C_{20}H_{14}BrF_2NO_4$ requiere 450,0147)

Ejemplo 272



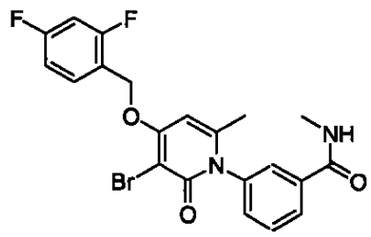

3-[3-Bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]benzoato de etilo

El compuesto del titulo (2,66 g, al 79%)se preparó Siguiendo el metodo del Ejemplo 271 y sustituyendo 3-aminobenzoato de metilo por 3-aminobenzoato de etilo $^1$H NMR (400 MHz, $CDCl_3$) δ 8,13 (dt, *J* = 1,41, 7,85 Hz, 1H), 7,84 (t, *J* = 1,88 Hz, 1H), 7,62-7,55 (m, 2H), 7,36 (*aprox* dq, *J* = 1,07, 7,85 Hz, 1H), 6,96 (*aprox* dt, *J* = 2,55, 8,35

956

Hz, 1H), 6,88-6,84 (m, 1H), 6,08 (s, 1H), 5,25 (s, 2H), 4,42-4,30 (m, 2H), 1,96 (s, 3H), 1,36 (t, *J* = 7,12 Hz, 3H) ES-HRMS *m/z* 478,0482 (M+H $C_{22}H_{18}BrF_2NO_4$ requiere 478,0460)

Ejemplo 273



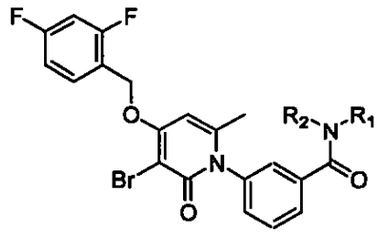
3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-*N*-metilbenzamida

A un recipiente de reaccion (un tubo de cultivo borosilicatado) se le agrego el compuesto del Ejemplo 271 (0,300 g, 0,666 mmol) Se agrego una disolución madre de 1-hidroxibenzotriazol en *N,N*-dimetilformamida (3 mL, 0,11 M) al recipiente de reaccion seguido por aproximadamente 0,97 g de la resina carbodiimida aglutinada con polimero (1,38 mmol/g) Luego se agrego *N,N*-dimetilformamida adicional (2 mL) al recipiente de reaccion Luego, se agitó orbitalmente el aparato de reacción en paralelo (Labline Benchtop Orbital Shaker) a aproximadamente 200 rpm a temperatura ambiente durante 15 minutos Luego se agrego *N*-metilamina (0,50 mL, 0,999 mmol) al recipiente de reaccion y se agito orbitalmente el aparato de reacción a temperatura ambiente durante la noche En este momento se diluyo la reaccion con tetrahidrofurano (30 mL) y se trató con aproximadamente 2,0 g de resina poliamina (2,63 mmol/g) y aproximadamente 3,6 g de poliestireno funcionalizado con metilisocianato (1,10 mmol/g) y se continuó la agitacion orbital a 200 rpm a temperatura ambiente durante 4 horas Luego se abrio el recipiente de reacción y los productos de fase de disolucion se separaron de los subproductos

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enfriados rapidamente insolubles mediante su filtración y recoleccion en un vial Despues de la evaporacion parcial, los subproductos insolubles se enjuagaron con tetrahidrofurano (2 x 10 mL) El filtrado se evaporo soplando $N_2$ sobre el vial mientras se calentaba (60 °C) en un bloque de reacc ón (KEM-Lab Parallel Reactor) para proporcionar un solido de color blanquecino (0,189 g, al 61%) $^1$H NMR (400 MH , DMF-$d_6$) δ 8,56 (br d, $J$ = 4,16 Hz, 1H), 8,05-7,76 (m, 3H), 7,66 (t, $J$ = 7,79 Hz, 1H), 7,56-7,19 (m, 3H), 6,74 (s, 1H), 5,43 (s, 2H), 3,46 (s, 3H), 2,03 (s, 3H) ES-HRMS $m/z$ 463,0476 (M+H $C_{21}H_{17}BrF_2N_2O_3$ requiere 463,0463)

Preparacion de los Ejemplos 274-289



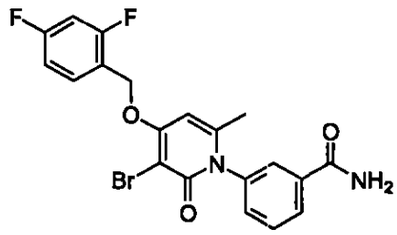

Los compuestos de los Ejemplos 274-289 se preparan siguiendo el metodo del Ejemplo 273 y reemplazando *N*-metilamina con la amina apropiada La desproteccion de los intermedios protegidos se logró con 4*N* HCl en dioxano para proporcionar los compuestos como sus sales de hidrocloruro

| Compuesto N° | R1 | R2 | % Rend | MF | M+H Requiere | ES-HRMS $m/z$ |
|---|---|---|---|---|---|---|
| Ej 274 | CH2CH2NH- | CH2CH2NH- | 92,8 | $C_{24}H_{22}BrF_2N_3O_3$ | 518,0885 | 518,0865 |
| Ej 275 | H | CH2CH2NH2 | 95,7 | $C_{22}H_{20}BrF_2N_3O_3$ | 492,0729 | 492,0711 |
| Ej 276 | H | CH2CH2CH2NH2 | 97,8 | $C_{23}H_{22}BrF_2N_3O_3$ | 506,0885 | 506,0889 |
| Ej 277 | H | OH | 91 0 | $C_{20}H_{15}BrF_2N_2O_4$ | 465 0256 | 465 0278 |
| Ej 278 | CH3 | CH3 | 67,7 | $C_{22}H_{19}BrF_2N_2O_3$ | 477,0620 | 477,0626 |
| Ej 279 | CH2CH2O- | CH2CH2O- | 86,7 | $C_{24}H_{21}BrF_2N_2O_4$ | 519,0726 | 519,0696 |

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| | | | | | | |
|---|---|---|---|---|---|---|
| Ej 280 | H | CH2CH2OH | 78 3 | $C_{22}H_{19}BrF_2N_2O_4$ | 493,0569 | 493,0575 |
| Ej 281 | CH2CH2CH2- | CH2CH2CH2- | 87,9 | $C_{25}H_{23}BrF_2N_2O_3$ | 517,0933 | 517,0918 |
| Ej 282 | H | CH(CH3)2 | 80,6 | $C_{23}H_{21}BrF_2N_2O_3$ | 491,0776 | 491,0797 |
| Ej 283 | CH2CH2- | CH2CH2- | 87 9 | $C_{24}H_{21}BrF_2N_2O_4$ | 503,0776 | 503,0732 |
| Ej 284 | CH2CH2N(CH3)- | CH2CH2N(CH3)- | 75,8 | $C_{25}H_{24}BrF_2N_3O_3$ | 532,1042 | 532,1038 |
| Ej 285 | H | CH2CH2N(CH3)2 | 86 1 | $C_{24}H_{24}BrF_2N_3O_3$ | 520,1042 | 520,1030 |
| Ej 286 | H | CH2CH2OCH3 | 90 2 | $C_{23}H_{21}BrF_2N_2O_4$ | 507,0726 | 507 0680 |
| Ej 287 | CH3 | CH2CH2N(CH3)2 | 60,0 | $C_{25}H_{26}BrF_2N_3O_3$ | 534 1198 | 534,1155 |
| Ej 288 | CH3 | CH2CH2OH | 81 6 | $C_{23}H_{21}BrF_2N_2O_4$ | 507,0726 | 507 0694 |
| Ej 289 | $CH3_3$ | CH2CH2OCH3 | 94,4 | $C_{24}H_{23}BrF_2N_2O_4$ | 521,0882 | 521,0862 |

Ejemplo 290



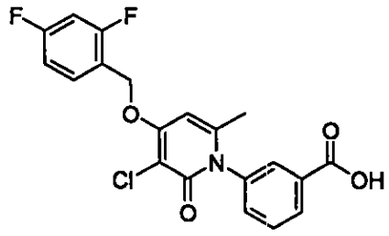
3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]benzamida

Se suspendieron el compuesto del Ejemplo 271 (2,00 g, 4,44 mmol) y 2-cloro-4,6-dimetoxi-1,3,5-triazina (0,94 g, 5,33 mmol) en tetrahidrofurano (20 mL) Se agrego 4-metilmorfolina (1,5 mL, 13,32 mmol) La mezcla resultante se agitó durante 1,5 horas a temperatura ambiente Se agrego $NH_4OH$ (10 mL, 148,00 mmol), y se agitó la reacción durante 0,5 horas a temperatura ambiente Se agregaron $H_2O$ (50 mL) y tetrahidrofurano (50 mL) y se separó la capa organica La fase acuosa se extrajo con acetato de etilo (75 mL) y los mater ales orgánicos combinados se lavaron con $Na_2CO_3$ saturado (50 mL), 1*N* HCl (50 mL), y salmuera (50 mL) La fase organica se secó sobre $Na_2SO_4$ y se evaporo El sólido resultante se lavo con éter dietílico para proporcionar un solido de color blanco (1,86 g, al 93%) $^1H$

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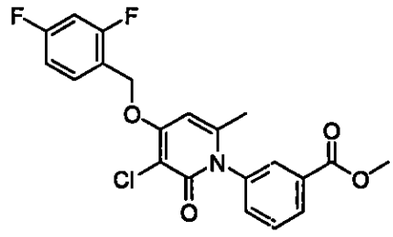
NMR (400 MHz, DMF-$d_6$) δ 8,20 (br s, 1H), 8,10-8,07 (m, 1H), 7,79 (s, 1H), 7,79 (*aprox* q, *J* = 7,83 Hz, 1H), 7,66 (*aprox* t, *J* = 7,79 Hz, 1H), 7,57-7,54 (m, 1H), 7,46 (br s, 1H), 7,36-7,19 (m, 2H), 6,74 (s, 1H), 5,43 (s, 2H), 2,04 (s, 3H) ES-HRMS *m/z* 449,0307 (M+H $C_{20}H_{15}BrF_2N_2O_3$ requiere 449,0307)

Ejemplo 291



Ácido 3-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]benzoico

Etapa 1 Preparación de 3-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]benzoato de metilo



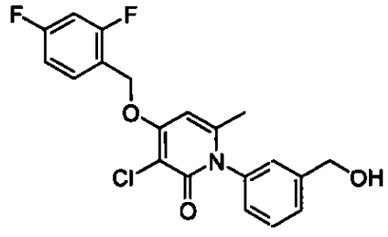
Se suspendieron el producto de la Etapa 2, Ejemplo 271 (4,54 g, 11,78 mmol) y *N*-clorosuccinimida (1,65 g, 12,37 mmol) en diclorometano (12 mL) Se agrego ácido dicloroacético (0,10 ml, 1,22 mmol) y la mezcla de reacción se agitó durante la noche a 40 °C La reacción se enfrio a temperatura ambiente y se formó un precipitado El precipitado se recogio mediante filtracion y se lavó con diclorometano (3 x 10 mL) para proporcionar un sólido blanco (1,75 g, al 35%) La reacción se concentro y se sometio a cromatografia (gel de sílice, acetato de etilo

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con metanol/hexanos al 10%) para proporcionar un solido de color blanquecino (1,29 g, al 26%) Luego se combinaron los dos solidos $^1$H NMR (400 MHz, $CDCl_3$) δ 8,12 (dt, *J* = 1,38, 7,83 Hz, 1H), 7,85 (t, *J* = 1,74 Hz, 1H), 7,60-7,52 (m, 2H), 7,37 (dq, *J* = 0,92, 7,92 Hz, 2H), 6,95 (*aprox* dt, *J* = 2,55, 8,32 Hz, 1H), 6,89-6,83 (m, 1H), 6,11 (s, 1H), 5,24 (s, 2H), 3,90 (s, 3H), 1,96 (s, 3H) ES-HRMS *m/z* 420,0783 (M+H $C_{21}H_{16}ClF_2NO_4$ requiere 420,809)

Etapa 2 Se disolvió 3-[3-cloro-4-[2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]benzoato de metilo (de la Etapa 1) (2,90 g, 6,91 mmol) en metanol (5 mL) y tetrahidrofurano (12 mL) Se agrego 4N NaOH (4,3 mL, 17,27 mmol) La mezcla resultante se agito durante 1,5 horas a temperatura ambiente La reaccion se acidificó (pH-2) con 4*N* HCl El precipitado se recogio mediante filtracion para propcrcionar un sólido de color blanquecino (2,36 g, al 84%) $^1$H NMR (400 MHz, DMSO-$d_6$ ) δ 8,01 (dt, *J* = 1,41, 7,65 Hz, 1H), 7,76 (*aprox* t, *J* = 1,68 Hz, 1H), 7,69-7,53 (m, 3H), 7,36-7,14 (m, 2H), 6,69 (s, 1H), 5,32 (s, 2H), 1,93 (s, 3H) ES-HRMS *m/z* 406,0662 (M+H $C_{20}H_{14}ClF_2NO_4$ requiere 406,0652)

Ejemplo 292



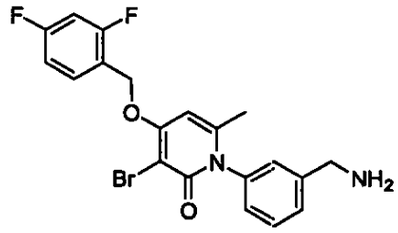

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[3-(hidroximetil)fenil]-6-metilpiridin-2(1H)-ona

El material inicial (0 550 g, 1 540 mmol) y *N*-clorosuccinimida (0,214 g, 1,602 mmol) se suspendieron en diclorometano (15 mL) Se agregó ácido dicloroacetico (0,01

961

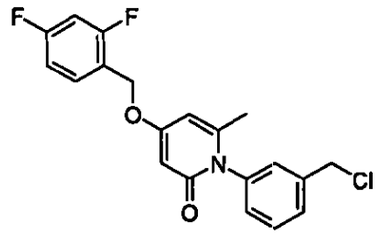
ml, 0,154 mmol) y la mezcla de reacción se calentó a 40 °C durante 9 horas La reacción se enfrió a temperatura ambiente y se formó un precipitado El precipitado se recogió mediante filtración y se lavó con diclorometano (3 x 10 mL) para proporcionar un solido blanco (0,286 g, al 47%) $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7,38 (*aprox* q, *J* = 7,35 Hz, 1H), 7,30-7,24 (m, 2H), 7,00 (br s, 1H), 6,85 (*aprox* dt, *J* = 2,37, 6,24 Hz, 1H), 6,82-6,67 (m, 2H), 6,01 (s, 1H), 5,07 (s, 2H), 4,48 (d, *J* = 5,24 Hz, 2H), 1,81 (*aprox* d, *J* = 0,40 Hz, 3H) ES-HRMS *m/z* 392,0885 (M+H $C_{20}H_{16}ClF_2NO_3$ requiere 392,0860)

Ejemplo 293




1-[3-(aminometil)fenil]-3-bromo-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona

Etapa 1 Preparacion de 1-[3-(clorometil)fenil]-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona

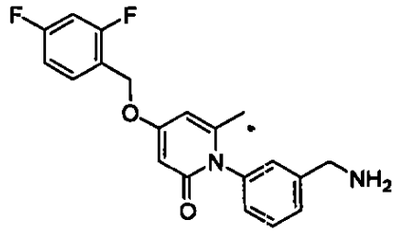



Se disolvio 2,4,6-tricloro-[1,3,5]-triazina (3,09 g, 16,78 mmol) en *N,N*-dimetilformamida (45 mL) La mezcla de reacción se agito a temperatura ambiente durante 1 hora y luego se agrego diclorometano (90 mL) Luego se agregó el alcohol (5,72 g, 15 99 mmol) La mezcla de reacción se agito a temperatura ambiente durante 1 hora La mezcla de

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reacción se diluyó con diclorometano (200 mL) y se lavo la fase orgánica con $H_2C$ (200 mL), $Na_2CO_3$ saturado (200 mL), 1*N* HCl (200 mL), y salmuera (200 mL) La fase organica se seco sobre $MgSO_4$ y se evaporó para proporcionar un solido de color naranja (5,95 g, al 99%)

Etapa 2 Preparación de 1-[3-(aminometil)fenil]-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona



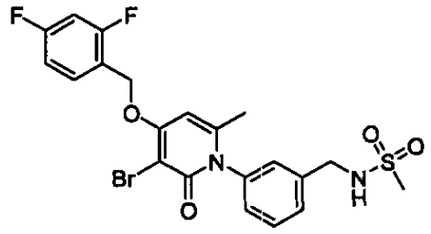
Se suspendio 1-[3-(clorometil)fenil]-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona de la Etapa 1 (1,00 g, 2,66 mmol) en metanol (5 mL) Luego, se llevo la suspension a -78 °C y se hizo burbujear $NH_3$ a traves de la mezcla de reacción durante 10 minutos Luego se permitió que la reaccion se entibiara lentamente hasta temperatura ambiente y se agitó a temperatura ambiente durante 4 dias La reaccion se concentro y el residuo se absorbió en $CH_2Cl_2$ y se filtro para eliminar el exceso de sal El filtrado se concentro para proporcionar un solido de color tostado (0,94 g, al 99%)

Etapa 3 Preparación del compuesto del titulo Se suspendió 1-[3-(aminometil)fenil]-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona de la Etapa 3 (3,89 g, 10,93 mmol) en acetonitrilo (42 mL) y se enfrio en un baño de hielo Se agregó *N*-bromosuccinimida (2,04 g, 11,47 mmol) y se elimino el baño de hielo La mezcla de reaccion se agitó durante 1,5 horas a temperatura ambiente La reacción se diluyo con acetonitrilo (100 mL) y el precipitado que se formo se recogio mediante filtración y

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se lavó con acetonitrilo (3 x 30 mL) para proporcionar un solido de color blanquecino (2,74 g, al 58%) $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7,67 7,59 (m, 3H), 7,34-7,31 (m, 2H), 7,04 (*aprox* t, *J* = 8,72 Hz, 2H), 7,05-6,88 (m, 2H), 6,13 (s, 1H), 5,30 (s, 2H), 3,95 (s, 1H), 2,01 (s, 3H) ES-HRMS *m/z* 435,0538 (M+H $C_{20}H_{17}BrF_2N_2O_2$ requiere 435,0514)

Ejemplo 294



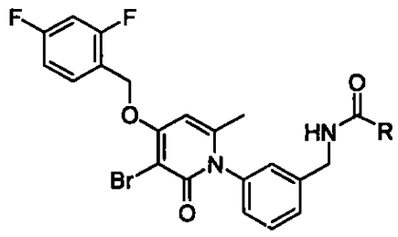
N-3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]bencil}metanosulfonamida

A un recipiente de reacción (tubo de cultivo borosilicatado) se le agrego el compuesto del Ejemplo 293 (0,200 g, 0,459 mmol) y *N,N*-dimetilformamida (4 mL) Se agrego una disolucion madre de 4-metilmorfolina en *N,N*-dimetilformamida (1,3 mL, 1,0 M) al recipiente de reacción y el aparato de reaccion en paralelo se agitó orbitalmente (Labline Benchtop Orbital Shaker) a aproximadamente 200 rpm a temperatura ambiente durante 10 minutos Luego se agregó una disolución madre de cloruro metanosulfonilico en *N,N*-dimetilformamida (4,50 mL, 0,15 mmol) al recipiente de reaccion y el aparato de reaccion se agito orbitalmente a temperatura ambiente durante 2 horas En este momento se diluyo la reaccion con diclorometano (4 mL) y se trato con aproximadamente 2,1 g de resina poliamina (2,63 mmol/g) y aproximadamente 0,8 g de poliestireno funcionalizado con metilisocianato (1,7 mmol/g) y se continuo la agitacion orbital a 200 rpm a temperatura ambiente durante la noche Luego se abrió el recipiente de reacción y los productos de

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fase de disolucion se separaron de los subproductos enfriados rapidamente insolubles mediante su filtración y recoleccion en un vial Despues de la evaporacion parcial, los subproductos insolubles se enjuagaron con diclorometano (2 x 5 mL) El filtrado resultante evaporado soplando $N_2$ sobre el vial mientras se calentaba (60 °C) en un bloque de reaccion (KEM-Lab Parallel Reactor) proporciono un solido de color amarillo (0,190 g, al 81%) $^1$H NMR (400 MHz, $CD_3OD$) δ 7,63 (*aprox* q, *J* = 7,00 Hz, 1H), 7,56-7,50 (m, 2H), 7,25 (m, 1H), 7,16 (dt, *J* = 1,94, 7,25 Hz, 1H), 7,04 (*aprox* t, *J* = 8,59 Hz, 2H), 6,58 (s, 1H), 5,34 (s, 2H), 4,30 (s, 2H), 2,87 (s, 3H), 2,03 (s, 3H) ES-HRMS *m/z* 513,0313 (M+H $C_{21}H_{19}BrF_2N_2O_4S$ requiere 513,0290)

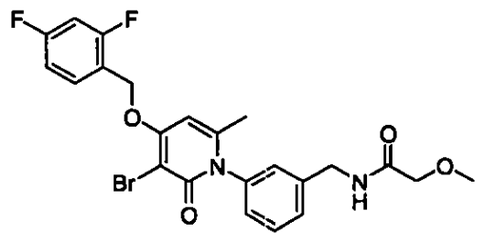
Preparación del Ejemplo 295-296



Los compuestos de los Ejemplos 295-296 se preparan siguiendo el metodo del Ejemplo 294 y reemplazando el cloruro metanosulfonilico con el cloruro acido apropiado

| Compuesto N° | R | % Rend | MF | M+H Requiere | ES-HRMS *m/z* |
|---|---|---|---|---|---|
| Ej 295 | $CH_3$ | 78,0 | $C_{22}H_{19}BrF_2N_2O_3$ | 477,0620 | 477,0640 |
| Ej 296 | $OCH_3$ | 84,0 | $C_{22}H_{19}BrF_2N_2O_4$ | 493,0569 | 493,0591 |

Ejemplo 297



965

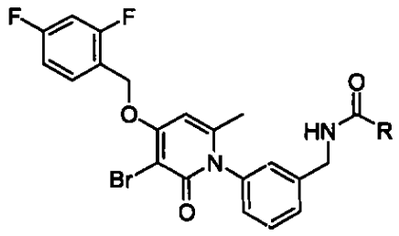
N-{3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]bencil}-2-metoxiacetamida

A un recipiente de reacción (tubo de cultivo borosilicatado) se le agrego aproximadamente 2,87 g de resina carbodiimida aglutinada con polimero (0,96 mmol/g) seguida por una disolucion madre de ácido metoxiacético (8,0 mL, 0,10 M) en *N,N*-dimetilacetamida Se agregaron una disolucion madre de 1-hidroxibenzotriazol en *N,N*-dimetilacetamida (3,0 mL, 0,10 M) y *N*-metilmorfolina (6,0 mL, 0,10 M) en 1,2-dicloroetano al recipiente de reaccion Luego, se agitó orbitalmente el aparato de reacción en paralelo (Labline Benchtop Orbital Shaker) a aproximadamente 200 rpm a temperatura ambiente durante 4 horas Luego se agrego una disolucion madre del Ejemplo 293 en *N,N*-dimetilacetamida (5,0 mL, 0,10 M) al recipiente de reacción y el aparato de reaccion se agito orbitalmente a temperatura ambiente durante la noche En este momento se diluyó la reaccion con 1,2-dicloroetano (10 mL) y se trato con aproximadamente 1,70 g de resina poliamina (2,63 mmol/g) y aproximadamente 0,84 g de poliestireno funcionalizado con metilisocianato (1,50 mmol/g) y se continuo la agitacion orbital a 200 rpm a temperatura ambiente durante 4 horas Luego se abrió el recipiente de reacción y los productos de fase de disolucion se separaron de los subproductos enfriados rapidamente insolubles mediante su filtración y recoleccion en un vial Despues de la evaporacion parcial, los subproductos insolubles se enjuagaron con *N,N*-dimetilacetamida (2 x 5 mL) El filtrado se evaporó soplando $N_2$ sobre el vial mientras se calentaba (60 °C) en un bloque de reacción (KEM-Lab Parallel Reactor) y se sometio a cromatografia (gel de silice, acetato de etilo con metanol/hexanos al 10%) para proporcionar un solido de color blanquecino (0,081 g, al 28%) $^1$H NMR (400

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MHz, DMF-$d_6$) δ 7,59 (q, *J* = 7,65 Hz, 1H), 7,46 (*aprox* t, *J* = 7,55 Hz, 1H), 7,40-7,37 (m, 1H), 7,11-7,07 (m, 2H), 7,00 (t, *J* = 8,56 Hz, 2H), 6,54 (s, 1H), 5,30 (s, 2H), 4,43 (s, 2H), 3,88 (s, 2H), 3,35 (*aprox* d, *J* = 0,80 Hz, 2H), 1,97 (s, 3H) ES-HRMS *m/z* 507,0699 (M+H $C_{23}H_{21}BrF_2N_2O_4$ requiere 507,0726)

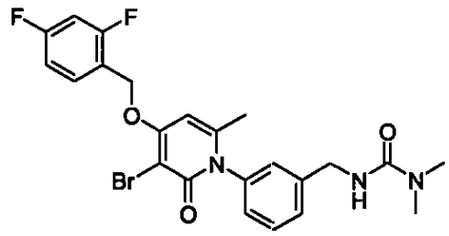
Preparación de los Ejemplos 298-300



Los compuestos de los Ejemplos 298-300 se preparan siguiendo el metodo de y reemplazando el acido metoxiacetico con el ácido apropiado La desproteccion de los intermedios protegidos se logró con 4*N* HCl en dioxano o 1 M $K_2CO_3$ para proporcionar los compuestos como sales de hidrocloruro

| Compuesto N° | R | % Rend | MF | M+H Requiere | ES-HRMS *m/z* |
|---|---|---|---|---|---|
| Ej 298 | $CH_2OCOCH_3$ | 35 5 | $C_{24}H_{21}BrF_2N_2O_5$ | 535,0675 | 535 0686 |
| Ej 299 | $CH_2NH_2$ | 32,6 | $C_{22}H_{20}BrF_2N_3O_3$ | 492,0729 | 492,0744 |
| Ej 300 | $CH_2OH$ | 33,4 | $C_{22}H_{19}BrF_2N_2O_4$ | 493,0569 | 493,0578 |

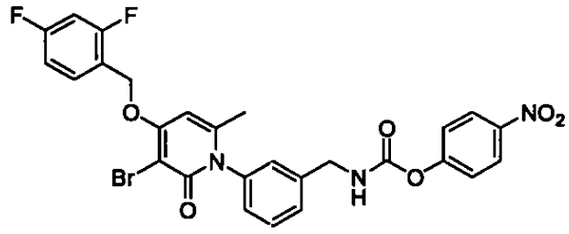
Ejemplo 301



N'-{3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]bencil}-N,N-dimetilurea

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Etapa 1 Preparación de 4-nitrofenil 3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]bencilcarbamato



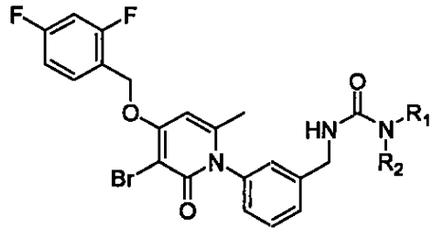
Se suspendio 1-[3-(aminometil)fenil]-3-bromo-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona (1,08 g, 2,48 mmol) en diclorometano (7,5 mL) Se agrego piridina (0,222 mL, 2,74 mmol) Despues de agitar durante 10 minutos a temperatura ambiente, se agregó gota a gota una disolución madre de cloroformato 4-nitrofenilico (5,0 mL, 0,50 M) en diclorometano Despues de agitar durante 4,5 horas a temperatura ambiente, se agregó nuevamente gota a gota una disolucion madre de cloroformato 4-nitrofenilico (2,5 mL, 0,50 M) en diclorometano y se continuo agitando a temperatura ambiente durante la noche La mezcla de reaccion se concentró y se sometio a cromatografia (gel de silice, acetato de etilo con metanol/hexanos al 10%) para proporcionar un solido de color amarillo (0,85 g, al 57%)

Etapa 2 Preparación del compuesto del titulo A un recipiente de reaccion (tubo de cultivo borosilicatado) se le agrego 4-nitrofenil 3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]bencilcarbamato (de la Etapa 1) (0,150 g, 2,5 mmol) y diclorometano (2,5 mL) Luego, se agito orbitalmente el aparato de reaccion en paralelo (Labline Benchtop Orbital Shaker) a aproximadamente 200 rpm a temperatura ambiente durante 15 minutos Luego se agrego una disolucion madre de *N*-metilamina (0,15 mL, 2,0 mmol) al recipiente de reacción

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y el aparato de reacción se agitó orbitalmente a temperatura ambiente durante la noche La mezcla de reaccion se concentrc y se sometio a cromatografia (gel de silice, acetato de etilo con metanol/hexanos al 10%) para proporcionar un sólido de color amarillento (0,065 g, al 51%) $^1$H NMR (400 MH', DMF-$d_6$) δ 7,58 (*aprox* q, *J* = 7,79 Hz, 1H), 7,42 (*aprox* t, *J* = 7,65 Hz, 1H), 7,37 (*aprox* d, *J* = 7,79 Hz, 1H), 7,08 (s, 1H), 7,03 (*aprox* dt, *J* = 1,58, 5,37 Hz, 1H), 6,96 (*aprox* dt, *J* = 2,55, 8,39 Hz, 1H), 6,88-6,83 (m, 1H), 6,06 (s, 1H), 5,24 (s, 2H), 4,95 (*aprox* t, *J* = 5,57 Hz, 1H) 4,42 (*aprox* dddd, *J* = 5,10, 5,71, 10,20, 15,17 Hz, 2H), 2,90 (s, 6H), 1,96 (s, 3H) ES-HRMS *m/z* 506,0848 (M+H $C_{23}H_{22}BrF_2N_3O_3$ requiere 506,0885)

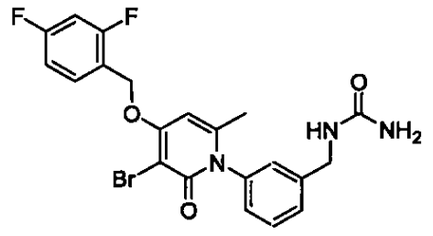
Preparacion de los Ejemplos 302-303



Los compuestos de los Ejemplos 302-303 se preparan siguiendo el metodo del Ejemplo 301 y sustituyendo *N,N*-dimetilamina con la amina apropiada

| Compuesto N° | R1 | R2 | % Rend | MF | M+H Requiere | ES-HRMS *m/z* |
|---|---|---|---|---|---|---|
| Ej 302 | H | $CH_3$ | 52,3 | $C_{22}H_{20}BrF_2N_3O_3$ | 492,0729 | 492,0737 |
| Ej 303 | $CH_2CH_2O$- | $CH_2CH_2O$- | 50,7 | $C_{25}H_{24}BrF_2N_3O_4$ | 548,0991 | 548,0962 |

Ejemplo 304

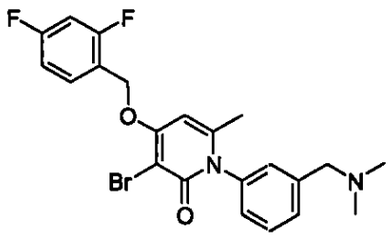


969

N-3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]bencil}urea

A un recipiente de reaccion (tubo de cultivo borosilicatado) se le agrego el compuesto del Ejemplo 293 (0,200 g, 0,459 mmol) y tetrahidrofurano (4,0 mL) Se agrego una disolución madre de tetrahidrofurano (1,8 mL, 1,0 M) al recipiente de reaccion y el aparato de reacción en paralelo se agito orbitalmente (Labline Benchtop Orbital Shaker) a aproximadamente 200 rpm a temperatura ambiente durante 10 minutos Luego se agregó una disolucion madre de cloruro metanosulfonilico en *N,N*-dimetilformamida (4,0 mL, 0,2 mmol) al recipiente de reaccion y el aparato de reacción se agito orbitalmente a temperatura ambiente durante 2 horas En este momento la reacción se diluyo con tetrahidrofurano (4 0 mL) y el precipitado resultante se recogio mediante filtración Luego se lavó el sólido con tetrahidrofurano (3 x 5 mL) para proporcionar un sólido de color blanco (0,214 g, al 97%) $^1$H NMR (400 MHz, $CD_3OD$) δ 7,72 (*aprox* q, *J* = ',83 Hz, 1H), 7,55 (*aprox* t, *J* = 8,06 Hz, 1H), 7,46 (d, *J* = 7,52 Hz, 1H), 7,25-7,14 (m, 4H), 6,65 (s, 1H), 5,65 (*aprox* t, *J* = 0,80 Hz, 1H), 5,40 (s, 2H), 4,38 (s, 2H), 2,05 (s, 3H) ES-HRMS *m/z* 478,0594 (M+H $C_{21}H_{18}BrF_2N_3O_3$ requiere 478,0572)

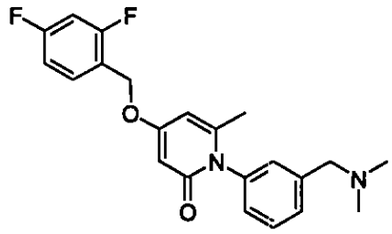
Ejemplo 305




3-bromo-4-[(2,4-difluorobencil)oxi]-1-{3-[(dimetilamino)metil]fenil}-6-metilpiridin-2(1H)-ona

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Etapa 1 Preparacion de 4-[(2,4-difluorobencil)oxi]-1-{3-[(dimetilamino)metil]fenil}-6-metilpiridin-2(1H)-ona



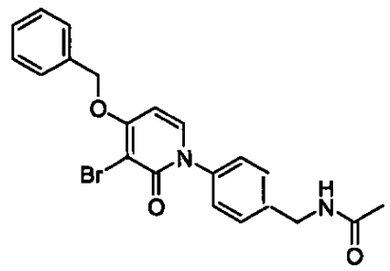
Se suspendio 1-[3-(clorometil)fenil]-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona (de la Etapa 1 de la sintesis del Ejemplo 293) (0,500 g, 1,330 mmol) en una disolución madre de *N,N*-dimetilamina en metanol (2,0 mL, 2,0 M) y se agito durante la noche a temperatura ambiente La reacción se concentro y el residuo se dividio en $H_2O$ (25 mL) y acetato de etilo (25 mL) La capa acuosa se extrajo mas con acetato de etilo (2 x 30 mL), y los materiales organicos combinados se lavaron con salmuera (30 mL), se secaron scbre $MgSO_4$, y se concentraron para proporcionar un sólido blanquecino (0,508 g, al 99%)

Etapa 2 Preparación del compuesto del titulo Se suspendió 4-[(2,4-difluorobencil)oxi]-1-{3-[(dimetilamino)metil]fenil}-6-metilpiridin-2(1H)-ona de la Etapa 1 (0,200 g, 0,521 mmol) en acetonitrilo (2,5 mL) y se enfrio en un baño de hielo Se agrego *N*-bromosuccinimida (0,097 g, 0,547 mmol) y se elimnó el baño de hielo La mezcla de reacción se agito durante 1,5 horas a temperatura ambiente La reaccior se diluyo con acetonitrilo (100 mL) El precipitado que se formo se recogio mediante filtracion y se lavo con acetonitrilo (3 x 15 mL) para proporcionar un sólido amarillo (0,160 g, al 66%) La cromatografia (C-18, acetonitrilo/$H_2O$ con ácido trifluoroacetico al 0 1%, seguido por cromatografia sobre gel de silice, acetato de

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etilo con metanol/hexanos al 10%) proporcionó un solido de color blanquecino (0,024 g, al 10%) $^1$H NMR (400 MHz, $CD_3OD$) δ 7,68 (*aprox* q, *J* = 7,85 Hz, 1H), 7,58 (*aprox* t, *J* = 7,65 Hz, 1H), 7,50 (*aprox* d, *J* = 7,85 Hz, 1H), 7,25-7,05 (m, 4H), 6,63 (s, 1H), 5,39 (s, 2H), 3,61 (*aprox* q, *J* = 12,08 Hz, 2H), 2,32 (s, 6H), 2,08 (s, 3H) ES-HRMS *m/z* 463,0782 (M+H $C_{22}H_{21}BrF_2N_2O_2$ requiere 463,0827)

Ejemplo 306



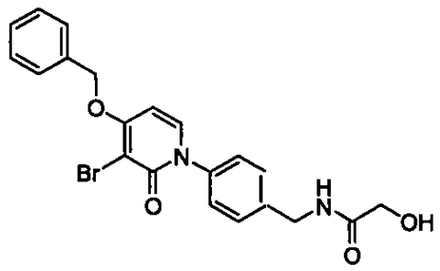
N-{4-[4-(benciloxi)-3-bromo-2-oxopiridin-1(2H)-il]bencil}acetamida

Se disolvió hidrocloruro de 1-[4-(aminometil)fenil]-4-(benciloxi)-3-bromopiridin-2(1H)-ona (0,150 g, 0,389 mmol) en *N,N*-dimetilformamida (3,5 mL) Se agrego una disolución madre de 4-metilmorfolina en *N,N*-dimetilformamida (1,5 mL, 1,0 M) y la reacción se agitó a temperatura ambiente durante 10 minutos Luego se agrego una disolucion madre de cloruro de acetilo en *N,N*-dimetilformamida (3,0 mL, 0,2 M) al recipiente de reaccion y el aparato de reaccion se agito orbitalmente a 200 rpm durante 2 horas a temperatura ambiente En este momento se diluyo la reaccion con diclorometano (4 mL) y se trato con aproximadamente 1,8 g de resina poliamina (2,63 mmol/g) y aproximadamente 0,8 g de poliestireno funcionalizado con metilisocianato (1,7 mmol/g) y se continuo la agitacion orbital a 200 rpm a temperatura ambiente durante la noche Luego se abrió el recipiente de reaccion y los productos de fase de disolución se separaron de los subproductos enfriados

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rapidamente insolubles mediante su filtracion y recoleccion en un vial Despues de una evaporacion parcial, los subproductos insolubles se enjuagaron mas con diclorometano (3 x 5 mL) y se combinaron con el filtrado parcialmente concentrado El filtrado resultante se concentro soplando $N_2$ sobre el vial mientras se calentaba (60 °C) en un bloque de reacción (KEM-Lab Parallel Reactor) para proporcionar un solido de color blanquecino (0,083 g, al 50%) $^1$H NMR (400 MHz, $CD_3OD$) δ 7,59 (d, *J* = 7,79 Hz, 1H), 7,48-7,29 (m, 9H), 6,55 (d, *J* = 7,79 Hz, 1H), 5,35 (s, 2H), 4,39 (s, 2H), 1,98 (s, 3H) ES-HRMS *m/z* 427,0625 (M+H $C_{21}H_{19}BrN_2O_3$ requiere 427,0652)

Ejemplo 307



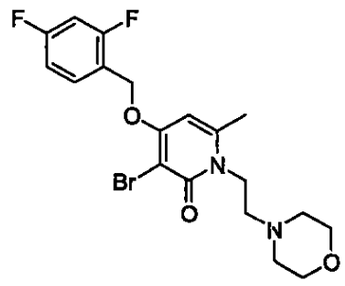

N-{4-[4-(benciloxi)-3-bromo-2-oxopiridin-1(2H)-il]bencil}-2-hidroxiacetamida

A un recipiente de reaccion (tubo de cultivo borosilicatado) se le agrego aproximadamente 1,95 g de resina carbodiimida aglutinada con polimero (0,96 mmol/g) seguida por una disolución madre de acido glicólico (5,8 mL, 0,10 M) en *N,N*-dimetilacetamida Se agregaron una disolucion madre de 1-hidroxibenzotriazol en *N,N*-dimetilacetamida (0,4 mL, 0,10 M) y *N*-metilmorfolina en 1,2-dicloroetano (3,9 mL, 0,10 M) al recipiente de reaccion Luego, se agitó orbitalmente el aparato de reaccion en paralelo (Labline Benchtop Orbital Shaker) a aproximadamente 200 rpm a temperatura ambiente durante 2 horas Luego se agrego una disolucion madre de hidrocloruro

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de 1-[4-(aminometil)fenil]-4-(benciloxi)-3-bromopiridin-2(1H)-ona en *N,N*-dimetilacetamida (0,05 M, 7,8 mL) al recipiente de reaccion y el aparato de reaccion se agito orbitalmente a temperatura ambiente durante la noche En este momento se diluyo la reaccion con 1,2-dicloroetano (8 mL) y se trato con aproximadamente 1,17 g de resina poliamina (2,63 mmol/g) y aproximadamente 0,58 g de poliestireno funcionalizado con metilisocianato (1,50 mmol/g) y se continuo la agitación orbital a 200 rpm a temperatura ambiente durante 4 horas Luego se abrio el recipiente de reaccion y los productos de fase de disolucion se separaron de los subproductos enfriados rapidamente insolubles mediante su filtracion y recoleccion en un vial Despues de una evaporacion parcial, los subproductos insolubles se enjuagaron con *N,N*-dimetilacetamida (2 x 5 mL) y se combinaron con el filtrado parcialmente concentrado El filtrado se concentro soplando $N_2$ sobre el vial mientras se calentaba (60 °C) en un bloque de reaccion (KEM-Lab Parallel Reactor) y se sometió a cromatografia (gel de silice, acetato de etilo con metanol/hexanos al 10%) lo que proporciono un solido de color blanquecino (0,081 g, al 21%) $^1$H NMR (400 MHz, $CD_3OD$) δ 7,55-7,30 (m, 10H), 6,51 (d, *J* = 7,85 Hz, 1H), 5,37 (s, 2H), 4,52 (s, 2H), 4,08 (s, 2H) ES-HRMS *m/z* 443,0605 (M+H $C_{21}H_{19}BrN_2O_4$ requiere 443,0601)

Ejemplo 308

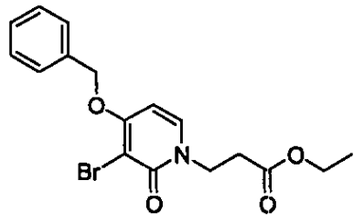


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3-Bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-(2-morfolin-4-iletil)piridin-2(1H)-ona

Se suspendieron 3-bromo-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona (0,100 g, 0,303 mmol), carbonato de cesio (0,296 g, 0,909 mmol), y 4-(2-cloroetil)morfolina (0,059 g, 0,394 mmol) en acetonitrilo (4 mL) La reacción se agito a 60 °C durante la noche Se agrego $H_2O$ (25 mL) y se recogio el precipitado resultante mediante filtración El solido se sometio a cromatografia (gel de silice, acetato de etilo con metanol/hexanos al 10%) para proporcionar un solido de color blanquecino (0,040 g, al 30%) $^1H$ NMR (400 MHz, $CDCl_3$) δ 7,55 (*aprox* q, *J* = 7,92 Hz, 1H), 6,93 (*aprox* t, *J* = 8,39 Hz, 1H), 6,84 (*aprox* t, *J* = 9,40 Hz, 1H), 5,95 (s, 1H), 5,18 (s, 2H), 4,16 (*aprox* t, *J* = 6,78 Hz, 2H), 3,68 (s, 4H), 2,65 (*aprox* t, *J* = 6,38 Hz, 2H), 2,54 (s, 4H), 2,43 (s, 3H) ES-HRMS *m/z* 443,0743 (M+H $C_{19}H_{21}BrF_2N_2O_3$ requiere 443,0776)

Ejemplo 309



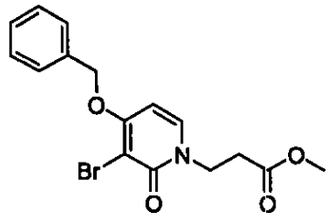

3-[4-(Benciloxi)-3-bromo-2-oxopiridin-1(2H)-il]propanoato de etilo

Se suspendieron 3-bromo-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona (0,50 g, 1,78 mmol) y fluoruro de cesio (0,0027 g, 0,178 mmol) en tetrahidrofurano (10 mL) seguido por la adicion gota a gota de tetraetilortosilicato (0,37 g, 1,78 mmol) a temperatura ambiente Despues de agitar durante 10 minutos a temperatura ambiente, se agregó gota a gota acrilato de etilo (0,23 g, 2,32 mmol) y la reacción se agito a temperatura ambiente

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durante la noche La mezcla de reacción se filtro a través de una almohadilla de Celite® La reaccion se concentró y el residuo resultante se sometio a cromatografia (gel de silice, acetato de etilo con metanol/hexanos al 10%) para proporcionar un solido de color blanco (0,62 g, al 92%) $^1$H NMR (400 MHz, $CDCl_3$) δ 7,42 (d, $J$ = 7,79 Hz, 1H), 7,41-7,29 (m, 5H), 6,03 (d, $J$ = 7,65 Hz, 1H), 5,20 (s, 2H), 4,17 (t, $J$ = 5,98 Hz, 2H), 4,07 (q, $J$ = 7,16 Hz, 2H), 2,83 (t, $J$ = 5,98 Hz, 2H), 1,19 (t, $J$ = 7,18 Hz, 3H) ES-HRMS *m/z* 380,0523 (M+H $C_{17}H_{18}BrNO_4$ requiere 380,0492)

Ejemplo 310



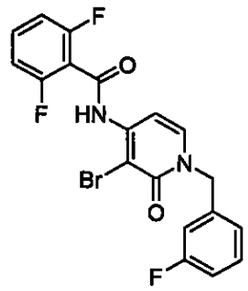

3-[4-(Benciloxi)-3-bromo-2-oxopiridin-1(2H)-il]propanoato de metilo

Se suspendieron 3-bromo-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona (5,00 g, 1,78 mmol) y fluoruro de cesio (0,27 g, 0,178 mmol) en tetrahidrofurano (50 mL) seguido por la adición gota a gota de tetrametilortosilicato (2,70 g, 17,85 mmol) a temperatura ambiente Despues de agitar durante 10 minutos a temperatura ambiente, se agregó gota a gota acrilato de metilo (2,00 g, 23,20 mmol) y la reacción se agitó a temperatura ambiente durante 48 horas La mezcla de reacción se filtro a traves de una almohadilla de Celite® La reacción se concentró y el residuo resultante se sometio a cromatografia (gel de silice, acetato de etilo con metanol/hexanos al 10%) para proporcionar un sólido de color blanco (6,10 g, al 93%) $^1$H NMR (400 MHz, $CDCl_3$) δ 7,42 (d, $J$ = 7,65 Hz, 1H), 7,41-7,29 (m, 5H), 6,04 (d, $J$ = 7,65 Hz, 1H), 5,20 (s, 2H), 4,17 (t,

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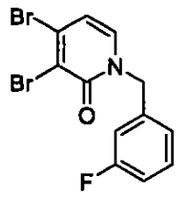
$J$ = 5,91 Hz, 2H), 3,63 (s, 3H), 2,85 (t, $J$ = 5,91 Hz, 2H) ES-HRMS $m/z$ 366,0350 (M+H $C_{16}H_{16}BrNO_4$ requiere 366,0335)

Ejemplo 311



N-[3-bromo-1-(3-fluorobencil)-2-oxo-1,2-dihidropiridin-4-il]-2,6-difluorobenzamida

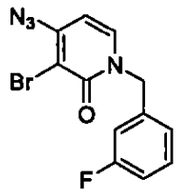
Etapa 1 Preparacion de 3,4-dibromo-1-(3-fluorobencil)piridin-2(1H)-ona



Se disolvieron 3-bromo-1-(3-fluorobencil)-2-oxo-1,2-dihidropiridin-4-il trifluorometanosulfonato (2,00 g, 4,65 mmol), KBr (5,53 g, 46,49 mmol), y 18-corona-6 (0,10 g, 0,38 mmol) en *N,N*-dimetilacetamida (26 mL) Luego, la mezcla de reaccion se calento a reflujo durante 16 horas La reaccion se concentro y el residuo resultante se dividió en agua (50 mL) y acetato de etilo (3 X 50 mL) Los materiales orgánicos combinados se lavaron con $H_2O$ (2 X 30 mL), salmuera (50 mL), se secaron sobre $MgSO_4$, se concentraron y se sometieron a cromatografia (gel de silice, acetato de etilo con metanol/hexano al 10%) para proporcionar un solico de color marron (0,850 g, al 51%)

Etapa 2 Preparación de 4-azido-3-bromo-1-(3-fluorobencil)piridin-2(1H)-ona

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Se suspendió azida de sodio (1,08 g, 16,62 mmol) en *N,N*-dimetilformamida (10 mL) y una disolución madre de 3,4-dibromo-1-(3-fluorobencil)piridin-2(1H)-ona (de la Etapa 1) en *N,N*-dimetilformamida (33,0 mL, 0,33 M) y la mezcla resultante se calentó hasta 60 °C durante 4 horas Se agrego agua helada (J0 mL) y la capa acuosa se extrajo con acetato de etilo (4 X 50 mL) Los materiales organicos combinados se lavaron con $H_2O$ (2 X 3 mL), salmuera (2 X 25 mL), se secaron sobre $MgSO_4$, se concentraron y se sometieron a cromatografia (gel de silice, acetato de etilo con metanol/hexano al 10%) para proporcionar un solido de color blanquecino (3,50 g, al 98%)

Etapa 3 Preparación de hidrocloruro de 4-amino-3-bromo-1-(3-fluorobencil)piridin-2(1H)-ona



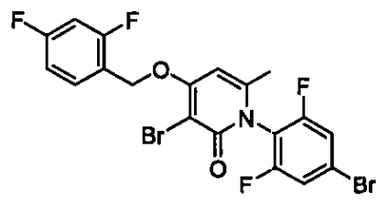
Se suspendio 4-azido-3-bromo-1-(3-fluorobencil)piridin-2(1H)-ona (de la Etapa 2) (4,00 g, 12,38 mmol) en acetato de etilo (300 mL) y se agrego Fe (2,07 g, 37,14 mmol) Se agregó una disolucion madre de $NH_4Cl$ en $H_2O$ (300 mL, 0 2 M) y la mezcla de reaccion se agito a temperatura ambiente durante 36 horas La reaccion se filtro a traves de una almohadilla de Celite® y se concentró El sólido resultante se disolvio en acetato de etilo (150 mL) y se lavo con agua (3 X 50 mL), salmuera (50 mL), se secó sobre $MçSO_4$, y se concentro $^1H$ NMR (400 MHz,

978

$CD_3OD$) δ 7,38-7,29 (m, 2H), 7,05 (d, *J* = 7 79 Hz, 1H), 6,99 (d, *J* = 8,99 Hz, 2H), 6,03 (d, *J* = 7,39 Hz 1H), 5,09 (s, 2H) ES-HRMS *m/z* 297,0023 (M+H $C_{20}H_{17}BrF_2N_2O_2$ requiere 297,0033)

Etapa 4 Preparación del compuesto del título Se suspendieron 4-amino-3-bromo-1-(3-fluorobencil)piridin-2(1H)-ona (de la Etapa 3) (0,30 g, 1,01 mmol) y 4-dimetilaminopiridina (0,002 g, 0,01 mmol) en acetonitrilo (5 mL) seguido por la adición gota a gota de trietilamina (0,2 mL, 1,41 mmol) Esta mezcla de reaccion se agito durante 10 minutos a temperatura ambiente antes de ser enfriada hasta 0 °C Se agrego gota a gota cloruro 2,6-difluorobenzoilico (0,37 g, 2,12 mmol) y la reacción se calento a reflujo durante la noche La reacción se enfrio a temperatura ambiente y se agrego 1*N* NaOH (10 mL) Luego, la reaccion se agito durante 45 minutos a temperatura ambiente La mezcla de reacción se extrajo con acetato de etilo (3 x 25 mL) y la capa orgánica se lavo con 1*N* NaOH (2 X 25 mL), $H_2O$ (hasta pH neutro), salmuera (50 mL), se secó sobre $MgSO_4$, se concentró, y se sometió a cromatografia (sobre C-18, acetonitrilo/ $H_2O$ con acido trifluoracético al 0,1%) para proporcionar un sólido de color blanco (0,19 g, al 43%) $^1H$ NMR (400 MHz, $CDCl_3$) δ 8,42 (br s, 1H), 7,67 (d, *J* = 7,65 Hz, 1H), 7,49 (*aprox* tt, *J* = 6,31, 8,60 Hz, 1H), 7,33-28 (m, 2H), 7,10-6,97 (m, 5H), 5,17 (s, 2H) ES-HRMS *m/z* 437,0083 (M+H $C_{19}H_{12}BrF_3N_2O_2$ requiere 437,0107)

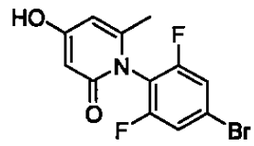
Ej 312



979

3-Bromo-1-(4-bromo-2,6-difluorofenil)-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona

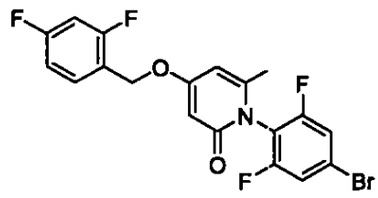
Etapa 1 Preparacion de 1-(4-bromo-2,6-difluorofenil)-4-hidroxi-6-metilpiridin-2(1H)-ona




Se suspendieron 4-hidroxi-6-metil-2-pirona (30,0 g, 238 mmol) y 4-bromo-2,6-difluoroanilina (49,5 g, 238 mmol) en 50 ml de 1,2-diclorobenceno en un matraz de fondo redondo, de tres cuellos de 250 ml, equipado con una sonda controladora de temperatura J-Kem, una trampa Dean-Stark y un manto calentador La reacción se calento a 165 °C durante 15 minutos, durante los cuales se recogio agua y algo de 1,2-diclorobenceno en la trampa Dean-Stark Se permitio que la reacción se enfriara hasta aproximadamente 80 °C El matraz se coloco en un baño de hielo y se agregaron aproximadamente 25 ml de tolueno y se agito Despues de aproximadamente 10 minutos, se formo un precipitado El precipitado se filtró y se lavo tres veces con tolueno, 3 veces con agua caliente para retirar el exceso de pirona y se secó *in vacuo* para proporcionar un solido de color tostado (22,1 g, al 29%) $^1$H NMR (400 MHz, DMSO-$d_6$) δ 11,00 (br s, 1H), 7,71 (d, $J$ = 6,98 Hz, 2H), 5,97 (t, $J$ = 0,88 Hz, 1H), 5,55 (d, $J$ = 2,28 Hz, 1H), 1,91 (s, 3H) LC/MS, $t_r$ = 1,96 minutos (acetonitrilo/agua al 95% a lo largo de 5 minutos a 1 ml/min con deteccion a 254 nm, a 50 °C) ES-MS $m/z$ 316 (M+H) ES-HRMS $m/z$ 315,9779 (M+H calculado para $C_{12}H_8BrF_2NO_2$ requiere 315,9779)

Etapa 2 Preparacion de 1-(4-bromo-2,6-difluorofenil)-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona

980



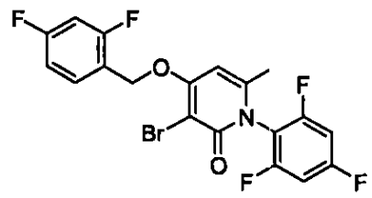
Se agitó enérgicamente 1-(4-bromo-2,6-difluorofenil)-4-hidroxi-6-metilpiridin-2(1H)-ona (de la Etapa 1) (5,0 g, 15,8 mmol) a temperatura ambiente con bromuro de 2,4-difluorobencilo (2,23 ml, 17,4 mmol) y $K_2CO_3$ (3,27 g, 23,7 mmol) en 50 ml de dimetilformamida Después de agitar durante la noche, la reaccion se vertió rapidamente en 900 ml de agua fria El precipitado resultante se filtro y se lavo con agua y hexano El producto se purifico usando un sistema de cromatografia de silice Biotage usando acetato de etilo/hexanos al 20% para proporcionar un sólido de color beis (4,32 g, al 62%) $^1$H NMR (400 MHz, $CDCl_3$) δ 7,41 (*aprox* q, *J* = 6,31 Hz, 1H), 7,25 (dd, *J* = 8,33, 1,74 Hz, 2H), 6,91 (dt, *J* = 9,2, 0,8 Hz, 1H), 6,86 (dt, *J* = 9,2, 0,8 Hz, 1H), 5,95 (d, *J* = 2,56 Hz, 1H), 5,92 (dd, *J* = 2,56, 0,94 Hz, 1H), 5,01 (s, 2H), 1,98 (s, 3H) LC/MS, $t_r$ = 3,04 minutos (acetonitrilo/agua al 95% a lo largo de 5 minutos a 1 ml/min con deteccion a 254 nm, a 50° C) ES-MS *m/z* 442 (M+H) ES-HRMS *m/z* 442,0057 (M+H calculado para $C_{19}H_{12}BrF_4NO_2$ requiere 442,0060)

Etapa 3 Preparación del compuesto del titulo Se agito 1-(4-bromo-2,6-difluorofenil)-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona (de la Etapa 2) (500 mg, 1,13 mmol) a temperatura ambiente con *N*-bromosuccinimida (221 mg, 1,24 mmol) en 5 ml de $CH_2Cl_2$ durante 1,5 horas La reaccion se evaporo en un rotavapor y se lavo 4 veces el solido resultante con acetonitrilo y se seco *in vacuo* para proporcionar un solido de color blanco (478 mg, al 92%) $^1$H NMR (300 MHz, $CDCl_3$) δ 7,62 (*aprox* q,

981

*J* = 6,64 Hz, 1H), 7,31 (d, *J* = 6,85 Hz, 2H), 7,01 (*aprox* t, *J* = 8,36 Hz, 1H), 6,96 (dt, *J* = 9,46, 2,21 Hz, 1H), 6,19 (s, 1H), 5,30 (s, 2H), 2,10 (s, 3H), LC/MS, $t_r$ = 3,17 minutos (acetonitrilo/agua al 5 a 95% a lo largo de 5 minutos a 1 ml/min con deteccion a 254 nm, a 50 °C) ES-MS *m/z* 520 (M+H) ES-HRMS *m/z* 521,9134 (M+H calculado para $C_{19}H_{11}Br_2F_4NO_2$ requiere 521,9146)

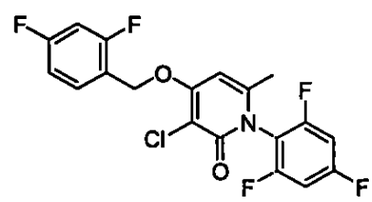
Ej 313



3-Bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-(2,4,6-trifluorofenil)piridin-2(1H)-ona

El compuesto del titulo se produjo esencialmente como en el Ejemplo 313, usando 2,4,6-trifluoroanilina en vez de 4-bromo-2,6-difluoroanilina $^1$H NMR (300 MHz, $CDCl_3$) δ 7,62 (*aprox* q, *J* = 7,79 Hz, 1H), 7,01 (*aprox* dt, *J* = 8,26, 2,01 Hz, 1H), 6,95 -6,85 (m, 3H), 6,19 (s, 1H), 5,30 (s, 2H), 2,11 (s, 3H), LC/MS, $t_r$ = 2,81 minutos (acetonitrilo/agua al 5 a 95% a lo largo de 5 minutos a 1 ml/min, a 254 nm, a 50 °C ), ES-MS *m/z* 460 (M+H) ES-HRMS *m/z* 459,9954 (M+H calculado para $C_{19}H_{11}BrF_5NO_2$ requiere 459,9966)

Ej 314

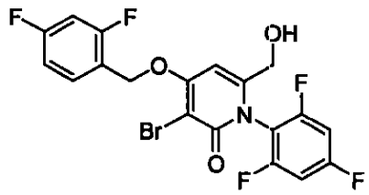


3-Cloro-4-[(2,4-difluorobencil)oxi]-6-metil-1-(2,4,6-trifluorofenil)piridin-2(1H)-ona

982

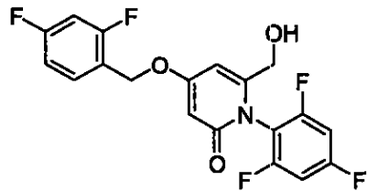
Se sometio a reflujo 4-[(2,4-difluorobencil)oxi]-6-metil-1-(2,4,6-trifluorofenil)piridin-2(1H)-ona (350 mg, 0,92 mmol) con *N*-clorosuccinimida (147 mg, 1,1 mmol) y acido dicloroacetico (0,038 ml, 0,46 mmol) en 5 ml de $CH_2Cl_2$ durante la noche La reaccion se evaporo en un rotavapor y se lavó 4 veces el sólido resultante con acetonitrilo y se seco *in vacuo* para proporcionar un solido de color blanco (217 mg, al 57%) $^1H$ NMR (300 MHz, $CDCl_3$) δ 7,60 (*aprox* q, *J* = 7,75 Hz, 1H), 7,00 (*aprox* dt, *J* = 8,23, 2,05 Hz, 1H), 6,93 -6,86 (m, 3H), 6,22 (s, 1H), 5,30 (s, 2H), 2,12 (s, 3H), LC/MS, $t_r$ = 2,78 minutos (acetonitrilo/agua al 5 a 95% a lo largo de 5 minutos a 1 ml/min, a 254 nm, a 50 °C ), ES-MS *m/z* 416 (M+H) ES-HRMS *m/z* 416,0472 (M+H calculado para $C_{19}H_{11}ClF_5NO_2$ requiere 416,0471)

Ej 315




3-Bromo-4-[(2,4-difluorobencil)oxi]-6-(hidroximetil-1-(2,4,6-trifluorofenil)piridin-2(1H)-ona

Etapa 1 Preparación de 4-[(2,4-difluorobencil)oxi]-6-(hidroximetil-1-(2,4,6-trifluorofenil)piridin-2(1H)-ona




Se calento 4-[(2,4-difluorobencil)oxi]-6-metil-1-(2,4,6-trifluorofenil)piridin-2(1H)-ona (9,0 g, 23,6 mmol) hasta 135 °C durante la noche con $SeO_2$ (13,1 g, 118 mmol) en 75 ml de 1,4-dioxano en un recipiente a presion de

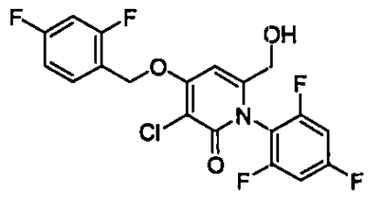
vidrio hermetico de 350 ml La mezcla de reaccion se enfrió y se coloco sobre un tapon de gel de silice y se lavo con metanol al 5% en $CH_2Cl_2$ El filtrado se evaporo y el solido resultante se lavó con eter dietilico y se disolvió en acetato de etilo caliente Se filtraron y retiraron las sales de Se insolubles y se evaporo la capa organica Se aislaron 7,01 g (17,6 mmol) con una relación de 3 1 de aldehido respecto del alcohol deseado La mezcla se agitó con $NaBH_4$ (802 mg, 21,2 mmol) en 30 ml de metanol a temperatura ambiente durante 1 hora La reacción se evaporo y se utilizaron $CH_2Cl_2$ y acetonitrilo para disolver el volumen del solido El solido insoluble remanente se filtró y retiro Se lavó 3 veces la capa orgánica con $NH_4Cl$, se seco sobre $MgSO_4$ y se evaporó El solido resultante se lavo 3 veces con eter dietilico y se seco *in vacuo* para proporcionar un solido de color naranja claro (4,35 g, al 46%) $^1$H NMR (300 MHz, DMSO-$d_6$) δ 7,68 (*aprox* q, $J$ = 7,92 Hz, 1H), 7,47 (*aprox* t, $J$ = 8,57 Hz, 2H), 7,35 (dt, $J$ = 9,87, 2,42 Hz, 1H), 7,18 (dt, $J$ = 8,31, 1,71 Hz, 1H), 6,21 (d, $J$ = 2,42 Hz, 1H), 6,07 (d, $J$ = 2,62 Hz, 1H), 5,67 (br s, 1H), 5,18 (s, 2H), 3,98 (s, 2H), LC/MS, $t_r$ = 2,31 minutos (acetonitrilo/agua al 5 a 95%/a lo largo de 5 minutos a 1 ml/min, a 254 nm, a 50 °C ), ES-MS *m/z* 398 (M+H)

Etapa 2 Preparacion del compuesto del titulo Se agitó 4-[(2,4-difluorobencil)oxi]-6-(hidroximetil)-1-(2,4,6-trifluorofenil)piridin-2(1H)-ona (de la Etapa 1) (2,1 g, 5,28 mmol) a temperatura ambiente con *N*-bromosuccinimida (1,13 g, 6,34 mmol) en 5 ml de $CH_2Cl_2$ durante 2 horas La reaccion se evaporo en un rotavapor y se lavo 4 veces el solido resultante con acetonitrilo y se seco *in vacuo* para proporcionar un sólido de color blanco (1,35 g, al 54%) $^1$H NMR (300 MHz, $CD_3OD$) δ 7,69 (*aprox* q,

984

*J* = 6,65 Hz, 1H), 7,20 (*aprox* t, *J* = 8,36 Hz, 2H), 7,09 (*aprox* t, *J* = 8,46 Hz, 2H), 6,88 (s, 1H), 5,46 (s, 2H), 4,21 (s, 2H), LC/MS, $t_r$ = 2,48 minutos (acetonitrilo/agua al 5 a 95% a lo largo de 5 minutos a 1 ml/min, a 254 nm, a 50 °C ), ES-MS *m/z* 476 (M+H) ES-HRMS *m/z* 475,9907 (M+H calculado para $C_{19}H_{11}BrF_5NO_3$ requiere 475,9915)

Ej 316

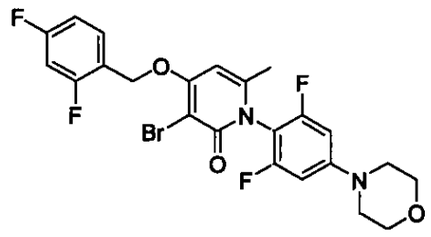


3-Cloro-4-[(2,4-difluorobencil)oxi]-6-(hidroximetil)-1-(2,4,6-trifluorofenil)piridin-2(1H)-ona

Se sometio a reflujo 4-[(2,4-difluorobencil)oxi]-6-(hidroximetil)-1-(2,4,6-trifluorofenil)piridin-2(1H)-ona (2,1 g, 5,28 mmol) con *N*-clorosuccinimida (846 mg, 6,34 mmol) y acido dicloroacético (0,87 ml, 10,56 mmol) en 5 ml $CH_2Cl_2$ durante la noche La reaccion se evaporó en un rotavapor y el aceite resultante se trituro con eter dietilico para obtener un solido El solido se lavo 4 veces con acetonitrilo Se realizo una cromatografia utilizando un sistema de gel de silice Biotage con acetato de etilo/hexanos al 60% La recuperacion de la columna fue pobre, y proporcionó un solido de color blanco (109 mg, 5%) $^1$H NMR (300 MHz, $CD_3OD$) δ 7,67 (*aprox* q, *J* = 7,85 Hz, 1H), 7,24 - 7,06 (m, 4H), 6,90 (s, 1H), 5,45 (s, 2H), 4,22 (s, 2H), LC/MS, $t_r$ = 2,71 minutos (acetonitrilo/agua al 5 a 95% a lo largo de 5 minutos a 1 ml/min, a 254 nm, a 50 °C ), ES-MS *m/z* 432 (M+H) ES-HRMS *m/z* 432,0413 (M+H calculado para $C_{19}H_{11}ClF_5NO_3$ requiere 432,0420)

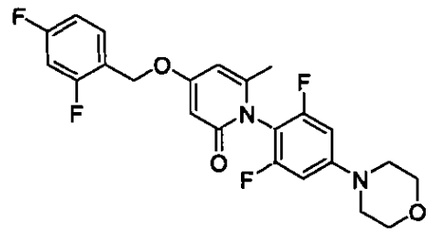
Ej 317

985



3-Bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-difluoro-4-morfolin-4-ilfenil)-6-metilpiridin-2(1H)-ona

Etapa 1 Preparacion de 4-[(2,4-difluorobencil)oxi]-1-(2,6-difluoro-4-morfolin-4-ilfenil)-6-metilpiridin-2(1H)-ona



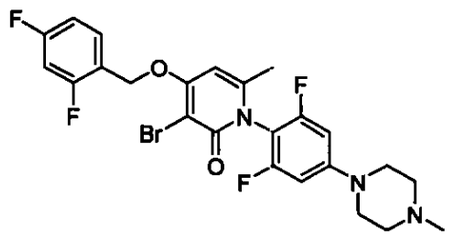
Se calento 4-[(2,4-difluorobencil)oxi]-6-metil-1-(2,4,6-trifluorofenil)piridin-2(1H)-ona (870 mg, 2,28 mmol) hasta 100 °C con $K_2CO_3$ (630 mg, 4,56 mmol) en 5 ml de morfolina durante 36 horas Se agregó la reaccion a 200 ml de agua fria y el solido resultante se lavó con agua y 50 50 de eter dietilico/hexanos y se seco *in vacuo* para proporcionar un solido de color beis (738 mg, al 72%) $^1H$ NMR (400 MHz, $CDCl_3$) δ 7,41 (*aprox* q, *J* = 7,70 Hz, 1H), 6,93 - 6,85 (m, 2H), 6,49 (d, *J* = 10,47 Hz, 2H), 5,96 (d, *J* = 2,41 Hz, 1H), 5,89 (d, *J* = 1,75 Hz, 1H), 5,00 (s, 2H), 3,83 (t, *J* = 4,83 Hz, 4H), 3,19 (t, *J* = 4,84 Hz, 4H), 1,99 (s, 3H), LC/MS, $t_r$ = 3,09 minutos (acetonitrilo/agua al 5 a 95% a lo largo de 5 minutos a 1 ml/min, a 254 nm, a 50 °C ), ES-MS *m/z* 449 (M+H) ES-HR/MS *m/z* 449,1485 (M+H calculado para $C_{23}H_{20}F_4N_2O_3$ requiere 449,1483)

Etapa 2 Preparacion del compuesto del titulo Se agitó 4-[(2,4-difluorobencil)oxi]-1-(2,6-difluoro-4-

986

morfolın-4-ılfenıl)-6-metılpırıdın-2(1H)-ona (de la Etapa 1) (500 mg, 1,12 mmol) a temperatura ambıente con *N*-bromosuccınımıda (236 mg, 1,33 mmol) en 5 ml de $CH_2Cl_2$ durante 2 horas La reaccion se evaporó en un rotavapor y el aceıte resultante se trıturó con éter dıetılıco para obtener un solıdo El solıdo se lavó 4 veces con acetonıtrılo y se seco *ın vacuo* para proporcıonar un solıdo de color blanco (171 mg, al 29%) $^1$H NMR (400 MHz, $CDCl_3$) δ 7,58 (*aprox* q, *J* = ',74 Hz, 1H), 6,96 (*aprox* t, *J* = 8,39 Hz, 1H), 6,86 (dt, *J* = 9,46, 2,28 Hz, 1H), 6,50 (d, *J* = 10,74 Hz, 2H), 6,09 (s, 1H), 5,24 (s, 2H), 3,84 (t, *J* = 4,84 Hz, 4H), 3,20 (t, *J* = 4,83 Hz, 4H), 2,07 (s, 3H), LC/MS, $t_r$ = 3,18 mınutos (acetonıtrılo/agua al 5 a 95% a lo largo de 5 mınutos a 1 ml/mın, a 254 nm, a 50 °C ), ES-MS *m/z* 527 (M+H) ES-HRMS *m/z* 527,0570 (M+H calculado para $C_{23}H_{19}BrF_4N_2O_3$ requıere 527,0588)

Ej 318



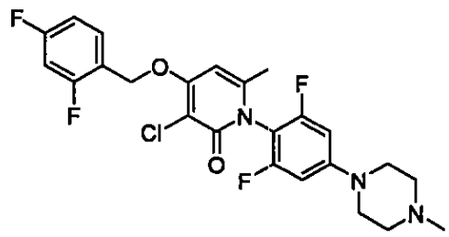
3-Bromo-4-[(2,4-dıfluorobencıl)oxı]-1-[2,6-dıfluoro-4-(4-metılpıperazın-1-ıl)fenıl]-6-metılpırıdın-2(1H)-ona

El compuesto del título se preparó esencıalmente como en el Ejemplo 317, utılızando 1-metılpıperazına en vez de morfolına $^1$H NMR (400 MHz, $CDCl_3$) δ 7,57 (*aprox* q, *J* = 7,79 Hz, 1H), 6,96 (dt, *J* = 8,19, 1,88 Hz, 1H), 6,86 (*aprox* dt, *J* = 9,44, 2,48 Hz, 1H), 6,52 (d, *J* = 10,61 Hz, 2H), 6,14 (s, 1H), 5,24 (s, 2H), 3,72 (br s, 4H), 3,51 (d, *J* = 11,27 Hz, 2H), 3,07 (br s, 2H), 2,85 (d, *J* = 4,29 Hz, 3H), 2,06 (s, 3H), LC/MS, $t_r$ = 2,50 mınutos

987

(acetonitrilo/agua al 5 a 95% a lo largo de 5 minutos a 1 ml/min, a 254 nm, a 50 °C ), ES-MS *m/z* 540 (M+H) ES-HRMS *m/z* 540,0930 (M+H calculado para $C_{24}H_{22}BrF_4N_3O_2$ requiere 540,0904)

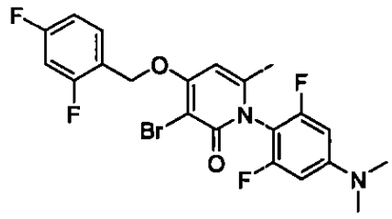
Ej 320



3-Cloro-4-[(2,4-difluorobencil)oxi]-1-[2,6-difluoro-4-(4-metilpiperazin-1-il)fenil]-6-metilpiridin-2(1H)-ona

Se agito a reflujo 4-[(2,4-difluorobencil)oxi]-1-[2,6-difluoro-4-(4-metilpiperazin-1-il)fenil]-6-metilpiridin-2(1H)-ona (1,3 g, 2,82 mmol) con *N*-clorosuccinimida (451 mg, 3,38 mmol) y ácido dicloroacetico (0,17 ml, 1,41 mmol) en 6 ml de $CH_2Cl_2$ durante la noche La LC-MS mostró una complecion del 33% Se agrego mas *N*-clorosuccinimida (271 mg, 2,23 mmol) y se sometio a reflujo durante la noche La reacción se evaporo en un rotavapor y el aceite resultante se trituro con acetato de etilo para obtener un solido El solido se lavo 4 veces con acetato de etilo y éter dietilico y se secó *in vacuo* para proporcionar un solido de color blanco (606 mg, al 43%) $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7,66 (br q, *J* = 7,74 Hz, 1H), 7,33 (br t, *J* = 9,00 Hz, 1H), 7,16 (br t, *J* = 7,65 Hz, 1H), 6,96 (d, *J* = 11,81 Hz, 2H), 6,79 (s, 1H), 5,33 (s, 2H), 3,61 (br m, 4H), 3,25 (br m, 4H), 3,21 (br s, 3H), 2,04 (s, 3H), LC/MS, $t_r$ = 2,45 minutos (acetonitrilo/agua al 5 a 95% a lo largo de 5 minutos a 1 ml/min, a 254 nm, a 50 °C ), ES-MS *m/z* 496 (M+H) ES-HRMS *m/z* 496,1400 (M+H calculado para $C_{24}H_{22}ClF_4N_3O_2$ requiere 496,1409)

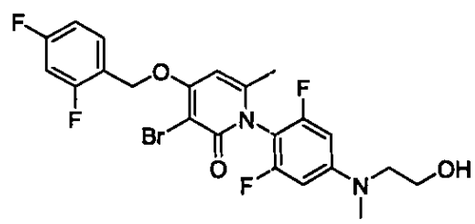
Ejemplo 321



3-bromo-4-[(2,4-difluorobencil)oxi]-1-[4-(dimetilamino)-2,6-difluorofenil]-6-metilpiridin-2(1H)-ona

El compuesto del título se preparó esencialmente como en el Ejemplo 317, utilizando dimetilamina en vez de morfolina $^1$H NMR (400 MHz, $CDCl_3$) δ 7,59 (q, *J* = 7,74 Hz, 1H), 6,95 (dt, *J* = 8,32, 1,61 Hz, 1H), 6,85 (*aprox* dt, *J* = 9,54, 2,41 Hz, 1H), 6,27 (d, *J* = 11,01 Hz, 2H), 6,08 (s, 1H), 5,23 (s, 2H), 2 98 (s, 3H), 2,07 (s, 3H), LC/MS, $t_r$ = 3,35 minutos (acetonitrilo/agua al 5 a 95% a lo largo de 5 minutos a 1 ml/min, a 254 nm, a 50 °C ), ES-MS *m/z* 485 (M+H) ES-HRMS *m/z* 485,0447 (M+H calculado para $C_{21}H_{17}BrF_4N_2O_2$ requiere 485,0482)

Ejemplo 322



3-Bromo-4-[(2,4-difluorobencil)oxi]-1-{2,6-difluoro-4-[(2-hidroxietil)(metil)amino]fenil}-6-metilpiridin-2(1H)-ona

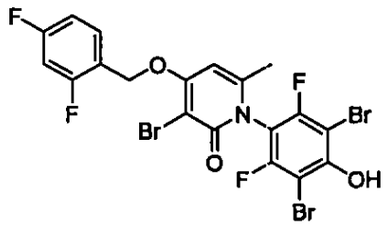
El compuesto del titulo se preparó esencialmente como en el Ejemplo 317, utilizando 2-(metilamino)etanol en vez de morfolina

$^1$H NMR (400 MHz, $CDCl_3$) δ 7,58 (q, *J* = 7,74 Hz, 1H), 6,95 (dt, *J* = 8,24, 1,66 Hz, 1H), 6,85 (*aprox* dt, *J* = 9,49, 2,37 Hz, 1H), 6,35 (d, *J* = 11,01 Hz, 2H), 6,10 (s,

989

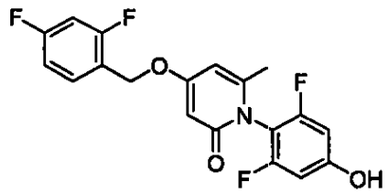
1H), 5,23 (s, 2H), 3,77 (t, $J$ = 5,77 Hz, 2H), 3,45 (t, $J$ = 5,78 Hz, 2H), 2,99 (s, 3H), 2,08 (s, 3H), LC/MS, $t_r$ = 2,96 minutos (acetonitrilo/agua al 5 a 95% a lo largo de 5 minutos a 1 ml/min, a 254 nm, a 50 °C ), ES-MS $m/z$ 515 (M+H) ES-HRMS $m/z$ 515,0576 (M+H calculado para $C_{22}H_{19}BrF_4N_2O_3$ requiere 515,0588)

Ejemplo 323



3-Bromo-1-(3,5-dibromo-2,6-difluoro-4-hidroxifenil)-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona

Etapa 1 Preparacion de 4-[(2,4-difluorobencil)oxi]-1-(2,6-difluoro-4-hidroxifenil)-6-metilpiridin-2(1H)-ona



Se calentó 4-[(2,4-difluorobencil)oxi]-6-metil-1-(2,4,6-trifluorofenil)piridin-2(1H)-ona (Etapa 2 anterior) (10,0 g, 26,2 mmol) hasta 45 °C con $KOSiMe_3$ (10,08 g, 78,6 mmol) en 50 ml de tetrahidrofurano durante 4 dias La reacción se diluyó con 30 ml de acetato de etilo y se lavo con 1N HCl y agua, se secó sobre $MgSO_4$, y se evaporo para proporcionar un sólido de color naranja El solido se agito en acetato de etilo/hexanos al 60% caliente y se filtró para proporcionar un sólido de color blanco, que se seco *in vacuo* para obtener un solido blanco (3,79 g, al 38%) Se descubrio que el filtrado contenia una mezcla del producto deseado y el regioisómero sustituido en orto $^1H$ NMR (400

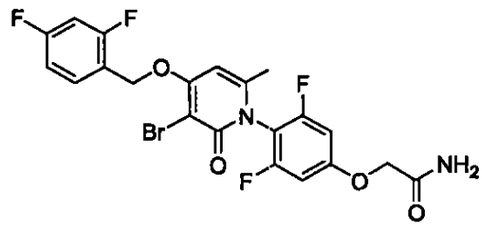
990
990

MHz, $CDCl_3$) δ 7,42 (*aprox* q, *J* = 7,70 Hz, 1H), 6,95 - 6,83 (m, 2H), 6,34 (d, *J* = 9,40 Hz, 2H), 6,05 (*aprox* s, 2H), 5,06 (s, 2H), 2,01 (s, 3H), LC/MS, $t_r$ = 2,80 minutos (acetonitrilo/agua al 5 a 95% a lo largo de 5 minutos a 1 ml/min, a 254 nm, a 50 °C ), ES-MS *m/z* 380 (M+H) ES-HRMS *m/z* 380,0926 (M+H calculado para $C_{19}H_{13}F_4NO_3$ requiere 380,0904)

Etapa 2 Preparacion del compuesto del titulo Se agito 4-[(2,4-difluorobencil)oxi]-1-(2,6-difluoro-4-hidroxifenil)-6-metilpiridin-2(1H)-ona (de la Etapa 1) (3,73 g, 8,14 mmol) como una suspension a temperatura ambiente con *N*-bromosuccinimida (1,52 g, 8,55 mmol) en 30 ml de $CH_2Cl_2$ durante la noche La LC-MS mostro un 60% de material inicial El sólido se filtró y se retiró, se disolvio en 30 ml de $CH_2Cl_2$/*N,N*-dimetilformamida y se agito con más *N*-bromosuccinimida (0,76 g, 4,28 mmol) durante la noche La LC-MS mostro el producto tri-brominado como el producto principal La reaccion se vertio en agua y se extrajo con n-butanol Las capas orgánicas combinadas se evaporaron en un rotavapor y el solido resultante se lavo con eter dietilico y se seco *in vacuo* para proporcionar un solido de color blanco (873 mg, al 17%) $^1$H NMR (400 MHz, $CDCl_3$) δ 7,67 (*aprox* q, *J* = 7,80 Hz, 1H), 7,32 (dt, *J* = 4,86, 2,11 Hz, 1H), 7,16 (dt, *J* = 8,48, 1,84 Hz, 1H), 6,79 (s, 1H), 5,35 (s, 2H), 2,08 (s, 3H), LC/MS, $t_r$ = 3,26 minutos (acetonitrilo /agua al 5 a 95% a lo largo de 5 minutos a 1 ml/min, a 254 nm, a 50 °C ), ES-MS *m/z* 616 (M+H) ES-HRMS *m/z* 615,8234 (M+H calculado para $C_{19}H_{10}Br_3F_4NO_3$ requiere 615,8200)

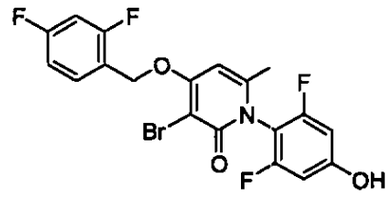
Ejemplo 324

991



2-{4-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-3,5-difluorofenoxi}acetamida

Etapa 1 Preparacion de 3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-difluoro-4-hidroxifenil)-6-metilpiridin-2(1H)-ona



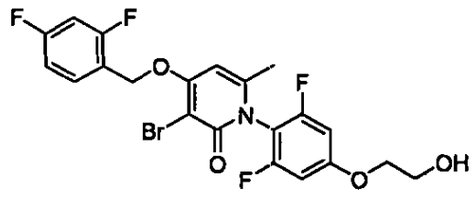
Se calentó 3- bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-(2,4,6-trifluorofenil)piridin-2(1H)-ona (anterior) (7,5 g, 16,3 mmol) hasta 45 °C con $KOSiMe_3$ (10,08 g, 78,6 mmol) en 50 ml de tetrahidrofurano durante 48 horas La reaccion se diluyó con 30 ml de acetato de etilo y se lavo con 1N HCl y agua, se secó sobre $MgSO_4$, y se evaporo para proporcionar un aceite de color negro El aceite se disolvio en acetato de etilo Se formo un precipitado al estacionarlo, que se filtro, se lavó con acetato de etilo y se seco in vacuo para obtener un solido de color blanco (2,80 g, al 37%) El filtrado mostró la presencia del producto deseado y su regioisómero sustituido en orto $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 7,66 (q, $J$ = 7,92 Hz, 1H), 7,32 (dt, $J$ = 8,77, 2,19 Hz, 1H), 7,15 (m, 1H), 6,73 (s, 1H), 6,67 (d, $J$ = 9,66 Hz, 2H), 5,33 (s, 2H), 2,03 (s, 3H), LC/MS, $t_r$ = 2,92 minutos (acetonitrilo/agua al 5 a 95% a lo largo de 5 minutos a 1 ml/min, a 254 nm, a 50 °C ), ES-MS

992

*m/z* 458 (M+H) ES-HRMS *m/z* 457,9995 (M+H calculado para $C_{19}H_{12}BrF_4NO_3$ requiere 458,0009)

Etapa 2 Preparacion del compuesto del titulo Se agito energicamente 3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-difluoro-4-hidroxifenil)-6-metilpiridin-2(1H)-ona (de la Etapa 1) (500 mg, 1,09 mmol) con 2-bromoacetamida (196 mg, 1,43 mmol) y $K_2CO_3$ (282 mg, 2,05 mmol) en 5 ml de *N,N*-dimetilformamida a temperatura ambiente durante 24 horas Se vertio rápidamente la reacción en agua fria y el solido resultante se filtro, se lavo con agua, acetonitrilo y éter dietilico y se seco *in vacuo* para proporcionar un solido de color blanco (289 mg, al 51%) $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7,66 (q, *J* = 7,92 Hz, 1H), 7,61 (br s, 1H), 7,45 (br s, 1H), 7,33 (dt, *J* = 10,07, 2,15 Hz, 1H), 7,16 (dt, *J* = 8,53, 1,88 Hz, 1H), 6,99 (d, *J* = 9,54 Hz, 2H), 6,76 (s, 1H), 5,34 (s, 2H), 2,03 (s, 3H), LC/MS, $t_r$ = 2,70 minutos (acetonirilo/agua al 5 a 95% a lo largo de 5 minutos a 1 ml/min, a 254 nm, a 50 °C ), ES-MS *m/z* 515 (M+H) ES-HRMS *m/z* 515,0245 (M+H calculado para $C_{21}H_{15}BrF_4N_2O_4$ requiere 515,0224)

Ejemplo 325



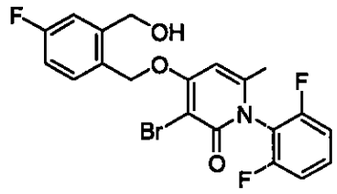

3-Bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-difluoro-4-(2-hidroxietoxi)fenil]-6-metilpiridin-2(1H)-ona

El compuesto del titulo se preparo mediante un procedimiento similar al descrito para el Ejemplo 324 $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7,66 (q, *J* = 7,92 Hz, 1H), 7,33 (dt, *J* = 10,04, 2,19 Hz, 1H), 7,17 (dt, *J* = 8,68, 1,84 Hz, 1H), 6,99 (d, *J* = 9,67 Hz, 2H), 6,75 (s, 1H), 5,34 (s, 2H),

993

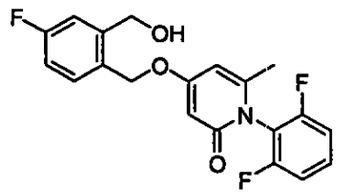
4,92 (t, $J$ = 4,86 Hz, 1H), 4,07 (t, $J$ = 4,77 Hz, 2H), 3,70 (t, $J$ = 4,83 Hz, 2H), 2,03 (s, 3H), LC/MS, $t_r$ = 2,81 minutos (acetonitrilo/agua al 5 a 95% a lo largo de 5 minutos a 1 ml/min, a 254 nm, a 50 °C ), ES-MS $m/z$ 502 (M+H) ES-HRMS $m/z$ 502,0291 (M+H calculado para $C_{21}H_{16}BrF_4NO_4$ requiere 502,0272)

Ejemplo 326




3-Bromo-1-(2,6-difluorofenil)-4-{[4-fluoro-2-(hidroximetil)bencil]oxi}-6-metilpiridin-2(1H)-ona

Etapa 1 Preparación de 1-(2,6-difluorofenil)-4-{[4-fluoro-2-(hidroximetil)bencil]oxi}-6-metilpiridin-2(1H)-ona




Se disolvió 1-(2,6-difluorofenil)-4-hidroxi-6-metilpiridin-2(1H)-ona (Etapa 1) (3,0 g, 12,65 mmol) en *N,N*-dimetilformamida (60 mL) y se enfrio hasta 0 °C Se agregaron trifenilfosfina (3,98 g, 15,18 mmol) y azodicarboxilato dietilico (2,39 ml, 15,18 mmol) y se agitó durante 10 minutos Se agrego 1,2-bis(hidroximetil)-4-fluorobenceno (2,57 q, 16,44 mmol)y se agito a 0 °C durante 1 hora, luego se dejó entibiar hasta temperatura ambiente y se agito durante la noche La LC-MS mostro solamente un producto, no una mezcla de regioisomeros, como se esperaba La reaccion se agrego a agua y se extrajo 3 veces con acetato de etilo Las capas organicas combinadas se secaron

994

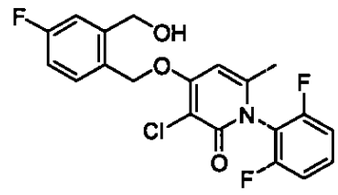
sobre $MgSO_4$ y se evaporaron Se utilizó una columna de sílice utilizando acetato de etilo/hexanos como eluyente El producto deseado se obtuvo con una impureza sustancial Se utilizo otra columna de sílice Biotage usando acetato de etilo/hexanos al 30% para obtener el producto puro El aceite resultante se trituro con eter dietílico para obtener un solido de color blanco (720 mg, al 15%) $^1$H NMR (300 MHz, $CDCl_3$) δ 7,51 - 7,39 (m, 2H), 7,26 (dd, *J* = 9,62, 2,51 Hz, 1H), 7,13 - 7,01 (m, 3H), 6,03 (d, *J* = 2,42 Hz, 1H), 5,96 (d, *J* = 2,41 Hz, 1H), 5,06 (s, 2H), 4,73 (s, 2H), 2,81 (br s, 1H), 2,02 (s, 3H), LC/MS, $t_r$ = 2,37 minutos (acetonitrilo/agua al 5 a 95% a lo largo de 5 minutos a 1 ml/min, a 254 nm, a 50 °C ), ES-MS *m/z* 376 (M+H) ES-HR/MS *m/z* 376,1181 (M+H calculado para $C_{20}H_{16}F_3NO_3$ requiere 376,1155) La identidad del isomero posicional se determino a partir de experimentos hmbc (experimento de correlación de enlace multiple heteronuclear), 2-D NMR (experimentos de resonancia magnetica nuclear en 2 dimensiones) usando H a C 2- y acoplamiento de triple enlace

Etapa 2 Preparacion del compuesto del titulo Se agitó 1-(2,6-difluorofenil)-4-{[4-fluoro-2-(hidroximetil)bencil]oxi}-6-metilpiridin-2(1H)-ona (de la Etapa 1) (350 mg, 0,93 mmol) a temperatura ambiente con *N*-bromosuccinimida (199 mg, 1,12 mmol) en 1,5 ml de $CH_2Cl_2$ durante 1,5 horas La reaccion se evaporo en un rotavapor y se lavo 4 veces el sólido resultante con acetonitrilo y se seco *in vacuo* para proporcionar un sólido de color blanco (197 mg, al 47%) $^1$H NMR (300 MHz, $CDCl_3$) δ 7,53 - 7,43 (m, 2H), 7,25 (dd, *J* = 9,46, 2,62 Hz, 1H), 7,11 -7,03 (m, 3H), 6,25 (s, 1H), 5,31 (s, 2H), 4,81 (s, 2H), 2,28 (br s, 1H), 2,10 (s, 3H), LC/MS, $t_r$ = 2,38 minutos (acetonitrilo/agua al 5 a 95% a lo largo de 5 minutos a 1 ml/min, a 254 nm, a

995

50 °C ), ES-MS *m/z* 454 (M+H) ES-HRMS *m/z* 454,0247 (M+H calculado para $C_{20}H_{15}BrF_3NO_3$ requiere 454,0260)

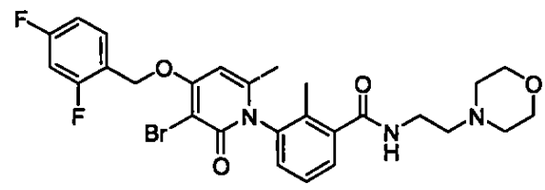
Ejemplo 327



3-cloro-1-(2,6-difluorofenil)-4-{[4-fluoro-2-(hidroximetil)bencil]oxi}-6-metilpiridin-2(1H)-ona

Se agito a reflujo 1-(2,6-difluorofenil)-4-{[4-fluoro-2-(hidroximetil)benc 1]oxi}-6-metilpiridin-2(1H)-ona (Etapa 1 anterior) (275 mg, 0,73 mmol) con *N*-clorosuccinimida (117 mg, 0,88 mmol) y acido dicloroacetico (0,03 ml, 0,36 mmol) en 1,5 ml de $CH_2Cl_2$ durante la noche La reaccion se evaporó en un rotavapor y el sólido resultante se lavó 4 veces el sólido resultante con acetato de etilo y eter dietilico y se secó *in vacuo* para obtener un solido de color blanco (65,5 mg, al 22%) $^1H$ NMR (300 MHz, $CDCl_3$) δ 7,52 - 7,43 (m, 2H), 7,26 (dd, *J* = 9,38, 2,52 Hz, 1H), 7,12 -7,04 (m, 3H), 6,27 (s, 1H), 5,32 (s, 2H), 4,82 (s, 2H), 2,29 (br s, 1H), 2,11 (s, 3H), LC/MS, $t_r$ = 2,32 minutos (acetonitrilo/agua al 5 a 95% a lo largo de 5 minutos a 1 ml/min, a 254 nm, a 50 °C ), ES-MS *m/z* 410 (M+H) ES-HRMS *m/z* 410,0755 (M+H calculado para $C_{20}H_{15}ClF_3NO_3$ requiere 410,0765)

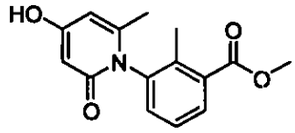
Ejemplo 328



996

3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-2-metil-N-(2-morfolin-4-iletil)benzamida

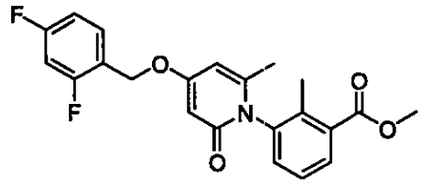
Etapa 1 Preparación de 3-(4-hidroxi-6-metil-2-oxopiridin-1(2H)-il)-2-metilbenzoato de metilo



Se suspendieron 4-hidroxi-6-metil-2-pirona (72,6 g, 576 mmol) y metil-3-amino-2-metilbenzoato (100 g, 605 mmol) en 75 ml de 1,2-diclorobenceno en un matraz de fondo redondo, de tres cuellos de 500 ml, equipado con una sonda controladora de temperatura J-Kem, una trampa Dean-Stark y un manto calentador La reacción se calento a 165 °C durante 15 minutos, durante los cuales se recogio agua y algo de 1,2-diclorobenceno en la trampa Dean-Stark Se permitió que la reaccion se enfriara hasta aproximadamente 80 °C El matraz se colocó en un baño de hielo y se agregaron aproximadamente 300 ml de tolueno y se agitó Despues de aproximadamente 30 minutos, se formo un precipitado El precipitado se filtro y se lavó tres veces con tolueno, 3 veces con agua caliente para eliminar el exceso de pirona y se secó *in vacuo* para proporcionar un solido de color tostado (44,6 g, al 28%) $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10,66 (br s, 1H), 7,80 (dd, $J$ = 7,72, 1,28 Hz, 1H), 7,33 (dd, $J$ = 7,78, 1,34 Hz, 1H), 5,91 (dd, $J$ = 2,41, 0,69 Hz, 1H), 5,55 (d, $J$ = 2,42 Hz, 1H), 3,82 (s, 3H), 2,06 (s, 3H), 1,73 (s, 3H), LC/MS, $t_r$ = 1,85 minutos (acetonitrilo/agua al 5 a 95% a lo largo de 5 minutos a 1 ml/min, a 254 nm, a 50 °C ), ES-MS *m/z* 274 (M+H) ES-HRMS *m/z* 274,1078 (M+H calculado para $C_{15}H_{15}NO_4$ requiere 274,1074)

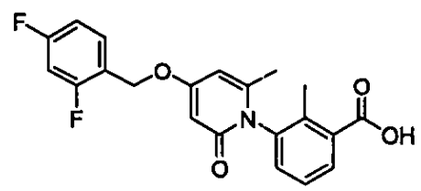
997

Etapa 2 Preparación de 3-[4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-2-metilbenzoato de metilo



Se agitó energicamente metil-3-(4-hidroxi-6-metil-2-oxopiridin-1(2H)-il) 2-metilbenzoato (de la Etapa 1) (42,0 g, 154 mmol) a temperatura ambiente con bromuro 2,4-difluorobencílico (19,7 ml, 154 mmol) y $K_2CO_3$ (31,8 g, 231 mmol) en 250 ml de *N,N*-dimetilformamida Después de agitar durante la noche, la reacción se vertio rapidamente en 1 L de agua fría La disolución se extrajo 3 veces con acetato de etilo y las capas organicas se secaron sobre $MgSO_4$, y se evaporaron El producto se llevo a la siguiente Etapa como un aceite en crudo(60,4 g, al 85%) $^1$H NMR (400 MHz, $CDCl_3$) δ 7,96 (dd, *J* = 7,85, 1,28 Hz, 1H), 7,45 - 7,34 (m, 2H), 7,27 - 7,23 (m, 1H), 6,94 - 6,84 (m, 2H), 5,98 (d, *J* = 2,68 Hz, 1H), 5,92 (dd, *J* = 2,69, 0,81 Hz, 1H), 5,01 (s, 2H), 3,88 (s, 3H), 2,28 (s, 3H), 1,81 (s, 3H), LC/MS, $t_r$ = 2,96 minutos (acetonitrilo/agua al 5 a 95% a lo largo de 5 minutos a 1 ml/min, a 254 nm, a 50 °C ), ES-MS *m/z* 400 (M+H) ES-HRMS *m/z* 400,1341 (M+H calculado para $C_{22}H_{19}F_2NO_4$ requiere 400,1355)

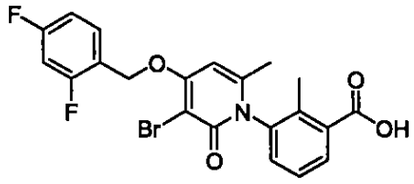
Etapa 3 Preparacion de acido 3-[4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-2-metilbenzoico



998

3-[4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-2-metilbenzoato de metilo (de la Etapa 2) (60,0 mg, 150 mmol) se agitó con 2,5 N NaOH (120 ml, 300 mmol) en 375 ml de tetrahidrofurano y 75 ml de agua a temperatura ambiente durante la noche La reaccion se acidificó con 1 N HCl, se agregaron 350 ml de agua y la disolución se extrajo 3 veces con acetato de etilo Las capas organicas combinadas se secaron sobre $MgSO_4$ se filtraron y se evaporaron El solido resultante se filtró, se lavo acetato de etilo y se seco *in vacuo* para proporcionar un sólido de color blanco (33,8 g, al 58%) $^1H$ NMR (400 MHz, $CDCl_3$) δ 7,98 (dd, *J* = 7,92, 1,20 Hz, 1H), 7,43 (*aprox* q, *J* = 7,70 Hz, 1H), 7,38 (t, *J* = 7,72 Hz, 1H), 7,35 (dd, *J* = 7,81, 1,21 Hz, 1H), 6,92 - 6,84 (m, 2H), 6,17 (d, *J* = 2,56 Hz, 1H), 6,00 (dd, *J* = 2,55, 0,81 Hz, 1H), 5,05 (s, 2H), 2,30 (s, 3H), 1,84 (s, 3H), LC/MS, $t_r$ = 2,61 minutos (acetonitrilo/agua al 5 a 95% a lo largo de 5 minutos a 1 ml/min, a 254 nm, a 50 °C), ES-MS *m/z* 386 (M+H) ES-HR/MS *m/z* 386,1228 (M+H calculado para $C_{21}H_{17}F_2NO_4$ requiere 386,1198)

Etapa 4 Preparacion de acido 3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-2-metilbenzoico




Se agitó acido 3-[4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-2-metilbenzoico (de la Etapa 3) (23,0 g, 59,7 mmol) a temperatura ambiente con *N*-bromosuccinimida (12,74 g, 71,6 mmol) en 120 ml de $CH_2Cl_2$ durante 2 horas La reaccion se evaporó en un rotavapor y

999

el solido resultante se agitó en acetonitrilo durante 1 hora, se lavó 7 veces con acetonitrilo y se secó *in vacuo* para proporcionar un solido de color blanco (19,14 g, al 69%) $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7,87 (dd, $J$ = 7,52, 1,61 Hz, 1H), 7,67 (*aprox* q, $J$ = 7,92 Hz, 1H), 7,45 - 7,37 (m, 2H), 7,33 (dt, $J$ = 9,87, 2,54 Hz, 1H), 7,17 (dt, $J$ = 8,50, 1,67 Hz, 1H), 6,71 (s, 1H), 5,32 (s, 2H), 2,08 (s, 3H), 1,86 (s, 3H), LC/MS, $t_r$ = 2,69 minutos (acetonitrilo agua al 95% a lo largo de 5 minutos a 1 ml/min, a 254 nm, a 50 °C ), ES-MS *m/z* 464 (M+H) ES-HRMS *m/z* 464,0284 (M+H calculado para $C_{21}H_{16}BrF_2NO_4$ requiere 464,0304)

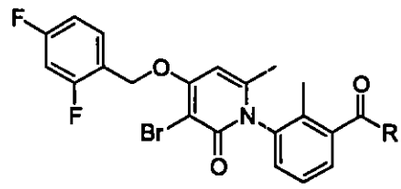
Etapa 5 Preparacion del compuesto del titulo Se disolvio ácido 3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-2-metilbenzoico (la Etapa 4 anterior) (500 mg, 1,08 mmol) en 5 ml de $CH_2Cl_2$ Se agregó 4-(2-aminoetil)morfolina (170 µl, 1,29 mmol), seguida, en orden, por EDCI (247 mg, 1,29 mmol), 1-hidroxibenzotriazol (174 mg, 1,29 mmol) y trietilamina (301 µl, 2,16 mmol) La reaccion se agito a temperatura ambiente durante la noche La reacción se enfrio repentinamente con $NH_4Cl$ y se extrajo 3 veces con acetato de etilo Las capa organica combinada se seco sobre $MgSO_4$ y se evaporo El aceite resultante se trituró con eter dietílico/hexano para obtener un sólido, que se seco *in vacuo* para proporcionar un sólido de color blanco (472 mg, al 76%) $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7,64 (*aprox* q, $J$ = 7,79 Hz, 1H), 7,47 (dd, $J$ = 7,65, 1,01 Hz, 1H), 7,39 (t, $J$ = 7,75 Hz, 1H), 7,17 (dd, $J$ = 7,65, 0,81 Hz, 1H), 7,01 (dt, $J$ = 8,26, 1,61 Hz, 1H), 6,91 (dt, $J$ = 9,42, 2,32 Hz, 1H), 6,49 (t, $J$ = 5,04 Hz, 1H), 6,18 (s, 1H), 5,30 (s, 2H), 3,73 (t, $J$ = 4,53 Hz, 4H), 3,68 - 3,47 (m, 2H), 2,59 (t, $J$ = 5,94 Hz, 2H), 2,51 (t, $J$ = 4,33 Hz, 4H), 2,15 (s, 3H), 1,98 (s, 3H), LC/MS, $t_r$ = 2,27 minutos (acetonitrilo/agua al 5 a 95% a lo largo de 5 minutos a 1

1000

ml/mın, a 254 nm, a 50 °C ), ES-MS *m/z* 576 (M+H) ES-HRMS *m/z* 576,1313 (M+H calculado para $C_{27}H_{28}BrF_2N_3O_4$ requıere 576,1304)

Ejemplos 329-337

Los sıguıentes compuestos se preparan esencıalmente conforme al procedımıento establecıdo para el Ejemplo 328



| Ejemplo N° | R | MF | M+H Requıere | ESHRMS m/z |
|---|---|---|---|---|
| Ej 329 | $-NHCH_2CH_2OCH_3$ | $C_{24}H_{22}BrF_2N_2O_4$ | 521,0882 | 521,0906 |
| Ej 330 | $-N(CH_3)_2$ | $C_{23}H_{20}BrF_2N_2O_3$ | 491,0776 | 491,0752 |
| Ej 331 | $-NHCH_2CH_2OH$ | $C_{23}H_{20}BrF_2N_2O_4$ | 507,0726 | 507,0689 |
| Ej 332 | $-NHCH_3$ | $C_{22}H_{18}BrF_2N_2O_3$ | 477,0620 | 477 0585 |
| Ej 333 | $-N(CH_3)CH_2CH_2OH$ | $C_{24}H_{22}BrF_2N_2O_4$ | 521,0882 | 521,0890 |
| Ej 334 | 4-metılpıperazın-1-ılo | $C_{26}H_{25}BrF_2N_3O_3$ | 546 1198 | 546,1187 |
| Ej 335 | morfol_n-4-ılo | $C_{25}H_{22}BrF_2N_2O_4$ | 533,0882 | 533,0856 |
| Ej 336 | $-N(CH_3)CH_2CH_2OCH_3$ | $C_{25}H_{24}BrF_2N_2O_4$ | 535,1039 | 535,1055 |
| Ej 337 | $-NH_2$ | $C_{21}H_{16}BrF_2N_2O_3$ | 463,0463 | 463,0492 |

Caracterızacıon por NMR (resonancıa magnetıca nuclear) de los compuestos de los Ejemplos 329-337

| Ejemplo N° | Datos de NMR |
|---|---|
| Ej 329 | $^1$H NMR (400 MHz, $CDCl_3$) δ 7,59 (*aprox* q, *J* = 7,79 Hz, 1H), 7,47 (dd, *J* = 7,65, 1,08 Hz, 1H), 7,34 (t, *J* = 7,72 Hz, 1H), 7,12 (dd, *J* = 7,78, 0,94 Hz, 1H), 6,96 (*aprox* dt, *J* = 7,92 2,27 Hz, 1H), 6 87 (dt, *J* = 9,46, 2,55 Hz, 1H) 6,29 (m, 1H) 6 12 (s, 1H), 5 25 (s, 2H), 3,73 - 3,65 (m, 1H), 3,56 - 3,48 (m, 3H), 3 35 (d *J* = 3 09 Hz 3H) 2 09 (s 3H) 1,93 (s, 3H) |

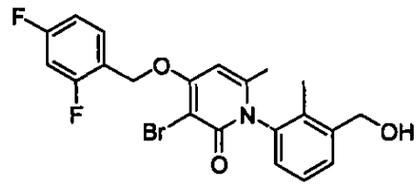
1001

| | |
|---|---|
| Ej 330 | $^1$H NMR (400 MHz $CDCl_3$) δ 7,59 (*aprox* q, *J* = 7 79 Hz 1H), 7,34 (t, *J* = 7,66 Hz, 1H) 7 28 (dd, *J* = 7,66, 1,21 Hz, 1H), 7,07 (dd, *J* = 7,65, 1,08 Hz, 1H), 6,96 (*aprox* dt, *J* = 8 52, 2,02 Hz, 1H), 6 87 (dt *J* = 9,46, 2,55 Hz, 1H), 6,29 (m 1H), 6,12 (s, 1H), 5,25 (s, 2H), 3,11 (s, 3H) 2,82 (s, 3H), 1,96 (s, 3H), 1,95 (s, 3H) |
| Ej 331 | $^1$H NMR (400 MHz $CDCl_3$) δ 7,59 (*aprox* q, *J* = 7 74 Hz 1H) 7 46 (d, *J* = 6,71 Hz 1H) 7 32 (t, *J* = 7,72 Hz 1H), 7,07 (d, *J* = 6 85 Hz, 1H), 6,98 (m, 2H), 6,87 (dt *J* = 9,47, 2,41 Hz, 1H), 6,15 (s, 1H), 5,26 (s, 2H) 3 71 (t, *J* = 4,97 Hz 2H) 3 60 - 3,45 (m, 2H), 2,06 (s, 3H), 1,95 (s, 3H) |
| Ej 332 | $^1$H NMR (400 MHz, $CDCl_3$) δ 7,59 (*aprox* q, *J* = 7 79 Hz 1H), 7,42 (dd, *J* = 7,66 0 94 Hz 1H), 7,31 (t, *J* = 7,72 Hz, 1H) 7,09 (dd, *J* = 7,79, 0,94 Hz, 1H), 6,96 (*aprox* dt, *J* = 8,26, 1,61 Hz, 1H), 6,87 (dt, *J* = 9,44, 2,49 Hz, 1H), 6,12 (s, 1H), 5,25 (s, 2H), 2,96 (d, *J* = 4,83 Hz, 3H), 2,07 (s, 3H), 1,93 (s, 3H) |
| Ej 333 | $^1$H NMR (300 MHz, DMSO-$d_6$) δ 7,73 (q *J* = 7 92 Hz 1H), 7,44 - 7,20 (m, 5H), 6,75 (s, 1H), 5 37 (s 2H), 4,83 (br s 1H) 3,65 (br s, 2H), 3,45 - 3,33 (m, 2H) 2 81 (s, 3H), 1,93 (d, *J* = 3 42 Hz, 3H) 1 85 (d *J* = 8,06 Hz, 3H) |
| Ej 334 | $^1$H NMR (300 MHz DMSO-$d_6$) δ 7,67 (*aprox* q, *J* = 7 92 Hz, 1H), 7,40 (t, *J* = 7,78 Hz, 1H), 7,34 (dt, *J* = 9,87, 2,55 Hz, 1H), 7,27 (d, *J* = 7,52 Hz, 1H), 7,24 (d *J* = 7,79 Hz, 1H), 7,17 (dt, *J* = 8,41, 1 97 Hz 1H), 6 71 (s, 1H), 5,32 (s, 2H), 3,63 (m, 2H), 3,29 (br s, 1H), 3,09 (br s, 2H), 2,34 (t, *J* = 4,57 Hz, 2H), 2 20 (br s, 2H), 2 16 (s, 3H), 1,88 (d, *J* = 8,86 Hz 3H) 1,80 (d, *J* = 4,83 Hz, 3H) |
| Ej 335 | $^1$H NMR (300 MHz, $CDCl_3$) δ 7,64 (*aprox* q, *J* = 7,79 Hz, 1H), 7 42 (t, *J* = 7 65 Hz 1H), 7,33 (d, *J* = 7,66 Hz, 1H), 7,14 (d, *J* = 7,65 Hz, 1H), 7,00 (dt, *J* = 8,76, 2,21 Hz, 1H), 6,91 (dt, *J* = 9,47, 2,42 Hz, 1H), 6,17 (s 1H), 5 29 (s 2H) 3 98 - 3 92 (m 1H), 3,80 - 3,77 (m, 3H) 3 59 (br s, 2H) 3 29 (t *J* = 4,43 Hz, |

1002

| | |
|---|---|
| | 2H) 2,04 (s, 3H) 2 00 (s, 3H) |
| Ej 336 | $^1$H NMR (300 MHz, $CDCl_3$) δ 7,65 (*aprox* q, *J* = 7,79 Hz, 1H), 7 43 - 7,32 (m 2H), 7,12 (dd *J* = 7,66, 1,21 Hz 1H) 7,0C (dt, *J* = 9 06, 1,51 Hz, 1H), 6,92 (dt, *J* = 9,42, 2,52 Hz, 1H), 6,16 (s, 1H), 5,30 (s, 2H), 3,69 (t, *J* = 5 04 Hz, 2H), 3,39 (s, 3H), 3,26 (s 1H), 3,19 (s, 1H) 2 91 (s, 3H), 2 04 (s 3H), 2,00 (s 3H) |
| Ej 337 | $^1$H NMR (300 MHz, DMSO-$d_6$) δ 7,91 (br s, 1H), 7,73 (*aprox* q, *J* = 7,85 Hz, 1H), 7,53 - 7,20 (m, 5H), 6 74 (s, 1H), 5,37 (s, 2H), 1,99 (s, 3H), 1,92 (s, 3H) |

Ejemplo 338



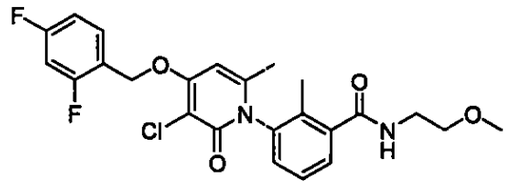

3-bromo-4-[(2,4-difluorobencil)oxi]-1-[3-(hidroximetil)-2-metilfenil]-6-metilpiridin-2(1H)-ona

Se enfrio ácido 3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-2-metilbenzoico (Etapa 4 anterior) (2,0 g, 4,31 mmol) hasta 0 °C en 10 ml de tetrahidrofurano Se agregaron 19,5 ml de 1M $BH_3$ THF en tetrahidrofurano y se agito durante la noche, permitiendo que la temperatura se eleve hasta temperatura ambiente Se enfrio nuevamente la reaccion hasta 0 °C y se agregaron astillas de hielo para enfriar repentinamente la reaccion La suspension se extrajo 3 veces con una mezcla de acetato de etilo/tetrahidrofurano Las capas orgánicas combinadas se lavaron con salmuera, se seco sobre $MgSO_4$, se filtro y se evaporo para proporcionar un solido de color blanco (1,73 g, al 89%) $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7,67 (*aprox* q, *J* = 7,92 Hz, 1H), 7,46 (d, *J* = 7,52 Hz, 1H), 7,32 (dt, *J* = 10,74, 2,42 Hz, 1H), 7,30 (t, *J* = 7,72 Hz, 1H), 7,17 (dt, *J* = 8,46, 1,88 Hz, 1H), 7,03 (d, *J* = 7,38 Hz, 1H), 6,68 (s, 1H), 5,32 (s, 2H), 4,51 (s, 2H), 3,29 (d,

1003

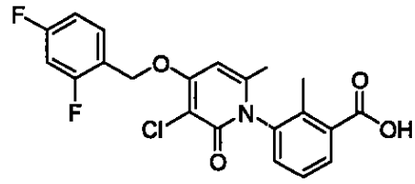
*J* = 9,40 Hz, 1H), 1,85 (s, 3H), 1,81 (s, 3H), LC/MS, $t_r$ = 2,64 minutos (acetonitrilo/agua al 5 a 95% a lo largo de 5 minutos a 1 ml/min, a 254 nm, a 50 °C ), ES-MS *m/z* 450 (M+H) ES-HRMS *m/z* 450,0480 (M+H calculado para $C_{21}H_{18}BrF_2NO_3$ requiere 450,0511)

Ejemplo 339



3-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-N-(2-metoxietil)-2-metilbenzamida

Etapa 1 Preparacion de ácido 3-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-2-metilbenzoico



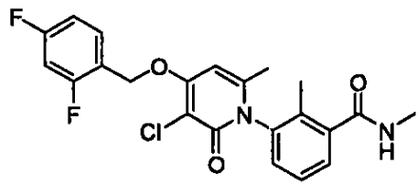
Se sometio a reflujo acido 3-[4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-2-metilbenzoico (Etapa 3 anterior) (10,0 g, 25,9 mmol) con *N*-clorosuccinimida (4,15 g, 31,1 mmol) y ácido dicloroacetico (1,06 ml, 12,9 mmol) en 50 ml de $CH_2Cl_2$ durante la noche La reaccion se evaporo en un rotavapor y el solido resultante se agitó en acetonitrilo durante 30 minutos, se lavo 4 veces con acetonitrilo y se secó *in vacuo* para proporcionar un sólido de color blanco (8,3 g, al 78%) $^1$H NMR (300 MHz, DMSO-$d_6$) δ 7,93 (dd, *J* = 7,15, 1,92 Hz, 1H), 7,72 (*aprox* q, *J* = 7,92 Hz, 1H), 7,52 - 7,35 (m, 3H), 7,22 (dt, *J* = 8,47, 2,01 Hz, 1H), 6,80 (s, 1H), 5,38 (s, 2H), 2,14 (s, 3H), 1,93 (s, 3H), LC/MS, $t_r$ = 2,64 minutos

1004

(acetonitrilo/agua a 5 a 95% a lo largo de 5 minutos a 1 ml/min, a 254 nm, a 50 °C ), ES-MS *m/z* 420 (M+H) ES-HRMS *m/z* 420,0806 (M+H calculado para $C_{21}H_{16}ClF_2NO_4$ requiere 420,0809)

Etapa 5 Preparación del compuesto del titulo Se disolvio ácido 3-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-2-metilbenzoico (de la Etapa 1 anterior) (500 mg, 1,19 mmol) en 5 ml de $CH_2Cl_2$ Se agrego 2-metoxietilamina (1'9 □l, 1,49 mmol), seguido, en orden, por EDCI (286 mg, 1,49 mmol), 1-hidroxibenzotriazol (202 mg, 1,49 mmol) y trietilamina (332 µl, 2,38 mmol) La reaccion se agito a temperatura ambiente durante la noche La reaccion se enfrio repentinamente con $NH_4Cl$ y se extrajo 3 veces con acetato ce etilo La capa organica combinada se secó sobre $MgSO_4$ y se evaporo El solido resultante se lavó *in vacuo* para proporcionar un solido de color blanco (401 mg, al 71%) $^1H$ NMR (400 MHz, $CDCl_3$) δ 7,56 (*aprox* q, *J* = 7,74 Hz, 1H), 7,47 (d, *J* = 6,98 Hz, 1H), 7,34 (t, *J* = 7,72 Hz, 1H), 7,11 (d, *J* = 7,25 Hz, 1H), 6,95 (dt, *J* = 8,23, 1,66 Hz, 1H), 6,87 (dt, *J* = 9,51, 2,46 Hz, 1H), 6,35 (br s, 1H), 6,15 (s, 1H), 5,25 (s, 2H), 3,72 - 3,63 (m, 1H), 3,58 - 3,49 (m, 3H), 3,35 (s, 3H), 2,09 (s, 3H), 1,93 (s, 3H), LC/MS, $t_r$ = 2,56 minutos (acetonitrilo/agua al 5 a 95% a lo largo de 5 minutos a 1 ml/min, a 254 nm, a 50 °C ), ES-MS *m/z* 477 (M+H) ES-HRMS *m/z* 477,1363 (M+H calculado para $C_{24}H_{23}ClF_2N_2O_4$ requiere 477,1387)

Ejemplo 340

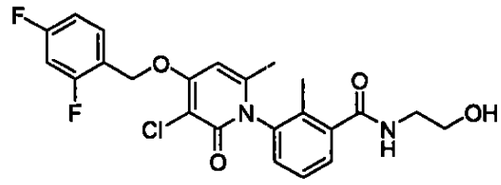


1005

3-[3-Cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-N,2-dimetilbenzamida

El compuesto del titulo se preparo siguiendo un procedimiento similar al descrito para el Ejemplo 337, en el que se utilizo metilamina como amina, y el producto se obtuvo con un rendimiento de un 73% $^1$H NMR (300 MHz, DMSO-$d_6$) δ 8,37 (*aprox* d, *J* = 4,64 Hz, 1H), 7,72 (*aprox* q, *J* = 7,92 Hz, 1H), 7,44 - 7,35 (m, 4H), 7,22 (dt, *J* = 8,54, 1,61 Hz, 1H), 6,78 (s, 1H), 5,37 (s, 2H), 2,79 (d, *J* = 4,43 Hz, 3H), 1,95 (s, 3H), 1,94 (s, 3H), LC/MS, $t_r$ = 2,46 minutos (acetonitrilo/agua al 5 a 95% a lo lardo de 5 minutos a 1 ml/min, a 254 nm, a 50 °C ), ES-MS *m/z* 433 (M+H) ES-HRMS *m/z* 433,1163 (M+H calculado para $C_{22}H_{19}ClF_2N_2O_3$ requiere 433,1125)

Ejemplo 341



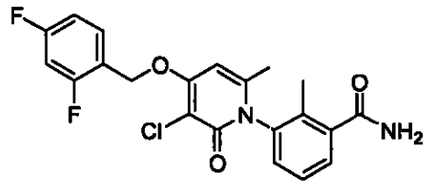

3-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-N-(2-hidroxietil)-2-metilbenzamida

El compuesto cel titulo se preparó siguiendo un procedimiento similar al descrito para, en el que se utilizó etanolamina como amina, y el producto se obtuvo con un rendimiento de un 65% $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8,39 (t, *J* = 5,51 Hz, 1H), 7,67 (*aprox* q, *J* = 7,88 Hz, 1H), 7,43 - 7,33 (m, 3H), 7,23 (d, *J* = 7,25 Hz, 1H), 7,17 (dt, *J* = 8,39, 1,66 Hz, 1H), 6,74 (s, 1H), 5,32 (s, 2H), 3,48 (br s, 2H), 3,31 - 3,26 (m, 2H), 1,90 (s, 3H), 1,89 (s, 3H), LC/MS, $t_r$ = 2,34 minutos (acetonitrilo/agua al 5 a 95% a lo largo de 5 minutos a 1 ml/min, a 254 nm, a 50 °C ), ES-MS

1006

*m/z* 463 (M+H) ES-HRMS *m/z* 463,1220 (M+H calculado para $C_{23}H_{21}ClF_2N_2O_4$ requiere 463,1231)

Ejemplo 342

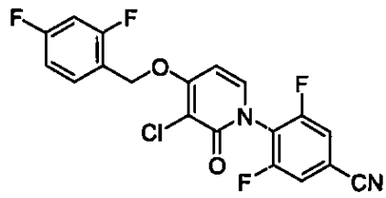


3-[3-Cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-2-metilbenzamida

Se agitó ácido 3-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-2-metilbenzoico (Etapa 1 anterior) (500 mg, 1,19 mmol) con 2-cloro-4,6-dimetoxi-1,3,5-triazina (251 mg, 1,43 mmol) y *N*-metilmorfolina (392 □l, 3,57 mmol) en 5 ml de tetrahidrofurano a temperatura ambiente durante 2 horas Se agregaron 2,5 ml de $NH_4OH$ y se agito a temperatura ambiente durante 2,5 horas La reaccion se diluyo con tetrahidrofurano y acetato de etilo y se extrajo Las capas orgánicas combinadas se lavaron con $NaHCO_3$, 1 N HCl, y salmuera, se secaron sobre $MgSO_4$, se filtraron y se evaporaron El solido resultante se lavó *in vacuo* para obtener un solido de color blanco (313 mg, al 63%) $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 7,87 (br s, 1H), 7,66 (q, *J* = 7,83 Hz, 1H), 7,48 - 7,30 (m, 3H), 7,23 (d, *J* = 7,52 Hz, 1H), 7,17 (t, *J* = 7,65 Hz, 1H), 6,73 (s, 1H), 5,32 (s, 2H), 1,94 (s, 3H), 1,88 (s, 3H), LC/MS, $t_r$ = 2,44 minutos (acetonitrilo/agua al 5 a 95% a lo largo de 5 minutos a 1 ml/min, a 254 nm, a 50 °C ), ES-MS *m/z* 419 (M+H) ES-HRMS *m/z* 419,0963 (M+H calculado para $C_{21}H_{17}ClF_2N_2O_3$ requiere 419,0969)

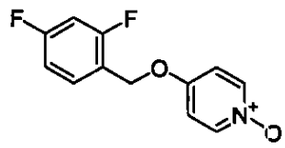
Ejemplo 343

1007



4-[3-Cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2H)-il]-3,5-difluorobenzonitrilo

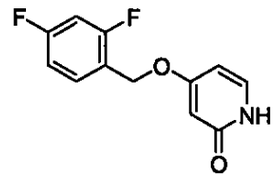
Etapa 1 Preparacion de 1-oxido de 4-[(2,4-difluorobencil)oxi]piridina



Se combinaron alcohol 2, 4-difluorobencilico (100 g, 0,694 mol) y N-oxido de nitropiridina (98 g, 0,700 mol) con 250 g $Cs_2CO_3$ (1,1 eq) en 2 5 L de dimetilformamida anhidro y se calento hasta 80°C con agitación A la reacción le siguio una $^{19}$F-NMR (mezcla de reaccion en crudo con referencia $D_2O$ externa) y se completó despues de 40 hs La mezcla se filtro en caliente, el producto se cristalizo al enfriarse Se recogieron 90,21 g (al 55%) de placas de color blanco mediante filtracion y lavado con eter dietilico El licor madre se diluyo con 2,5 L de eter dietilico y se almaceno en el congelador durante una noche, produciendo una segunda cosecha de 68,76 g (al 41%, rendimiento combinado 96%) $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 8,06 (m, 2 H), 7,61 (cuarteto, $J$ = 8,45 Hz, 1H), 7,30 (t, $J$ = 10,37 Hz,1H), 7,12, (t, $J$ = 8,45 Hz, 1H), 7,09 (d, $J$ = 5,06 Hz, 2H), 5,14 (s, 2H) $^{19}$F-NMR (400 MHz, DMSO-$d_6$) δ -109,43 (quinteto, $J$ = 7,78 Hz, 1F), -113,82 (cuarteto, $J$ = 9,55 Hz, 1F) LC/MS $t_r$ = 3,90 minutos (acetonitrilo/agua al 0-95%, acido trifluoroacético al 0,05%, a lo largo de 6 minutos a 1 ml/min con deteccion a 215 nm, a 50°C) ES-MS $m/z$ 238 (M+H)

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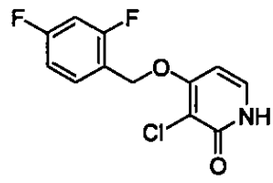
Etapa 2 Preparacion de 4-[(2,4-difluorobencil)oxi]-piridin-2(1H)-ona



Se combinaron 1-oxido de 4-[(2,4-difluorobencil)oxi]piridina (de la Etapa 1) (30,0 g , 0,127 mol), acetato de potasio anhidro (25 g, 0,25 mol), anhidrido acetico (25 g, 0,25 mol), y 10 ml de acido acetico en un matraz de fondo redondo con agitacion superior y se calentaron hasta 130 °C durante 4 horas La mezcla se concentró bajo vacio, los solidos se disolvieron en 95 ml de acetonitrilo 5 ml de agua, se filtraron a traves de carbon y se vertieron en 600 ml de hielo con agitacion Se permitio que la mezcla reposara durante la noche a temperatura ambiente, luego se recogieron 9,62 g (al 30%) de producto mediante filtracion en forma de solido de color marrón medio (adecuado para la siguiente Etapa sin purificacion) $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 11,10 (s, 1H), 7,59 (cuarteto, $J$ = 9,91 Hz, 1H), 7,29 (t, $J$ = 10,36 Hz, 1H), 7,21 (d, $J$ = 8,20 Hz, 1H), 7,11 (t, $J$ = 8,48 Hz, 1H), 5,83 (m, 2H), 5,02 (s, 2H) $^{19}$F-NMR (400 MHz, DMSO-$d_6$) δ -109,57(quinteto, $J$ = 7 66 Hz, 1F) -113 88 (cuarteto, $J$ = 8,93 Hz, 1F) LC/MS $t_r$ = 4,29 minutos (acetonitrilo/agua al 0-95%, acido trifluoroacético al 0,05%, a lo largo de 6 minutos a 1 ml/min con deteccion a 254 nm, a 50°C) ES-MS $m/z$ 238 (M+H)

Etapa 3 Preparacion de 3-cloro-4-[(2,4-difluorobencil)oxi]piridin-2(1H)-ona

1009



Se agito 4-[(2,4-difluorobencil)oxi]-piridin-2(1H)-ona (de la Etapa 2) (8,60 g, 36,3 mmol) en 150 ml dimetilformamida y se trato con N-clorosuccinimida (5,4 g, 39,9 mmol) Despues de 15 horas, se recogio el precipitado mediante filtracion (5,11 g, al 52%) proporcionando un sólido de color blanco lustroso El licor madre se diluyo en 500 ml con eter dietilico, proporcionando 2,47 g (al 25%) en una segunda cosecha $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 11,87 (s, 1H), 7,60 (cuarteto, $J$ = 6,34 Hz, 1H), 7,43 (d, $J$ = 7,58 Hz, 1H), 7,3 (dt, $J$ = 10,08, 2,21 Hz, 1H), 7,14 (dt, $J$ = 8,65, 1,79 Hz, 1H), 6,44 (d, $J$ = 7,49 Hz, 1H), 5,28 (s, 1H) $^{19}$F-NMR (400 MHz, DMSO-$d_6$) δ -109,58 (quinteto, $J$ = 7,75 Hz, 1F), -113,68 (cuarteto, $J$ = 8,68 Hz, 1F) LC/MS $t_r$ = 4,47 minutos (acetonitrilo/agua al 0-95% , acido trifluoroacetico al 0,05%, a lo largo de 6 minutos a 1 ml/min con deteccion a 254 nm, a 50°C) ES-MS *m/z* 272 (M+H)

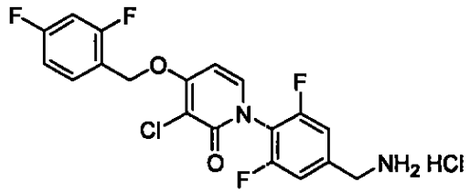
Etapa 4 Preparacion del compuesto del titulo

Se combinó 3-clcro-4-[(2,4-difluorobencil)oxi]piridin-2(1H)-ona (de la Etapa 3) (3,25 g, 11,9 mmol) con $Cs_2CO_3$ (3,93 g, 12,1 mmol) en 50 ml de dimetilformamida y se calento a 70°C, agitando bajo nitrogeno Se agrego 3,4,5-trifluorobenzonitrilc (1,83 g, 11,9 mmol) Despues de 4 horas, la mezcla se filtro, se concentro *in vacuo*, se lavo tres veces con ciclohexano caliente, se disolvio en tetrahidrofurano, se trato con $MgSO_4$ y carbon y se filtró La disolución se evaporo dejando un solido blanco fino (3,99 g, al 82%) $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 8,12 (d, $J$ =

1010

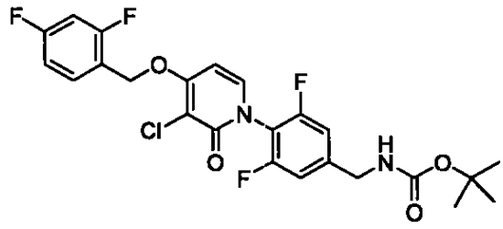
7,59 Hz, 2H), 7,92 (d, $J$ = 8,31 Hz, 1H), 7,65 (cuarteto, $J$ = 6,77, 1H), 7,34 (dt, $J$ = 9,81, 2,71 Hz, 1H), 7,16 (dt, $J$ = 8,59, 2,50 Hz, 1H), 6,87 (d, $J$ = 8,01 Hz, 1H), 5,39 (s, 2H) $^{19}$F-NMR (400 MHz, DMSO-$d_6$) δ -109,17 (quinteto, $J$ = 8,97 Hz, 1F), -113,51(cuarteto, $J$ = 9,53 Hz, 1F), -116,32 (d, $J$ = 7,69 Hz, 2F) LC/MS $t_r$ = 5,51 minutos (acetonitrilo/agua al 0-95% , acido trifluoroacético al 0,05%, a lo largo de 6 minutos a 1 ml/min con deteccion a 215 nm, a 50°C) ES-MS $m/z$ 409 (M+H) ES-HRMS $m/z$ 409,0351 (M+H calculado para $C_{19}H_{10}ClF_4N_2O_2$ requiere 409,0361)

Ejemplo 344




Hidrocloruro de 1-[4-(aminometil)-2,6-difluorofenil]-3-cloro-4-[(2,4-difluorobencil)oxi]piridin-2(1H)-ona

Etapa 1 Preparacion de 4-[3-Cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2H)-il]-3,5-difluorobencilcarbamato




Se combinaron 4-[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2H)-il]-3,5-difluorobenzonitrilo (2,84 g, 6,95 mmol), di-$t$-butil-dicarbonato (3,18 g, 14,6 mmol), y cloruro de niquel(II) (0,90 g, 6,95 mmol) con 40 ml de metanol y 40 ml de tetrahidrofurano y se enfriaron hasta 0°C agitando en baño de hielo Se agrego borohidruro de

1011

sodio (1,33 g, 35,2 mmol) en pequeñas porciones a lo largo de 10 minutos para controlar la formacion de espuma, y se agitó la reacción 1 hora Se requirió borohidruro de sodio adicional (0,50 g, 13,2 mmol) para forzar la complecion de la reaccion mediante LC A su compleción, persistio un cambio de color de amarillo a negro La mezcla se filtro a traves de una cama e carbon colocada en capas sobre $MgSO_4$ anhidro y se evaporo hasta sequedad Se elimino el exceso de di-*t*-butil-dicarbonato y el subproducto *t*-butanol mediante el calentamiento repetido con agua hasta 80°C *in vacuo*, proporcionando el producto como un fino polvo de color blanco (3,11 g, al 87%) $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 7,89 (d, *J* = 8,04 Hz, 1H), 7,65 (cuarteto, *J* = 6,73 Hz, 1H), 7,55 (t, *J* = 6,73 Hz,1H), 7,34, (dt, *J* = 10,05, 2,51 Hz, 1H), 7,16 (m, 3H), 6,77 (d, *J* = 8,18 Hz, 1H), 5,34 (s, 2H), 4,18 (d, *J* = 5,68 Hz, 2H), 1,34 (s, 9H) $^{19}$F-NMR (400 MHz, DMSO-$d_6$) δ -109,26 (quinteto, *J* = 6,91 Hz, 1F), -113,53(cuarteto, *J* = 7,73 Hz, 1F), -120,32 (d, *J* = 8,91 Hz, 2F) LC/MS $t_r$ = 5,90 minutos (acetonitrilo/agua al 0-95% , acido trifluoroacético al 0,05%, a lo largo de 6 minutos a 1 ml/min con detecc ón a 215 nm, a 50°C) ES-MS *m/z* 513 (M+H) ES-HRMS *m/z* 513,1164 (M+H calculado para $C_{24}H_{22}ClF_4N_2O_4$ requiere 513,1199)

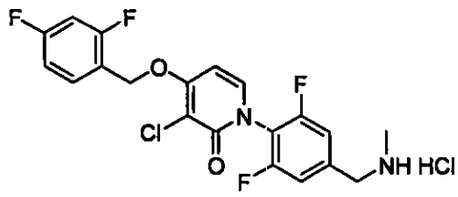
Etapa 2 Preparacion del compuesto del título

Se disolvió 4-[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2H)-il]-3,5-difluorobencilcarbamato terc-butilico (de la Etapa 3) (1,39 g, 2,71 mmol) en 20 ml de tetrahidrofurano y se trato con 4 ml de acido hidroclorico concentrado La disolución se evaporó y se secó *in vacuo* hasta lograr un solido blanco fino (1,20 g, al 99%) $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 8,54 (m, 2H), 7,86 (d, *J* = 7,57 Hz, 1H), 7,65 (cuarteto, *J* = 7,62, 1H), 7,50 (d, *J* = 9,25

1012

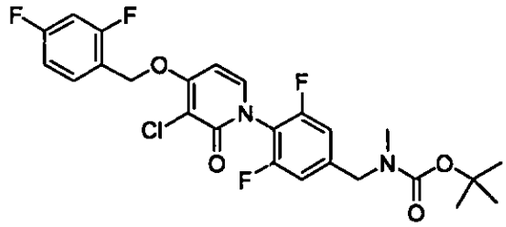
Hz, 2H), 7,34 (dt, J = 10,50, 2,45 Hz, 1H), 7,16 (dt, J = 8,38, 2,55 Hz, 1H), 6,78 (d, J = 7,86 Hz, 1H), 5,37 (s, 2H), 4,10 (br s, 2H), 4,97-3,14 (v br s, 3H) $^{19}$F-NMR (400 MHz, DMSO-$d_6$) δ -109,21 (quinteto, J = 7,77 Hz, 1F), -113,51(cuarteto, J = 8,95 Hz, 1F), -119,56 (d, J = 9,44 Hz, 2F) LC/MS $t_r$ = 4,33 minutos (acetonitrilo/agua al 0-95%, ácido trifluoroacetico al 0,05%, a lo largo de 6 minutos a 1 ml/min con deteccion a 215 nm, a 50°C) ES-MS *m/z* 413 (M+H) ES-HRMS *m/z* 413,0712 (M+H calculado para $C_{19}H_{14}ClF_4N_2O_2$ requiere 413,0674)

Ejemplo 345



Hidrocloruro de 3-cloro-4-[(2,4-difluorobencil)oxi]-1-{2,6-difluoro-4-[(metilamino)metil]fenil}piridin-2(1H)-ona

Etapa 1 Preparacion de 4-[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2H)-il]-3,5-difluorobencil(metil)carbamato terc-butilico



Se combinaron 4-[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2H)-il]-3,5-difluorobencilcarbamato terc-butilico (de Etapa 1) (252 mg, 0,491 mmol) y yodometano (75 mg, 0,528 mmol) en 8 ml de dimetilformamida anhidro Se agregó hidruro de sodio al 60% en aceite mineral (30 mg, 0,75 mmol) y la mezcla se agito bajo nitrogeno a temperatura ambiente durante 1 hora Se agregó $NH_4Cl$ acuoso

1013

saturado (4 ml) seguido de 20 ml de agua y el producto se extrajo en acetato de etilo, se lavo con salmuera, se seco sobre $MgSO_4$, se filtro y se evaporo para proporcionar el producto como un polvo blanco (208 mg, al 80%) $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 7,87 (d, $J$ = 7,85 Hz, 1H), 7,64 (cuarteto, $J$ = 6,66 Hz, 1H), 7,32, (dt, $J$ = 9,39, 3,29 Hz, 1H), 7,13 (m, 3H), 6,77 (d, $J$ = 7,94 Hz, 1), 5,38 (s, 2H), 4,43 (s, 2H), 2,90 (s, 3H), 1,40 (br m, 9H) $^{19}$F-NMR (400 MHz, DMSO-$d_6$) δ -109,25 (quinteto, $J$ = 8,93 Hz, 1F), -113,53(cuarteto, $J$ = 9,73 Hz, 1F), -119,89 (d, $J$ = 9,35 Hz, 2F) LC/MS $t_r$ = 6,16 minutos (acetonitrilo/agua al 0-95%, acido trifluoroacetico 0,05%, a lo largo de 6 minutos, luego acetonitrilo al 95% durante 2 minutos, a 1 ml/min con deteccion a 215 nm, a 50°C) ES-MS $m/z$ 527 (M+H) ES-HRMS $m/z$ 527,1338 (M+H calculado para $C_{25}H_{24}ClF_4N_2O_4$ requiere 527,1355)

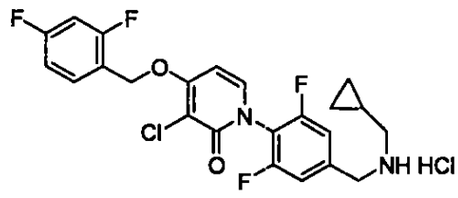
Etapa 2 Preparacion del compuesto del titulo

Se sometió 4-[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2H)-il]-3,5-difluorobencilcarbamato terc-butilico (de la Etapa 1) (188 mg, 0,357 mmol) a las condiciones de la Etapa 2, proporcionando un solido blanco fino (165 mg, al 100%) $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 9,30 (br s, 2H), 7,89 (d, $J$ = 7,99 Hz, 1H), 7,65 (cuarteto, $J$ = 7,64, 1H), 7,55 (d, $J$ = 8,66 Hz, 2H), 7,34 (dt, $J$ = 9,93, 2,57 Hz, 1H), 7,17 (dt, $J$ = 8,49, 2,48 Hz, 1H), 6,81 (d, $J$ = 8,01 Hz, 1H), 5,39 (s, 2H), 4,21 (s, 2H), 2,56 (s, 3H) $^{19}$F-NMR (400 MHz, DMSO-$d_6$) δ -109,20 (quinteto, $J$ = 7,56 Hz, 1F), -113,52(cuarteto, $J$ = 9,67 Hz, 1F), -119,21 (d, $J$ = 8,79 Hz, 2F) LC/MS $t_r$ = 4,30 minutos (acetonitrilo/agua al 0-95% , ácido trifluoroacetico al 0,05%, a lo largo de 6 minutos a 1 ml/min con deteccion a 215 nm, a 50°C) ES-MS

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*m/z* 427 (M+H) ES-HRMS *m/z* 427,0816 (M+H calculado para $C_{20}H_{16}ClF_4N_2O_2$ requiere 427,0831)

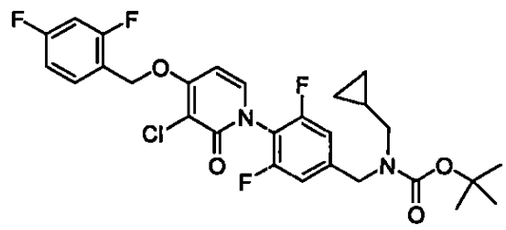
Ejemplo 346



Hidrocloruro de 3-cloro-1-(4-{[(ciclopropilmetil)amino]metil}-2,6-difluorofenil)-4-[(2,4-difluorobencil)oxi]piridin-2(1H)-ona

El compuesto del titulo se preparó mediante analogia directa con PHA-773122A, reemplazando yodometano con bromociclopropilmetaro y ampliando el tiempo de reacción a 6 horas en la Etapa 1

Etapa 1



4-[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2H)-il]-3,5-difluorobencil(ciclopropilmetil)carbamato 1 terc-butilico

$^1$H-NMR (400 MHz, DMSO-$d_6$) δ 7,89 (d, $J$ = 7,91 Hz, 1H), 7,65 (cuarteto, $J$ = 6,81 Hz, 1H), 7,33, (dt, $J$ = 9,90, 2,26 Hz, 1H), 7,17 (m, 3H), 6,77 (d, $J$ = 7,90 Hz, 1), 5,38 (s, 2H), 4,51 (s, 2H), 3,10 (br s, 2H), 1,36 (m, 9H), 0,97 (br s, 1H), 0,38 (m, 2H), 0,18 (m, 2H) $^{19}$F-NMR (400 MHz, DMSO-$d_6$) δ -109,25 (quinteto, $J$ = 7,77 Hz, 1F), -113,54 (cuarteto, $J$ = 9,02 Hz, 1F), -120,24(m, 2F) LC/MS $t_r$ = 5,99 minutos (acetonitrilo/agua al 0-95%, ácido trifluoroacético 0,05%, a lo largo de 6 minutos, luego

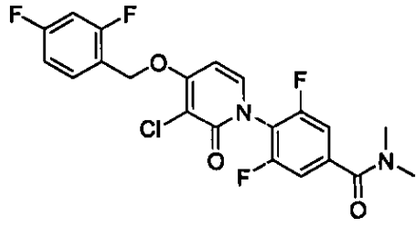
1015

acetonitrilo al 95% durante 2 minutos, a 1 ml/min con detección a 215 nm, a 50°C) ES-MS *m/z* 567 (M+H) ES-HRMS *m/z* 567,1653 (M+H calculado para $C_{28}H_{28}ClF_4N_2O_4$ requiere 567,1668)

Etapa 2 Compuesto del título

$^1$H-NMR (400 MHz, DMSO-$d_6$) δ 9,51 (br s, 2H), 7,87 (d, *J* = 7,96 Hz, 1H), 7,63 (m, 3H), 7,33 (dt, *J* = 9,93, 2,65 Hz, 1H), 7,16 (dt, *J* = 8,36, 2,32 Hz, 1H), 6,81 (d, *J* = 7,92 Hz, 1H), 5,38 (s, 2H), 4,22 (br s, 2H), 2,82 (br s, 2H), 1,10 (m, 1H), 0,57 (m, 2H), 0,36 (m, 2H) $^{19}$F-NMR (400 MHz, DMSO-$d_6$) δ -109,25 (quinteto, *J* = 7,69 Hz, 1F), -113,54 (cuarteto, *J* = 9,35 Hz, 1F), -120,24(m, 2F) LC/MS $t_r$ = 4,55 minutos (acetonitrilo/agua al 0-95%, ácido trifluoroacetico al 0,05%, a lo largo de 6 minutos a 1 ml/min con deteccion a 215 nm, a 50°C) ES-MS *m/z* 467 (M+H) ES-HRMS *m/z* 467,1119 (M+H calculado para $C_{23}H_{20}ClF_4N_2O_2$ requiere 467,1144)

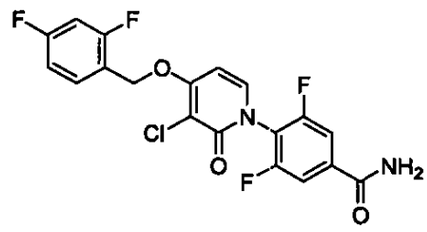
Ejemplo 347



4-[3-Cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2H)-il]-3,5-difluoro-*N*,*N*-dimetilbenzamida

Etapa 1 Preparacion de 4-[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2H)-il]-3,5-difluorobenzamida

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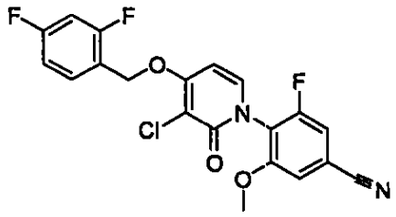
Se combinaron 4-[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2H)-il]-3,5-difluorobenzonitrilo (540 mg, 1,32 mmol) y trimetilsilonato de potasio al 90% (375 mg, 2,63 mmol) en 8 ml de tolueno anhidro y se calentó a reflujo con agitacion Despues de 10 minutos, se dejo enfriar la mezcla y luego se dividio en cloruro de amonio acuoso saturado y acetato de etilo La capa acuosa se extrajo dos veces con acetato de etilo, los materiales orgánicos combinados se lavaron con salmuera, se secaron sobre $MgSO_4$, y se evaporaron *in vacuo* El producto en crudo se absorbe en tetrahidrofurano y se filtro a traves de carbon colocado en forma de capa sobre gel de silice, y la disolución se evaporó *in vacuo* para proporcionar el producto como un polvo blanco (468 mg, al 83%) $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 8,22 (br s, 2H), 7,92 (d, $J$ = 7,84 Hz, 1H), 7,78 (d, $J$ = 8,45, 2H), 7,65 (cuarteto, $J$ = 8,40 Hz, 1H), 7,34, (dt, $J$ = 10,09, 2,58 Hz, 1H), 7,17 (dt, $J$ = 8,72, 2,30 Hz, 1H), 6,83 (d, $J$ = 7,91 Hz, 1H), 5,39 (s, 2H) $^{19}$F-NMR (400 MHz, DMSO-$d_6$) δ -109,21 (quinteto, $J$ = 7,43 Hz, 1F), -113,52(cuarteto, $J$ = 9,62 Hz, 1F), -118,74 (d, $J$ = 8,88 Hz, 2F) LC/MS $t_r$ = 4,67 minutos (acetonitrilo/agua al 0-95%, acido trifluoroacetico 0,05%, a lo largo de 6 minutos, luego acetonitrilo al 95% durante 2 minutos, a 1 ml/min con deteccion a 215 nm, a 50°C) ES-MS *m/z* 427 (M+H) ES-HRMS *m/z* 427,0454 (M+H calculado para $C_{19}H_{12}ClF_4N_2O_3$ requiere 427,0467)

Etapa 2 Preparación del compuesto del titulo

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Se sometio 4-[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2H)-il]-3,5-difluorobenzamida (de la Etapa 1) (243 mg, 0,357 mmol) a las condiciones de la Etapa 1, con la excepcion de se utilizaron dos equivalentes de hidruro de sodio al 60% en aceite mineral y yodometano en vez de uno(46 mg, 0 69 mmol y 103 mg, 0,724 mmol respectivamente) $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 7,92 (d, $J$ = 7,76 Hz, 1H), 7,66 (cuarteto, $J$ = 7,33, 1H), 7,44 (d, $J$ = 7,59 Hz, 2H), 7,34 (dt, $J$ = 9,88, 2,63 Hz, 1H), 7,17 (dt, $J$ = 8,35, 2,06 Hz, 1H), 6,83 (d, $J$ = 7,55 Hz, 1H), 5,39 (s, 2H), 2,98 (s, 3H), 2,91 (s, 3H) $^{19}$F-NMR (400 MHz, DMSO-$d_6$) δ -109,22 (quinteto, $J$ = 8,10 Hz, 1F), -113,53(cuarteto, $J$ = 9,18 Hz, 1F), -118,88 (d, $J$ = 7,77 Hz, 2F) LC/MS $t_r$ = 5,13 minutos (acetonitrilo/agua al 0-95%, acido trifluoroacético al 0,05%, a lo largo de 6 minutos a 1 ml/min con detección a 215 nm, a 50°C) ES-MS *m/z* 455 (M+H) ES-HRMS *m/z* 455,0791 (M+H calculado para $C_{21}H_{16}ClF_4N_2O_3$ requiere 455,0780)

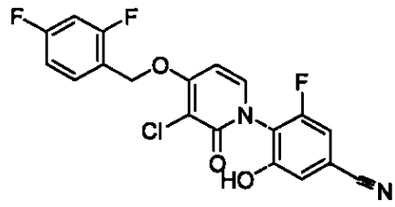
Ejemplo 348



4-[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2H)-il]-3-fluoro-5-metoxibenzonitrilo

Etapa 1 Preparación de 4-[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2H)-il]-3-fluoro-5-hidroxibenzonitrilo

1018



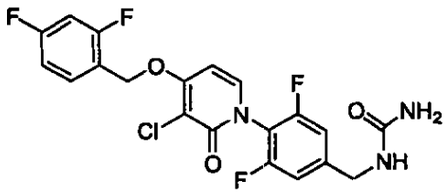
Se combinaron 4-[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2H)-il]-3,5-difluorobenzonitrilo (522 mg, 1,28 mmol) y trimetilsilonato de potasio al 90% (655 mg, 4,60 mmol) en 8 ml ce tetrahidrofurano anhidro y se agito bajo nitrogeno a temperatura ambiente durante 2 horas Se recogio la sal de potasio de PHA-789396 precipitada mediante filtracior, se lavo con un minimo de tetrahidrofurano, y se seco *in vacuo* Se disolvio una porcion de esta sal (275 mg, 0,618 mmol) en 5 ml de agua, se ajustó el pH por debajo de 6 con ácido hidroclorico concentrado, se recogio el producto por filtración, se lavo con agua, se secó po~ absorcion bajo un manto de nitrogeno seco, y se secó aun mas *in vacuo* durante la noche (251 mg, al 100%, al 98% en general) $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 11,46 (br s, 1H), 7,74 (d, $J$ = 7,81 Hz, 1H), 7,67 (cuarteto, $J$ = 6,76 Hz, 1H), 7,52 (d, $J$ = 8,76, 1H), 7,364, (dt, $J$ = 10,18, 2,37 Hz, 1H), 7,24 (br s, 1H), 7,17 (br t, $J$ = 8,75, 1H), 6,74 (d, $J$ = 8,04 Hz, 1H), 5,39 (s, 2H) $^{19}$F-NMR (400 MHz, DMSO-$d_6$) δ -109,26 (quinteto, $J$ = 8,50 Hz, 1F), -113,52 (cuarteto, $J$ = 9,29 Hz, 1F), -118,06 (d, $J$ = 9,38 Hz, 1F) LC/MS $t_r$ = 5,13 minutos (acetonitrilo/agua al 0-95%, ácido trifluoroacético 0,05%, a lo largo de 6 minutos, luego acetonitrilo al 95% durante 2 minutos, a 1 ml/min con deteccion a 215 nm, a 50°C) ES-MS *m/z* 407 (M+H) ES-HRMS *m/z* 407,0381 (M+H calculado para $C_{19}H_{11}ClF_3N_2O_3$ requiere 407,0405)

Etapa 2 Preparación del compuesto del titulo

1019

La sal de potasio de 4-[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2H)-il]-3-fluoro-5-hidroxibenzonitrilo (de la Etapa 1) (273 mg, 0,614 mmol) se agito en 5 ml de dimetilformamida anhidro bajo nitrogeno Se agregó yodometano (93 mg, 0,66 mmol) y la agitación continuó durante 2 h: La mezcla se diluyo hasta 50 ml con agua helada, y se recogió el precipitado blanco por filtración El precipitado se lavó tres veces con agua, se dejó secar por absorcion bajo un manto de nitrógeno y se secó más *in vacuo* durante la noche (242 mg, al 87%) $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 7,73 (m, 2H), 7,65 (m, 2H), 7,34 (dt, $J$ = 9,90, 2,39 Hz, 1H), 7,17 (dt, $J$ = 8,75, 2,47 Hz, 1H), 6,75 (d, $J$ = 7,97 Hz, 1H), 5,37 (s, 2H), 3,84 (s, 3H) $^{19}$F-NMR (400 MHz, DMSO-$d_6$) δ -109,24 (quinteto, $J$ = 7,85 Hz, 1F), -113,54 (cuarteto, $J$ = 9,83 Hz, 1F), -118,33 (d, $J$ = 7,77 Hz, 1F) LC/MS $t_r$ = 5,40 minutos (acetonitrilo/agua al 0-95%, acido trifluoroacetico al 0,05%, a lo largo de 6 minutos a 1 ml/min con deteccion a 215 nm, a 50°C) ES-MS *m/z* 421 (M+H) ES-HRMS *m/z* 421,0522 (M+H calculado para $C_{20}H_{13}ClF_3N_2O_3$ requiere 421,0561)

Ejemplo 349




*N*-{4-[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2H)-il]-3,5-difluorobencil}urea

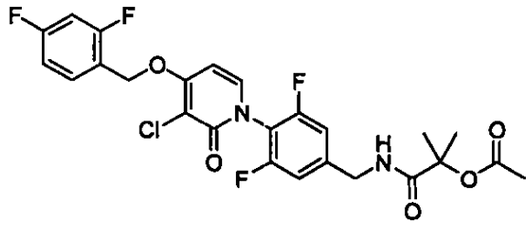
Etapa 1 Preparacion del compuesto del titulo

Se disolvio hidrocloruro de 1-[4-(aminometil)-2,6-difluorofenil]-3-cloro-4-[(2,4-difluorobencil)oxi]piridin-2(1H)-ona (162 mg, 0,361 mmol) en 4 ml de acido acetico acuoso al 50% y se trató con cianato de potasio (59 mg,

1020

0,72 mmol) La mezcla se agitó 2 hs, luego se diluyó la mezcla hasta alcanzar 50 ml con agua fría, y el producto en crudo, contaminado con la acetamida, se purificó mediante cromatografía sobre gel de sílice, eluyendo primero con etanol al 20% en hexano luego etanol al 40% en hexano Las fracciones al 50% se unieron mediante TLC (cromatografía de capa fina) y se evaporaron, proporcionando el producto como un fino polvo blanco (65 mg, al 40%) $^{1}$H-NMR (400 MHz, DMSO-$d_6$) δ 7,87 (d, $J$ = 8,07 Hz, 1H), 7,64 (cuarteto, $J$ = 6,53 Hz, 1H), 7,33, (dt, $J$ = 9,47, 1,99 Hz, 1H), 7,15 (m, 3H), 6,76 (d, $J$ = 7,97 Hz, 1H), 6,59 (m, 1H), 5,65 (br s, 2H), 5,38 (s, 2H), 4 22 (m, 2H) $^{19}$F-NMR (400 MHz, DMSO-$d_6$) δ -109,22 (quinteto, $J$ = 7,86 Hz, 1F), -113,51 (cuarteto, $J$ = 9,40 1F), -120,65 (d, $J$ = 8,75 Hz, 2) LC/MS $t_r$ = 4,85 minutos (acetonitrilo/agua al 0-95%, ácido trifluoroacético al 0,05%, a lo largo de 6 minutos a 1 ml/min con detección a 215 nm, a 50°C) ES-MS $m/z$ 456 (M+H)

Ejemplo 350



Acetato de 2-({4-[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2H)-il]-3,5-difluorobencil}amino)-1,1-dimetil-2-oxoetilo

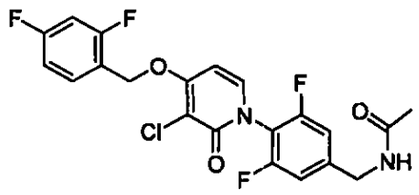
Etapa 1 Preparacion del compuesto del titulo

Se disolvió hidrocloruro de 1-[4-(aminometil)-2,6-difluorofenil]-3-cloro-4-[(2,4-difluorobencil)oxi]piridin-2(1H)-ona (225 mg, 0,501 mmol) en una disolución de 10 ml de tetrahidrofurano y trietilamina (111 mg, 1,10 mmol) Se agrego cloruro de 2-acetoxi-2-metil-propionilo (85 mg,

1024

0,516 mmol), y la mezcla se agito durante 30 minutos antes de dividirlo entre cloruro de amonio acuoso saturado y acetato de etilo Se separaron las capas y la fase acuosa se extrajo dos veces con acetato de etilo Los materiales organicos combinados se lavaron con agua y salmuera, luego se secaron sobre $MgSO_4$, se filtraron y se evaporaron in vacuo, proporcionando el producto como un fino polvo blanco (254 mg, al 94%) $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8,47 (t, $J$ = 6,16 Hz, 1H), 7,88 (d, $J$ = 7,71 Hz, 1H), 7,65 (cuarteto, $J$ = 7,24 Hz, 1H), 7,34, (dt, $J$ = 10,04, 2,49 Hz, 1H), 7,16 (m, 3H), 6,77 (d, $J$ = 7,78 Hz, 1H), 5,38 (s, 2H), 4,32 (d, $J$ = 5,93 2H), 2,02 (s, 3H), 1,48(s, 6H) $^{19}$F-NMR (400 MHz, DMSO-$d_6$) δ -109,26 (quinteto, $J$ = 9,00 Hz, 1F), -113,52(cuarteto, $J$ = 9,52 Hz, 1F), -120,62 (d, $J$ = 9,09 Hz, 2F) LC/MS $t_r$ = 5,43 minutos (acetonitrilo/agua al 0-95% , acido trifluoroacetico al 0,05%, a lo largo de 6 minutos a 1 ml/min con detección a 215 nm, a 50°C) ES-MS $m/z$ 541 (M+H) ES-HRMS $m/z$ 541,1128 (M+H calculado para $C_{25}H_{22}ClF_4N_2O_5$ requiere 541,1148)

Ejemplo 351



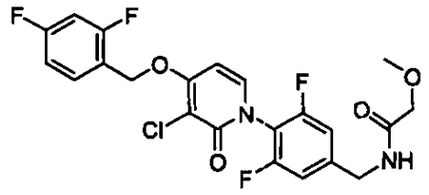

*N*-{4-[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2H)-il]-3,5-difluorobencil}acetamida

El compuesto se preparo siguiendo el procedimiento del Ejemplo 350, sustituyendo cloruro de 2-acetoxi-2-metil-propionilo por cloruro de acetilo (24 mg, 0,30 mmol) (128 mg, al 96%) $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 8,48 ( br s, 1H), 7,87 (d, $J$ = 7,28 Hz, 1H), 7,64 (cuarteto, $J$ = 8,01 Hz, 1H), 7,33, (dt, $J$ = 9,87, 2,25 Hz, 1H), 7,17 (m, 3H), 6,76

1022

(d, $J$ = 8,25 Hz, 1H), 5,38 (s, 2H), 4,30 (m, 2H), 1,88(s, 3H) $^{19}$F-NMR (400 MHz, DMSO-$d_6$) δ -109,22 (quinteto, $J$ = 8,04 Hz, 1F), -113,52(cuarteto, $J$ = 9,91 Hz, 1F), -120,43 (d, $J$ = 8,77 Hz, 2F) LC/MS $t_r$ = 5,04 minutos (acetonitrilo/agua al 0-95% , acido trifluoroacetico al 0,05%, a lo largo de 6 minutos a 1 ml/min con deteccion a 215 nm, a 50°C) ES-MS $m/z$ 555 (M+H) ES-HRMS $m/z$ 455,0824 (M+H calculado para $C_{21}H_{16}ClF_4N_2O_3$ requiere 455,0780)

Ejemplo 352



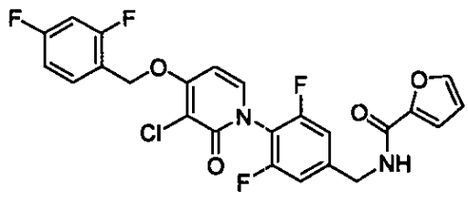
*N*-{4-[3-cloro-4 [(2,4-difluorobencil)oxi]-2-oxopiridin-1(2H)-il] 3,5-difluorobencil}-2-metoxiacetamida

El compuesto se preparo siguiendo el procedimiento del Ejemplo 350, sustituyendo cloruro de 2-acetoxi-2-metil-propionilo por cloruro de 2-metoxi-acetilo (45 mg, 0,415 mmol) (124 mg, al 78%) $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 8,56 (t, $J$ = 6,77 Hz, 1H), 7,90 (d, $J$ = 7,85 Hz, 1H), 7,67 (cuarteto, $J$ = 7,67 Hz, 1H), 7,36, (dt, $J$ = 10,03, 2,36 Hz, 1H), 7,20 (m, 3H), 6 79 (d, $J$ = 8,07 Hz, 1H), 5,40 (s, 2H), 4,37 (d, $J$ = 6,28 Hz, 2H), 3,91(s, 2H), 3,35 (s, 3 H) $^{19}$F-NMR (400 MHz, DMSO-$d_6$) δ -109,23 (quinteto, $J$ = 8,29 Hz, 1F), -113,50(cuarteto, $J$ = 9,36 Hz, 1F), -120,43 (d, $J$ = 9,07 Hz, 2F) LC/MS $t_r$ = 5,13 minutos (acetonitrilo/agua al 0-95% , acido trifluoroacético al 0,05%, a lo largo de 6 minutos a 1 ml/min con deteccion a 215 nm, a 50°C) ES-MS $m/z$ 485 (M+H) ES-hRMS $m/z$ 485,0856 (M+H calculado para $C_{22}H_{18}ClF_4N_2O_4$ requiere 485,0886)

Ejemplo 353

~~1023~~

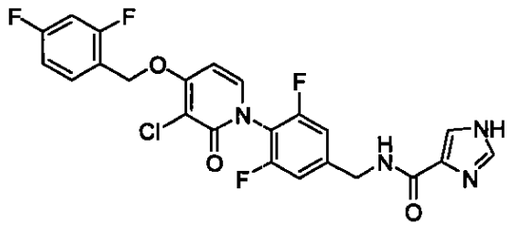
1023



*N*-{4-[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2H)-il]-3,5-difluorobencil}-2-furamida

El compuesto se preparó siguiendo el procedimiento del Ejemplo 350, sustituyendo cloruro de 2-acetoxi-2-metil-propionilo por cloruro de furoilo (62 mg, 0,48 mmol) Rendimiento 142 mg, al 85% $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 9,07 (t, *J* = 6,14 Hz 1H), 7,90 (d, *J* = 7,88 Hz, 1H), 7,87 (dd, *J* = 1,69, 0,80 Hz, 1H), 7,67 (td, *J* = 8,46, 6,80 Hz, 1H), 7,35, (dt, *J* = 10,00, 2,81 Hz, 1H), 7,26 (d, *J* = 8,78 Hz, 2H), 7,18 (ddt, *J* = 8,58, 2,30, 1,07 Hz, 1H), 7,16 (dd, *J* = 3,52, 0,77 Hz, 1H), 6,79 (d, *J* = 8,07 Hz, 1H), 6,64 (dd, *J* = 3,16, 1,73 Hz, 1H), 5,40 (s, 2H), 4,49 (d, *J* = 6,13 Hz, 2H) $^{19}$F NMR (400 MHz, DMSO-$d_6$) δ -109,23 (quinteto, *J* = 7,65 Hz, 1F), -113,50(cuarteto, *J* = 9,84 Hz, 1F), -120,29 (d, *J* = 9,41 Hz, 2F) LC/MS $t_r$ = 5,32 minutos (acetonitrilo/agua al 0-95% , acido trifluoroacetico al 0,05%, a lo largo de 6 minutos a 1 ml/min con deteccion a 215 nm, a 50°C) ES-MS *m/z* 507 (M+H) ES-HRMS *m/z* 507,0716 (M+H calculado para $C_{24}H_{16}ClF_4N_2O_4$ requiere 507,0729)

Ejemplo 354



*N*-{4-[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2H)-il]-3,5-difluorobencil}-1H-imidazol-4-carboxamida

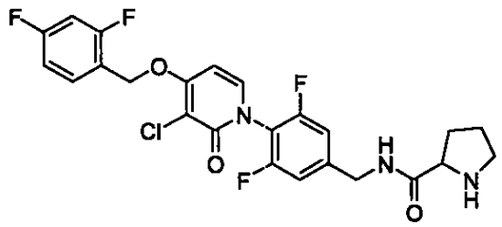
1024

Etapa 1 Preparación del compuesto del título

Se disolvió hidrocloruro de 1-[4-(aminometil)-2,6-difluorofenil]-3-cloro-4-[(2,4-difluorobencil)oxi]piridin-2(1H)-ona (150 mg, 0,334 mmol) en una disolucion de 4 ml de tetrahidrofurano y trietilamina (35 mg, 0,35 mmol) Se combinaron ácido 4-imidazolcarboxílico (62 mg, 0,56 mmol), hidrato de 1-hidroxibenzotriazol (90 mg, 0,67 mmol), hidrocloruro 1-[3-(dimetilamino)propil]-3-etilcarbodiimida (128 mg, 0,668 mmol), y trietilamina (100 mg, 0,989 mmol) en 5 ml de tetrahidrofurano y se agito bajo nitrogeno Se agrego la disolucion que contenia hidrocloruro de 1-[4-(aminometil)-2,6-difluorofenil]-3-cloro-4-[(2,4-difluorobencil)oxi]piridin-2(1H)-ona en una porción, enjuagando con 2 ml de tetrahidrofurano Se continuo con la agitacion a temperatura ambiente durante la noche, luego la reaccion se vertio en 90 ml de agua helada, y el producto se recogio por filtracion y se seco *in vacuo* (254 mg, al 94%) $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 12,55 (br s, 1H), 8,73 (t, $J$ = 6,57 Hz, 1H), 7,90 (d, $J$ = 7,87 Hz, 1H), 7,75 (s, 1H), 7,67 (m, 2H), 7,35, (dt, $J$ = 10,04, 2,54 Hz, 1H), 7,21 (m, 3H), 6,78 (d, $J$ = 8,04 Hz, 1H), 5,39 (s, 2H), 4,47 (m, 2H) $^{19}$F-NMR (400 MHz, DMSO-$d_6$) δ -109,26 (quinteto, $J$ = 7,87 Hz, 1F), -113,52(cuarteto, $J$ = 9,30 Hz, 1F), -120,59 (d, $J$ = 9,21 Hz, 2F) LC/MS $t_r$ = 4,48 minutos (acetonitrilo/agua al 0-95% , ácido trifluoroacetico al 0,05%, a lo largo de 6 minutos a 1 ml/min con deteccion a 215 nm, a 50°C) ES-MS *m/z* 507 (M+H) ES-HRMS *m/z* 507,0818 (M+H calculado para $C_{23}H_{16}ClF_4N_4O_3$ requiere 507,0842)

Ejemplo 355

1025

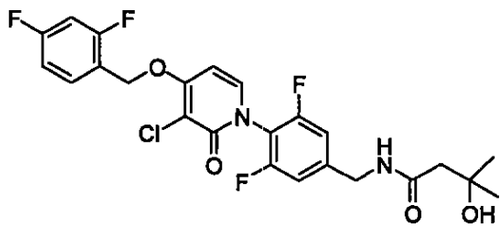


*N*-{4-[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2H)-il]-3,5-difluorobencil}-5-oxoprolinamida

Etapa 1 Preparacion del compuesto del titulo

El compuesto se preparo siguiendo el procedimiento del Ejemplo 354, sustituyendo acido 4-imidazolcarboxilico por acido 2-pirrolidona-5-carboxilico $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 8,67 (t, *J* = 6,08 Hz, 1H), 7,88 (m, 1H), 7,65 (qr, *J* = 7,57, 1H), 7,34, (dt, *J* = 9,32, 2,63 Hz, 1H), 7,22 (d, *J* = 9,36, 2H), 7,17 (dt, *J* = 8,51, 2,55 Hz, 1H), 6,77 (d, *J* = 7,66 Hz, 1H), 5,73 (s, 1H), 5,38 (s, 2H), 4,35 (d, *J* = 5,74, 2H), 4,05 (m, 1H), 2,15 (m, 2H), 1,90 (m, 2H) $^{19}$F-NMR (400 MHz, DMSO-$d_6$) δ -109,25 (quinteto, *J* = 7,72 Hz, 1F), -113,52(cuarteto, *J* = 8,94 Hz, 1F), -120,39 (d, *J* = 9,11 Hz, 2F) LC/MS $t_r$ = 4,81 minutos (acetonitrilo/agua al 0-95%, acido trifluoroacético al 0,05%, a lo largo de 6 minutos a 1 ml/min con deteccion a 215 nm, a 50°C) ES-MS *m/z* 524 (M+H) ES-HRMS *m/z* 524,0998 (M+H calculado para $C_{24}H_{19}ClF_4N_3O_4$ requiere 524,0995)

Ejemplo 356



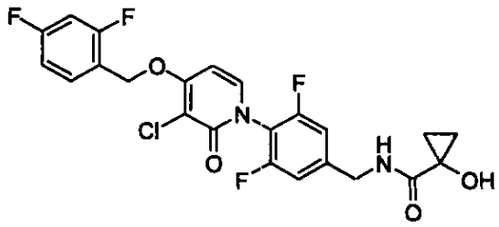
*N*-{4-[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2H)-il]-3,5-difluorobencil}-3-hidroxi-3-metilbutanamida

1026

Etapa 1 Preparacion del compuesto del titulo

El compuesto se preparó siguiendo el procedimiento del Ejemplo 354, sustituyendo ácido 4-imidazolcarboxilico por acido 2-hidroxi-2-metil-butirico $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 8,43 (t, $J$ = 6,04 Hz, 1H), 7,88 (d, $J$ = 8,01, 1H), 7,65 (qr, $J$ = 6,84, 1H), 7,34, (dt, $J$ = 10,13, 2,55 Hz, 1H), 7,22 (d, $J$ = 8,74, 2H), 7,16 (dt, $J$ = 8,57, 2,45 Hz, 1H), 6,77 (d, $J$ = 7,89 Hz, 1H), 5,38 (s, 2H), 4,75 (s, 0,5H (OH)), 4,35 (d, $J$ = 6,48, 2H), 2,28 (s, 2H), 1,47 (s, 0,5H(OH)), 1,16 (s, 6H) $^{19}$F-NMR (400 MHz, DMSO-$d_6$) δ -109,26 (quinteto, $J$ = 7,79 Hz, 1F), -113,53(cuarteto, $J$ = 9,23 Hz, 1F), -120,49 (d, $J$ = 9,39 Hz, 2F) LC/MS $t_r$ = 5,08 minutos , (acetonitrilo/agua al 0-95%, acido trifluoroacetico al 0,05%, a lo largo de 6 minutos a 1 ml/min con deteccion a 215 nm, a 50°C) ES-MS $m/z$ 513 (M+H) ES-HRMS $m/z$ 513,1177 (M+H calculado para $C_{24}H_{22}ClF_4N_2O_4$ requiere 513,1199)

Ejemplo 357



*N*-{4-[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2H)-il]-3,5-difluorobencil}-1-hidroxiciclopropanocarboxamida

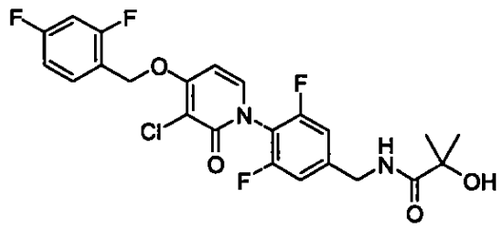
Etapa 1 Preparación del compuesto del titulo

El compuesto se preparo siguiendo el procedimiento del Ejemplo 354 sustituyendo acido 4-imidazolcarboxilico por acido 1-hidroxi-1-ciclopropanocarboxílico $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 8,70 (t, $J$ = 6,26 Hz, 1H), 7,89 (d, $J$ = 6,31, 1H), 7,65 (qr, $J$ = 6,83, 1H), 7,34 (t, $J$ = 10,58 Hz, 1H),

1027

7,19 (m, 3H), 6,77 (d, $J$ = 7,70 Hz, 1H), 5,38 (s, 2H), 4,35 (d, $J$ = 5,66, 2H), 1,14 (s, 1H), 1,02 (m, 2H), 0,84 (m, 2H) $^{19}$F-NMR (400 MHz, DMSO-$d_6$) δ -109,25 (quinteto, $J$ = 8,05 Hz, 1F), -113,53(cuarteto, $J$ = 8,27 Hz, 1F), -120,59 (d, $J$ = 8,99 Hz, 2F) LC/MS $t_r$ = 5,01 minutos (acetonitrilo/agua al 0-95% , acido trifluoroacético al 0,05%, a lo largo de 6 minutos a 1 ml/min con deteccion a 215 nm, a 50°C) ES-MS $m/z$ 497 (M+H) ES-HRMS $m/z$ 497,0873 (M+H calculado para $C_{23}H_{18}ClF_4N_2O_4$ requiere 4970886)

Ejemplo 358



*N*-{4-[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2H)-il]-3,5-difluorobencil}-2-hidroxi-2-metilpropanamida

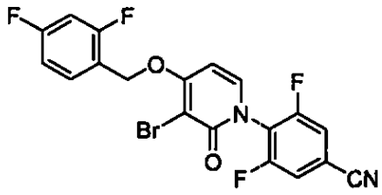
Etapa 1 Preparacion del compuesto del titulo

El compuesto se preparo siguiendo el procedimiento del Ejemplo 354, sustituyendo acido 4-imidazolcarboxilico por acido 2-hidroxiisobutirico $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 8,48 (t, $J$ = 6,41 Hz, 1H), 7,89 (d, $J$ = 7,78, 1H), 7,65 (qr, $J$ = 9,10, 1H), ',33 (dt, $J$ = 10,12, 2,41 Hz, 1H), 7,17 (m, 3H), 6,77 (d, $J$ = 7,69 Hz, 1H), 5,38 (s, 2H), 4,31 (d, $J$ = 6,50, 2H), 1,41 (s, 1H), 1,33 (s, 6H) $^{19}$F-NMR (400 MHz, DMSO-$d_6$) δ -109,25 (quinteto, $J$ = 7,49 Hz, 1F), -113,53(cuarteto, $J$ = 9,64 Hz, 1F), -120,59 (d, $J$ = 8,68 Hz, 2F) LC/MS $t_r$ = 5,05 minutos (acetonitrilo/agua al 0-95%, acido trifluoroacetico al 0,05%, a lo largo de 6 minutos a 1 ml/min con detección a 215 nm, a 50°C) ES-MS $m/z$ 499

1028

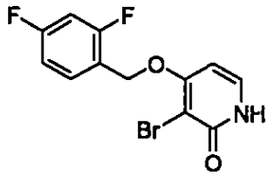
(M+H) ES-HRMS *m/z* 499,1020 (M+H calculado para $C_{23}H_{20}ClF_4N_2O_4$ requiere 499,1042)

Ejemplo 359



4-[3-bromo-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2H)-il]-3,5-difluorobenzonitrilo

Etapa 1 Preparación de 3-bromo-4-[(2,4-difluorobencil)oxi]piridin-2(1H)-ona



El compuesto se preparó siguiendo el procedimiento para 3-cloro-4-[(2,4-difluorobencil)oxi]piridin-2(1H)-ona (Etapa 3), sustituyendo *N*-clorosuccinimida por *N*-bromosuccinimida $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 11,85 (br s, 1H), 7,61 (m, 1H), 7,46 (d, *J* = 7,36 Hz, 1H), 7,30, (m, 1H), 7,14 (m, 1H), 6,40 (d, *J* = 7,71 Hz, 1H), 5,26 (s, 2H) $^{19}$F-NMR (400 MHz, DMSO-$d_6$) δ -109,69 (quinteto, *J* = 7,93 Hz, 1F), -113,63 (cuarteto, *J* = 9,55 Hz, 1F) LC/MS $t_r$ = 4,48 minutos (acetonitrilo/agua al 0-95% , acido trifluoroacético al 0,05%, a lo largo de 6 minutos a 1 ml/min con detección a 215 nm, a 50°C) ES-MS *m/z* 316 (M+H)

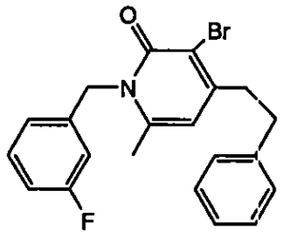
Etapa 2 Preparación del compuesto del titulo

El compuesto se preparo siguiendo el procedimiento para 4-[3-cloro-4- (2,4-difluorobencil)oxi]-2-oxopiridin-1(2H)-il]-3,5-difluorobenzonitrilo (Etapa 4), sustituyendo 3-cloro-4-[(2,4-difluorobencil)oxi]piridin-2(1H)-ona (de Etapa 3) por 3-bromo-4-[(2,4-difluorobencil)oxi]piridin-

1029

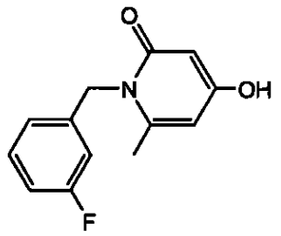
2(1H)-ona (de la Etapa 1) (1,92 g, 6,06 mmol) $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 8,13 ( d, $J$ = 7,24 Hz, 2H), 7,95 (d, $J$ = 7,76 Hz, 1H), 7,66 (cuarteto, $J$ = 8,71 Hz, 1H), 7,34, (dt, $J$ = 9,94, 2,53 Hz, 1H), 7,17 (dt, $J$ = 8,64, 2,33 Hz, 1H), 6,82 (d, $J$ = 7,77 Hz, 1H), 5,39 (s, 2H) $^{19}$F-NMR (400 MHz, DMSO-$d_6$) δ -109,28 (quinteto, $J$ = 7,98 Hz, 1F), -113,45(cuarteto, $J$ = 9,29 Hz, 1F), -116,30 (d, $J$ = 7,44 Hz, 2F) LC/MS $t_r$ = 5,48 minutos (acetonitrilo/agua al 0-95%, acido trifluoroacetico al 0,05%, a lo largo de 6 minutos a 1 ml/min con deteccion a 215 nm, a 50°C) ES-MS $m/z$ 453 (M+H) ES-HRMS $m/z$ 452,9836 (M+H calculado para $C_{19}H_{10}BrF_4N_2O_2$ requiere 452,9856)

Ejemplo 360




3-Bromo-1-(3-fluorobencil)-6-metil-4-(2-feniletil)piridin-2(1H)-ona

Etapa 1 Preparación de 1-(3-fluorobencil)-4-hidroxi-6-metilpiridin-2(1H)-ona

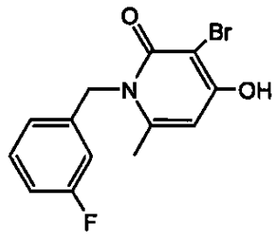



Se calentaron a reflujo una mezcla de 4-hidroxi-6-metil-2-pirona (2,5 g, 0,02 mol) y 3-fluorobencilamina (2,5 g, 0,02 mol) en n-butanol (15,0 mL) durante 16 hs bajo atmósfera de argon Se destiló butanol in vacuo, se trituro el residuo con EtOAc, se enfrio y se filtro el precipitado

1030

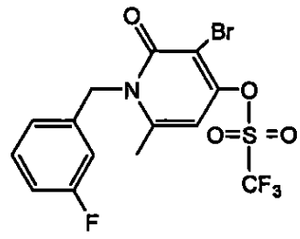
Se lavó con EtOAc frío y se secó para proporcionar 0,86 g del compuesto del título como un polvo amarillo pálido 1H-NMR (CD3OD/400 MHz) □ 7,31 (m, 1H), 7,0 - 6,85 (m, 2H), 6,83 (d, 1H, J = 9,5 Hz), 5,96 (d, 1H, J = 2,0 Hz), 5,80 (d, 1H, J = 2,0 Hz) 5,30 (s, 2H), y 2,24 (s, 3H), ES MS m/z = 234 ( MH+)

Etapa 2 Preparación de 3-bromo-1-(3-fluorobencil)-4-hidroxi-6-metilpiridin-2(1H)-ona




Se agitó una mezcla de 1-(3-fluorobencil)-4-hidroxi-6-metilpiridin-2(1H)-ona (0,8 g, 0,0034 mol), NBS (0,64 g, 0,0036 mol) en diclorometano (15,0 mL) a temperatura ambiente bajo atmosfera de argón Despues de 1,5 hs, la mezcla de reaccion se diluyó con diclorometano (15,0 mL), se enfrio y se filtraron los solidos El residuo se lavó con diclorometano y se secó in vacuo para proporcionar 0,93 g del compuesto del titulo como un polvo blanco 1H- NMR (CD3OD/400 MHz) □ ? 7,33 (m, 1H), 7,2 - 6,8 (m, 3H), 6,07 (s, 1H), 5,34 (s, 2H), 2,26 (s, 3H), ESHRMS m/z 312,0016 (M+H C13H12NO2BrF requiere 312,0035)

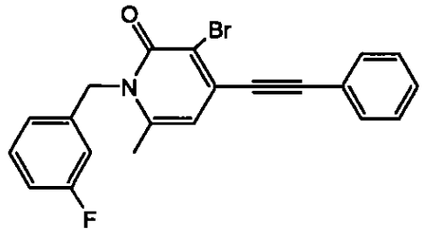
Etapa 3 Preparación de 3-bromo-1-(3-fluorobencil)-6-metil-2-oxo-1,2-dihidropiridin-4-il trifluorometanosulfonato



1031

A una suspension de 3-bromo-1-(3-fluorobencil)-4-hidroxi-6-metilpiridin-2(1H)-ona (0 86 g, 0 0028 mol) en diclorometano (15,0 mL) enfriada a -30 °C, se le agrego trietilamina (0,5 mL, 0,004 mol) y anhidrido triflico (0,7 mL, 0,0042 mol) y se agito durante 1 hora La disolución de color naranja resultante se vertio en agua helada (25 mL) y se extrajo con diclorometano ( 2 x 25 mL) Los extractos organicos combinado se lavaron con agua, se secaron (Na2SO4) y se concentraron bajo presion reducida El residuo resultante se purifico mediante cromatografia rapida sobre gel de silice usando 1 1 EtOAc/hexano vol/vol para proporcionar 1,0 g (al 85%) del compuesto del titulo como un solido marrón claro $^1$H- NMR (CDCl3/400 MHz)δ 7,32 (m,1H), 7,0 - 6,85 (m, 3H), 6,18 (s, 1H), 5,32 (s, 2H), y 2,34 (s, 3H), ESHRMS m/z 443,9492 (M+H C14H11NO4BrF4S requiere 443,9528)

Etapa 4 Preparación de 3-bromo-1-(3-fluorobencil)-6-metil-4-(feniletinil)piridin-2(1H)-ona




Se desgasifico una disolucion de trifluorometanosulforato de 3-bromo-1-(3-fluorobencil)-6-metil-2-oxo-1,2-dihicropiridin-4-il (1,0 g, 0,0022 mol) y fenilacetileno (0,3 mL, 0,0029 mol) en DMF (5,0 mL) utilizando una bomba de vacio, y se purgo con argón (3 ciclos)

Luego se agrego diisopropiletilamina, (0 5 mL) seguido de la adición de PdCl2(PPh3)2 (0,36 g) La mezcla de reacción se calento a 65 °C durante 1,5 hs bajo atmosfera

1032

de argón Los disolventes se destilaron in vacuo, y el residuo se purifico mediante cromatografia rápida sobre gel de silice utilizando EtOAc/hexano (2 3 vol/vol) para proporcionar 0,65 g (al 70%) del compuesto del titulo como un sólido amorfo coloreado $^{1}$H- NMR (CD3OD/400 MHz)δ 7,59 (m, 2H), 7,45 - 7,3 (m, 4H), 7,05 - 6,85 (m, 3H), 6,44 (s, 1H), 5,41 (s, 2H), y 2,31 (s, 3H), $^{19}$F-NMR (CD3OD/400 MHz) δ -116,33 (m ), ESHRMS m/z 396,0373 (M+H C21H16NOBrF 396,0399)

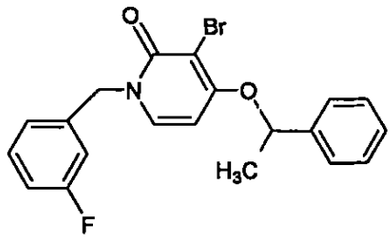
Etapa 5 Preparacion de 3-bromo-1-(3-fluorobencil)-6-metil-4-(2-feniletinil)piridin-2(1H)-ona

A una disolución de 3-bromo-1-(3-fluorobencil)-6-metil-4-(feniletinil)piridin-2(1H)-ona (0,55 g, 0,0014 mol) en EtOAc (10,0 mL) y EtOH (10,0 mL) se le agregó PtO2 (0,05 g) y se agitó en una atmosfera de hidrogeno gaseoso y se agito a 15 libras por pulgada cuadrada durante 30 minutos Se elimino el catalizador mediante filtracion, se concentro el filtrado y se purifico el residuo mediante cromatografia rapida en gel de silice, usando EtOAc al 25% en hexano como eluyente

Se combinaron las fracciones apropiadas (visualizadas bajo UV) y se concentraron hasta alcanzar la sequedad $^{1}$H-NMR (CD3OD/400 MHz)δ 7,35 (m, 1H), 7,31 - 7,16 (m, 5H), 6,99(m, 1H), 6,91 (m, 1H), 6,81 (m, 1H), 6,20 (s, 1H), 5,41 (s, 2H), 2,94 (m, 4H), y 2,24 (s, 3H), $^{19}$F-NMR (CD3OD/400 MHz)δ -115,01 (m ), ESHRMS m/z 400,0695 (M+H C21H20NOBrF 400,0712)

Ejemplo 361

1033

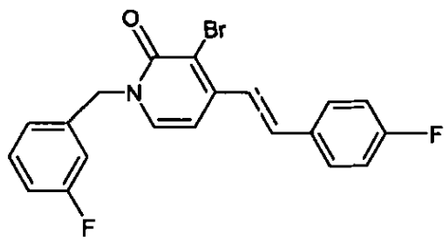


3-bromo-1-(3-fluorobencil)-4-(1-feniletoxi)piridin-2(1H)-ona

Se agito una mezcla de 3-bromo-1-(3-fluorobencil)-4-hidroxipiridin-2(1H)-ona (0 2 g, 0,72 mmol), carbonato de potasio (0,1 g, 0,72 mmol) y (1-bromoetil)benceno (0,19 g, 1 mmol) en DMF (3 0 mL) a temperatura ambiente durante 16 hs Se destiló DMF in vacuo, y se purificó el residuo mediante cromatografia rapida (EtOAc en hexano (1 3 vol/vol) para proporcionar un jarabe amarillo pálido Este material se purifico mas mediante HPLC (cromatografia liquida de alto rendimiento) de fase inversa utilizando un gradiente de acetonitrilo agua al 10 - 90% (30 min), a un caudal de 100 mL/min Se concentraron las fracciones adecuadas, se concentraron hasta obtener un volumen pequeño 20 mL), se agrego EtOAc (25 mL) y se lavo sucesivamente con bicarbonato de sodio, agua y se secó ($Na_2SO_4$) Se elimino el EtOAc bajo presion reducida y se seco el residuo in vacuo para proporciorar el compuesto del titulo (0,15 g, al 52%) como una sustancia amorfa $^1H$ NMR ($CD_3OD$/ 400 MHz) δ 7,56 (d, 1H, J = 7,6 Hz), 7,4 - 7,2 (m, 5H), 7,0 (m, 3H), 6,28 (d, 1H, J = 7,6 Hz), 5,65 (m, 1H), 5,19 (d x d, 2H, J = 14,8 Hz), y 1,64 (d, 3H, J = 6,4 Hz), ES-HRMS m/z 402,0492(M+H $C_{20}H_{18}NO_2Br$, requiere 402,0499)

Ejemplo 362

1034

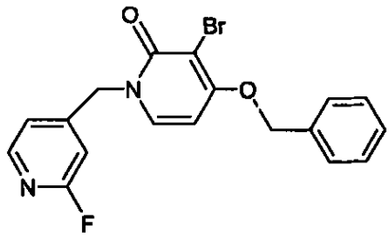



3-bromo-1-(3-fluorobencil)-4-[(*E*)-2-(4-fluorofenil)etenil]piridin-2(1*H*)-ona,

Una mezcla de 3-bromo-1-(3-fluorobencil)-2-oxo-1,2-dihidropiridin-4-il trifluorometanosulfonato (1,0 g, 0,0023 mol), y 4-fluoroestireno (0,33 mL, 0,0028 mol) en DMF desgasificado (10,0 ml) que contenia diisopropil etil amina (0,37 g, 0,0029 mol) se trato con $PdCl_2(PPh_3)_2$ (0,32 g, 0,46 mmol) y se calentó hasta 65 °C bajo atmosfera de argon durante 16 hs Se destilo DMF in vacuo, y se purificó el residuo mediante cromatografia rapida (EtOAc/ hexano 1 4 vol/vol) para proporcionar una sustancia amarilla que se purificó más mediante HPLC de fase inversa usando un gradiente de acetonitrilo agua al 10 - 90% (30 min), a un caudal de 100 mL/min Se combinaron las fracciones adecuadas, se concentro hasta lograr un volumen (20 mL), se agrego EtOAc (25 mL) y se lavo sucesivamente con bicarbonato de sodio saturado, agua y se seco ($Na_2SO_4$) Se elimino el EtOAc bajc presion reducida y se seco el residuo in vacuo para proporcionar el compuesto del titulo (0,06 g, al 6%) como un polvo amarillo $^1H$ NMR ($CD_3OD$/ 400 MHz)δ 7,68 (m, 3H), 7,39 (m, 3H), 7,2 - 7,0 (m, 5H), 6,82 (d, 1H, J = 7,2 Hz), y 5,22 (s, 2H), $^{19}F$ NMR($CD_3OD$/ 400 MHz)δ -113,9(m) y -115 (m), ES-HRMS m/z 402,0305 ($M+HC_{20}H_{15}NOF_2Br$, requiere 402,0300)

Ejemplo 363

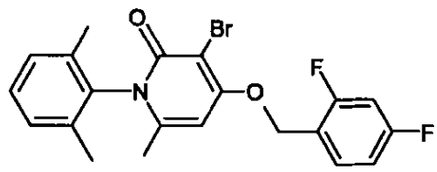
1035



4-(Benciloxi)-3-bromo-1-[(6-fluoropiridin-3-il)metil]piridin-2(1*H*)-ona

Una mezcla de 4-(benciloxi)-3-bromopiridin-2(1H)-ona (0,2 g, 0,00076 mol , 5-bromometil-2-fluoropiridina (0,25 g, 0,0013 mol) y carbonato de potasio (0,15 g, 0,0011 mol) en DMF (3,0 ml) se agito a temperatura ambiente durante 16 hs bajo atmósfera de argón Se destilo DMF in vacuo y el residuo se dividio en agua (15 ml) y EtOAc (25 mL) La fase organica se lavo con agua, se seco ($Na_2SO_4$), y se concentró bajo presión reducida $^1$H NMR ($CD_3OD$/ 400 MHz)δ 8,22 (m, 1H, 2,4 Hz), 7,92(m, 1H), 7,82 (d, 1H, J = 7,6 Hz), 7,44 - 7,31 (m 5H), 7,03( m, 1H) 6,49 (d, 1H, J = 7,6 Hz),5,29 (s, 2H), y 5,20 (s, 2H), $^{19}$F NMR($CD_3OD$/ 400 MHz)δ -72,30 (d, J = 6,0 Hz) y -115 (m), ES-HRMS m/z 389,0295 (M+H $C_{18}H_{15}N_2O_2FBr$, requiere 389,0309)

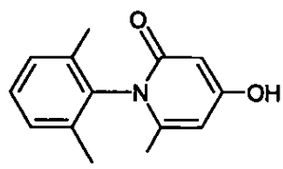
Ejemplo 364



3-Bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-dimetilfenil)-6-metilpiridin-2(1*H*)-ona

Etapa 1

Preparacion de



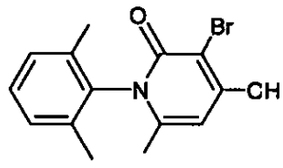
1036

1-(2,6-dimetilfenil)-4-hidroxi-6-metilpiridin-2(1H)-ona

Una mezcla de 4-hidroxi-6-metil-2-pirona (2,5 g, 0,02 mol), 2,6 dimetilan lina (2,4 g, 0,02 mol), y ácido p-toluenosulfonico (0,2 g) se calentó hasta 140 °C durante 3 hs bajo atmosfera de nitrógeno La mezcla de reaccion se enfrió, se trituró con acetonitrilo, se enfrio y se filtraron los solidos $^1$H NMR ($CD_3OD$/ 400 MHz) δ 7,22 (m, 3H), 6,12 (d, 1H, J = 1,6 Hz), 5,83 (d, 1H, J = 1,8 Hz), 2,00 (s, 6H), y 1,82 (s, 3H), ES MS m/z 229 (M+H)

Etapa 2

Preparacion de




3-Bromo-1-(2,6-cimetilfenil)-4-hidroxi-6-metilpiridin-2(1H)-ona

Se agito una mezcla de 1-(2,6-dimetilfenil)-4-hidroxi-6-metilpiridin-2(1H)-ona (0,4 g, 0,00175 mol) y NBS (0,35 g, 0,0019 mol) en ciclorometano (10,0 mL) a temperatura ambiente bajo atmósfera de nitrógeno Despues de 1 hora, se filtraron los sólidos, se lavaron con diclorometano para proporcionar 0,42 g (al 78%) del compuesto del titulo como un polvo amarillo pálido $^1$H NMR ($CD_3OD$/ 400 MHz) δ 7,22 (m, 3H ), 6,21 (s, 1H), 1,99 (s, 6H), y 1,82 (s, 3H), ES MS m/z 308/310 (M+H),

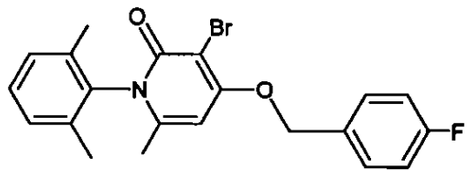
Etapa 3

Se agito una mezcla de 3-Bromo-1-(2,6-dimetilfenil)-4-hidroxi-6-metilpiridin-2(1H)-ona (0,15 g, 0,00049 mol), bromuro de 2,4 difluorobencilo (0,12 g, 0,00058 mol) y carbonato de potasio (0,075 g, 0,00054 mol) en DMF 3,00 mL) a temperatura ambiente bajo atmosfera de argon durante 2

1037

hs Luego, se calento hasta 60 °C durante 30 mın y se concentró ın vacuc El resıduo se purıfıco medıante cromatografıa rápıda $^1$H NMR ($CD_3OD$/ 400 MHz) δ 7,62 (m, 1H), 7,28 ( m,3H), 7,04 (m, 2H), 6,68 (s, 1H), 5,35 (m, 1H), 1,98 (s, 6H), y 1,92 (s, 3H), ES-HRMS m/z 434,0574 (M+H $C_{21}H_{19}NO_2F_2Br$, requıere 434,0562)

Ejemplo 365




3-Bromo-1-(2,6-dımetılfenıl)-4-[(4-fluorobencıl)oxı]-6-metılpırıdın-2(1*H*) ona

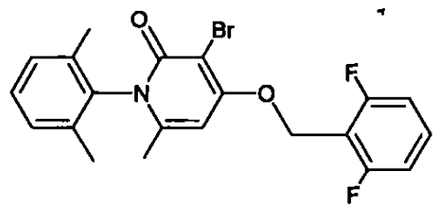
El compuesto del tıtulo se preparo medıante un procedımıento sımılar al descrıto para el Ejemplo 364 $^1$H NMR ($CD_3OD$/ 400 MHz) δ 7,58 (m, 2H), 7,23 (m, 3H), 7,15 (m, 2H), 6,62 (s, 1H), 5,32 (s, 2H), 1,98 (m, 6H), y 1,91 (s, 3H), ES-HRMS m/z 416,0670 (M+H $C_{21}H_{20}NO_2FBr$, requıere 416,0656)

Ejemplo 366

3-Bromo-1-(2,6-dımetılfenıl)-6-metıl-4-[(2,4,6-trıfluorobencıl)oxı]pırıdın-2(1*H*)-ona,

El compuesto del tıtulo se preparo medıante un procedımıento sımılaı al descrıto para el Ejemplo 364 $^1$H NMR ($CD_3OD$/ 400 MHz) δ 7,19 (m, 3H), 6,95 (m, 2H), 6,69 (s, 1H), 5,29 (s, 2H), 1,95 (s, 6H), y 1,90 (s, 3H), ES-HRMS m/z 452,0471 (M+H $C_{21}H_{18}NO_2F_3Br$, requıere 452,0468)

Ejemplo 367

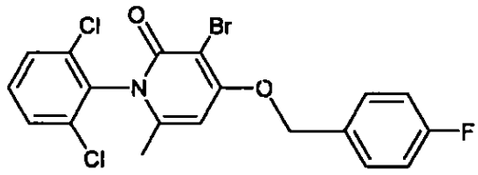


1038

3-Bromo-4-[(2,6-difluorobencil)oxi]-1-(2,6-dimetilfenil)-6-metilpiridin-2(1*H*)-ona

El compuesto del titulo se preparo mediante un procedimiento similar al descrito para el Ejemplo 364 $^1$H NMR ($CD_3OD$/ 400 MHz)δ 7,46 (m, 1H), 7,24 (m, 3H), 7,08 (m, 2H), 6,74 (s, 1H), 5,38 (s, 2H), 1,99 (s, 6H), y 1,94 (s, 3H), ES-HRMS m/z 434,0589 (M+H $C_{21}H_{19}NO_2F_2Br$, requiere 434,0562)

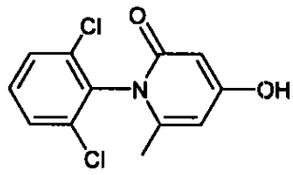
Ejemplo 368




3-Bromo-1-(2,6-diclorofenil)-4-[(4-fluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona

Etapa 1

Preparacion de 1-(2,6-diclorofenil)-4-hidroxi-6-metilpiridin-2(1H)-ona

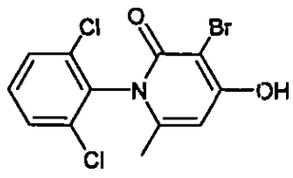



Este compuesto se preparó mediante el procedimiento descrito en la Etapa 1 para el Ejemplo 364 Rendimiento 28%, $^1$H NMR (CD3OD) δ 7,6 (m, 2H), 7,48 (m,1H)6,10 (dd, 1H), 5,78 (d, 1H, J = 2,4 Hz), 1,91 (s, 3H), (ES-MS m/z = 270 ($MH^+$),

Etapa 2

Preparacion de 3-bromo-1-(2,6-diclorofenil)-4-hidroxi-6-metilpiridin-2(1H)-ona

1039

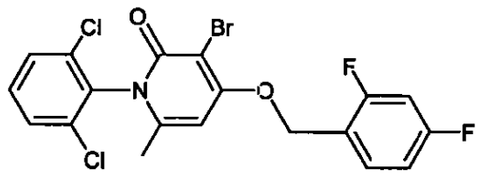


Este compuesto se preparo mediante el procedimiento descrito en la Etapa 2 para el Ejemplo 364 Rendimiento 78%, $^1$H NMR (400 MHz) $CD_3OD$ δ 7,61 (m, 2H), 7,49 (m, 1H), 6,2 (s, 1H), y 1,91 (s, 3H), ES-MS, m/z = 348 ($MH^+$)

Etapa 3

Este compuesto se preparó mediante el procedimiento descrito en la Etapa 3 para el Ejemplo 364 Rendimiento 44%, $^1$H NMR ($CD_3OD$) δ 7,62 (d, 2H, J = 8,0 Hz), 7,51 (m, 3H), 7,15 (m, 2H), 6,64 (s, 1H), 5,33 (s, 2H), y 2,0 (s, 3H), $^{19}$F NMR ($CD_3OD$) δ -166,21 (m), ES-HRMS m/z 455,9541(M+H $C_{19}H_{14}NO_2Cl_2BrF$, requiere 455,9564)

Ejemplo 369

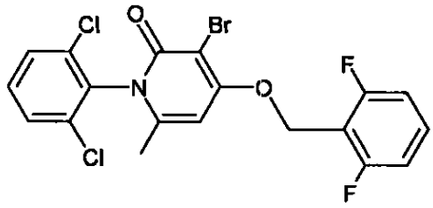


3-Bromo-1-(2,6-diclorofenil)-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona

El compuesto se preparó mediante un procedimiento similar al descrito para el Ejemplo 368 Rendimiento 64%, $^1$H NMR ($CD_3OD$/400 MHz δ7,62 (m,3H), 7,48 (m, 1H)7,05 (m, 2H), 6,70 (s, 1H), 5,36 (s, 2H), y 2,02 (s, 3H), $^{19}$F NMR ($CD_3OD$) δ -111,43 (m) y -115,89 (m), ES-HRMS m/z 473,9450 (M+H $C_{19}H_{13}NO_2Cl_2BrF_2$, requiere 473,9469)

Ejemplo 370

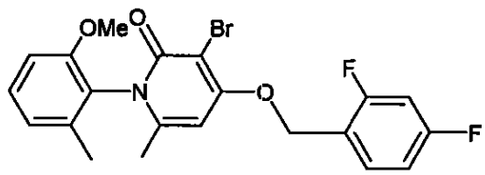
1040



3-Bromo-1-(2,6-ciclorofenil)-4-[(2,6-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona

Este compuesto se preparo mediante un procedimiento similar al descrito para el Ejemplo 368 Rendimiento 78%, $^1$H NMR ($CD_3OD$/400 MHz) δ 7,62 (d, 2H, J = 8,0 Hz) 7,52 (m, 2H), 7,1 (m, 2H), 6,77 (s, 1H), y 2,04 (s, 3H), $^{19}$F NMR ($CD_3OD$) δ -117,04 (m), ES-HRMS m/z 473,9468 (M+H $C_{19}H_{13}NO_2Cl_2BrF_2$, requiere 473,9469)

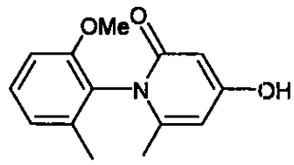
Ejemplo 371



3-Bromo-4-[(2,4-difluorobencil)oxi]-1-(2-metoxi-6-metilfenil)-6-metilpiridin-2(1*H*)-ona

Etapa 1

Preparacion de 4-hidroxi-1-(2-metoxi-6-metilfenil)-6-metilpiridin-2(1H)-ora

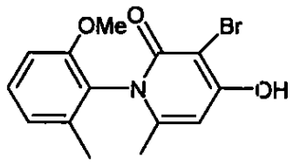


Este compuesto se preparo mediante un procedimiento similar al descrito en la Etapa 1 para el Ejemplo 368 Rendimiento 21%, $^1$H NMR ($CD_3OD$/400 MHz) δ 7,31 (m, 1H), 6,94 (m, 2H), 6,05 (d, 1H, J = 2,4 Hz), 5,78 (d, 1H, J = 2,4 Hz), 3,76 (s, 3H), 2,00 (s, 3H), y 1,83 (s, 3H), ES-HRMS m/z 246,1092 (M+H $C_{14}H_{16}NO_3$, requiere 246,1123)

1041

Etapa 2

Preparación de 3-bromo-4-hidroxi-1-(2-metoxi-6-metilfenil)-6-metilpiridin-2(1H)-ona

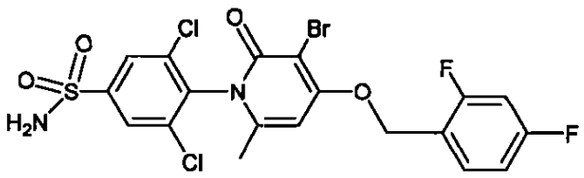



Este compuesto se preparo mediante un procedimiento similar al descrito en la Etapa 2 para el Ejemplo 368 Rendimiento 58%, $^1$H NMR ($CD_3OD$/400 MHz) δ 7,34 (m, 1H), 6,96 m (2H), 6,15 (s, 1H), 3,76 (s, 3H), 1,99 (s, 3H), y 1,83 (s, 3H), ES MS m/z 324 (M+H)

Etapa 3

Este compuesto se preparo mediante un procedimiento similar al descrito para el Ejemplo 368 Rendimiento 60%, $^1$H NMR ($CD_3OD$/400 MHz) δ 7,63 (m, 1H), 7,36 (m, 1H), 7,01 (m, 4H), 6,61 (s, 1H), 5,33 (s, 2H), 3,76 (s, 3H), 1,99(s, 3H), y 1,95 (s, 3H), $^{19}$F NMR ($CD_3OD$/400 MHz) δ-111,64 (m), y -116,03 (m), ES-HRMS m/z 450,0532 (M+H $C_{21}H_{19}NO_3Cl_2BrF_2$, requiere 450,0511)

Ejemplo 372

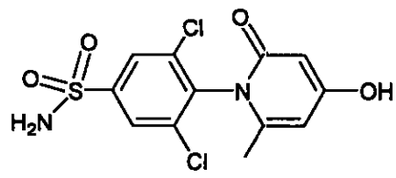



4-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-3,5-diclorobencenosulfonamida

Etapa 1

Preparacion de 3,5-dicloro-4-(4-hidroxi-6-metil-2-oxopiridin-1(2H)-il)bencenosulfonamida

1042



Se calento una mezcla de 4-hidroxi-6-metilpirona (1,2 g, 0,0095 mol), y 2,6-diclorosulfanilamida (2,4 g, 0,0099 mol) hasta 170 °C bajo argon durante 20 min Se enfrió el fundido de color oscuro resultante y el material en crudo se purifico por primera vez mediante cromatografia rapida (EtOAc) para proporcionar un material parcialmente purificado que contenía el producto deseado Éste se purificó mas mediante HPLC de fase inversa utilizando $CH_3CN$/Agua al 10 - 90% (gradiente de 30 min) a un caudal de 100 mL/min Se combinaron las fracciones adecuadas (m/z = 349) y se deshidrataron por congelación para proporcionar 0,19 g de 3,5-dicloro-4-(4-hidroxi-6-metil-2-oxopiridin-1(2H)-il)benzenosulfcnamida como un solido amarillo pálido $^1H$ NMR ($CD_3OD$/400 MHz) ) δ 8,06 (s, 2H), 6,13 (d, 1H, J = 1,6 Hz), 5,78 (d, 1H, J = 1,6 Hz), y 1,94 (s, 3H)), ES-HRMS m/z 348,9819 (M+H $C_{12}H_{11}N_2O_4SCl_2$ requiere 348,9811)

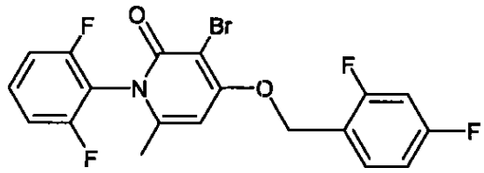
Etapa 2

Se agito una mezcla de 3,5-dicloro-4-(4-hidroxi-6-metil-2-oxopiridin-1(2H)-il)benzenosulfonamida (0,18 g, 0,0005 mol), N-bromosuccinimida (0,1 g, 0,00056 mol) en acido acético (2,0 mL) a temperatura ambiente bajo atmósfera de argon durante 1 hora Se eliminó el ácido acético in vacuo, el residuo se disolvió en DMF (2 0 mL), y se agrego bromuro de 2,4 difluorobencilo (0,128 g, 0,0006 mol), carbonato de potasio (0,1 g, 0,0007 mol) La mezcla resultante se agito a temperatura ambiente durante 1 hora Los disolventes se destilaron in vacuo, y el residuo se purificó mediante cromatografia rapida (EtOAc/ hexano 1 3 vol/vol) para proporcionar 0,14 g de producto parcialmente

1043

purificado Este se purifico mediante HPLC de fase inversa utilizando $CH_3CN$/Agua al 10-90% (30 min en gradiente) a un caudal de 100 mL/min Las fracciones apropiadas (m/z = 553) se combinaron y se deshidrataron por congelacion para producir 0,045 g de polvo amarillo pálido Este se dividio en EtOAc (25 ml) y bicarbonato de sodio al 5% La fase organica se lavo con agua, se seco ($Na_2SO_4$), y se concentro bajo presión reducida Este material se seco in vacuo para proporcionar el compuesto del titulo (0,033 g) como una sustancia blanca amorfa $^1H$ NMR ($CDCl_3$/400 MHz) ) δ 7 99 (s, 2H), 7,59 (m, 1H), 6,98 (m, 1H), 6,85 (m, 1H), 6,23 (s, 1H), 5,69 (s, 2H), 5,28 (s, 2H), 1,97 (s, 3H), y 1,76 (br, 2H), ES-HRMS m/z 552,7214 (M+H $C_{19}H_{14}BrCl_2N_2O_4S$ requiere 552,9197)

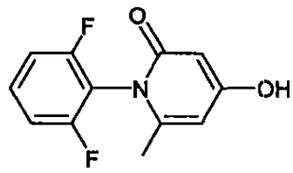
Ejemplo 373




3-Bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorofenil)-6-metilpiridin-2(1*H*)-ona

Etapa 1

Preparacion de 1-(2,6-difluorofenil)-4-hidroxi-6-metilpiridin-2(1H)-ona



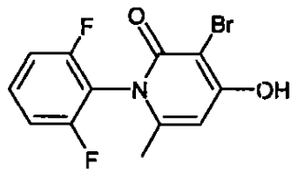

Se calento una mezcla de 4-hidroxi-6-metil-2-pirona (10,0 g, 0,079 mol) y 2,6 difluoroanilina (9,5 g, 0,073 mol) a 170 °C bajo atmósfera de argon durante 20 min Se elimino el agua que se formo utilizando un aparato Dean-Stark Se enfrió el fundido, se trituro el sólido oscuro

1044

con EtOAc, y se filtro Este material se lavo minuciosamente con EtOAc para proporcionar el producto deseado 1-(2,6-difluorofenil)-4-hidroxi-6-metilpiridin-2(1H)-ona 6,5 g (al 35%) como un solido marrón claro $^1$H NMR ($CD_3OD$/400 MHz) δ 7,56 (m, 1H), 7,19 (m, 2H), 6,09 (m, 1H ), 5,77 (d, 1H, J = 2,4 Hz), y 1,99 (s, 3H), ES-HRMS m/z 238,0679 (M+H $C_{12}H_{10}NO_2F_2$ requiere 238,0674)

Etapa 2

Preparacion de 3-bromo-1-(2,6-difluorofenil)-4-hidroxi-6-metilpiridin-2(1H)-ona

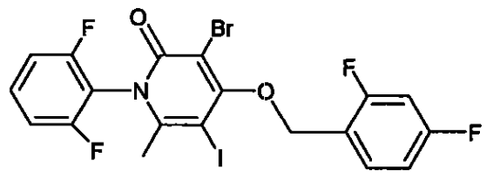



El compuesto del titulo se preparo mediante el procedimiento descrito en la Etapa 2 para el Ejemplo 364 Rendimiento 79%, $^1$H NMR ($CD_3OD$/400 MHz) δ 7,58 (m, 1H), 7,21 (m, 2H), 6,19 (d, 1H, J = 0,8 Hz), 1,99 (s, 3H), ES-HRMS m/z 315,9811 (M+H $C_{12}H_9NO_2F_2Br$ requiere 315,9779)

Etapa 3

Este compuesto se preparó mediante el procedimiento descrito en la Etapa 3 para el Ejemplo 364 Rendimiento 63%, $^1$H NMR ($CD_3OD$) δ 7,58 (m, 2H), 7,23 (m, 2H), 7,06 (m, 2H), 6,68 (s, 1H), 5,36 (s, 2H), y 2,10 (s, 3H), $^{19}$F NMR ($CD_3OD$) δ −111,50 (m), -115,96(m), y −121,93 (m), ES-HRMS m/z 442,0061 (M+H $C_{19}H_{13}NO_2F_4Br$ requiere 442,0060)

Ejemplo 374

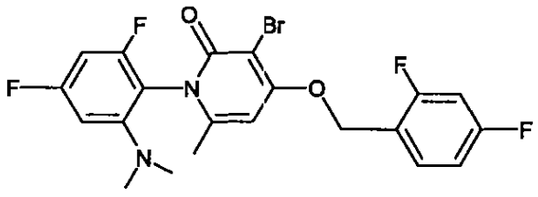


1045

3-Bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorofenil)-5-yodo-6-metilpiridin-2(1*H*)-ona

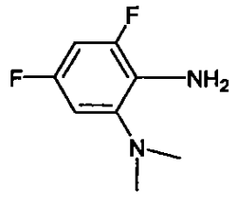
Se calento a reflujo una disolucion de 3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorofenil)-6-metilpiridin-2(1H)- ona (0,3 g, 0,00098 mmol) y N-yodosuccinimida (0,22 g, 0,00098 mmol) en dicloroetano que contenia ácido dicloroacetico (0,01 mL) durante 6 horas bajo atmosfera de argón Despues de eliminar los disolventes bajo presion reducida, se dividio el residuo en diclorometano (20 mL) y sulfito de sodio al 5% (10 mL) La fase organica se lavo con agua, se seco ($Na_2SO_4$), y se concentró bajo presión reducida El residuo se purifico mediante cromatografia rapida (EtOAc al 25% en hexano) para producir el compuestc del titulo (0,125 g, al 32 %) como un polvo amarillo palido $^1$H NMR ($CDCl_3$/400 MHz) δ 7,68 (m, 1H), 7,46 (m, 1H), 7,11 (m, 2H), 6,95 (m, 1H), 6,85 (m, 1H), 5,23 (s, 2H), y 2,38 (s, 3H), $^{19}$F NMR ($CDCl_3$) δ -109,15 (m), -112,95 (m), -118,50 (m), ES-HRMS m/z 567,9014 (M+H $C_{19}H_{12}NO_2F_4BrI$ requiere 567,9027)

Ejemplo 375




3-Bromo-4-[(2,4-difluorobencil)oxi]-1-[2-(dimetilamino)-4,6-difluorofenil]-6-metilpiridin-2(1*H*)-ona

Etapa 1

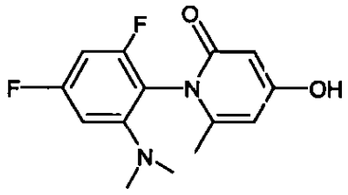


1046

3,5-difluoro-N~1~,N~1~-dimetilbenceno-1,2-diamina

A una disolución de 2,4,6-trifluoronitrobenceno (2,58 g, 0,0145 mol) en THF (20,0 ml) se agregó una disolución de N,N-dimetilamina en THF (8,5 mL de sol 2M) y se agito durante 45 min a 0 °C Luego, se agito a temperatura ambiente durante 30 min y se concentró hasta alcanzar la sequedad El material resultante se disolvio en EtOH (25 mL), se agrego Pd/C (al 10%, 0,6 g) y se hidrogeno a 50 libras por pulgada cuadrada durante 4 hs El catalizador se elimino mediante filtracion, y se concentro el filtrado hasta alcanzar la sequedad bajo presion reducida El residuo se dividió en bicarbonato de sodio (al 10%, 25 mL) y EtOAc (30 mL) La fase organica se lavó con agua, se secó ($Na_2SO_4$) y se concentró hasta alcanzar la sequedad para producir el compuesto del titulo (1,3 g, al 50%) como sólido de color oscuro $^1$H NMR ($CDCl_3$/400 MHz) δ 6,52 (m, 2H), 3,64 (br, 2H), y 2,65 (s, 6H), ES-HRMS m/z 172,0772 (M+ $C_8H_{10}N_2F_2$ requiere 172,0810)

Etapa 2




1-[2-(dimetilamino)-4,6-difluorofenil]-4-hidroxi-6-metilpiridin-2(1H)-ona

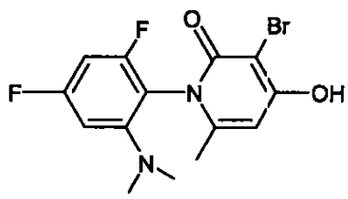
Se calento una mezcla estrecha de 4-hidroxi-6-metil-2-pirona (1,3 gr, 0,0103 mol), y 3,5- difluoro-N,N-dimentilbenceno-1,2-diamina (1,4 gr, 0,008 mol) a 160 °C en atmosfera de argon durante 15 minutos La mezcla de reaccion de color oscuro se enfrio, se trituro con EtOAc (15 ml), y se filtro Los solidos se lavaron con EtOAc caliente, luego con hexano y se secaron para proporcionar

46
1047

el compuesto del título como un sólido azul claro (0,4 gr, 14%) Se preparó una muestra analíticamente pura mediante purificación por HPLC de fase inversa utilizando $CH_3CN$/agua al 10-90% (en gradiente de 30 minutos) a un caudal de 100 mL/min Las fracciones apropiadas se combinaron y se deshidrataron por congelación para dar el compuesto del título $^1H$ NMR ($CD_3OD$/400 MHz) δ6,61 (m, 2H), 6,08 (d, 1H, J = 2,0 Hz), 6,78 (d, 1H, J = 2,0 Hz), 2,69 (s, 6H), y 1,94 (s, 3H), ES-HRMS m/z 281,1084 (M+H $C_{14}H_{15}N_2O_2F_2$ requiere 281,1096)

Etapa 2

Preparación de




3-bromo-1-[2-(dimetilamino)-4,6-difluorofenil]-4-hidroxi-6-metilpiridin-2(1H)-ona

El compuesto del título se preparó mediante el procedimiento que se describe en la Etapa 2 del EJEMPLO 364 Rendimiento 71%, $^1H$ NMR ($CD_3OD$/400 MHz) δ6,62 (m, 2H), 6,17 (s, 1H), 2,67 (s, 6H), y 1,94 (s, 3H), ES-HRMS m/z 359,0188 (M+H $C_{14}H_{14}N_2O_2F_2Br$ requiere 359,0201)

Etapa 3

Este compuesto se preparó mediante el procedimiento descrito en la Etapa 3 para el EJEMPLO 364

Rendimiento 34%, $^1H$ NMR ($CDCl_3$/400 MHz) δ7,62 (m, 1H), 6,98 (m, 1H), 6,85 (m, 1H), 6,46 (m, 2H), 6,11(s, 1H), 5,24 (s, 2H), 2,66 (s, 6H), y 1,98 (s, 3H), $^{19}F$ NMR ($CDCl_3$/400 MHz) δ -103,06 (m), -109,60 (m), - 115,02 (m), y

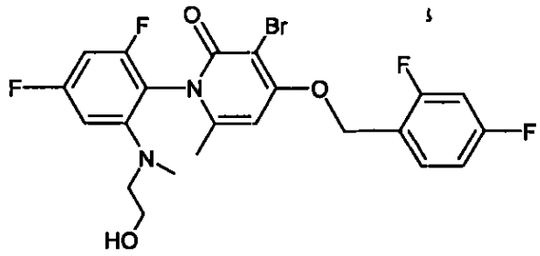
1048

-116,01 (m), ES-HRMS m/z 485,0451 (M+H $C_{21}H_{18}N_2O_2F_4Br$ requiere 485,0482)

El compuesto del título se preparó agitando una suspensión del producto de la Etapa 3, precedente, (0,14 g) con 4N HCl en dioxano (0,7 mL) a temperatura ambiente durante 30 min La mezcla se concentró hasta lograr la sequedad $^1H$ NMR ($CD_3OD$/400 MHz) δ7,62 (m, 1H), 7,02 (m, 2H), 6,65 (m, 3H), 5,34 (s, 2H), 2,66 (s, 6H), y 2,05 (s, 3H), ESMS m/z = 485

1049

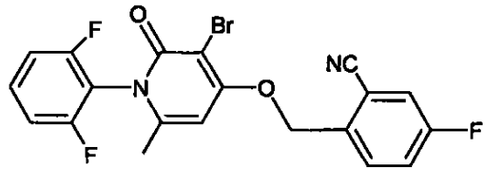
Ejemplo 376



3-Bromo-4-[(2,4-difluorobencil)oxi]-1-{2,4-difluoro-6-[(2-hidroxietil)(metil)amino]fenil}-6-metilpiridin-2(1H)-ona

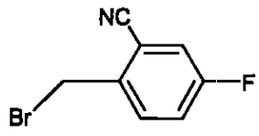
El compuesto se preparo mediante un procedimiento similar al descrito para el EJEMPLO 375, reemplazando el grupo N,N-dimetilo por N-Metil-aminoetanol $^1$H NMR ($CDCl_3$/400 MHz)δ 7,59 (m, 1H), 6,98 (m, 1H), 6,85 (m, 1H), 6,61(m, 1H), 6,52 (m, 1H), 6,17 (m, 1H), 5,25 (s, 2H), 3,63 (m, 1H), 3,53 (m, 1H), 3,26 (m, 1H), 3,0 (m, 1H), 2,66 (s, 6H), y 2,09 (s, 3H), ES-HRMS m/z 515,0512 (M+H $C_{22}H_{20}N_2O_3F_4Br$ requiere 515,0588)

Ejemplo 377



2-({[3-bromo-1-(2,6-difluorofenil)-6-metil-2-oxo-1,2-dihidropiridin-4-il]oxi}methil)-5- fluorobenzonitrilo

Etapa 1



2-(Bromometil)-5-fluorobenzonitrilo

Se calento a reflujo durante 6 horas una mezcla de 5-fluoro-2-metilbenzonitrilo (2,0 g, 0,015 mol), NBS (N-

1050

bromosuccinimida) (3,2 g, 0,018 mol) y benzoilperoxido (0,25 g) en tetracloruro de carbono (25,0 ml)

bajo atmósfera de argon La mezcla de la reacción se enfrió y se filtro El filtrado se concentró bajo presion reducida, y el residuo se purificó por cromatografia rápida (5% EtOAc en hexano) para proporcionar 2-(bromometil)-5-fluorobenzonitrilo

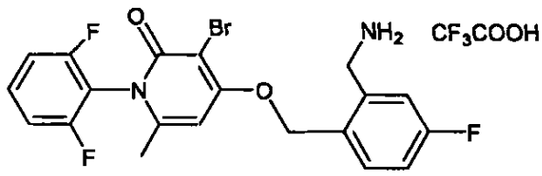
(1,9 g, 60%) como un líquido incoloro $^1$H NMR ($CDCl_3$/400 MHz) δ7,59 (m) 7,58 (m, 1H), 7,38 (m, 1H) y 7,25 (m, 1H)

Etapa 2

Una mezcla de 3-bromo-1-[2,6-(difluorofenil)-4-hidroxi-6-metilpiridin-2(1H)-ona(1,0 g, 0,0032 mol), carbonato de potasio (0,65 g, 0,0047 mol) y 2-(Bromometil) 5-fluorobenzonitrilo (0,95 g, 0,0045 mol) en dimetilacetamida (15,0 ml) se agito a temperatura ambiente en atmosfera de argon Despues de 1 hora, se destilo dimetilacetamida en el vacio y el residuo se dividió entre diclorometano (50 ml) y acido citrico 55 (15 mL) La fase organica se lavó con agua, se seco ($Na_2SO_4$), y se concentro hasta lograr la sequedad El material resultante se trituró con EtOAc, se filtro, se lavo con EtOAc y se seco para proporcionar el compuesto del titulo (0,86 g, 60%) como un polvo blanco $^1$H NMR ($CDCl_3$/400 MHz) δ7,95 (m, 1H), 7,81 (m, 1H), 7,68 (m, 1H), 7,37 (m, 2H), 6,79(s, 1H), 5,45 (s, 2H), y 2,03 (s, 3H), $^{19}$F- NMR (DMSO-$d_6$) δ -111,31 (m), -120,34 (m), ES-HRMS m/z 449,0094 (M+H $C_{20}H_{13}N_2O_2F_3Br$ requiere 449,0107)

Ejemplo 378

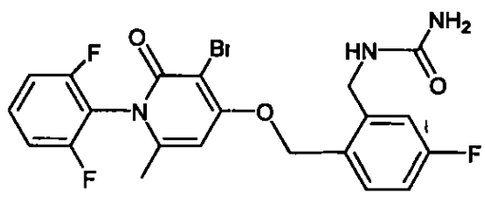
1051



trifluoroacetato 4-{[2-(aminometil)-4-fluorobencil]oxi}-3-bromo-1-(2,6-difluorofenil)-6-metilpiridin-2(1H)-ona

A una suspension fria de 2-({[3-bromo-1-(2,6-difluorofenil)-6-metil-2-oxo-1,2-dihidropiridin-4-il]oxi}metil)-5-fluorobenzonitrilo (0,3 g, 0,00066 mol) en tetrahidrofurano (THF) (3,0 mL), se agregó $BH_3$ THF (1,0 mL) Despues de agitar a temperatura ambiente durante 15 min, la mezcla de reaccion se calento a reflujo durante 30 min en atmósfera de argón La disolucion transparente resultante se dejo enfriar, se le agregó MeOH (2,0 mL), se concentro bajo presion reducida y el residuo se purificó mediante purificación por HPLC de fase inversa utilizando $CH_3CN$/agua al 10 -90% (gradiente de 30 min) a un caudal de 100 mL/min Las fracciones apropiadas (m/z= 453 M+H) se combinaron y se congelaron y deshidrataron en el vacio para producir el compuesto del titulo (0,16 g, 43%) como su sal de trifluoroacetato $^1$H NMR (DMSO-$d_6$/400 MHz) δ8,19 (br, 3H), 7,65 (m, 2H), 7,37 (m, 4H), 6,78 (s, 1H), 5,42 (s, 2H), 4,21 (br, 2H), y 2,04 (s, 3H), $^{19}$F- NMR (DMSO-$d_6$/400 MHz) δ -112,96(m), y -120,41 (m), ES-HRMS m/z 453,0387 (M+H $C_{20}H_{17}N_2O_3F_3Br$ requiere 453,0420)

Ejemplo 379



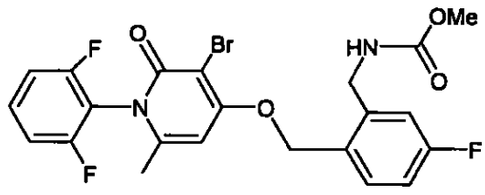
1052

N-[2-({[3-bromo-1-(2,6-difluorofenil)-6-metil-2-oxo-1,2-dihidropiridin-4-il]oxi}metil)-5- fluorobencil]urea

A una suspension de trifluoroacetato 4-{[2-(aminometil)-4-fluorobencil]oxi}-3-bromo-1-(2,6-difluorofenil)-6-metilpiridin-2(1H)-ona (0,13g, 0,00023 mol) en THF (3,0 mL), se agrego trietil amina (0,07 mL, 0,0005 mol) seguido por el agregado de trimetilsililisocianato ( 0,066 mL) La mezcla de reacción se agitó a temperatura ambiente durante 1 hora, y el producto deseado se aislo mediante purificacion por HPLC de fase inversa utilizando $CH_3CN$/agua al 10-90% (gradiente de 30 min) a un caudal de

100 mL/min Las fracciones apropiadas (m/z= 496 M+H) se combinaron y se deshidrataron por congelación, y el residuo se dividió entre bicarbonato de sodio al 5% (20 mL) y diclorometano (20 mL) La fase organica se lavo con agua, se seco ($Na_2SO_4$) y se concentro hasta lograr la sequedad bajo presion reducida, para producir el compuesto del titulo como un polvo blanco amorfo (0,065 g) $^1H$ NMR (DMSO-$d_6$/400 MHz) δ7,62 (m, 1H), 7,52 (m, 1H), 7,35 (m, 2H), 7,09 (m, 2H), 6,77(s, 1H), 6,51 (t, 1H), 5,61 (s, 2H), 5,38 (s 2H), 4,28 (d, 2H, J= 6,0 Hz), y 2,02 (s, 3H), $^{19}F$ NMR (DMSO-$d_6$/400 MHz) δ -114,044 (m), y -120,31 (m), ES-HRMS m/z 496,0460 (M+H $C_{21}H_{18}N_3O_3F_3Br$ requiere 496,0478)

Ejemplo 380

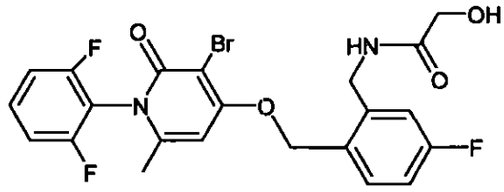


1053

Metil 2-({[3-bromo-1-(2,6-difluorofenyl)-6-metil-2-oxo-1,2-dihidropiridin-4-il]oxi}metil)-5-fluorobencilcarbamato

A una disolucion de trifluoroacetato 4-{[2-(aminometil)-4-fluorobencil]oxi}-3-bromo-1-(2,6-difluorofenil)-6-metilpiridin-2(1H)-ona (0,12g, 0,00021 mol) en dimetilacetamida (2,0 mL) a 0°C, se agregó trietilamina (0,06 mL, 0,00043 mol) seguido por el agregado de metilcloroformato ( 0,05 mL) La mezcla de reaccion se agitó a temperatura ambiente durante 30 min en atmosfera de argon La dimetilacetamida se destiló in vacuo y el residuo se dividió entre diclorometano (10 mL) y 5% acido citrico (10 mL) La fase orgánica se lavo con agua, se seco ($Na_2SO_4$), y se concentro hasta lograr la sequedad El residuo resultante se purifico mediante cromatografia rápida (60%EtOAc en hexano) para producir el compuesto del titulo (0,09 g, 75%) como un polvo amorfo blanco $^1H$ NMR (DMSO-$d_6$/400 MHz) δ7,68 (m, 1H), 7,62 (m, 1H), 7,59 (m, 1H), 7,38 (m, 2H), 7,115 (m, 2H), 6,78 (s, 1H), 5,38 (s 2H), 4,31 (d, 2H, J= 6,0 Hz), 3,53 (s, 3H), y 2,03 (s, 3H), $^{19}F$ NMR (DMSO-$d_6$/400 MHz) δ -113,77 (m), y -120,33 (m), ES-HRMS m/z 511,0508 (M+H $C_{22}H_{19}N_2O_4F_3Br$ requiere 511,0475)

Ejemplo 381




N-[2-({[3-bromo-1-(2,6-difluorofenil)-6-metil-2-oxo-1,2-dihidropiridin-4-il]oxi}metil)-5-fluorobencil]-2-hidroxiacetamida

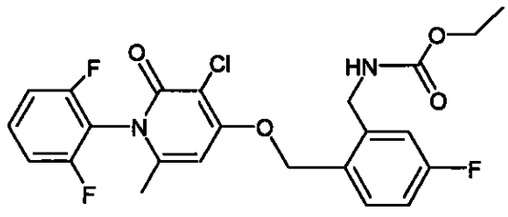
A una suspensión de trifluoroacetato 4-{[2-(aminometil)-4-fluorobencil]oxi}-3-bromo-1-(2,6-

1054

difluorofenil)-6-metilpiridin-2(1H)-ona (0,12g, 00021 mol) en

THF (2,0 mL) a 5 °C, se agrego trietil amina (0,036 g, 0,00035 mol) seguido del agregado de cloruro de acetoxiacetilo (0,05 mL) La mezcla se agitó a temperatura ambiente durante 30 min, se diluyó con agua fria (10 mL), y se extrajeron los productos con diclorometano (2 x 10 mL) Los extractos orgánicos combinados se lavaron con agua, se secaron ($Na_2SO_4$), / se concentraron hasta lograr la sequedad El residuo se disolvio en etanol (0,5 mL), se agrego 1 N NaOH (0,5 mL) y se agito a temperatura ambiente durante 1 hora La disolución resultante se diluyó con agua (15 mL), y se extrajo con diclorometano (2 x 10 mL) Los extractos de diclorometano combinados se lavaron con agua, se secaron ($Na_2SO_4$), y se concentraron hasta lograr la sequedad El residuo se purifico mediante cromatografia rapida (MeOH al 1% en EtOAc) para producir el compuesto del titulo (0,032 g, 30 %) como un polvo amorfo blanco $^1H$ NMR ($CDCl_3$/400 Hz) δ7,45(m, 2H), 7,18 (m, 1H), 7,05 (m, 3H), 6,23 (s, 1H), 5,24 (s, 2H), 4,56 (d, 2H, J = 6,4 Hz), 4,08 (d, 2H, J = 5 2 Hz), 2,79 (t, 1H), and 2,08 (s, 3H,) $^{19}F$ NMR ($CDCl_3$/400 MHz)δ -111,88(m), y -118,62 (m), ES-HRMS m/z 511,0482 (M+H $C_{22}H_{19}N_2O_4F_3Br$ requiere 511,0475)

Ejemplo 382

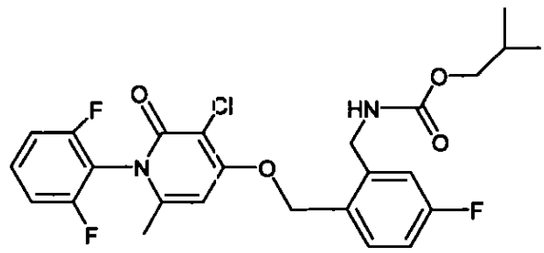



Etil 2-({[3-cloro-1-(2,6-difluorofenil)-6-metil-2-oxo-1,2-dihidropiridin-4-il]oxi}metil)-5-fluorobencilcarbamato

1055

A la disolución de trifluoracetato 4-{[2-(aminometil)-4-fluorobencil]oxi}-3-cloro-1-(2,6-difluorofenil)-6- metilpiridin-2(1H)-ona (0,3 g, 0,00057 mol) en dimetilacetamida (3,0 mL) se le agrego N-metimorfolina (0,064 g, 0,00064 mol), seguido del agregado de etilcloroformato (0,06 mL) y se agito a -10 °C, durante 30 min Los disolventes se destilaron in vacuo y el residuo se purificó mediante purificacion por HPLC de fase inversa utilizando $CH_3CN$/agua al 10 -90% (gradiente de 30 min) a un caudal de 100 mL/min Las fracciones apropiadas (m/z=481 M+H) se combinaron y se deshidrataron por congelacion, y el residuo se dividio entre bicarbonato de sodio al 5% (20 mL) y diclorometano (20 mL) La fase orgánica se lavó con agua, se seco ($Na_2SO_4$) y se concentro hasta lograr la sequedad bajo presion reducida, para producir el compuesto del titulo como un polvo blanco amorfo (0,15 g, 55%) $^1H$ NMR ($CD_3OD$/400MHz) δ7,61 (m, 1H), 7,52 (m, 1H), 7,26 ~t, 2H, J = 8,4 Hz), 7,12 (dd, 1H), 7,05 (3d, 1H, J = 2,4 Hz), 6,74 (s, 1H), 5,40 (s, 2H), 4,42 (s, 2H), 4,05 (q, 2H, J = 7,2 Hz), 2,12 (s, 3H), y 1,21 (t, 3H, J = 7,2 Hz ), ES-HRMS m/z 481,1118 (M+H $C_{23}H_{21}N_2O_4F_3Cl$ requiere 481,1136)

Ejemplo 383

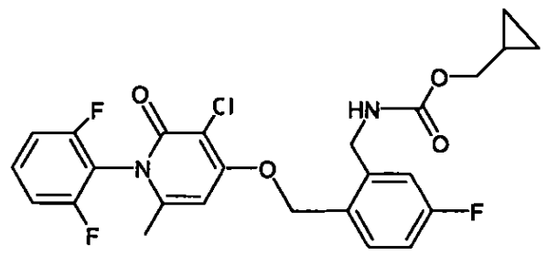



2-({[3-cloro-1-(2,6-difluorofenil)-6-metil-2-oxo-1,2-dihidropiridin-4-il]oxi}metil)-5-fluorobencilcarbamato de isobutilo

1056

El compuesto del título se preparo mediante un procedimiento similar al que se describe para el EJEMPLO 382 Rendimiento 57%, $^1$H NMR ($CD_3OD$/400 MHz) δ7,61 (m, 1H), 7,51 (m, 1H), 7,24 (~t, 2H, J = 8,0 Hz), 7,18 (m, 1H), 7,06 (m, 1H), 6,74 (s, 1H), 5,40 (s, 2H), 4,21 (s, 2H), 3,79 (d 2H, J = 6,8 Hz), 2,12 (s, 3H), 1,85 (m, 1H), y 0,91 (d, 6H, J = 6,4 Hz), ES-HRMS m/z 509,1422 (M+H $C_{25}H_{25}N_2O_4F_3Cl$ requiere 509,1449)

Ejemplo 384

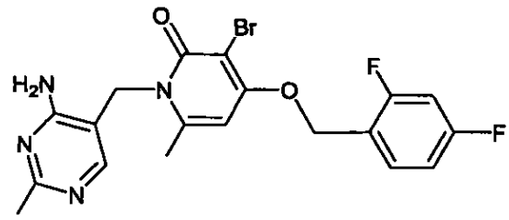


Ciclopropilmetil 2-({[3-cloro-1-(2,6-difluorofenil)-6-metil-2-oxo-1,2-dihidropiridin-4-il]oxi}metil)-5-fluorobencilcarbamato de ciclopropilmetilo

El compuesto del título se preparó mediante un procedimiento similar al que se describe para el EJEMPLO 382 Rendimiento 46%, $^1$H NMR ($CD_3OD$/400 Hz) δ7,61 (m, 1H), 7,55 (m, 1H), 7,24 (~t, 2H, J = 7,6 Hz), 7,18 (m, 1H), 7,05 (m, 1H), 6,73 (s, 1H), 5,40 (s, 2H), 4,42 (s, 2H), 3,83 (d 2H, J = 7,2 Hz), 2,12 (s, 3H), 1,1 (m, 1H), 0,58 (~d, 2H), y 0,22 (~ d, 2H), ES-HRMS m/z 507,1316 (M+H $C_{25}H_{23}N_2O_4F_3Cl$ requiere 507,1293)

Ejemplo 385

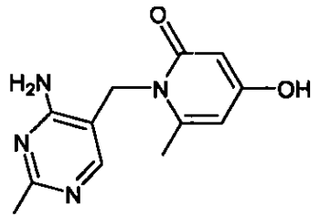
1057



$CF_3COOH$

Trifluoroacetato 1-[(4-amino-2-metilpirimidin-5-il)metil]-3-bromo-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona

Etapa 1



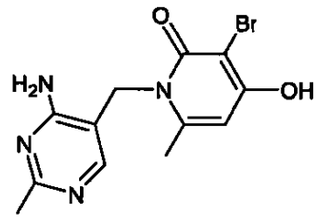
1-[(4-amino 2-metilpirimidin-5-il)metil]-4-hidroxi-6-metilpiridin-2(1H)-ona

Una mezcla de 4 hidroxi-6-metil-2-pirona (0,9 g, 0,007 mol) y 4-amino-5-aminometil-2-metilpirimidina (1,0 g, 0,007 mol) en agua (10,0 ml) se mezclo a 100 °C durante 1 hora en atmosfera de argon La mezcla de la reaccion se enfrió y se filtró el precipitado amarillo Se lavó sucesivamente con agua fria, etanol y se seco in vacuo para proporcionar el compuesto del titulo (1,01 g, 51%) como un polvo amarillo pálido $^1H$ NMR (DMSO-$d_6$/400 MHz) δ7,62 (s, 1H), 7,04 (s, 1H), 5,83 (d, 1H, J = 2,0 Hz), 5,58 (d, 1H, J = 2,0 Hz), 4,92 (s, 2H), 2,24 (s, 3H), y 2,22 (s, 3H), ES-HRMS m/z 325,0304 (M+H $C_{12}H_{14}N_4O_2Br$ requiere 325,0295)

Etapa 2

1058

1058



1-[(4-amino-2-metilpirimidin-5-il)metil]-3-bromo-4-hidroxi-6-metilpiridin-2(1H)-ona

Una mezcla de 1-[(4-amino-2-metilpirimidin-5-il)metil]-4-hidroxi-5-metilpiridin-2(1H)-ona (0,5 g, 0,002 mol), y NBS (0,4 g, 0,002 mol) en acido acetico glacial (5,0 ml) se agito a temperatura ambiente durante 1 hora en atmósfera de argon El acido acetico se elimino in vacuo, el residuo se trituro con EtOAc que contenia 10% de EtOH, y se filtró El precipitado amarillo palido se lavó con EtOAc que contenia EtOH al 10% y se seco in vacuo para producir el compuesto del título (0,47 g, 725) como un polvo amarillo palido

$^1$H NMR ((CD$_3$OD/400 MHz) δ7,62 (s, 1H), 6,09 (s, 1H), 5,15 (s, 2H), 2,42 (s, 3H) y 2,33 (s, 3H) ES-HRMS m/z 247,1160 (M+H $C_{12}H_{15}N_4O_2$ requiere 247,1190)

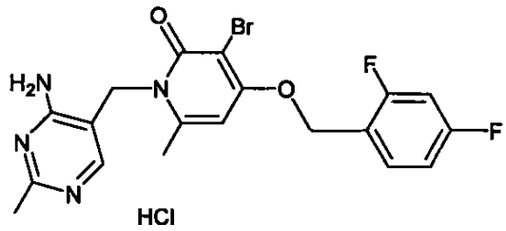
Etapa 3

A la suspensión de 1-[(4-amino-2-metilpirimidin-5-il)metil]-3-bromo-4-hidroxi-6-metilpiridin-2(1H)-ona (1,0 g, 0,0031 mol) y carbonato de potasio (0,0 g, 0004 mol) en dimetilacetamida (10,0 mL) se agregó bromuro de 2,4 difluorobencilo (0,62 mL, 0,0048 mol) y se agito a temperatura ambiente durante 2 horas La dimetilacetamida se destiló in vacuo y el residuo se purifico mediante HPLC de fase inversa utilizando $CH_3CN$/agua al 10-90% (gradiente de 30 min) a un caudal de 100 mL/min Las fracciones apropiadas (m/z = 566) se combinaron y se deshidrataron por congelacion para producir 0,65 g (37 %) del compuesto del titulo como su sal de trifluoroacetato $^1$H NMR (CD$_3$OD/400

1059

MHz) δ7,65 (s, 1H), 7,58 (m, 1H), 7,05 (m, 2H), 6,61 (s, 1H), 5,31 (s, 2H), 5,18 (s, 2H), 2,51 (s 3H) y 2,46 (s, 3H), $^1$H NMR ($CD_3OD$/400 MHz)δ -111,39(m ) y -115,98(m), ES-HRMS m/z 451,0590 (M+H $C_{19}H_{18}N_4O_2BrF_2$ requiere 451,0576)

Ejemplo 386

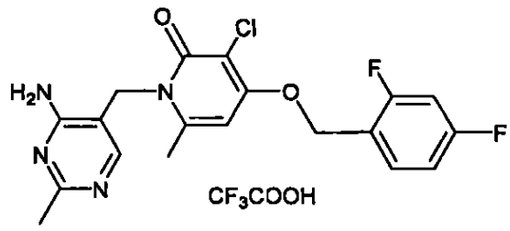



Hidrocloruro de 1-[(4-amino-2-metilpirimidin-5-il)metil]-3-bromo-4-|(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona

La resina BioRad AG 2X8 de intercambio iónico (en forma de cloruro de 200-400 mallas) se lavó con 1M HCl (150 mL), y se dejo equilibrar durante 2,5 hrs Esta resina se cargó sobre una columna, y se agrego la disolución del Ejemplo 385 (3,3 g, 5,8 mmol) en agua/$CH_3CN$ (1 1) La columna se eluyo lentamente durante mas de 1 hora, se recogieron las fracciones y se deshidrataron por congelacion para proporcionar la sal HCl deseada (2,2 g, 72%) como un sólido blanco $^1$H-NMR ($CD_3OD$, 400Hz) δ 7,60 (m, 2H), 7,21 (m, 2H), 6,62 (s, 1H), 5,31 (s, 2H), 5,18 (s, 2H), 2,52 (s, 3H), 2,47 (s,3H), ES-HRMS m/z 451,0544/453,0577 (M+H $C_{19}H_{17}N_4O_2F_2Br$ requiere 451,0581/453,0563)

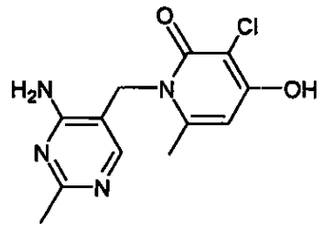
Ejemplo 387

1060



trifluoroacetato 1-[(4-amino-2-metilpirimidin-5-il)metil]-3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona

Etapa 1 Preparacion de 1-[(4-amino-2-metilpirimidin-5-il)metil]-3-cloro-4-hidroxi-6-metilpiridin-2(1H)-ona



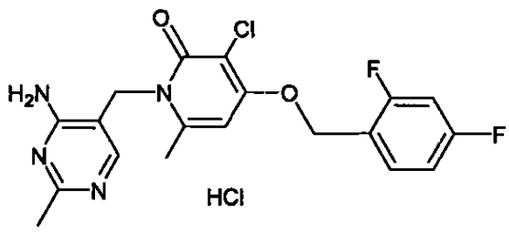
$^1$H NMR ($CD_3OD$,400Hz)δ 7,62 (m, 1H), 6,11 (s, 1H), 5,13 (s, 2H), 2,66 (s, 3H) y 2,42 (s, 3H), ES-HRMS m/z 281,0793 (M+H $C_{12}H_{13}N_4O_2Cl$ requiere 281,0800)

Etapa 2 Preparación de trifluoroacetato de 1-[(4-amino-2-metilpirimidin-5-il)metil]-3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona

El compuesto del titulo se preparo mediante un procedimiento similar al que se describe para el Ejemplo 385 Etapa 2 $^1$H NMR ($CD_3OD$, 400Hz) δ 7,59 (m, 2H), 7,03 (m, 2H), 6,63 (s, 1H), 5,31 (s, 2H), 5,17 (s, 2H), 2,48 (s, 3H), 2,46 (s, 3H), ES-HRMS m/z 407,1097 (M+H $C_{19}H_{17}N_4O_2ClF_2$ requiere 407 1081)

Ejemplo 388

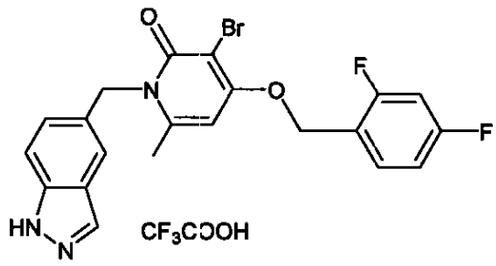
1061




hidrocloruro 1-[(4-amino-2-metilpirimidin-5-il)metil]-3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona

La resina BioRad AG 2X8 (12,5 g)de intercambio ionico (en forma de cloruro de 200-400 mallas) se lavo con 1M HCl (150 mL), y se dejo equilibrar durante 2,5 hrs Esta resina se cargo sobre una columna, y se agrego la disolucion del Ejemplo 387 (1,2 g, 2,4 mmol) en agua/$CH_3CN$ (1 1) La columna se eluyó lentamente durante mas de 1 hora, se recogieron las fracciones y se deshidrataron por congelacion para proporcionar la sal de HCl deseada (1,03 g, 97%) como un solido blanco $^1$H-NMR ($CD_3OD$, 400Hz) δ 7,60 (m, 2H), 7,04 (m, 2H), 6,64 (s, 1H), 5,31 (s, 2H), 5,17 (s, 2H), 2,50 (s, 3H), 2,47 (s,3H), ES-HRMS m/z 407,1079(M+H $C_{19}H_{17}N_4O_2ClF_2$ requiere 407,1081)

Ejemplo 389

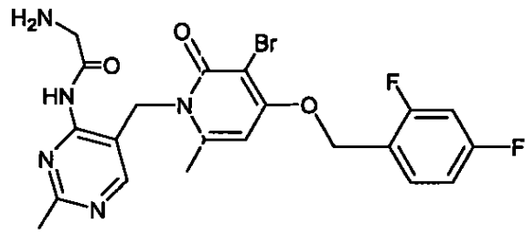



Trifluoroaceto 3-bromo-4-[(2,4-difluorobencil)oxi]-1-(1H-indazol-5-ilmetil)-6-metilpiridin-2(1H)-ona

1062

A una mezcla de 3-bromo-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona (0,55 g, 0,0017 mol) y 5-(bromometil)-1-tetrahidro-2H-piran-2-il-1H-indazol (0,5 g, 0,0017 mol) en THF (10,0 mL) se agregó NaH (0,045 g, 0,0019 mol) y se calento a 60 °C durante 16 hs en atmosfera de argón El THF se destilo bajo presión reducida, y el residuo se suspendio en EtOAc, se agregó acido acetico (0,5 mL) y el producto se purificó mediante cromatografia rapida (EtOAc al 80% en hexano) Las fracciones apropiadades se combinaron y se concentraron para producir una sustancia amorfa (0,31 g) Esto se agitó con trifluoroacético (0,5 mL) durante 30 min, la disolución se diluyo con acetonitrilo (5 mL) y el producto se aislo mediante HPLC de fase inversa utilizando $CH_3CN$/agua al 10-90% (gradiente de 30 min) a un caudal de 100 mL/min Las fracciones apropiadas (m/z = 460) se combinaron y se deshidrataron por congelacion para producir 0,14 g (52%) del compuesto del título como su sal de trifluoroacetato $^1H$ NMR ($CD_3OD$/400 MHz) δ7,97 (s, 1H), 7,62 (m, 1H), 7,51 (m, 1H), 7,45 (s, 1H), 7,25 (m, 1H), 7,03 (t, 2H), 6,49 (s 1H), 5,53 (s, 2H), 5,29 (s, 2H), y 2,40 (s,3H), $^{19}F$ NMR ($CD_3OD$/400 MHz)δ -111,69 (m ), -116 09 (m), ES-HRMS m/z 460,0432 (M+H $C_{21}H_{17}N_3O_2BrF_2$ requiere 460,0467)

Ejemplo 390



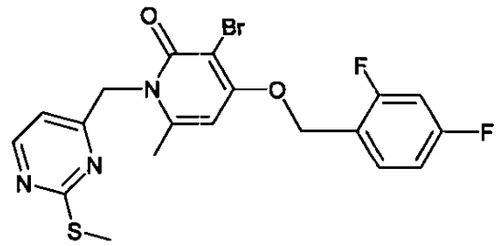

Trifluoroacetato N~1~-(5-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}-2-metilpirimidin-4-il)glicinamida

1063

A una disolucion de BOC-Gly-OH (0,19 g, 0,0011 mol) en DMF (dimetilformamida) (2,0 mL) se agrego N-metilmorfolina (0,14 mL, 0,0011 mol), seguido del agregado de cloroformato de isobutilo (0,15 mL, 0,0011 mol) y se agitó a -10 °C durante 15 min Despues se agregó una disolucion de trifluoroacetato 1- [(4-amino-2-metilpirimidin-5-il)metil]-3-bromo-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona (0/125 g, 0,00022 mol) en DMF (2,0 mL) que contenia diisopropiletilamina (0,1 g, 0,006 mL) y la mezcla resultante se agito durante 16 hs, a temperatura ambiente Los disolventes se destilaron in vacuo y el residuo se purificó mediante HPLC de fase inversa utilizando $CH_3CN$/agua al 10-90% (gradiente de 30 min) a un caudal de 100 mL/min Las fracciones apropiadas (m/z = 608/610) se combinaron y se deshidrataron por congelación para producir 0,025 g (37 %) de polvo blanco Esto se agito con acido trifluoroacetico (0,5 mL) durante 1 hora y el producto se aisló por HPLC de fase inversa utilizando $CH_3CN$/agua al 10-90% (gradiente de 30 min) a un caudal de 100 mL/min Las fracciones apropiadas (m/z = 508/510) se combinaron y se deshidrataron por congelacion para producir el compuesto del titulo (0,02 g) como un polvo blanco $^1H$ NMR ($CD_3OD$/400 MHz) δ8,18 (s, 1H), 7,61 (m, 1H), 7,02 (m, 2H), 6,59 (s, 1H), 5,30 (s, 4H), 4,23 (s, 2H), 2,60 (s 3H) y 2,47 (s, 3H), ES-HRMS m/z 508,0797 (M+H $C_{21}H_{21}N_5O_3BrF_2$ requiere 508,0790)

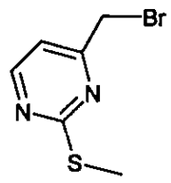
Ejemplo 391

1064



3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-{[2-(metiltio)pirimidin-4-il]metil}piridin-2(1H)-ona

Etapa 1



4-(bromometil)-2-(metiltio)pirimidina

A una disolucior de 4-metil-2-metiltiopirimidina (12,6 g, 0,09 mol) en acido acetico (50,0 mL) se agregó bromo (5,5 mL, 0,11 mol) y se calento a 80 °C bajo atmosfera de argon durante 2 hs El ácido acetico se destilo in vacuo, el residuo se tritu·o con diclorometano (100,0 mL) y se vertio en una disolución de bicarbonato de sodio saturado (200,0 mL) Se agreço diclorometano adicional (100,0 ml) y se agito durante 15 min La fase orgánica se lavo con agua (3 x 100 mL), se seco ($Na_2SO_4$), y se concentro bajo presion reducida El residuo oscuro se purifico mediante cromatografia rapida (EtOAc/hexano 1 4 vol/vol) para producir 4-(bromometil)-2-(metiltio)pirimidina (10,9 g, 55%) como un liquido de color oscuro $^1H$ NMR ($CDCl_3$/400 MHz) δ 8,50 (d, 1H, J = 4,8 Hz), 7,09 (d, 1H, J = 4,8 Hz), 4,34 (s, 2H), y 2,56 (s, 3H), ESMS m/z 219 (M+H)

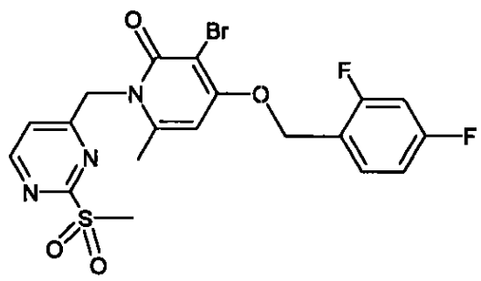
Etapa 2

A una mezcla de 3-bromo-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona (5,0 g, 0,015 mol) y 4-(bromometil)-2-(metiltio)pirimidina (4,0 g, 0,018 mol) en THF (50,0 mL)

1065

se agregó NaH (0,4 g, 0,0017) y se agito a 55 °C en argon durante 16 hs La mezcla de reaccion se concentro bajo presion reducida y el residuo se dividio entre ácido cítrico al 5% (25 mL) y EtOAc (50 mL) Se formo un precipitado, el cual se filtro, se lavo con agua, EtOAc, y se seco in vacuo para proporcionar el compuesto del titulo (4,2 g, 59 %) como un polvo color marron claro, $^1$H NMR ($CD_3OD$/400 MHz) δ 8,45 (d, 1H, J = 5,2 Hz), 7,6 (m, 1H), 7,06 (d sobre m, 2H, J = 5,2 Hz), 6,54 (s, 1H), 5,39 (s, 2H), 5,32 (s, 2H), 2,43 (s, 3H), ES-HRMS m/z 468,0173 (M+H $C_{19}H_{17}N_3O_2BrSF_2$ requiere 468,0187)

Ejemplo 392



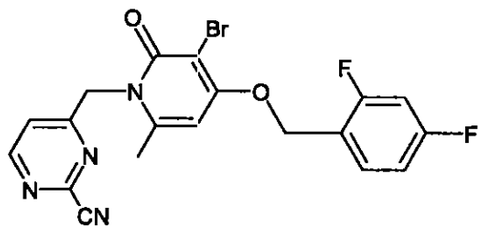
3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-{[2-(metilsulfonil)pirimidin-4-il]metil}piridin-2(1H)-ona

Una suspensión de 3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-{[2-(metiltio)pirimidin-4-il]metil}piridin-2(1H)-ona (0,28 g, 0,0006mol), y hexahidrato de monoperoxiftalato de magnesio (90,6 g, 0,0012 mol) en acetonitrilo (8,0 ml) y agua (2,0 ml) se agitó a temperatura ambiente durante 16 hs La disolucion transparente resultante se concentro bajo presión reducida, y el residuo se dividió entre diclorometano (30 mL) y agua (20 mL) La fase orgánica se lavo con agua, se seco ($Na_2SO_4$) y se concentro para producir el compuesto del titulo (0,27 g, 90%) como una sustancia color amarillo pálido $^1$H NMR ($CD_3OD$/400 MHz)δ

1066

8,91 (d, 1H, J= 5,2 Hz), 7,63 (d sobre m, 2H, J= 5,2 Hz), 7,03 (m, 2H), 6,58 (s, 1H), 5,54 (s, 2H), 5,33 (s, 2H), 3,28 (s, 3H) y 2,49 (s, 3H), $^{19}F$ NMR ($CD_3OD$/400 MHz) δ-111,58 (m ), -115,98(m), ES-HRMS m/z 500,0113 (M+H $C_{19}H_{17}N_3O_4BrF_2$ requiere 500,0086)

Ejemplo 393




$CF_3COOH$

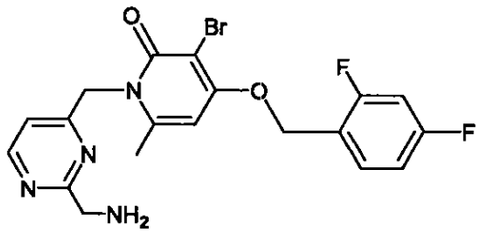
Trifluoroacetato 4-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}pirimidina-2-carbonitrilo

Una mezcla de 3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-{[2-(metilsulfonil)pirimidin-4-il]metil}piridin-2(1H)-ona (1,0 g, 0,C02 mol) y NaCN (0,15 g, 0,0031 mol) en DMF (5,0 mL) se ag to a temperatura ambiente durante 2 horas bajo atmosfera de argón Se destilo DMF in vacuo, el residuo se trituro con acetonitrilo (10 mL) y agua (10 mL), y se filtro el precipitado de color rojo Se lavo con acetonitrilo y se ›eco para producir el compuesto del titulo (0,26 g) Los lavados y el filtrado se combinaron y se purificaron mediante HPLC de fase inversa utilizando acetonitrilo/agua al 10 -90% (gradiente de 30 min) a un caudal de 100 mL/min para proporcionar 0,5 g adicionales del compuesto del titulo $^1H$ NMR ($CD_3OD$/400 MHz) δ8,83 (d, 1H, J= 5,2 Hz), 7,6› (d sobre m, 2H, J= 5,2 Hz), 7,00 (m, 2H), 6,58 (s, 1H), 5,46 (s, 2H), 5,33 (s, 2H), y 2,47 (s,

1067

3H), $^{19}F$ NMR ($CD_3OD$/400 MHz) δ-111,64(m ), -116,03(m), ES-HRMS m/z 447,0278 (M+H $C_{19}H_{14}N_4O_2BrF_2$ requiere 447,0263)

Ejemplo 394



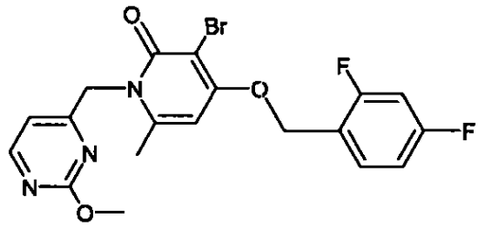

$CF_3COOH$

trifluoroacetatc 4-{[2-(aminometil)-4-fluorobencil]oxi}-3-bromo-1-(2,6-difluorofenil)-6-metilpiridin-2(1H)-ora

A una disolucion de trifluoroacetato 4-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}pirimidina-2-carbonitrilo (0,3 g, 0,00066 mol) en una mezcla de disolvente de EtOAc (15,0 mL) y ácido acetico (5,0 mL), se agregc Pd/C (10%, 0,18 g) y se agito en atmosfera de hidrogeno a 15 libras por pulgada cuadrada (lppc) durante 2 hs El catalizador se elimino por filtracion El fi'trado se concentro hasta lograr la sequedad y el residuo se purifico mediante HPLC de fase inversa utilizando $CH_3CN$/agua al 10-90% (gradiente de 30 min) a un caudal de 100 mL/min Las fracciones apropiadas (m/z = 451) se combinaron y se deshidrataron por congelación para producir (0,32 g, 645) del compuesto del titulo como su sal de trifluoroacetato $^1H$ NMR (DMSO-$d_6$/400 mHz) δ 8,78 (d, 1H, J = 5,2 Hz), 8,28 (br, 2H), 7,62 (m, 1H), 7,38 (m, 1H), 7,25 (d, 1H, J = 5,2 Hz), 7,18 (m 1H), 6,62 (s, 1H), 5,32 (s, 2H), 5,29 (s, 2H), 4,24 (s, 2H), y 2,46 (s, 3H) $^{19}F$ NMR (DMSO-$d_6$/400 MHz)δ -109,59(m), -113,67 (m), ES-HRMS m/z 451,0530 (M+H $C_{19}H_{18}N_4O_2BrF_2$ requiere 451,0576)

Ejemplo 395

1068



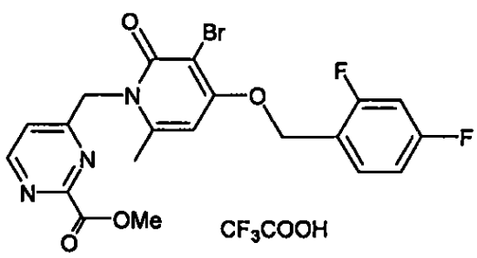
$CF_3COOH$

Trifluoroaceto 3-bromo-4-[(2,4-difluorobencil)oxi]-1-[(2-metoxipirimidin-4-il)metil]-6 metilpiridin-2(1H)-ona

Una disolución de trifluoroacetato 4-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}pirimidina-2-carbonitrilo (0,13 g, 0,00023 mol) en MeOH (2,0 mL) se trató con 1N NaOH (0,5 mL) Despues de agitar a temperatura ambiente durante 3 hs, se calentó a 60 °C durante 3 hs adicionales y se dejo a temperatura ambiente durante la noche La disolución resultante se diluyo con acetonitrilo, y se purifico mediante HPLC de fase inversa utilizando gradiente de $CH_3CN$/agua al 10-90% (30 min) a un caudal de 100 mL/min Las fracciones apropiadas (m/z = 452) se combinaron y se deshidrataron por congelación para producir el compuesto del titulo (0,015g) como un polvo blanco $^1H$ NMR ($CD_3OD$) δ8,84(d, 1H, J = 5,2 Hz)

7,62 (d, 1H, J=5,2 Hz), 7,05 (m, 2H), 6,57 (s, 1H), 5,49 (s, 2H), 5,32 (s, 2H), 3,96 (s, 3H), y 2,49 (s, 3H), ES-HRMS m/z 452,044C(M+H $C_{19}H_{17}N_3O_3BrF_2$ requiere 452,0416)

Ejemplo 396



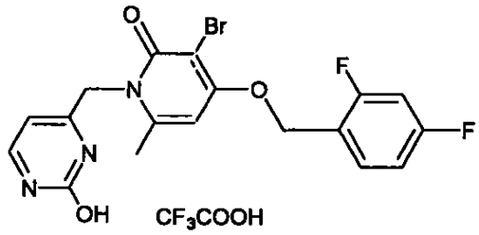
$CF_3COOH$

1069

Trifluoroacetato 4-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}pirimidina-2-carboxilato

El compuesto del titulo se obtuvo como un segundo producto en la formacion de trifluoroaceto 3-bromo-4-[(2,4-difluorobencil)oxi]-1-[(2-metoxipirimidin-4-il)metil]-6 metilpiridin-2(1H)-ona $^1$H NMR ($CD_3OD$/400 MHz) δ 8,46 (d, 1H, J = 5,2 Hz), 7,62 (m, 1H), 7,00 (m 2H), 6,93 (d, 1H, J= 5,2 Hz), 6,55 (s, 1H), 5,39 (s, 2H), 5,32 (s, 2H), 3,85 (s, 3H), y 2,44 (s, 3H), ES-HRMS m/z 480,0340 (M+H $C_{20}H_{17}N_3O_4BrSF_2$ requiere 480,0365)

Ejemplo 397




Trifluoroaceto 3-bromo-4-[(2,4-difluorobencil)oxi]-1-[(2-hidroxipirimidin-4-il)metil]-6 metilpiridin-2(1H)-ona

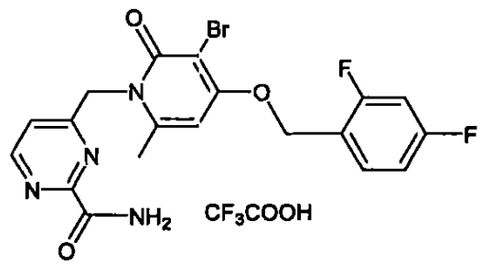
Una mezcla de trifluoroacetato 4-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}pirimidina-2-carbonitrilo (0,2 g, 0,00035 mol) fluoruro de potasio sobre óxido de aluminio (0,25 g) en t-butanol (5,0 mL) se hizo refluir durante 4 hs en atmosfera de argon La mezcla de la reacción se enfrió, se filtro el precipitado y se lavo con etanol El filtrado y los lavados combinados se concentraron hasta lograr la sequedad y el residuo se purificó mediante HPLC de fase inversa utilizando gradiente de acetonitrilo/agua al 10-90% (30 min) a un caudal de 100 mL/min Las fracciones apropiadas (m/z = 452) se combinaron y se deshidrataron por

1070

congelacion para producir el compuesto del titulo (0,05 g) como un polvo blanco

$^1$H NMR (DMSO-$d_6$/400 Mz) δ7,85 (d, 1HJ= 6,4 Hz), 7,64 (m, 1H), 7,30 (m, 1H), 7,15 (m, 1H), 6,55(s, 1H), 6,22 (d, 1H, J= 6,4 Hz), 5,28 (s, 2H), 5,12 (d, 2H) y 2,29 (s, 3 H), $^{19}$F NMR (DMSO-$d_6$/400 MHz) δ -109,69 (m), y -113,67 (m), ES-HRMS m/z 438,0228 (M+H $C_{21}H_{18}N_3O_3BrF_2$ requiere 438,0259)

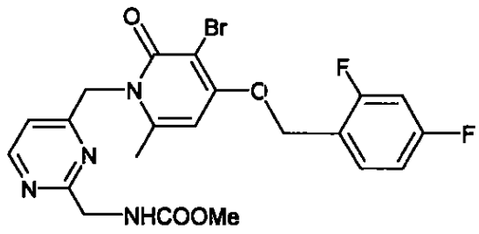
Ejemplo 398




Trifluoroacetato 4-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}pirimidina-2-carboxamida

El compuesto del titulo se obtuvo mediante un procedimiento que se describe para el Ejemplo 397 $^1$H NMR (DMSO-$d_6$/400 MHz) δ8,82 (d, 1H J=5,2 Hz), 8,01 (br, 1H), 7,79(br, 1H), 7,64(m 1H), 7,34 (m, 2H), 7,16 (m, 1H), 6,62 (s, 1H), 5,36 (s, 2H), 5,30 (s, 2H) y 2,38 (s, 3H), $^{19}$F NMR (DMSO-$d_6$/400 MHz) δ -109,64 (m), y -113,66 (m), ES-HRMS m/z 465,0385 (M+H $C_{19}H_{16}N_4O_3BrF_2$ requiere 465,0368)

Ejemplo 399

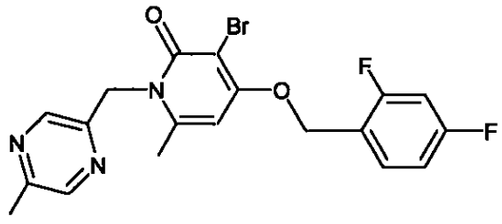


1071

4-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}pirimidin-2-il) metilcarbamato de metilo

A una disolución de trifluoroacetato de 4-{[2-(aminometil)-4-fluorobencil]oxi}-3-bromo-1-(2,6-difluorofenil)-6-metilpiridin-2(1H)-ona (0,13 g, 0,00023 mol) en dimetilacetamida (1,0 mL) a 0 °C, se agrego trietilamina (0,04 mL, 0,0003 mol) seguido por el agregado de metilcloroformato ( 0,05 mL) y se agitó a 0° C durante 30 min en atmósfera de argón La mezcla de reaccion se diluyo con agua (10 mL) y se extrajo con EtOAc (2 x 20 mL) Los extractos organicos combinados se lavaron con agua, se secaron ($Na_2SO_4$) y se concentraron hasta lograr la sequedad El residuo resultante se purifico mediante cromatografia rapida (MeOH al 5% en EtOAc) para producir el compuesto del titulo (0,055 g, 37%) como un polvo amorfo blanco $^1H$ NMR (DMSO-$d_6$/400 Mz) δ8,65 (d, 1HJ= 5,6 Hz), 7,63 (m, 1H), 7,5 (m, 1H), 7,28 (m, 1H), 7,13(s, 1H), 6,22 (d, 1H, J= 6,4 Hz), 5,28 (s, 2H), 6,59 (d, 2H) y 2,46 (s, 3 H), $^{19}F$ NMR (DMSO-$d_6$/400 MHz) δ -109,64 (m), y -113,71 (m), ES-HRMS m/z 509,0621 (M+H $C_{21}H_{20}N_4O_4BrF_2$ requiere 509,0630)

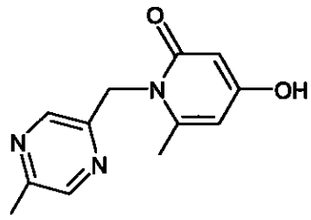
Ejemplo 400




3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-[(5-(metilpirazin-2-il)metil]piridin-2(1H)-ona

Etapa 1

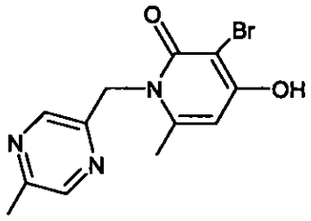
1072



4-hıdroxı-6-metıl-1-[(5-metılpırazın-2-ıl)metıl]pırıdın-2(1H)-ona

Una mezcla de 4 hıdroxı-6-metıl-2-pırona (5,0 g, 0,04 mol) y 5-amıno-5-amınometıl-2-metılpırazına (5,0 g, 0,041 mol) en agua (25,0 ml) se mezcló a 100 °C durante 1 hora en atmosfera de argon La mezcla de la reaccıon se enfrıo y se fıltró el precıpıtado amarıllo Se lavó con etanol y se secó ın vacuo para proporcıonar el compuesto del tıtulo (5,8 g, 63%) como un polvo amarıllo palıdo $^1$H NMR (DMSO-$d_6$/400 MHz) δ 10,43(br, 1H), 8,38 (d, 2H, J = 5,2 Hz), 5,77 (d, 1H, J = 2,0 Hz), 5,58 (d, 1H, J = 2,0 Hz), 4,92 (s, 2H), 2,24 (s, 3H), y 2,22 (s, 3H), ESMS m/z 232 (M+H)

Etapa 2



3-bromo-4-hıdroxı-6-metıl-1-[(5-metılpırazın-2-ıl)metıl]pırıdın-2(1H)-ona

El compuesto del tıtulo se preparó medıante el procedımıento descrıto en la Etapa 2 para el EJEMPLO 385

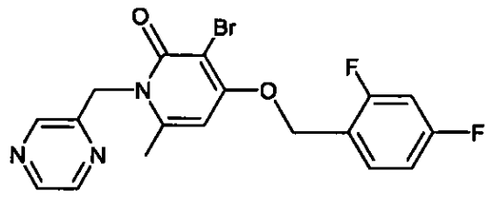
Rendımıento 64%, $^1$H NMR ((CD$_3$OD/400 MHz) δ 8,47 (s, 1H), 8,42 (s, 1H), 6,07 (s, 1H), 5,38 (s, 2H), 2,51 (s, 3H) y 2,44 (s, 3H), ESMS m/z 310 y 312 (M+H)

1073

Etapa 3

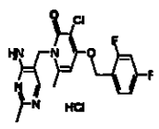
A una mezcla de 3-bromo-4-hıdroxı-6-metıl-1-[(5-metılpırazın-2-ıl)metıl]pırıdın-2(1H)-ona (0,45 g, 0,0015 mol), y carbonato de potasıo (0,25g, 0,0018 mol) en dımetılacetamıda (5,0 mL) se agrego bromuro de 2,4 dıfluorobencılo (0,25 mL) 0,0019 mol) y se agıto a temperatura ambiente en argon durante 1 hora La dımetılacetamıda se destıllo ın vacuo y el resıduo se dıvıdıo entre $CH_2Cl_2$ (20 mL) y agua (20 mL) La fase organıca se lavo con agua, se seco ($Na_2SO_4$), y se concentró bajo presión reducida El materıal resultante se purıfıco mediante cromatografía rápida (EtOAc/hexano 4 1 vol/vol) como el eluyente Las fracciones apropıadas (m/z=451/453) se combınaron y concentraron bajo presión reducıda para proporcıonar un solıdo (0,25 g, 38% ) blanco $^1$H NMR ($CD_3OD$/400 MHz) δ 8,49 (s, 1H), 8,40 (s, 1H), 7,60 (m, 1H), 6,99 (m, 2H), 6,51 (s, 1H), 5,42 (s, 2H), 5,29 (s 2H), 2,54 (s, 3H) y 2,50 (s, 3H), $^{19}$F NMR ($CD_3OD$/400 MHz) -δ117,70(m ), y -1_6,09(m), ES-HRMS m/z 436,0439 (M+H $C_{19}H_{17}N_3O_2BrF_2$ requıere 436,0467)

Ejemplo 401




3-bromo-4-[(2,4-dıfluorobencıl)oxı]-6-metıl-1-(pırazın-2-ılmetıl)pırıdın-2(1H)-ona

Etapa 1



1074

2-Clorometilpirazina

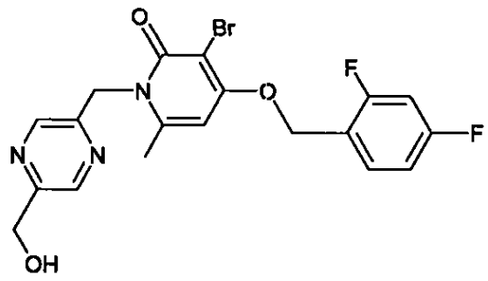
Una mezcla de 2-metilpirazina (3,5 g, 0,037 mol), NCS (N-clorosuccinimida) (6,3 g, 0,047 mol) y peroxido de benzoilo (0,05 g) se calento hasta reflujo durante 16 hs bajo atmosfera de argón Se filtro y el filtrado se concentro hasta lograr la sequedad El residuo resultante se purificó mediante cromatografia rápida utilizando EtOAc al 30% en hexano para proporconar 2-clorometilpirazina como un liquido de color oscuro (1,7 g,365) $^{1}H$ NMR ($CD_3OD$/400 MHz) δ 8,75 (d, 1H, J = 1,2 Hz), 8,58 (m, 1H, 8,56 (m, 1H) y 4,75 (s, 2H), ESMS m/z =129 (M+H)

Etapa 2

3-bromo-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona (1,8 g, 0,0055 mol) y 2-cloropirazina (0,8 g, 0,00625) se suspendieron en THF (25 mL), despues se agregó NaH (0,15 g, 0,0062 mol), KI (0,1 g) y la mezcla se calento a 65 °C en atmosfera de argon durante 16 hs La mezcla de reaccion se enfrio, se agregó ácido acetico (0,5 mL) y se concentró hasta lograr la sequedad bajo presion reducida El residuo se agito con una mezcla de agua (50 mL) y EtOAc (25 mL) y se filtró el precipitado Se lavo con agua y acetonitrilo y se secó in vacuo para proporcionar 1,7 g de polvo marron claro $^{1}H$ NMR ($CD_3OD$/400 MHz) δ 8,65 (d, 1H), 8,49 (m, 1H), 8,47 9m, 1H), 7,61 (~ q, 1H), 7,02 (m, 2H), 6,52 (s, 1H), 5,47 (s, 2H), 5,23 (s, 2H), y 2,53 (s, 3H), $^{19}F$ NMR ($CD_3OD$/400 MHz) δ -111,72 (m), y -115,07 (m), ES-HRMS m/z 422,0283 (M+H $C_{18}H_{15}N_3O_2BrF_2$ requiere 422,0310)

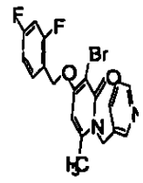
Ejemplo 402

1075



3-bromo-4-[(2,4-difluorobencil)oxi]-1-{[5-(hidroximetil)pirazin-2-il]metil}-6- metilpiridin-2(1H)-ona

Etapa 1



5-metilpirazina-2-carboxilato de etilo

Una disolución de acido 5-metilpirazina-2-carboxilico (15,0 g, 0,109 mol) en etanol (70,0 mL) que contiene (1,5 g, 0,0079 mol) se calentó hasta reflujo durante 4 hs bajo atmosfera de argón La disolución de color oscuro se enfrio, se le agrego bicarbonato de sodio (1,0 g) y se concentro bajo presion reducida El residuo se dividió entre agua (50 mL) y EtOAc (100 mL) La capa organica se lavo con agua (2 x 25 mL), se seco ($Na_2SO_4$) y se concentro bajo presión reducida para proporcionar 5-metilpirazina-2-carboxilato de etilc (12,05 g, 67%) como un liquido de color naranja $^1H$ NMR ($CD_3OD$/400 MHz) δ 9,1 (d, 1H, J = 1,2 Hz), 8,62 (d, 1H, J = 1,2 Hz), 4,45 (q, 2H, J = 7,2 Hz), 2,63 (s, 3H) y 1,41 (t, 3H, J = 7,2 Hz), ESMS m/z 167 (M+H)

Etapa 2

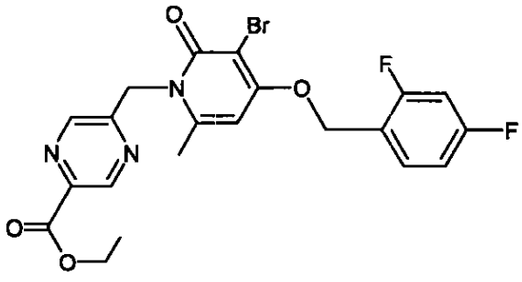
1076



5-(bromometil)pirazina-2-carboxilato de etilo

Una disolucion de 5-metilpirazina-2-carboxilato de etilo (12,0 g, 0,072 mol) en ácido acetico glacial (60 mL) que contenia bromuro (4,0 mL) se calento a 80 °C bajo condiciones anhidro durante 45 min Luego de eliminar el acido acetico in vacuo, el residuo se dividió entre bicarbonato saturado (100 mL) y EtOAc (3 x 30 mL) Los extractos de EtOAc combinados se lavaron con agua (2 x 25 mL), se secaron ($Na_2SO_4$) y se concentraron bajo presion reducida El liquido resultante se purifico mediante cromatografia rapida (EtOAc al 20% en hexano) para proporcionar (5 bromometilpirazina-2)-carboxilato de etilo (7,7 g, 44%) como un liquido de color naranja $^1H$ NMR ($CD_3OD$/400 MHz) δ 9,18 (d, 1H, J = 1,2 Hz), 8,85 (d, 1H, J = 1,2 Hz), 4,71 (q, 2H), 4,47 (q, 2H, J = 7,2 Hz), y 1,42 (t, 3H, J = 7,2 Hz), ES-HRMS m/z 244,9942 (M+H $C_8H_{10}N_2O_2Br$ requiere 244,9920)

Etapa 3



5-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}pirazina-2-carboxilato de etilo

1077

A una mezcla de 3-bromo-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona (6,0 g, 0,018 mol) y 5-(bromometil)pirazina-2-carboxilato de etilo (4,9 g, 0,02 mol) en THF (50,0 mL se agregó NaH (0,5 g) y se calento a 55 °C bajo atmosfera de argón durante 3 hs La mezcla de reaccion se enfrió, se le agrego acido acético (1,2 ml) y se concentro bajo presion reducida El residuo se trituro con agua y se filtro el solido Se lavo con agua, despues con etanol y se seco in vacuo para proporcionar el compuesto del titulo (3,0 g, 78%) como un polvo marron claro $^1$H NMR ($CD_3OD$/400 MHz) δ 9,10 (d, 1H, J= 1,2 Hz), 8,77 (d, 1H, J= 1,2 Hz), 7,61 (m, 1H), 7,01 (m, 2H), 6,54 (s, 1H), 5,54 (s 2H), 5,30 (s, 2H), 4,43 (~ t, 1H), 3,66 (m, 2H), 3,56 (t, 1H J = 6,8 Hz), 2,52 (d, 3H J = 1,39 Hz), 6,8 (s, 3H), $^{19}$F NMR ($CD_3OD$/400 MHz) δ -111,64 (m ), y -116,04 (m), ES-HRMS m/z 494,0482 (M+H $C_{21}H_{19}N_3O_4BrF_2$ requiere 494,0522)

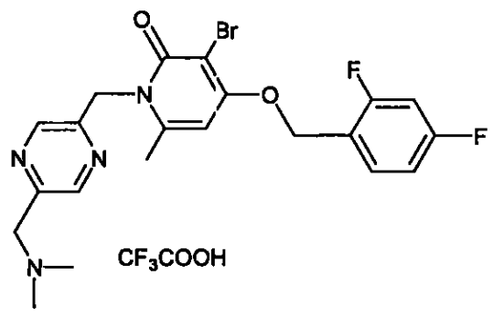
Etapa 4

A una suspensión de 5-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}pirazina-2-carboxilato de etilo (2,0 g, 0,004 mol) en t-butanol (15,0 mL y THF (5,0 mL) se agregó $NaBH_4$ (0,18 g, 0,0047 mol) y la mezcla se agito a temperatura ambiente durante 16 hs bajo atmosfera de argon Se enfrió, se agrego MeOH (5,0 mL) y acido acetico (1,0 mL) y se concentró hasta lograr la sequedad El residuo se trituro con agua y se filtro Se lavo con agua, se seco in vacuo y se purifico mediante cromatografia rapida (MeOH al 1% en EtOAc) para proporcionar el compuesto del titulo (0,75 g, 41%) como un polvo amarillo palido $^1$H NMR ($CD_3OD$/400 MHz) δ 8,58 (d, 1H, J= 1,6 Hz), 8,56 (d, 1H, J= 1,6 Hz), 7,6 (m, 1H), 7,01 (m, 2H), 6,52 (s, 1H), 5,46 (s, 2H), 5,29 (s, 2H), 4,71 (s, 2H), y 2,54 (s, 3H), $^{19}$F NMR ($CD_3OD$/400 MHz) δ

1078

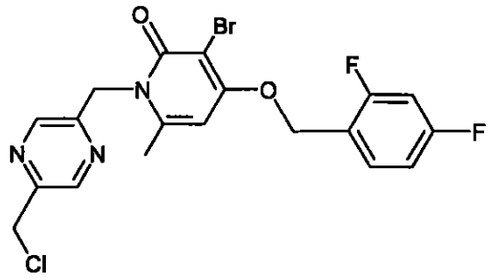
-111,70 (m), y -116,06 (m), ES-HRMS m/z 452,0394 (M+H $C_{19}H_{17}N_3O_3BrF_2$ requiere 452,0416)

Ejemplo 403




3-bromo-4-[(2,4-difluorobencil)oxi]-1-({5-[dimetilamino)metil]pirazin-2-il}metil)-6- metilpiridin-2(1H)-ona

Etapa 1




3-bromo-1-{[5-(clorometil)pirazin-2-il]metil}-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona

Se agrego cloruro de cianurilo (0,42g, 0,0023 mol) a DMF (0,52 mL) y se agito a temperatura ambiente durante 15 min Después se agrego diclorometano (15 mL) seguido por el agregado de 3-bromo-4-[(2,4-difluorobencil)oxi]-1-{[5-(hidroximetil)pirazin-2-il]metil}-6-metilpiridin-2(1H)-ona (1,0 g, 0,0022 mol) y la mezcla de reaccion se agitó a temperatura ambiente bajo atmosfera de argon Despues de 1 hora, se agrego 1,0 mL adicional de DMF (dimetilformamida) y se dejó que continuara la reaccion durante otra hora, cuando se obtuvo una disolución clara

1079

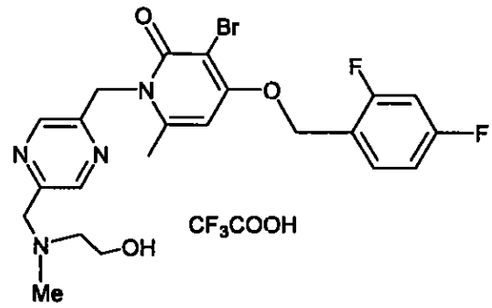
La disolucion se diluyó con diclorometano (20 mL) y se lavo con agua, se secó ($Na_2SO_4$), y se concentró hasta lograr la sequedad bajo presión reducida El residuo se trituró con EtOAc, se filtro, se lavó con EtOAc y se seco para proporcionar 0,79 g (77%) del compuesto del titulo como un polvo amarillo pálico $^1$H-NMR ($CD_3OD$, 400MHz) δ 8,66 (s, 2H), 7,73 (m, 1H), 7,05 (m, 2H), 6,56 (s, 1H), 5,52 (s, 2H), 5,33 (s, 2H), 4,74 (s, 2H) y 2,57 (s, 3H), ES-HRMS m/z 470,0051(M+H $C_{19}H_{16}N_3O_2BrClF_2$ requiere 470,0077)

Etapa 2

Una suspensión de 3-bromo-1-{[5-(clorometil)pirazin-2-il]metil)-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona (0,25 g, 0,00053 mol) en THF (1,0 mL) se trató con N,N,-dimetil amina (1,0 mL de disolucion 2M en THF) y se agitó a temperatura ambiente durante 16 hs La mezcla de reaccion se concentró y el compuesto del titulo se aislo mediante HPLC de fase inversa utilizando gradiente de acetonitrilo/agua al 10 -90% (30 min) a un caudal de 100 mL/min Las fracciones apropiadas (m/z= 479) se combinaron y deshidrataron por congelacion para proporcionar el compuesto del titulo (0,27 g, 87%) como un polvo blanco $^1$H NMR ($CD_3OD$/400 MHz) 5 8,78 (d, 1H, J Hz), 8,56 (d, 1H, J= 1,2 Hz), 7,61 (m, 1H), 7,01 (m, 2H), 6,55 (s, 1H), 5,49 (s, 2H), 5,30 (s, 2H), 4,52 (s, 2H), 2,94 (s, 6H) y 2,57 (s, 3H), $^{19}$F NMR ($CD_3OD$) = δ -111,56 (m ) y -116,02(m), ES-HRMS m/z 479,0885 (M+H $C_{21}H_{22}N_4O_2BrF_2$ requiere 479,0889)

Ejemplo 404

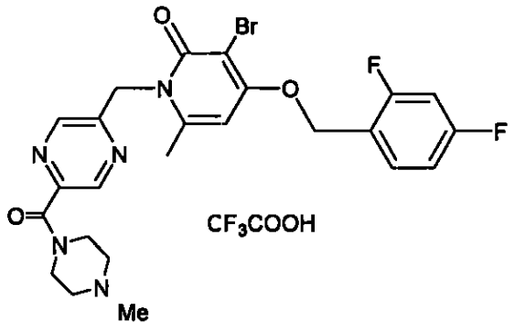
1080




Trifluoroacetato de 3-bromo-4-[(2,4-difluorobencil)oxi]-1-[(5-{[2-hidroxietil)(metil)amino]-metil}pirazin-2-il)metil]-6-metilpiridin-2(1H)-ona

El compuesto del titulo se preparo en una manera similar a la descrita para el Ejemplo 403 sustituyendo N, N-dimetilamina por N-metilaminoetanol Rendimiento = 78%, $^1$H NMR ($CD_3OD$/400 MHz) δ 8,78 (d, 1H, J Hz), 8,59 (d, 1H, J= 1,2 Hz), 7,6 (m, 1H), 7,01 (m, 2H), 6,55 (s, 1H), 5,49 (s, 2H), 5,30 (s, 2H), 3,89 (~t, 2H), 2,97 (s, 3H) y 2,57 (s, 3H), $^{19}$F NMR ($CD_3OD$/400 MHz) = δ -111,56 (m ) y -116,04(m), ES-HRMS m/z 509,0964 (M+H $C_{22}H_{24}N_4O_3BrF_2$ requiere 509,0994)

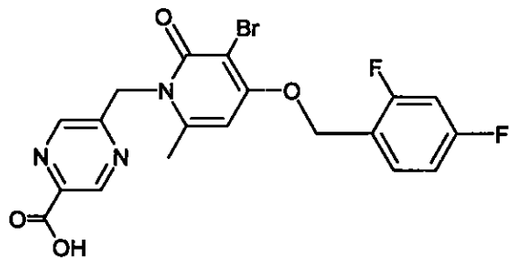
Ejemplo 405




Trifluoroacetato 3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-({5-[(4-metilpiperazin-1-il)carbonil]pirazin-2-il}metil)piridin-2(1H)-ona

Etapa 1

1081



acido 5-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}pirazina-2-carboxilico

Una suspensión de 5-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}pirazina-2-carboxilato de etilo (0,18 g, 0,002 mol) y 1N NaOH (0,6 mL en EtOH/agua 1 1 vol/vol) se agito a temperatura ambiente durante 1,5 hora La mezcla de reacción se acidifico con acido citrico al 5% y se filtro el precipitado Se lavo con agua, despues con etanol y se seco in vacuo para proporcionar el compuesto del titulo (0,14 g, 77%) como un polvo marron claro $^{1}H$ NMR ($CD_3OD$/400 MHz) = δ9,03 (s 1H), 8,60 (s, 1H), 7,61 (m 1H), 7,00 (m, 2H), 6,52 (s, 1H), 5,51 (s, 2H), 5,30 (s 2H), y 2,52 (s, 3H), $^{19}F$ NMR ($CD_3OD$/400 MHz) = δ-111,75 (m ) y -116,06 (m), ES-HRMS m/z 466,0209 (M+H $C_{19}H_{15}N_4O_3BrF_2$ requiere 466,0209)

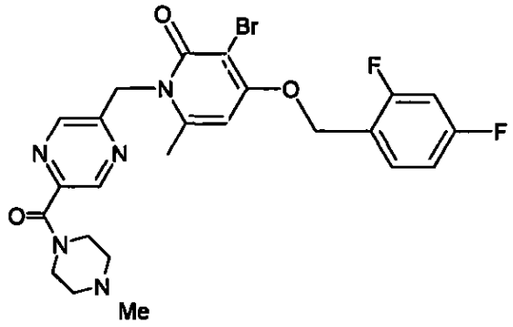
Etapa 2

A una disolución de acido 5-{[3-bromo-4-[(2,4-diflurobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}pirazina-2-carboxilico (0,28 g, 0,0006 mol) en DMF (3,0 mL), a -15 °C, se agrego cloroformato de isobutilo (0,082g, 0,0006 mol), seguido del agregado de N-metilmorfolinona (0,06 g, 0,00063 mol) y se agitó bajo argon durante 15 min Despues se agregó a la reacción N-metilpiperazina (0,072 g, 0,00072 mol) en DMF (2,0 mL) y la mezcla se agito a temperatura ambiente durante 3 hs Luego de eliminar los solventes in vacuo, el residuo se purificó mediante HPLC de fase inversa utilizando gradiente de

1082

acetonitrilo/agua al 10 -90% (30 min) a un caudal de 100 mL/min Las fracciones apropiadas (m/z = 548) se combinaron y deshidrataron por congelacion para proporcionar el compuesto del titulo (0,32 g, 80%) como un polvo blanco $^1$H NMR ($CD_3OD$/400 MHz) δ 8,89 (d 1H, J= 1,6 Hz), 8,73 (d, 1H, J= 1,6 Hz), 7,61 (m, 1H), 7,01 (m, 2H), 6,56 (s, 1H), 5,50 (s, 2H), 5,30 (s, 2H), 2,9 (s, 3H), y 2,57 (s, 3H), $^{19}$F NMR ($CD_3OD$/400 MHz) = δ 109,36(m ), y -114,91(m), ES-HRMS m/z 548,1090 (M+H $C_{24}H_{25}N_3O_3BrF_2$ requiere 548,1103)

Ejemplo 406



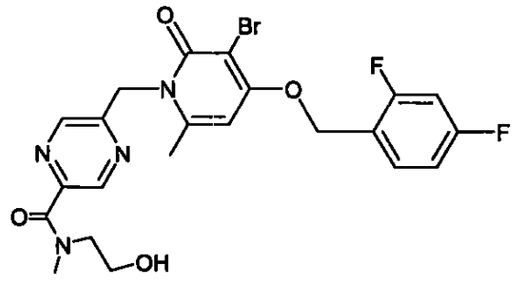

3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-({5-[(4-metilpiperazin-1-il)carbonil]pirazin-2-il}metil)piridin-2(1H)-ona

Una disolucion de trifluoroacetato de 3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-({5-[(4-metilpiperazin-1-il)carbonil]pirazin-2-il}metil)piridin-2(1H)-ona (0,17 g, 0,00026 mol) en 0,1N NaOH (25 mL) se agito a temperatura ambiente durante 15 min y se extrajo el producto en acetato de etilo (2 x 20 mL) Los extractos organicos combinados se lavaron con agua (2 x 20 mL), se secaron ($Na_2SO_4$), y se concentraron hasta lograr la sequedad El residuo se secó in vacuo para proporcionar el producto del titulo (0,09 g, 64%) como un polvo blanco $^1$H NMR ($CD_3OD$/400 MHz) δ 8,69 (d 1H, J= 1,2 Hz), 8,67 (d, 1H, J=

1083

1,2 Hz), 7,60 (m, 1H), 7,00 (m, 2H), 6,54 (s, 1H), 5,50 (s, 2H), 5,30 (s, 2H), 3 78 (t, 2H, J = 4,8 Hz), 3,58 (t, 2H, J = 4,8 Hz), 2,526 (s, 3H), 2,53 (t, 2H, J = 4,8 Hz), 2,44 (t, 2H, J = 4,8 Hz), y 2,31 (s, 3H), $^{19}F$ NMR ($CD_3OD$/400 MHz) = δ -111,65(m ), y -116,06 (m), ES-HRMS m/z 548,1123 (M+H $C_{24}H_{25}N_5O_3BrF_2$ requiere 548,1103)

Ejemplo 407

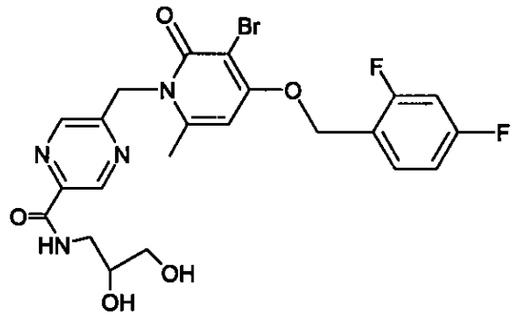



5-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}-N-(2-hidroxietil)-N-metilpirazina-2-carboxamida

El compuesto del titulo se preparó en una manera similar a la descrita para el Ejemplo 405, sustituyendo N-metilapiperazina por N, metiletanolamina Rendimiento = 60%,

$^1H$ NMR ($CD_3OD$/400 MHz)δ 8,69 (d, 1H, J= 1,2 Hz), 8,64 (d, 1H, J= 1,2 Hz), 7,61 (m, 1H), 7,00 (m, 2H), 6,54 (s, 1H), 5,49 (s 2H), 5,30 (s, 2H), 3,81 (~ t, 1H), 3,66 (m, 2H), 3,56 (t, 1H J = 5,2 Hz), 3,12 (d, 3H J = 7,6 Hz), 2,56 (s, 3H), $^{19}F$ NMR ($CD_3OD$/400 MHz) δ -109,64(m), y -113,66(m), ES-HRMS m/z 523,0743 (M+H $C_{22}H_{22}N_4O_4BrF_2$ requiere 523,0797)

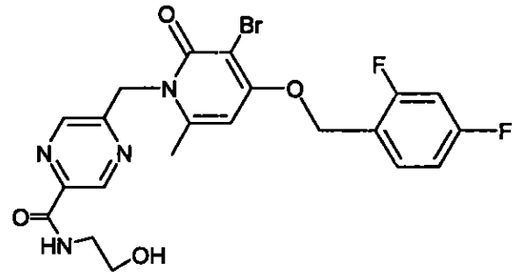
Ejemplo 408



5-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}-N-(2,3-dihidroxipropil)pirazina-2-carboxamida

El compuesto del titulo se preparo en una manera similar a la descrita para el EJEMPLO 405 sustituyendo N-metilpiperazina por 3-amino-1,2-propanodiol Rendimiento = 56% $^1$H NMR ($CD_3OD$/400 MHz)δ 9,09 (d, 1H, J= 1,2 Hz), 8,70 (d, 1H, J= 1,2 Hz), 7,60 (m, 1H), 7,00 (m, 2H), 6,54 (s, 1H), 5,53 (s 2H), 5,30 (s, 2H), 3,80 (~ t, 1H), 3,61 (m, 2H), 5,53 (t, 1H J = 5,2 Hz), 3,12 (d, 3H J = 3,42 Hz), 2,55 (s, 3H), $^{19}$F NMR ($CD_3OD$/400 MHz) δ -109,65(m), y -113,67(m), ES-HRMS m/z 539,0703 (M+H $C_{22}H_{22}N_4O_4BrF_2$ requiere 539,0736)

Ejemplo 409

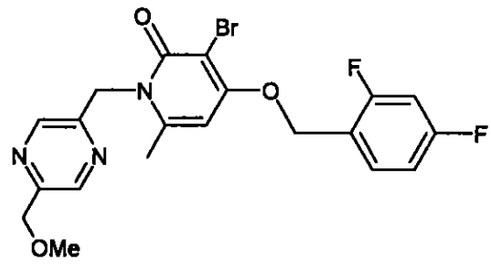


5-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}-N-(2-hidroxietil)pirazina-2-carboxamida

1085

El compuesto del titulo se preparo en una manera similar a la descrita para el EJEMPLO 405, sustituyendo N-metilpiperazina por 2-aminoetanol Rendimiento = 46%, $^1$H NMR ($CD_3OD$/400 MHz) δ 9,08 (d 1H, J = 1,2 Hz), 8,70 (d, 1H, J = 1,2 Hz), 7,601 (m, 1H), 7,01 (m, 2H), 6,54 (s, 1H), 5,53 (s 2H), 5,30 (s, 2H), 3,69 (t, 2H, J = 6,0 Hz), 3,53 (t, 2H, J = 6,0 Hz), 2,55 (s, 3H), ), $^{19}$F NMR ($CD_3OD$/400 MHz) -111,67 (m), y -116,07(m), ES-HRMS m/z 509,0616 (M+H $C_{21}H_{20}N_4O_4BrF_2$ requiere 509,0630)

Ejemplo 410




3-bromo-4-[(2,4-difluorobencil)oxi]-1-{(5-metoximetil)pirazin-2-il]-metil}-6-metilpiridin-2(1H)-ona

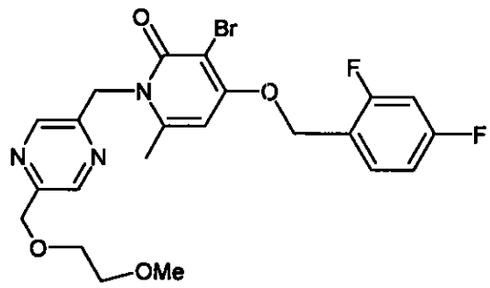
A una disolución de 3-bromo-4-[(2,4-difluorobencil)oxi]-1-{[5-(hidroximetil)pirazin-2-il]metil}-6-metilpiridin-2(1H)-ona (0,35 g, 0,00078 mol) en DMF a 0 °C, se agrego NaH (0,022 g, 0,00092 mol) y se agito durante 10 min Se agrego yodometano (0,05 mL) a la reaccion y la mezcla se agitó a 10 °C durante 3 hs Se destilo DMF in vacuc y el residuo se dividio entre acido citrico y EtOAc (15,0 mL) al 5% La fase orgánica se lavo con agua, se seco ($Na_2SO_4$), y se concentró hasta lograr la sequedad El residuo se purifico mediante cromatografía rápida (EtOAc), y las fracciones apropiadas

1086

se combinaron y se concentraron hasta lograr un polvo amarillo palido

$^1$H NMR ($CD_3OD$/400 MHz)δ 8,59 (s), 8,55 s,1H), 7,60 (m, 1H), 6,99 (m, 2H), 6,52 (s, 1H), 5,47 (s, 2H), 5,30 (s, 2H), 4,57 (s, 2H), 3,44 (s, 2H) y 2,54 (s, 3H), $^{19}$F NMR ($CD_3OD$/400 Hz) δ-111,69 (m) y -116,09(m), ES-HRMS m/z 466,0577 (M+H $C_{21}H_{19}N_3O_3BrF_2$ requiere 466,0572)

Ejemplo 411



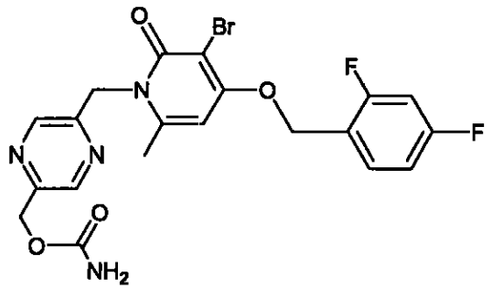

3-bromo-4-[(2,4-difluorobencil)oxi]-1-({5-[(2-metoxietoxi)metil]pirazin-2-il} metil)-6- metilpiridin-2(1H)-ona

A una disolucion de 3-bromo-4-[(2,4-difluorobencil)oxi]-1-{[5-(hidroximetil)pirazin-2-il]metil}-6- metilpiridin-2(1H)-ona (0,25 g, 0,00055 mol) en dimetil acetamida a 0 °C, se agregó NaH (0,016 g, 0,00067 mol) y se agito durante 15 min Despues se agrego bromuro de 2-metoxietilo (0,09 g, 0,0065 mol), y la mezcla se agito a temperatura ambiente durante 6 hs La dimetilacetamida se destilo in vacuo y el producto se purifico mediante HPIC de fase inversa utilizando gradiente de acetonitrilo/agua al 10-90% (30 min) a un caudal de 100 mL/min Las fracciones apropiadas (m/z = 510) se combinaron y deshidrataron por congelamiento para proporcionar el compuesto del titulo (0,32 g, 80%) como un polvo blanco

1087

$^1$H NMR ($CD_3OD$/400 MHz) δ 8,59 (s 1H), 8,58 s,1H), 7,60 (m, 1H), 7,02 (m, 2H), 6,52 (s, 1H), 5,45 (s, 2H), 5,29 (s, 2H), 4,67 (s, 2H), 3,71 (~t, 2H), 3,57 (~t, 2H), 3,34 (s, 3H) y 2,54 (s, 3H), ES-HRMS m/z 510,0852 (M+H $C_{20}H_{18}N_4O_4BrF_2$ requiere 510,0835)

Ejemplo 412



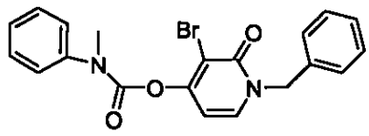

(5-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}pirazin-2-il) metil carbamato

A una suspensión de 3-bromo-4-[(2,4-difluorobencil)oxi]-1-{[5-(hidroximetil)pirazin-2-il]metil}-6-metilpiridin-2(1H)-ona (0,21 g, 0,00055 mol) en THF (5,0 mL) y DMF (2,0 mL), se agregó 4-nitrofenilcloroformato (0,1 g, 0,0005mol) y se enfrió a 0 °C Después se agregó trietilamina (0,052g, 0,0005 mol), se agitó a temperatura ambiente durante 1 hora, y a 65 °C durante 1 hora mas Se enfrió en un baño de hielo y se agregó 2M amoniaco en propanol (1,0 mL) y se agitó a temperatura ambiente durante 2 hs Luego de eliminar los disolventes bajo presion reducida, el residuo se dividio entre bicarbonato de sodio al 5% y EtOAc (25 mL) La fase organica se lavó con bicarbonato de sodio al 5%, (3 x 25 mL), agua (3 x 25 mL), se seco ($Na_2SO_4$) y se concentro bajo presion reducida Ia sustancia resultante se purifico y aislo mediante HPLC de fase inversa utilizando $CH_3CN$/agua al 10-90% (gradiente de 30 min) a un caudal de 100 mL/min Las fracciones apropiadas (m/z=495 M+H) se combinaron y se

deshidrataron por congelacion, y el residuo se dividio entre bicarbonato de sodio al 5% (20 mL) y EtOAc (25 mL) La fase organica se lavo con agua, se secó ($Na_2SO_4$) y se concentró hasta lograr la sequedad bajo presion reducida, para producir el compuesto del titulo como un polvo blanco (0,065 g)

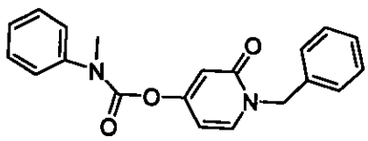
$^1$H NMR ($CD_3OD$/400 MHz) δ 8,61(br s, 1H), 8,54 (br s, 1H), 7,60 )m, 1H), 7,02 (m, 2H), 6,52 (s, 1H), 5,47 (s, 2H), 5,29 (s, 2H), 5,15 (s, 2H) y 2,54 (s, 3H) $^{19}$F NMR ($CD_3OD$) δ-111,70(m), y -116,09 (m), ES-HRMS m/z 495,0449 (M+H $C_{20}H_{18}N_4O_4BrF_2$ requiere 495,0474)

Ejemplo 413




1-bencil-3-bromc-2-oxo-1,2-dihidropiridin-4-il metil(fenil)carbamatc

Etapa 1 Preparación de 1-bencil-3-oxo-1,2-dihidropiridin-4-il metil(fenil)carbamato

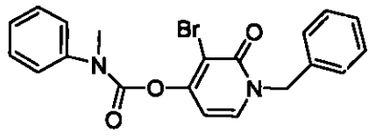



A una disolucion enfriada de 1-bencil-4-hidroxipiridin-2(1H)-ona (0,375 g, 1,86 mmol) en acetonitrilo anhidro (10 mL) se agrego trietilamina (0,206 g, 2,04 mmol) y luego cloruro de N-metil-N-fenilcarbamoilo La mezcla de reaccion se agito bajo atmosfera de nitrógeno a 0° C durante 30 minutos y despues a temperatura ambiente durante 1 hora La reaccion se vigilo mediante TLC (cromatografia de capa fina) (metanol al 5% en diclorometano) El disolvente se elimino bajo presión

1089

reducida y el residuo se lavo con acido citrico al 10% y se extrajo con acetato de etilo Los extractos organicos se combinaron, se lavaron con agua y se secaron sobre $Na_2SO_4$ anhidro El disolvente se eliminó bajo presión reducida para proporcionar un jarabe amarillo El residuo se purifico mediante cromatografia rapida (gel de silice) utilizando MeOH al 5% en $CH_2Cl_2$ para proporcionar el producto deseado (0,382g, 61%) como un semisolido blanco $^1$H-NMR ($d_6$-DMSO, 400 MHz) δ7,8 (d, 1H, J= 7,2 Hz), 7,39 (m, 10H), 6,19 (s, 2H), 5,03 (s, 2H), 3,29 (s, 3H), ES-HRMS m/z 335,1396 (M+H calculado para $C_{20}H_{19}N_2O_3$ requiere 335,1418)

Etapa 2 Preparación de 1-bencil-3-bromo-2-oxo-1,2-dihidropiridin-4-il metil(fenil)carbamato

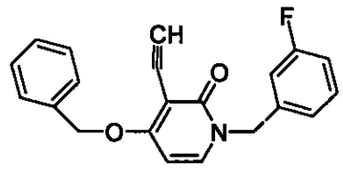



A una disolucion de 1-bencil-2-oxo-1,2-dihidropiridin-4-il metil(fenil)carbamato (0,38 g, 1,13 mmol) en $CH_2Cl_2$ anhidro (7 mL) se agrego N-bromosuccinimida (NBS, 0,24 g, 1,34 mmol) La reacción se agitó durante la noche a temperatura ambiente bajo atmósfera de nitrogeno La mezcla de reacción se purificó mediante cromatografia rapida (gel de silice) utilizando acetato de etilo/hexano (1 1 vol/vol) Las fracciones apropiadas se recogieron de acuerdo con ES MS (M+H 413) y se concentraron El producto deshidratado mostro alrededor del 14% del producto dibromonado por HPLC analitica Los compuestos se separaron mediante HPLC de fase inversa utilizando acetonitrilo al 10-90% en agua (gradiente de 30 minutos) a un caudal de 100 mL/min para proporcionar (luego de la

1090

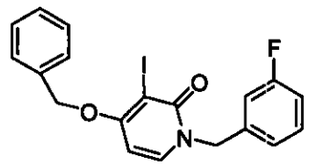
liofilización) la sal del compuesto deseado La sal se diluyo en acetato de etilo y se lavo con $NaHCO_3$ Los extractos organicos se secaron sobre $Na_2SO_4$ anhidro y se concentro para proporcionar el compuesto deseado (0,271 g, 58%) como un solido de color beige $^1$H-NMR ($d_6$-DMSO, 400 MHz) δ7,94 (d, 1H, J= 7,2 Hz), 7,29 (m, 10H), 6,48 (s, 1H), 5,12 (s, 2H), 3,33 (s, 3H), ES-HRMS m/z 413,0495 (M+H calculado para $C_{20}H_{18}O_3$ requiere 413,0496)

Ejemplo 414




4-(benciloxi)-3-etinil-1-(3-fluorobencil)piridin-2(1H)-ona

Etapa 1 Preparación de 4-(benciloxi)-1-(3-fluorobencil)-3-yodopiridin-2(1H)-ona

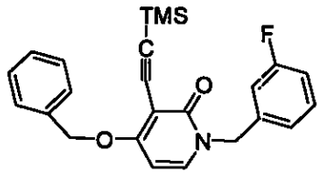



Una mezcla de 4-(benciloxi)-1-(3-fluorobencil)piridin-2(1H)-ona (4,83 g, 15,6 mmol) en acetonitrilo anhidro (55 mL) y N-yodosuccinimida (NIS, 3,86 g, 17,1 mmol) se calento a 65° C bajo nitrogero durante 4 hs La mezcla de reaccion se concentro bajo presion reducida y el residuo se purifico mediante cromatografia rapida (gel de silice) utilizando acetato de etilo/hexano (1 1 vol/vol) Las fracciones apropiadas se recogieron de acuerdo con ES MS (M+H 436) y se lavo con $Na_2SO_3$ para eliminar las impurezas del color Las fracciones se concentraron bajo presion reducida y se

1091

secaron in vacuo para proporcionar el producto deseado (6,15 g, 90%) como un sólido amarillo claro $^1$H-NMR ($CD_3OD$, 400 MHz) δ7,73 (d, 1H, J= 7,6 Hz), 7,47 (d, 2H, J= 7,2 Hz), 7,39 (m, 4H), 7,08 (m, 3H), 6,39 (d, 1H, J= 8,0 Hz), 5,29 (s, 2H), 5,19 (s, 2H), ES-HRMS m/z 436,0210 (M+H calculado para $C_{19}H_{16}NO_2FI$ requiere 436,0196)

Etapa 2 Preparacion de 4-(benciloxi)-1-(3-fluorobencil)-3-[(trimetilsilil)etinil]piridin-2(1H)-ona

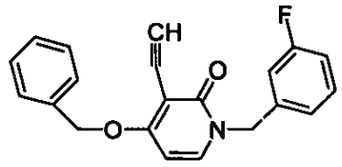



Se desgasifico una disolución de 4-(benciloxi)-1-(3-fluorobencil)-3-yodopiridin-2(1H)-ona (2,01 g, 4,62 mmol) en acetonitrilo anhidro (25 mL) bajo atmosfera de argón Se agregó trietilamina (1,11 g, 11 mmol) y se desgasifico rapidamente La mezcla de reaccion se enfrió en un baño de hielo durante 15 minutos antes de agregar cloruro de bistrifenilfosfina-paladio (0,34 g, 0,48 mmol) y yoduro cuproso (0,2 g) La reaccion se agito a temperatura ambiente durante 30 minutos antes de calentarla a 60° C bajo atmosfera de argon durante 2 horas La mezcla de reacción se filtro a través de un lecho de Celite y el filtrado se concentro bajo presion reducida El residuo marron oscuro se diluyó con $CH_2Cl_2$ (100 mL) y se lavó con agua Los extractos orgánicos se combinaron, se secaron sobre $Na_2SO_4$ anhidro y se concentraron bajo presión reducida El residuo marrón oscuro se purifico mediante cromatografia rapida utilizando acetato de etilo al 30% en hexano Las fracciones apropiadas se combinaron y concentraron bajo presion reducida para proporcionar el

1092

producto deseado (1 34 g, 72%) como un solido amarillo claro $^1$H-NMR ($CD_3OD$, 400 MHz) δ7,74 (d, 1H, J= 7,6 Hz), 7,47 (d, 2H, J= 7,6 Hz), 7,35 (m, 4H), 7,09 (m, 3H), 6,46 (d, 1H, J= 7,6 Hz), 5,26 (s, 2H), 5,13 (s, 2H), 0,18 (s, 9H), ES-HRMS m/z 406,1638 (M+H calculado para $C_{24}H_{25}NO_2FSi$ requiere 406,1610)

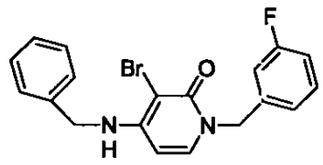
Etapa 3 Preparación de 4-(benciloxi)-3-etinil-1-(3-fluorobencil)piridin-2(1H)-ona




A una disolucion de 4-(benciloxi)-1-(3-fluorobencil)-3-[(trimetilsilil)etinil]piridin-2(1H)-ona (1,31 g, 3,2 mmol) en acetonitrilo anhidro (25 mL) a 0 °C se agregó fluoruro de tetrabutilamonio (0,611 g, 1,93 mmol) La reacción se agito a 0° C durante 15 mintuos y luego durante 1 hora a temperatura ambiente La reacción se concentro bajo presión reducida y el residuo se diluyo con acetato de etilo y se lavo con agua Los extractos organicos se combinaron, se secaron sobre $Na_2SO_4$ anhidro y se concentro bajo presion reducida El residuo se purifico mediante cromatografia rapida (gel de silice) utilizando acetato de etilo/hexano (1 1 vol/vol) Las fracciones apropiadas se combinaron y concentraron bajo presión reducida para proporcionar el producto deseado (0,779 g, 72%) como un solido color dorado $^1$H-NMR ($CD_3OD$, 400 MHz) δ7,73 (d, 1H, J= 7,6 Hz), 7,43 (d, 2H, J= 7,2 Hz), 7,35 (m, 4H), 7,09 (m, 3H), 6,45 (d, 1H, J= 7,6 Hz), 5,27 (s, 2H), 5,13 (s, 2H), 3,78 (s, 1H), ES-HRMS m/z 334,1243 (M+H calculado para $C_{21}H_{17}NO_2F$ requiere 334,1234)

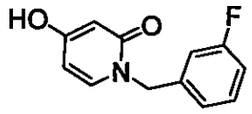
Ejemplo 415

1093




4-(bencılamıno) 3-bromo-1-(3-fluorobencıl)pırıdın-2(1H)-ona

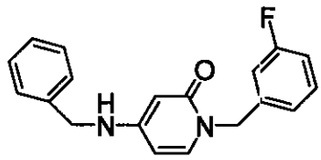
Etapa 1 Preparación de 1-(3-fluorobencıl)-4-hıdroxıpırıdın-2(1H) ona




En una botella Fıscher Porter, se agrego una dısolucıon de 4 (bencıloxı)-1-(3-fluorobencıl)pırıdın-2(1H)-ona (4,5 g, 14,56 mmol) en etanol absoluto (20 mL) La dısolución se lavo con nıtrogeno y después se agregó catalızador de paladıo (1,05 g, Pd/C al 10%) Se sello la botella y se vació el sıstema El sıstema se purgo con gas hıdrogeno (2 X 15 lppc) para vıgılar las fugas La reacción se cargó con hıdrogeno (35 lppc) y se agıtó a temperatura ambıente durante 45 mınutos El sıstema se vacıo y se lavo con nıtrogeno La reacción se fıltró y el catalızador se lavo cuıdadosamente con etanol nuevo El fıltrado se concenıro bajo presıon reducıda $^{1}$H-NMR ($CD_3OD$, 400 MHz) δ7,54 (d, 1H, J= 7,6 Hz), 7,32 (m, 1H), 7,06 (d, 1H, J= 7,6 Hz), 6,99 (m, 2H), 6,05 (dd, 1H, J= 2,4 Hz, 2,8 Hz), 5,83 (d, 1H, J= 2,4 Hz), 5,09 (s, 2H), ES-HRMS m/z 220,0774 (M+H calculado para $C_{12}H_{11}NO_2F$ requıere 220,0787)

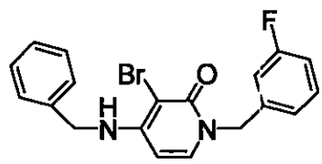
Etapa 2 Preparacıon de 4-(bencılamıno)-1-(3-fluorobencıl)pırıdın 2(1H)-ona

1094



Una mezcla de 1-(3-fluorobencil)-4-hidroxipiridin-2(1H) ona (1,005 g, 4,5 mmol) en bencilamina (15 mL) se calento a reflujo (185° C) bajo atmosfera de nitrogeno durante 24 horas La reaccion se vigilo por ES-MS (MH+ 309) El d solvente se elimino por destilación en vacio para proporcionar un residuo amarillo $^1$H-NMR ($CD_3OD$, 400 MHz) δ7,31 (m, 7H), 7,03 (m, 3H), 5,98 (d, 1H, J= 7,2 Hz), 5,45 (s, 1H), 5,00 (s, 2H), 4,30 (s, 2H), ES-HRMS m/z 309,1403 (M+H calculated for $C_{19}H_{18}N_2OF$ requiere 309,1375)

Etapa 3 Preparación de 4-(bencilamino)-3-bromo-1-(3-fluorobencil)piridin 2(1H)-ona

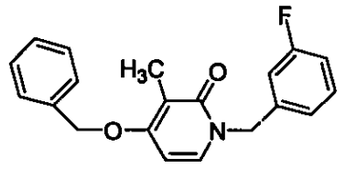


A una disolucion de 4-(bencilamino)-1-(3-fluorobencil)piridin 2(1H)-ona (0,50 g, 1,62 mmol) en $CH_2Cl_2$ anhidro (10 mL) se agregó N-bromosuccinimida (NBS, 0,30 g, 1,7 mmol) La reacción se agitó a temperatura ambiente bajo atmosfera de nitrogeno durante 3 horas La mezcla de reaccion se purifico mediante cromatografia rapida (gel de silice) utilizando acetato de etilo en hexano (1 1 vol/vol) Las fracciones apropiadas se combinaron y concentraron $^1$H-NMR ($CD_3OD$, 400 MHz) δ7,41 (d, 1H, J= 7,6 Hz), 7,31 (m, 6H), 7,04 (m, 3H), 5,99 (d, 1H, J= 7,6 Hz), 5,08 (s, 2H), 4,53 (s, 2H), ES-HRMS m/z

1095

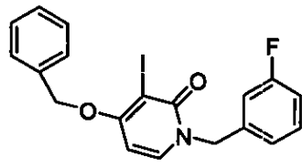
387,0508 (M+H calculado para $C_{19}H_{17}N_2OBrF$ requiere 387,0504)

Ejemplo 416



4-(benciloxi)-1-(3-fluorobencil)-3-metilpiridin-2(1H)-ona

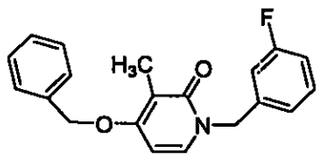
Etapa 1 Preparacion de 4-(benciloxi)-1-(3-fluorobencil)-3-yodopiridin-2(1H)-ona



Una mezcla de 4-(benciloxi)-1-(3-fluorobencil)piridin-2(1H)-ona (4,83 g, 15,6 mmol) y N-yodosuccinimida (NIS, 3,86 g, 17,1 mmol) en acetonitrilo anhidro se calento a 65° C durante 4 horas bajo atmosfera de nitrogeno La mezcla de reaccion se concentro bajo presion reducida y el residuo se purificó mediante cromatografia rápida (acetato de etilo/hexano 1 1 vol/vol) Las fracciones apropiadas se recogieron de acuerdo con ES MS (M+H 436) y se lavó con $Na_2SO_3$ para eliminar las impurezas del color Las fracciones se concentraron bajo presión reducida y se secaron in vacuo para proporcionar el producto deseado (6,15 g, 90%) como un sólido amarillo claro $^1$H-NMR ($CD_3OD$, 400 MHz) δ7,73 (d, 1H, J= 7,6 Hz), 7,36 (m, 6H), 7,08 (m, 3H), 6,39 (d, 1H, J= 8,0 Hz), 5,28 (s, 2H), 5,19 (s, 2H), ES-HRMS m/z 436,0196 (M+H calculado para $C_{19}H_{16}NO_2FI$ requiere 436,0210)

Etapa 2 Preparacion de 4-(benciloxi)-1-(3-fluorobencil)-3-metilpiridin-2(1H)-ona

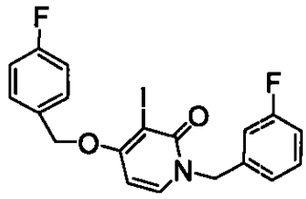
1096
1096




A una disolución desgasificada de 4-(benciloxi)-1-(3-fluorobencil)-3-yodopiridin-2(1H)-ona (1,03 g, 2,36 mmol) en DMF anhidro (15 mL) bajo atmosfera de argon se agrego trietilamina (1,11 g, 11 mmol) La mezcla de reaccion se enfrió en un baño de hielo durante 15 mintuos antes de agregar tetrametil estaño (2,10 g, 11,75 mmol) seguido por cloruro de bistrifenilfosfina-paladio (0,166 g, 0,24 mmol) La reaccion se agitó a temperatura ambiente durante 30 minutos antes de calentarla a 95° C bajo atmósfera de argon durante 3 horas La mezcla de reaccion se filtró a traves de un lecho de Celite y el filtrado se concentro bajo presion reducida El residuo marron oscuro se diluyo con acetato de etilo (100 mL) y se lavo con agua Los extractos organicos se combinaron, se secaron sobre $Na_2SO_4$ anhidro y se concentraron bajo presion reducida El residuo marron oscuro se purificó mediante cromatografia rapida (acetato de etilo al 30% en hexano) Las fracciones apropiadas se combinaron y concentraron bajo presion reducida para proporcionar el producto deseado (0,1758 g, 22%) como un solido amarillo claro El producto se purificó adicionalmerte por HPLC de fase inversa utilizando acetonitrilo/agua al 10-90% (gradiente de 30 minutos) a un caudal de 100 mL, para proporcionar un producto mas puro como un solido amarillo claro (0,0975g, 8%) $^1$H-NMR ($CD_3OD$, 400 MHz) δ7,58 (d, 1H, J= 7,6 Hz), 7,35 (m, 6H), 6,98 (m, 3H), 6,46 (d, 1H, J= 7,6 Hz), 5,19 (s, 2H), 5,15 (s, 2H), 2,0 (s, 3H), ES-HRMS m/z 324,1366 (M+H calculado para $C_{20}H_{19}NO_2F$ requiere 324,1394)

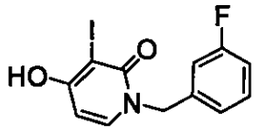
1097

Ejemplo 417



1-(3-fluorobencil)-4-[(4-fluorobencil)oxi]-3-yodopiridin-2(1H)-ona

Etapa 1 Preparacion de 1-(3-fluorobencil)-4-hidroxi-3-yodopiridin-2(1H)-ona



A una mezcla de 1-(3-fluorobencil)-4-hidroxipiridin-2(1H)-ona (1,1 g, 5 mmol) en acetonitrilo (15 mL) se agregó N-yodosuccinimida (1,1 g, 5,5 mmol) junto con una cantidad aproximada de acido dicloroacetico (0,1 mL) La mezcla de reaccion se agito a temperatura ambiente durante 1 hora bajo nitrógeno La mezcla se enfrió en un baño de hielo y se filtro fria con $MeCl_2$ nuevo El sólido beige se secó para proporcionar el intermedio yodado deseado(1,21 g, 69%) ES-LRMS m/z 346

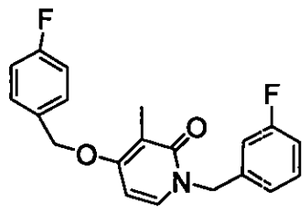
Etapa 2 Preparacion de 1-(3-fluorobencil)-4-[(4-fluorobencil)oxi]-3-yodopiridin-2(1H)-ona

A una mezcla de 1-(3-fluorobencil)-4-hidroxi-3-yodopiridin-2(1H)-ona (0,5 g, 1,44 mmol) en DMF (5 mL) se agregó $K_2CO_3$ (0,199 g, 1,44 mmol) seguido del agregado de bromuro 4-fluorobenc lo (0,189 mL, 1,51 mmol) La mezcla de reaccion se agitó a temperatura ambiente durante 30 minutos El residuo marron oscuro se diluyo con acetato de

1098

etilo (50 mL) y se lavo con agua Los extractos organicos se secaron sobre $Na_2SO_4$ anhidro y se concentraron hasta lograr la sequedad $^1$H-NMR ($CD_3OD$, 400 MHz) δ7,75 (d, 1H, J= 7,6 Hz), 7,49 (q, 2H), 7,34 (q, 1H), 7,11 (m, 5H), 6,40 (d, 1H, J= 7,6 Hz), 5,26 (s, 2H), 5,19 (s, 2H), ES-HRMS m/z 454,0098 (M+H calculado para $C_{19}H_{15}NO_2F_2I$ requiere 454,0110)

Ejemplo 418

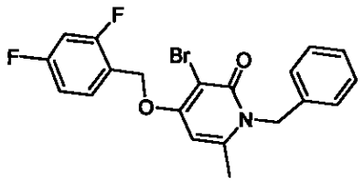


1-(3-fluorobencil)-4-[(4-fluorobencil)oxi]-3-metilpiridin-2(1H)-ona

A una disolucion desgasificada de of 1-(3-fluorobencil)-4-[(4-fluorobencil)oxi]-3-yodopiridin-2(1H)-ona (0,804g, 1,7 mmcl) en DMF (10 mL) y LiCl (0,25g, 5,9 mmol) se agregó tetrametilestaño (0,49 mL, 3,54 mmol) y luego el catalizador cloruro de bistrifenilfosfina-paladio (0,124g, 0,177 mmol) La mezcla de reacción se calento en un baño de aceite (85° -90° C) bajo nitrogeno durante 3 horas La reaccion se concentro y el residuo se diluyo con acetato de etilo y se lavó con agua Los extractos organicos se secaron sobre $Na_2SO_4$ anhidro y se concentraron hasta lograr la sequedad El residuo se purificó mediante cromatografia rápida de columna (acetato de etilo al 20% en hexano) Las fracciones apropiadas se concentraron $^1$H-NMR ($CD_3OD$, 400 MHz) δ7,59 (d, 1H, J= 7,6 Hz), 7,46 (m, 2H, 7,34 (m, 1H), 7,10 (m, 4H), 4,46 (d, 1H, J=7,6 Hz), 5,17 (s, 2H), 5,15 (s, 2H), 1,99 (s, 3H), ES-HRMS m/z 342,1314 (M+H calculado para $C_{20}H_{18}NO_2F_2$ requiere 342,1300)

1099

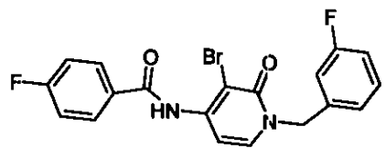
Ejemplo 419



1-bencil-3-bromo-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona

A una disolucion fria desgasificada de DMF (10 mL) y $PPh_3$ (resina, 0,93 g, 2,75 mmol) se agrego DEAD (0,44 mL, 2,75 mmol) La mezcla de reaccion se agitó a -10 °C durante 20 minutos bajo nitrógeno Una disolucion de 1-bencil-3-bromo-4-hidroxi-6-metilpiridin-2(1H)-ona (0,62 g, 2,1 mmol) y alcohol 2,4-difluorobencilico (0,283 mL, 2,5 mmol) en DMF (10 mL) se agregó a la suspension de resina La mezcla de reaccion se agito a -10 °C durante 30 minutos y luego se permitió que se agitara a temperatura ambiente durante 1 hora La resina se filtró y se enjuagó con MeOH nuevo y el filtrado se concentro El residuo se disolvio en acetato de etilo y se purifico por cromatografia de columna rapida (acetato de etilo/hexano 1 1 vol/vol) Las fracciones apropiadas se concentraron $^1$H-NMR ($CD_3OD$, 400 MHz) δ7,62 (m, 1H), 7,31 (m, 3H), 7,1 (d, 2H, J = 7,2 Hz), 7,02 (t, 2H, J = 8,6 Hz), 6,48 (s, 1H), 5,42 (s, 2H), 5,28 (s, 2H), 2,34 (s, 3H), ES-HRMS m/z 420,0399/422,0380 (M+H calculado para $C_{20}H_{17}NO_2F_2Br$ requiere 420,0405/422,0387)

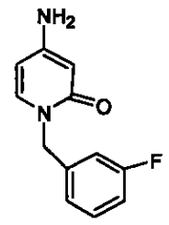
Ejemplo 420



1100

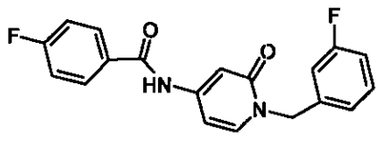
N-[3-bromo-1-(3 fluorobencil)-2-oxo-1,2-dihidropiridin-4-il] 4-fluorobenzamida

Etapa 1 Preparacion de 4-amino-1-(3-fluorobencil)pirídin 2(1H)-ona



En una botella Fischer Porter, se agregó una disolucion de 4-(bencilamino)-1-(3-fluorobencil)pirídin-2(1H)-ona (2,5g, 8,11 mmol) en ácido acético glacial (20 mL) Despues de lavar la disolucion con nitrógeno, se agrego el catalizador (10% Pd/C, 2,0g) Se selló el recipiente, se vació y se purgo con gas hidrogeno Se cargo el sistema con gas hidrógeno (50 lppc) y la mezcla se agito a temperatura ambiente durante 4 horas El sistema se vació y se lavó con nitrogeno La mezcla de reaccion se filtro a través de un lecho de celite y se lavo con etanol nuevo El filtrado se concentró bajo presion reducida y el residuo se purificó mediante cromatografia de columna rapida (hexano/acetato de etilo 3 4 vol/vol) El filtrado se concentró $^1$H-NMR ($CD_3OD$, 400 MHz) δ7,32 (q, 1H), 7,02 (m, 3H), 5,93 (dd, 1H, J= 2,4 Hz, 2,8 Hz), 5,58 (d, 1H, J= 2,4 Hz), ES-HRMS m/z 219,0966 (M+H calculado para $C_{12}H_{12}N_2OF$ requiere 219,0928)

Etapa 2 Preparacion de 4-fluoro-N-[1-(3-fluorobencil)-2-oxo-1,2-dihidropiridin-4-il]benzamida



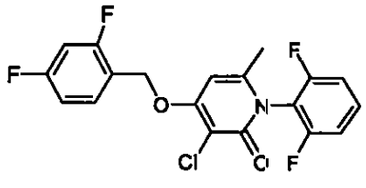
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A una disolución de 4-amino-1-(3-fluorobencil)piridin-2(1H)-ona (0,263 g, 1,2 mmol) en acetonitrilo (7 mL) se le agrego (aprox ) DMAP, trietilamina (0,25 mL, 1,8 mmol) y cloruro de 4-fluorobenzoilo (0,213 mL, 1,8 mmol) La mezcla de reaccion se agito a 0° C durante 25 minutos y luego se filtro El sólido se lavó con ácido cítrico y agua al 10% para proporcionar el compuesto deseado (0,326 g, 79%) luego de secar $^1$H-NMR ($d_6$DMSO, 400 MHz) δ 7,98 (m, 2H), 7,71 (d, 1H, J= 7,6 Hz), 7,35 (m, 3H), 7,08 (m, 3H), 6,98 (d, 1H, J= 2,4 Hz), 6,61 (dd, 1H, J= 2,4 Hz, 2,4 Hz), 5,03 (s, 2H), ESLRMS m/z 341,1

Etapa 3 Preparación de N-[3-bromo-1-(3-fluorobencil)-2-oxo-1,2-dihidropiridin-4-il]-4-fluorobenzamida

A una mezcla de 4-fluoro-N-[1-(3-fluorobencil)-2-oxo-1,2-dihidropiridin-4-il]benzamida (0,305g, 0,89 mmol) en acetonitrilo (7 mL) se agrego NBS (0,159g, 0,89 mmol) La mezcla de reacción se agito a temperatura ambiente durante 1,5 horas El filtrado se elimino bajo presion reducida y el residuo se purificó mediante cromatografia de columna rapida (acetato de etilo/hexano 1 1 vol/vol) Las fracciones se concentraron $^1$H-NMR ($CD_3OD$, 400 MHz) δ 8,03 (m, 2H), 7,79 (d, 1H, J= 7,6 Hz), 7,47 (d, 1H, J=8,0 Hz), 7,28 (m, 3H), 7,12 (m, 3H), 5,23 (s, 2H) ES-HRMS m/z 419,0202/421,0191 (M+H calculado para $C_{19}H_{14}NO_2F_2Br$ requiere 419,0201/421,0183)

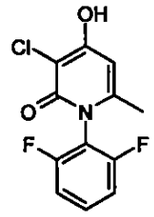
Ejemplo 421



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3-cloro-4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorofenil)-6-metilpiridin-2(1H)-ona

Etapa 1 Preparacion de 3-cloro-1-[2,6-(difluorofenil)-4-hidroxi-6-metilpiridin-2(1H)-ona



A una mezcla de 1-(2,6-difluorofenil)-4-hidroxi-6-metilpiridin-2(1H)-ona (0,30 g, 1,26 mmol) en diclorometano (5 mL) se agregó NCS (2,52 g, 1,90 mmol) La mezcla de reacción se agitó a temperatura ambiente bajo nitrogeno durante 4,5 horas La suspension se enfrio en un baño de hielo, se filtró y el solido se enjuago con diclorometano nuevo para proporcionar el producto deseado (0,271 g, 79%) como un sólido blanco $^1$H-NMR ($CD_3OD$, 400 MHz) δ 7,58 (m, 1H), 7,22 (m, 2H), 6 20 (s 1H), 2 00 (s, 3H), ES-HRMS m/z 272 0287 (M+H calculado para $C_{12}H_9NO_2F_2Cl$ requiere 272,0290)

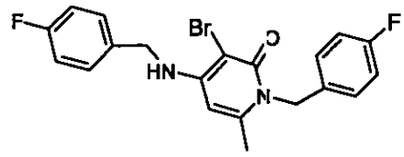
Etapa 2 Preparacion de 3-cloro-4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorofenil)-6-metilpiridin-2(1H)-ona

A una disolucion de 3-cloro-1-(2,6-difluorofenil)-4-hidroxi-6-metilpiridin-2(1H)-ona (0,27 g, 1,00 mmol) en DMA (5 mL) se agrego $K_2CO_3$ seguido por el agregado de bromuro 2,4-difluorobencil (0,128 mL, 1 mmol) La mezcla de reaccion se agitó a temperatura ambiente durante 2 horas y luego se diluyo en agua La mezcla de reaccion se extrajo con acetato de etilo, los extractos orgánicos se secaron sobre $Na_2SO_4$ y se concentro el filtrado El residuo resultante se purificó mediante cromatografia de columna rapida (acetato de etilo/hexano 3 4 vol/vol) para proporcionar el producto deseado $^1$H-NMR ($CD_3OD$, 400 MHz)

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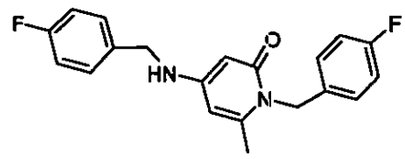
δ 7,60 (m, 2H), 7,25 (m, 2H), 7,04 (m, 2H), 6,71 (s, 1H), 5,36 (s, 2H), 2,11 (s, 3H), ES-HRMS m/z 398,0551 (M+H calculado para $C_{19}H_{13}NO_2F_4Cl$ requiere 398,0571)

Ejemplo 422



3-bromo-1-[4-fluorobencil)-4-[(4-fluorobencil)amino]-6-metilpiridin-2(1H)-ona

Etapa 1 Preparacion de 1-(4-fluorobencil)-4-[(4-fluorobencil)amino]-6-metilpiridin-2(1H)-ona



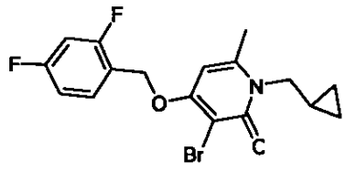
Una mezcla de 4-hidroxi-6-metilpirona (5,0 g, 0,04 mol) y 4-fluorobencilamina (10,0 g, 0,08 mol) en n-butanol (25,0 mL) se calento a reflujo durante 24 horas bajo atmósfera de argón La disolución resultante se concentro hasta lograr la sequedad bajo presion reducida El residuo se trituró con acetato de etilo y se filtro Se lavo minuciosamente con acetato de etilo y se secó hasta proporcionar el compuesto del título como un polvo amarillo palido (4,1 g, 30%) $^1$H-NMR ($CD_3OD$, 400 MHz) δ 7,33 (q, 2H), 7,04 (m, 5H), 5,85 (d, 1H, J = 2,0 Hz), 5,44 (d, 2H, J = 2,4 Hz), 5,20 (s, 1H), 4,29 (s, 2H), 2,17 (s, 3H), ES-HRMS m/z 341,1488(M+H calculado para $C_{20}H_{19}N_2OF_2$ requiere 341,1460)

Etapa 2 Preparación de 3-bromo-1-[4-fluorobencil)-4-[(4-fluorobencil)amino]-6-metilpiridin-2(1H)-ona

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A una disolucion de 1-(4-fluorobencil)-4-[(4-fluorobencil)amino]-6-metilpiridin-2(1H)-ona (0,2857 g, 0,84 mmol) en $MeCl_2$ se agregó NBS (0,156 g, 0,88 mmol) La reaccion se agito a temperatura ambiente bajo nitrogeno durante 45 minutos La mezcla de reaccion se diluyo con $MeCl_2$ y se lavo con $NaHCO_3$ Los extractos organicos se lavaron con agua, se secaron sobre $Na_2SO_4$ y se concentraron para proporcionar el producto deseado (0,3242 g, 92%) como un solido amarillo $^1$H-NMR ($CD_3OD$, 400 MHz) δ 7,32 (q, 2H), 7,04 (m, 6H), 5,91 (s, 1H), 5,28 (s, 2H), 4,50 (s, 2H), 2,17 (s, 3H), ES-HRMS m/z 419,0549/421,0537 (M+H calculado para $C_{20}H_{18}N_2OBrF_2$ requiere 419,0565/421,0547)

Ejemplo 423



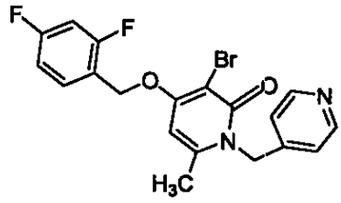

3-bromo-1-(ciclopropilmetil)-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona

A una mezcla de 3-bromo-1-(ciclopropilmetil)-4-hidroxi-6-metilpiridin-2(1H)-ona (0,276 g, 1,07 mmol) y $K_2CO_3$ (0,148 g, 1,07 mmol) en DMA (4 mL) se agregó bromuro de 2,4-difluorobencilo (0,14 ml, 1,07 mmol) La mezcla se agito a temperatura ambiente durante 1,5 horas La mezcla de reaccion se diluyo en agua y se extrajo con acetato de etilo Los extractos organicos se secaron sobre $Na_2SO_4$ y se concentraron El residuo se purifico mediante cromatografia de columna rapida (acetato de etilo/hexano 1 1 vol/vol) Las fracciones apropiadas se combinaron y se concentraron $^1$H-NMR ($CD_3OD$, 400 MHz) δ 7,60 (q, 1H), 7,04 (m, 2H), 6,42 (s, 1H), 5,26 (s, 2H), 4,06 (s, 1H), 4,04 (s, 1H), 2,50 (s, 3H), 0,53 (m, 2H), 0,43 (m, 2H), ES-

1105

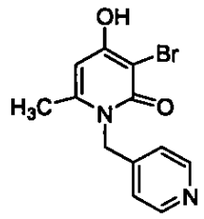
HRMS m/z 384,0392 (M+H calculado para $C_{17}H_{17}N_2OBrF_2$ requiere 384,0405)

Ejemplo 424



3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-(piridin-4-ilmetil)piridin-2(1H)-ona

Etapa 1 Preparacion de 3-bromo-4-hidroxi-6-metil-1-(piridin-4-ilmetil)piridin-2(1H)-ona



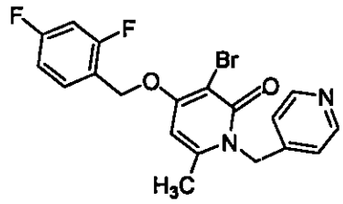
Se condensó 4-hidroxi-6-metil pirona (10 g, 79,3 mmol) que está a la venta con 4-(aminometil) piridina también en venta (8 mL, 79,3 mmol) en agua (50 mL) La mezcla se calentó en un baño de aceite a reflujo durante 1 hora bajo nitrogeno El disolvente se evaporo MS y $^1$H-NMR concordaron con la estructura desbromada deseada $^1$H-NMR ($CD_3OD$, 400 MHz) δ 8,45 (dd, 2H, J= 1,6 Hz,1,6 Hz), 7,15 (d, 2H, J= 6,0 Hz), 6,00 (d, 1H, J= 2,0 Hz), 5,80 (d, 1H, J= 2,4 Hz), 5,34 (s, 2H), 2,23 (s, 3H), ES-LRMS (M+H) m/z 217

A una suspensión del compuesto precedente (0,801 g, 3,7 mmol) en $MeCl_2$ (10 mL) se agrego NBS (0,725 g, 4,07 mmol) La mezcla de reacción se agitó a temperatura ambiente durante 30 minutos bajo nitrogeno La suspensión se enfrio en un baño de hielo y se filtro Se lavó el solido con $MeCl_2$ nuevo y se secó para proporcionar un

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solido de color beige (0,9663 g, 88%) luego de secar $^1$H-NMR ($CD_3OD$, 400 MHz) δ 8,47 (d, 2H, J= 5,2 Hz), 7,16 (d, 2H, J= 6,0 Hz), 6,09 (s, 1H), 5,40 (s, 2H), 2,24 (s, 3H), ES-LRMS (M+H) m/z 295/297

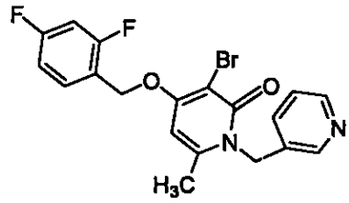
Etapa 2 Preparación de 3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-(piridin-4-ilmetil)piridin-2(1H)-ona




A una disolucion fria de alcohol 2,4-difluorobencil (0,569 mL, 5,1 mmol) en THF (5 mL) se le agrego $PPh_3$ (resina, 2,55 g, 7,65 mmol) seguido por el agregado de DIAD (1,48 mL, 7,65 mmol) La mezcla de reaccion se agito a -10 °C durante 15 minutos bajo nitrogeno Una disolucion de 3-bromo-4-hidroxi-6-metil-1-(piridin-4-ilmetil)piridin-2(1H)-ona (1,0 g, 3,4 mmol), en DMF (10 mL) se agrego a la suspensión de resina La mezcla de reaccion se agito a 0 °C durante 1,5 horas y luego se permitio que continuara agitándose a temperatura ambiente durante la noche La resina se filtro y se enjuago con MeOH nuevo y el filtrado se concentro El residuo se disolvio en acetato de etilo y se purificó por cromatografia de columna rápida (acetato de etilo) Las fracciones apropiadas se concentraron $^1$H-NMR ($CD_3OD$, 400 MHz) δ 8,47 (d, 2H, J= 5,6 Hz), 7,63 (q, 1H), 7,15 (d, 1H, J=5,6 Hz), 7,05 (m, 2H), 6,55 (s, 1H), 5,45 (s, 2H), 5,31 (s, 2H), 2,35 (s, 3H), ES-HRMS m/z 421,0366/423, 0355 (M+H calculado para $C_{19}H_{16}N_2O_2F_2Br$ requiere 421,0358/423,0339)

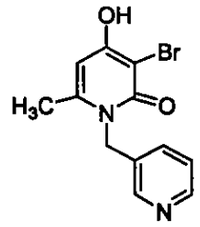
1107

Ejemplo 428



3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-(piridin-3-ilmetil)piridin-2(1H)-ona

Etapa 1 Preparacion de 3-bromo-4-hidroxi-6-metil-1-(piridin-3-ilmetil)piridin-2(1H)-ona



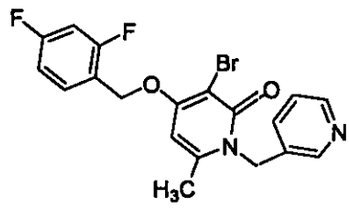
Se condenso 4-hidroxi-6-metil pirona (15 g, 119,0 mmol) que está a la venta con 3-(aminometil) piridina tambien en venta (12,10 mL, 119,0 mmol) en agua (75 mL) La mezcla se calento en un baño de aceite a reflujo durante 1 hora bajo nitrógeno El solvente se evaporó $^1$H-NMR ($CD_3OD$, 400 MHz) δ 8,43 (d, 1H, J= 4,8 Hz), 8,38 (s, 1H), 7,60 (d, 1H, J= 8,0 Hz), 7,39 (dd, 1H, J= 4,8 Hz, 4,8 Hz), 5,97 (d, 1H, J= 2,0 Hz), 5,79 (d, 1H, J= 2,4 Hz), 5,33 (s, 2H), 2,28 (s, 3H), ES-LRMS (M+H) m/z 217

A una suspension del compuesto precedente (5,01 g, 23,1 mmol) en $MeCl_2$ (50 mL) se agregó NBS (4,53 g, 25,4 mmol) La mezcla de reaccion se agito a temperatura ambiente durante 30 minutos bajo nitrógeno La suspensión se enfrió en un baño de hielo y se filtro Se lavo el solido con $MeCl_2$ nuevo y se secó para proporcionar un solido de color beige (7,89 g, 114%) luego de secar $^1$H-NMR ($CD_3OD$, 400 MHz) δ 8,44 (d, 1H, J= 4,4 Hz), 8,39 (s,

1108

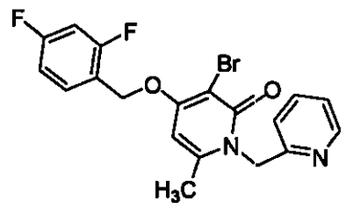
1H), 7,62 (d, 1H, J= 7,6 Hz), 7,39 (dd, 1H, J= 5,2 Hz, 4,4 Hz), 6,07 (s, 1H), 5,39 (s, 2H), 2,29 (s, 3H), ES-LRMS (M+H) m/z 295/297

Etapa 2 Preparacion de 3-bromo-4-[(2,4-difourobencil)oxi]-6-metil-1-(piridin-3-ilmetil)piridin-2(1H)-ona



El compuesto se preparó esencialmente como se describe en la Etapa 2 del Ejemplo 424 utilizando 3-bromo-4-hidroxi-6-metil-1-(piridin-3-ilmetil)piridin-2(1H)-ona $^1$H-NMR ($CD_3OD$, 400 MHz) δ 8,45 (d, 1H, J= 4,4 Hz), 8,41 (s, 1H), 7,63 (m, 2H), 7,41 (dd, 1H, J=5,2 Hz, 4,8 Hz), 7,02 (m, 2H), 6,52 (s, 1H), 5,44 (s, 2H), 5,29 (s, 2H), 2,40 (s, 3H), ES-HRMS m/z 421,0355/423, 0358 (M+H calculado para $C_{19}H_{16}N_2O_2F_2Br$ requiere 421,0358/423,0339)

Ejemplo 435



3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-(piridin-2-ilmetil)piridin-2(1H)-ona

Etapa 1 Preparacion de 3-bromo-4-hidroxi-6-metil-1-(piridin-2-ilmetil)piridin-2(1H)-ona

1109

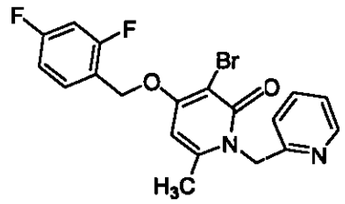



Se condensó 4-hıdroxı-6-metıl pırona (5 g, 39,6 mmol) que esta a la venta con 2-(amınometıl) pırıdına tambıen en venta (4,03 mL, 39,6 mmol) en agua (25 mL) La mezcla se calento en un baño de aceıte a reflujo durante 1,5 hora bajo nıtrogeno El solvente se evaporo MS y $^1$H-NMR concordaron con la estructura desbromada deseada $^1$H-NMR ($CD_3OD$, 400 MHz) δ 8,47 (d, 1H, J= 4,8 Hz), 7,75 (ddd, 1H, J= 2,0 Hz, 1,6 Hz, 1,6 Hz), 7,28 (dd, 1H, J= 4,8 Hz, 4,8 Hz), 7,11(d, 1H, J= 7,6 Hz), 5,98 (d, 1H, J= 2,4 Hz), 5,77 (d, 1H, J= 2,4 Hz), 5,35 (s, 2H), 2,28 (s, 3H), ES-LRMS (M+H) m/z 217

A una suspensıon del compuesto precedente (3,0 g, 13,8 mmol) en $MeCl_2$ (30 mL) se agrego NBS (2,71 g, 15,18 mmol) La mezcla de reaccıon se agıto a temperatura ambıente durante 2,5 horas bajo nıtrógeno La suspensión se enfrió en un baño de hıelo y se fıltro Se lavo el sólıdo con $MeCl_2$ nuevo y se secó para proporcıonar un solıdo de color beıge (3,18 g, 77%) luego de secar $^1$H-NMR ($CD_3OD$, 400 MHz) δ 8,46 (d, 1H, J= 4,8 Hz), 7,76 (ddd, 1H, J= 2,0 Hz, 1,6 Hz, 1,6 Hz), 7,29 (dd, 1H, J= 5,2 Hz, 5,2 Hz), 7,17 (d, 1H, J= 8,0 Hz), 6,07 (s, 1H), 5,40 (s, 2H), 2,30 (s, 3H), ES-LRMS (M+H) m/z 295/297

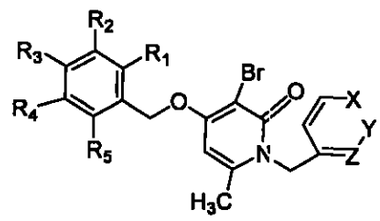
Etapa 2 Preparación de 3-bromo-4-[(2,4-dıfourobencıl)oxı]-6-metıl-1-(pırıdın-2-ılmetıl)pırıdın-2(1H)-ona

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El compuesto se preparó esencialmente como se describe en la Etapa 2 del Ejemplo 424 utilizando 3-bromo-4-hidroxi-6-metil-1-(piridin-2-ilmetil)piridin-2(1H)-ona $^1$H-NMR ($CD_3OD$, 400 MHz) δ 8,45 (d, 1H, J= 4,4 Hz), 7,76 (ddd, 1H, J= 2,0 Hz, 2,0 Hz, 1,6 Hz), 7,62 (q, 1H), 7,29 (dd, 1H, J= 5,2 Hz, 5,6 Hz), 7,21 (d, 1H, J= 8,0 Hz), 7,04 (m, 2H), 6,51 (s, 1H), 5,45 (s, 2H), 5,29 (s, 2H), 2,42 (s, 3H), ES-HRMS m/z 421,0254/423,0332 (M+H calculado para $C_{19}H_{16}N_2O_2F_2Br$ requiere 421,0358/423,0339)

Ejemplos 425-427, 429-435, 436-437



Se prepararon los siguientes compuestos esencialmente conforme a los procedimientos establecidos precedentemente para el Ejemplo 424, utilizando los productos de la Etapa 1 de los Ejemplos 424, 428 o 435

| Ej N° | R1 | R2 | R3 | R4 | R5 | X | Y | Z | MF | M+H m/z requerido | ES-HRMS m/z |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 425 | H | H | F | H | H | N | CH | CH | $C_{19}H_{16}N_2O_2FBr$ | 403,0452/ 405,0434 | 403,0444/ 405,0414 |

111

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 426 | F | H | F | H | F | N | CH | CH | $C_{19}H_{14}N_2O_2F_3Br$ | 439,0264/ 441,0245 | 439 027 0/ 441,027 4 |
| 427 | F | H | H | H | F | N | CH | CH | $C_{19}H_{15}N_2O_2F_2Br$ | 421,0358/ 423,0339 | 421,037 8/ 423,036 8 |
| 429 | H | H | F | H | H | CH | N | CH | $C_{19}H_{16}N_2O_2FBr$ | 403,0487/ 405 0438 | 403,048 7/ 405 043 8 |
| 430 | F | H | F | H | F | CH | N | CH | $C_{19}H_{14}N_2O_2F_3Br$ | 439,0264/ 441,0245 | 439,026 7/ 441 024 1 |
| 431 | F | H | H | H | H | CH | N | CH | $C_{19}H_{16}N_2O_2FBr$ | 403,0452/ 405 0434 | 403,048 9/ 405,047 4 |
| 432 | F | H | F | F | H | CH | N | CH | $C_{19}H_{14}N_2O_2F_3Br$ | 439,0264/ 441,0245 | 439,026 6/ 441 023 1 |
| 433 | F | H | Cl | H | H | CH | N | CH | $C_{19}H_{15}N_2O_2FClBr$ | 437,0062/ 439,0041 | 437,006 8/ 439 004 1 |
| 434 | Cl | H | F | H | H | CH | N | CH | $C_{19}H_{15}N_2O_2FClBr$ | 437,0062/ 439,0041 | 437,004 8/ 439,004 3 |
| 435 | F | H | H | H | F | CH | N | CH | $C_{19}H_{15}N_2O_2F_2Br$ | 421,0358/ 423,0339 | 421,037 1/ 423,033 6 |
| 436 | H | H | F | H | H | CH | CH | N | $C_{19}H_{16}N_2O_2FBr$ | 403,0452/ 405 0434 | 403,045 4/ 405,037 |

1112

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | 9 |
| 437 | F | H | F | H | F | CH | CH | N | $C_{19}H_{14}N_2O_2F_3Br$ | 439,0264/ 441,0245 | 439,026 6/ 441,024 2 |
| 438 | F | H | F | F | H | CH | CH | N | $C_{19}H_{14}N_2O_2F_3Br$ | 439,0264/ 441,0245 | 439,026 4/ 441,024 1 |

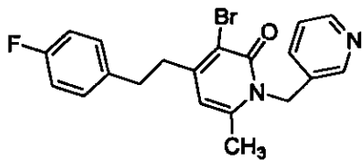
Caracterizacion de NMR de los compuestos de los Ejemplos 425-427, 429-435, 436-437

| Ej N° | Datos de NMR |
|---|---|
| 425 | $^1$H-NMR ($CD_3OD$, 400 MHz) δ 8,47 (d, 2H, J= 5,6 Hz), 7,50 (q, 2H), 7,14 (m, 4H), 6,49 (s, 1H), 5,44 (s, 2H), 5,27 (s 2H) 2,32 (s, 3H |
| 426 | $^1$H-NMR ($CD_3OD$, 400 MHz) δ 8,48 (dd, 2H, J= 1,6 Hz), 7,15 (d, 2H J= 6 0 Hz) 6 98 (t 2H J=1 2 Hz) 6 60 (s 1H) 5 45 (s, 2H), 5 29 (s 2H), 2,36 (s, 3H) |
| 427 | $^1$H NMR ($CD_3OD$ 400 MHz) δ 8 47 (d 2H J = 1 6 Hz) 7 5 (m 1H), 7,6 (d, 2H, J = 5,6 Hz), 7,06 (t, 2H, J = 8,4 Hz), 6,62 (s, 1H), 5,46 (s, 2H), 5,34 (s, 2H), y 2,37 (s, 3H) |
| 429 | $^1$H-NMR ($CD_3OD$ 400 MHz) δ 8,45 (d, 1H, J= 4,4 Hz), 8,40 (s, 1H), 7,62 (d, 1H, J= 8,0 Hz), 7,49 (q, 2H), 7,41 (dd, 1H, J= 4,8 Hz, 4,8 Hz), 7,14 (t, 2H, J= 8,8 Hz), 6,46 (s, 1H), 5,43 (s, 2H), 5,26 (s, 2H), 2,38 (s 3H) |
| 430 | $^1$H-NMR ($CD_3OD$ 400 MHz) δ 8,45 (d, 1H, J= 3,6 Hz), 8,42 (d, 1H, J= 1 2 Hz), 7,60 (d, 1H, J= 8,4 Hz), 7,41 (dd, 1H, J= 5,2 Hz 4 8 Hz), 6,97 (m, 2H), 6,57 (s, 1H), 5,45 (s, 2H) 5,27 (s, 2H) 2,42 (s, 3H) |
| 431 | $^1$H-NMR ($CD_3OD$, 400 MHz) δ 8,45 (d 1H, J= 4,4 Hz), 8,41 (d, 1H, J= 1,6 Hz), 7,58 (m 2H), 7,41 (m, 2H), 7,22 (m, 2H), 6 51 (s, 1H), 5,44(s, 2H), 5,34 (s 2H), 2 39 (s 3H) |

1113

| | |
|---|---|
| 432 | $^1$H-NMR ($CD_3OD$, 400 MHz) δ 8,45 (d 1H, J= 4,0 Hz), 8,41 (d 1H, J= 1,6 Hz) 7 63 (d, 1H, J= 7,6 Hz) 7 53 (m, 1H), 7,41 (dd, 1H, J= 5,6 Hz 5 2 Hz), 7,26 (m, 1H), 6,51 (s 1H), 5,45 (s, 2H) 5,29 (s 2H), 2,40 (s, 3H) |
| 433 | $^1$H-NMR ($CD_3OD$, 400 MHz) δ 8,45 (d 1H, J= 4,0 Hz), 8,41 (d 1H, J= 1,6 Hz), 7,60 (m, 2H), 7 39 (dd, 1H, J= 5,2 Hz) 7 28 (s,1H) 7 26 (s, 1H), 6,50 (s 1H), 5,44 (s, 2H), 5,31 (s, 2H), 2,40 (s, 3H) |
| 434 | $^1$H-NMR ($CD_3OD$, 400 MHz) δ 8,45 (d, 1H, J= 4,0 Hz), 8,41 (d 1H, J= 1,6 Hz), 7 68 (m 2H), 7,39 (dd, 1H, J= 4,8 Hz, 4,8 Hz) 7,31 (dd, 1H, J= 2 4 Hz, 2,8 Hz), 7,16 (ddd, 1H J= 2,8 Hz, 2,8 Hz 2 8 Hz), 6,50 (s, 1H) 5 45 (s, 2H), 5,32 (s, 2H), 2 41 (s 3H) |
| 435 | $^1$H-NMR ($CD_3OD$, 400 MHz) δ 8,45 (d 1H, J= 4,0 Hz), 8,42 (s, 1H), 7,60 (d 1H J= 8,0 Hz), 7,47 (m, 1H), 7,40 (dd 1H J= 5,2 Hz, 4,8 Hz), 7,07 (m 2H), 6 59 (s, 1H), 5,45 (s, 2H), 5,32 (s, 2H), 2,11 (s, 3H) |
| 436 | $^1$H-NMR ($CD_3OD$, 400 MHz) δ 8,45 (d, 1H, J= 4 8 Hz), 7,76 (ddd, 1H, J= 2 0 Hz, 1,6 Hz, 1,6 Hz), 7,51 (q, 2H), 7,30 (dd 1H, J= 5,2 Hz), 7,19 (d, 1H, J= 7,6 Hz), 7,14 (t, 2H, J= 8,8 Hz), 6,46 (s, 1H) 5,14 (s 2H), 5 26 (s 2H), 2,40 (s, 3H) |
| 437 | $^1$H-NMR ($CD_3OD$ 400 MHz) δ 8 46 (d, 1H, J= 4 8 Hz), 7,76 (ddd, 1H, J= 2 0 Hz 1,6 Hz, 1,6 Hz), 7,29 (dd, 1H, J= 4,8 Hz, 5,2 Hz) 7 21 (d, 1H, J= 7,6 Hz), 6,69 (dd, 2H, J= 8,0 Hz, 7,6 Hz), 6,57 (s, 1H), 5,46 (s, 2H), 5,28 (s, 2H), 2,43 (s, 3H) |
| 438 | $^1$H-NMR ($CD_3OD$, 400 MHz) δ 8,45 (d, 1H J= 4,4 Hz) 7 76 (ddd 1H, J= 2,0 Hz, 1,6 Hz, 1,6 Hz), 7,55 (m, 1H), 7,26 (m, 3H), 6,50 (s, 1H), 5,46 (s, 2H), 5,29 (s, 2H) 2,42 (s, 3H) |

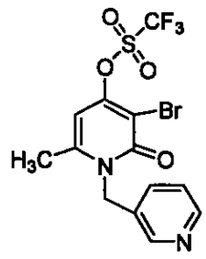
Ejemplo 439




3-bromo-4-[2-(4-fluorofenil)etil]-6-metil-1-(piridin-3-ilmetil)piridin-2(1H)-ona

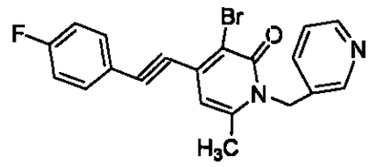
1114

Etapa 1 Preparacion de trifluorometanosulfonato de 3-bromo-6-metil-2-oxo-1-(piridin-3-ilmetil)-1,2-dihidropiridin-4-il



A una suspension (-30° C) de 3-bromo-4-hidroxi-6-metil-1-(piridin-3-ilmetil)piridin-2(1H)-ona (0,481g, 1,63 mmol) en diclorometano (6 mL) se le agrego trietilamina (0,28 mL, 2,04 mmol), seguido del agregado de una disolucion de trifluorometanosulfonico anhidro (0,4 mL, 2,44 mmol) en diclorometano (3 mL) La mezcla de reacción se agito a -30° C bajo nitrógeno durante 1 hora La mezcla de reacción se diluyo con diclorometano y se lavó con $NaHCO_3$/agua frios Los extractos organicos se secaron sobre $Na_2SO_4$ y el filtrado se concentró bajo presion reducida para proporcionar el compuesto deseado como un semisólido amarillo (0,6675 g, 95%) luego de secar ES-LRMS (M+H) m/z 427,1/429,1

Etapa 2 Preparacion de 3-bromo-4-[(4-fluorofenil)etinil]-6-metil-1-(piridin-3-ilmetil)piridin-2(1H)-ona

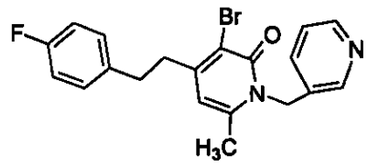


A una disolucion desgasificada de trifluorometanosulfonato de 3-bromo-6-metil-2-oxo-1-

1115

(piridin-3-ilmetil)-1,2-dihidropiridin-4-il (0,6675 g, 1,56 mmol) en DMF (9 mL) se agrego DIEA (0,35 mL, 2,03 mmol), 4-fluorofenilacetileno (0,235 mL, 1,95 mmol) y $PdCl_2(PPh_3)_2$ (0,11 g) La mezcla de reaccion se agito a temperatura ambiente bajo nitrogeno durante 1 hora y luego se calentó en un baño de aceite (65° C) bajo nitrogeno durante la noche Los disolventes se destilaron in vacuo y el residuo se purificó mediante cromatografia de columna rápida (metanol en acetato de etilo al 5%) Los extractos se concentraron para proporcionar el compuesto deseado (0,432 g, 69%) luego de secar $^1$H-NMR ($CD_3OD$, 400 MHz) δ 8,45 (s, 2H), 7,96 (s, 1H), 7,64 (m, 3H), 7,41 (dd, 1H, J = 4,8 Hz, 4,8 Hz), 7,18 (t, 2H, J = 8,8 Hz), 6,46 (s, 1H), 5,45 (s, 2H), 2,37 (s, 3H), ES-HRMS m/z 397,0361/399,0310 (M+H calculado para $C_{20}H_{15}N_2OFBr$ requiere 397,0346/399,0328)

Etapa 3 Preparacion de 3-bromo-4-[2-(4-fluorofenil)etil]-6-metil-1-(piridin-3-ilmetil)piridin-2(1H)-ona

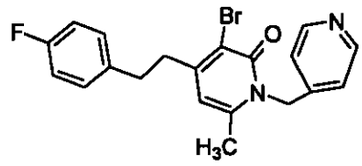



Una suspensión de 3-bromo-4-[(4-fluorofenil)etinil]-6-metil-1-(piridin-3-ilmetil)piridin-2(1H)-ona (0,430 g, 1,01 mmol) en acetato de etilo (5 mL) y EtOH (5 mL), que contenia $PtO_2$ (0,015 g) se agitó en atmósfera de hidrógeno (15 lppc) en una botella Fischer- Porter durante 2 horas La mezcla de reaccion se filtro y el filtrado se concentro para reducir el volumen El material se purifico mediante cromatografia de columna rápida (acetato de etilo) Las fracciones apropiadas se combinaron y concentraron bajo

1116

presion reducida para proporcionar el producto deseado (0,0943 g, 22 %) como un semisólido pegajoso luego de secar $^1$H-NMR ($CD_3OD$, 400 MHz) δ 8,46 (d, 2H, J= 26,4 Hz), 7,60 (d, 1H, J= 8,0 Hz), 7,41 (dd, 1H, J= 4,8 Hz, 4,8 Hz), 7,21 (m, 2H), 6,97 (t, 2H, J= 8,8 Hz), 6,24 (s, 1H), 5,43 (s, 2H), 2,93 (m, 4H), 2,31 (s, 3H), ES-HRMS m/z 401,0645/403,0603 (M+H calculado para $C_{20}H_{19}N_2OFBr$ requiere 401,0659/403,0641)

Ejemplo 440



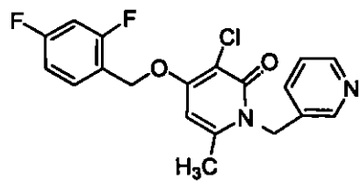

3-bromo-4-[2-(4-fluorofenil)etil]-6-metil-1-(piridin-4-ilmetil)piridin-2(1H)-ona

El compuesto del titulo se preparo mediante un procedimiento similar al descrito para la etapa 1 a la etapa 3 (0,374 g, 25%) Para la etapa 1 MS y $^1$H-NMR fueron compatibles con la estructura deseada $^1$H-NMR ($CD_3OD$, 400 MHz) δ 8,80 (d, 2H, J= 6,8 Hz), 7,89 (d, 2H, J=6,8 Hz), 6,61 (s, 1H), 5,66 (s, 2H), 2,45 (s, 3H), ES-HRMS m/z 427,9645/429,9625 (M+H calculado para $C_{13}H_{11}N_2O_4SF_3Br$ requiere 427,9599/429,9578)

MS y $^1$H-NMR para la Etapa 3 fueron compatibles con la estructura deseada $^1$H-NMR ($CD_3OD$, 400 MHz) δ 8,48 (d, 2H, J= 5,2 Hz), 7,21 (m, 2H), 7,13 (d, 2H, J= 5,2 Hz), 6,98 (t, 2H, J= 9,0 Hz), 6,26 (s, 1H), 5,43 (s, 2H), 2,95 (m, 4H), 2,25 (s, 3H), ES-HRMS m/z 401,0682/403,0636 (M+H calculado para $C_{20}H_{19}N_2OFBr$ requiere 401,0659/403,0641)

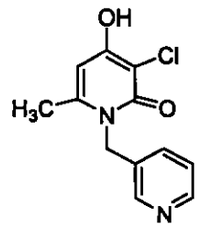
Ejemplo 441

1117



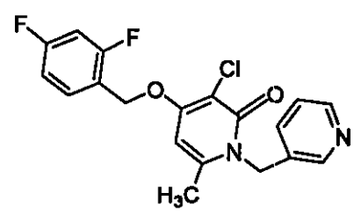
3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-1-(piridin-3-ilmetil)piridin-2(1H)-ona

Etapa 1 Preparación de 3-cloro-4-hidroxi-6-metil-1-(piridin-3-ilmetil)piridin-2(1H)-ona



A una suspensión de 4-hidroxi-6-metil-1-(piridin-3-ilmetil)piridin-2(1H)-ona (1,016 g, 4,7 mmol) en $MeCl_2$ (10 mL) se agregó NCS (1,21 g, 1,78 mmol) La mezcla de reacción se agitó a temperatura ambiente durante 24 horas bajo nitrogeno La suspensión se enfrió en un baño de hielo y se filtró Se lavo el sólido con $MeCl_2$ nuevo y se secó para proporcionar un sólido de color amarillo (1,00 g, 85%) luego de secar $^1$H-NMR ($CD_3OD$, 400 MHz) δ 8,54 (m, 2H), 7,85 (d 1H, J=1,6 Hz), 7,61 (m, 1H), 6,10 (s, 1H), 5,41 (s, 2H), 2,33 (s, 3H), ES-LRMS (M+H) m/z 251/253

Etapa 2 Preparacion de 3-cloro-4-[(2,4-difourobencil)oxi]-6-metil-1-(piridin-3-ilmetil)piridin-2(1H)-ona

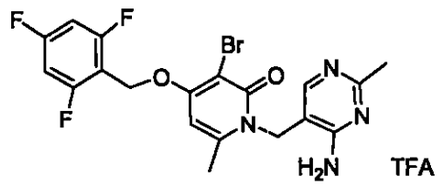


1118

7+88

A una disolución fría desgasificada de DMF (10 mL) y $PPh_3$ (resina, 2,2 g, 6,6 mmol) se agregó DEAD (1,038 mL, 6,6 mmol) La mezcla de reaccion se agitó a -10 °C durante 20 minutos bajo nitrogeno Una disolución de 3-cloro-4-hidroxi-6-metil-1-(p ridin-3-ilmetil)piridin-2(1H)-ona (1,00 g, 4,0 mmol), y alcohol 2,4-difluorobencilo (0,66 mL, 6,0 mmol) en DMF (10 mL) se agrego a la suspensión de resina La mezcla de reacción se agito a -10 °C durante 30 mintuos y luego se permitió que se agitara a temperatura ambiente durante 1 hora La resina se filtró y se enjuago con MeOH nuevo y el filtrado se concentro El residuo se disolvio en acetato de etilo y se purifico por cromatografia de columna rapida (metanol al 5% en acetato de etilo) Las fracciones apropiadas se concentraron $^1$H-NMR ($CD_3OD$, 400 MHz) δ 8,45 (ddd, 2H, J= 1,6 Hz, 1,6 Hz, 1,6 Hz), 7,61 (m, 2H), 7,41 (dd, 1H, J=4,4 Hz, 4,8 Hz), 7,02 (m, 2H), 6,55 (s, 1H), 5,43 (s, 2H), 5,29 (s, 2H), 2,41 (s, 3H), ES-HRMS m/z 377,0882/379,0840 (M+H calculado para $C_{19}H_{16}N_2O_2F_2Cl$ requiere 377,0863/379,0840)

Ejemplo 442



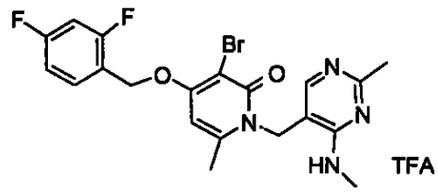

Trifluoroacetatc 1-[(4-amino-2-metilpirimidin-5-il)metil]-3-bromo-6-metil-4-[(2,4,6-trifluorobencil)oxi]piridin-2(1H)-ona

El compuesto del titulo se preparo mediante un procedimiento similar al descrito para el Ejemplo 385, etapa 2 (0,142 g, 9%) $^1$H-NMR ($CD_3OD$, 400 MHz) δ 7,64 (s, 1H), 7,00 (m, 2H), 6,66 (s, 1H), 5,29 (s, 2H), 5,18 (s,

2H), 2,50 (s, 3H), 2,47 (s,3H), ES-HRMS m/z 469,0488/471,0464 (M+H calculado para $C_{19}H_{17}N_4O_2F_3Br$ requiere 469,0481/471,0463)

1119

Ejemplo 443

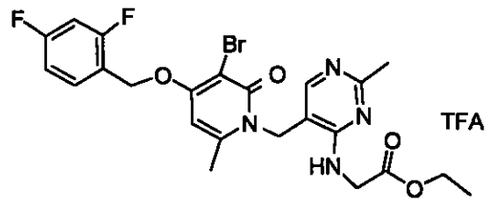



3-bromo-4-[(2,4 difluorobencil)oxi]-6-metil-1-{[2-metil-4-(metilamino)pirimidin-5-il]metil}piridin-2(1H)-ona

A una disolucion de hidrocloruro 1-[(4-amino-2-metilpirimidin-5-il)metil]-3-bromo-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona (0,15 g, 0,3 mmol) en DMF (3 mL) se agrego DBU (0,09 mL, 0,6 mmol) La disolución se enfrio en un baño de hielo y se agregó yodometano (0,019 mL, 0,3 mmol) La mezcla de reacción se agito a temperatura ambiente bajo nitrogeno durante 2 horas La reaccion se purifico mediante HPLC de fase inversa utilizando $CH_3CN$/agua al 10-90% (gradiente de 30 min) a un caudal de 100 mL/min Las fracciones apropiadas (m/z = 465 M+H) se combinaron y se deshidrataron por congelación para procucir el producto deseado (0,036 g, 25% ) como un polvo blanco $^1$H-NMR ($CD_3OD$, 400 MHz) δ 7,72 (s, 1H), 7,60 (m, 1H), 7,03 (m, 2H), 6,62 (s, 1H), 5,31 (s, 2H), 5,16 (s, 2H), 3,77 (s,3H), 2,60 (s, 3H), 2,47 (s, 3H), ES-HRMS m/z 465,0717/467,0712 (M+H calculado para $C_{20}H_{20}N_4O_2F_2Br$ requiere 465,0732/467,0714)

Ejemplo 444

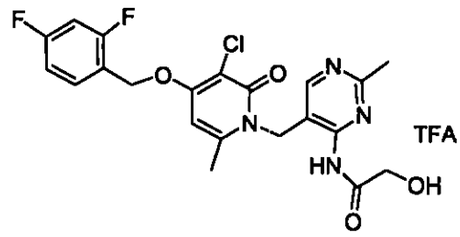
1120




N-(5-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}-2-metilpirimidin-4-il)glicinato trifluoroacetato de etilo

El compuesto del titulo se preparo mediante un procedimiento similar al descrito para el Ejemplo 442E excepto que la mezcla de reaccion tenia que calentarse a una temperatura de baño de aceite de 70° C durante 2 dias (0,1384 g, 51%) $^1$H-NMR ($CD_3OD$, 400 MHz) δ 7,78 (s, 1H), 7,61 (m, 1H), 7,03 (m, 2H), 6,61 (s, 1H), 5,30 (s, 2H), 5,18 (s, 2H), 5,03 (s,2H), 4,27 (q, 2H), 2,55 (s, 3H), 2,46 (s, 3H), 1,28 (t, 3H, J=7,0 Hz), ES-HRMS m/z 537,0936/539,0932 (M+H calculado para $C_{23}H_{24}N_4O_4F_2Br$ requiere 537,0943/539,0926)

Ejemplo 445



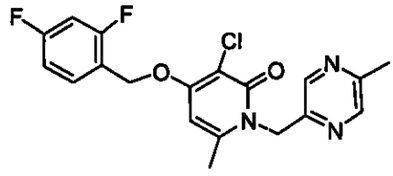

Trifluoroacetatc N-(5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}-2-metilpirimidin-4-il)-2-hidroxiacetamida

A una disolución enfriada de trifluoroacetato 1-[(4-amino-2-metilpirimidin-5-il)metil]-3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona (0,200 g, 0,38 mmol) en DMF (20 mL)y una cantidad catalitica de DMAP se agrego trietilamina(0,064 mL, 0,38 mmol) La reaccion se

174

agito a -20° C y se agregó cloruro de acetoxiacetilo (0,082 mL, 0,76 mmol) La reaccion se agitó fria durante 15 minutos y luego se permitió que se calentara a temperatura ambiente durante 3 horas La reacción se vigilo mediante LR-ESMS (m/z) = 466 Despues de 3 horas la reaccion estaba incompleta Se agregó cloruro de acetoxiacetilo (0,05 mL, 0,466 mmol) y trietilamina (0,2 mL, 1,43 mmol) a la mezcla de reaccion y se continuo agitando durante la noche a temperatura ambiente A la mañana siguiente se calento la reaccion a 65° C durante 3 horas Se elimino el disolvente in vacuo y se agregó 1N LiOH (2,5 mL) al residuo La reacción se calento a 60° C durante 5 horas La reaccion se diluyó con acetonitrilo y agua (1 1) y se purifico mediante HPLC de fase inversa en $CH_3CN$/water al 10-90% (gradiente de 30 minutos) a un caudal de 50 mL/min Las fracciones apropiadas se deshidrataron por congelacion para proporcionar el producto deseado (0,020 g, 9%) $^1$H-NMR ($CD_3OD$, 400 MHz) δ 8,04 (s, 1H), 7,6 (m, 1H), 7,02 (m, 1H), 6,59 (s, 1H), 5,30 (s, 2H), 5,24 (s, 2H), 4,26 (s,1H), 2,60 (s, 3H), 2,43 (s, 3H), ES-HRMS m/z 465,1161(M+H calculado para $C_{21}H_{20}N_4O_4F_2Cl$ requiere 465,1136)

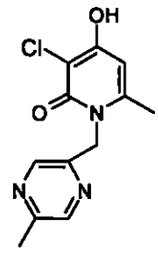
Ejemplo 446




3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-1-[(5-metilpirazin-2-il)metil]piridin-2(1H)-ona

Etapa 1 Preparación de 3-cloro-4-hidroxi-6-metil-1-[(5-metilpirazin-2-il)metil]piridin-2(1H)-ona

1122



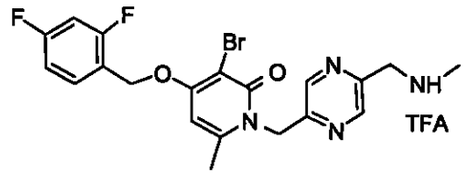
A una disolucion de 4-hidroxi-6-metil-1-[(5-metilpirazin-2-il)metil]piridin-2(1H)-ona (1,00g, 4,3 mmol) en acido acético glacial (10 mL) se agrego NCS (0,79 g, 5,94 mmol) La reacción se agitó a 60° C durante 6 horas El disolvente se eliminó bajo presion reducida y el residuo resultante se trituro con acetato de etilo El producto deseado se filtro y seco (0,80 g, 69%) $^1$H NMR ((CD$_3$OD/400 MHz) δ 8,47 (s, 1H), 8,42 (s, 1H), 6,08 (s, 1H), 5,36 (s, 2H), 2,50 (s, 3H), 2,43 (s, 3H) ES-HRMS m/z 266,0691 (M+H calculado para $C_{12}H_{13}N_3O_2Cl$ requiere 266,0691)

Etapa 2 Preparacion de 3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-1-[(5-metilpirazin-2-il)metil]piridin-2(1H)-ona

A una disolución de 3-cloro-4-hidroxi-6-metil-1-[(5-metilpirazin-2-il)metil]piridin-2(1H)-ona (2,48 g, 9,3 mmol) en DMA (7 mL) se agrego $K_2CO_3$ (1,54 g, 11,0 mmol) y luego bromuro 2,4-difluorobencil (1,2 mL, 9,3 mmol) La mezcla de reaccion se agito a temperatura ambiente bajo nitrógeno durante 1,5 horas El disolvente se destiló in vacuo El residuo resultante se diluyó en diclorometano y se lavó con agua Los extractos organicos se concentraron y el residuo resultante se purifico mediante cromatografia de columna rapida (acetato de etilo) Las fracciones apropiadas se combinaron y se concentraron $^1$H NMR (CD$_3$OD/400 MHz) δ 8,49 (d, 1H, J=1,2 Hz), 8,40 (s, 1H), 7,59 (m, 1H), 7,04 (m, 2H), 6,54 (s, 1H), 5,41 (s, 2H),

5,28 (s, 2H), 2,54 (s, 3H), 2,40 (s,3H), ES-HRMS m/z 392,1014 (M+H calculado para $C_{19}H_{17}N_3O_2ClF_2$ requiere 392,0972)

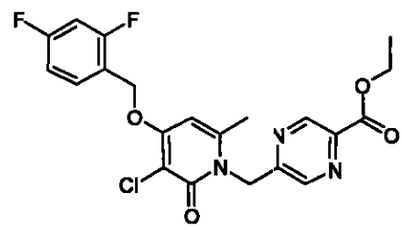
Ejemplo 447




Trifluoroacetato 3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-({5-[(metilamino)metil]pirazin-2-il}metil)piridin-2(1H)-ona

A una suspension de 3-bromo-1-{[5-(clorometil)pirazin-2-il]metil}-4-[(2,4-cifluorobencil)oxi]-6-metilpiridin-2(1H)-ona (0,25 g, 0,53 mmol) en THF se agrego metilamina (1 mL, 2,1 mmol) La reacción se sello y se agito a temperatura ambiente durante la noche La mezcla de reaccion se diluyo con acetonitrilo agua (1 1) y se purificó mediante HPLC de fase inversa en $CH_3CN$/water al 10-90% (gradiente de 30 minutos) a un caudal de 70 mL/min Las fracciones apropiadas se combinaron y se deshidrataron por congelacion para proporcionar el producto deseado (0,22 g, 71%) como un solido amorfo $^1H$ NMR ($CD_3OD$/400 MHz) δ 8,73(s, 1H), 8,55 (s, 1H), 7,6 (m, 2H), 7,02 (m, 1H), 6,54 (s, 1H), 5,47 (s, 2H), 5,29 (s, 2H), 4,37 (s, 2H), 2,78 (s, 3H), 2,56 (s, 3H) ES-HRMS m/z 465,0732/467 0709 (M+H calculado para $C_{20}H_{20}N_4O_2BrF_2$ requiere 465,0732/467,0714)

Ejemplo 448

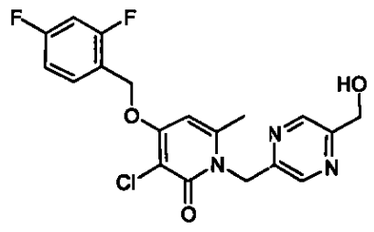


1124

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}pirazina-2-carboxilato de etilo

A una mezcla de 3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona (0,59 g, 2,07 mmol) y 5-(bromometil)pirazina-2-carboxilato de etilo(0,62 g, 2,4 mmol) en THF (15 mL) se agregó NaH (0,06 g, 2,4 mmol) La reacción se agito a 60° C durante 3,5 horas El disolvente se elimino bajo presion reducida y el residuo se dividio sobre diclorometano y acido citrico (5%) Los extractos organicos se lavaron con agua y se secaron sobre $Na_2SO_4$ (anhidro) Los extractos orgánicos se concentraron y el residuo resultante se purifico mediante cromatografía de columna rapida (acetato de etilo al 100%) Las fracciones apropiadas se combinaron y se concentraron bajo presión reducida para eliminar el disolvente $^1H$ NMR ($CD_3OD$/400 MHz) δ 9,11 (d, 1H, J = 1,6 Hz), 8,77 (s, 1H), 7,52 (m 1H), 7,02 (m, 2H), 6,57 (s, 1H), 5,53 (s, 2H), 5,30 (s, 2H), 4,49 (q, 2H), 2,52 (s, 3H), 1,39 (t, 3H, J= 7,2 Hz), ES-HRMS m/z 450,1045 (M+H calculado para $C_{21}H_{19}N_3O_4ClF_2$ requiere 450,01027)

Ejemplo 449



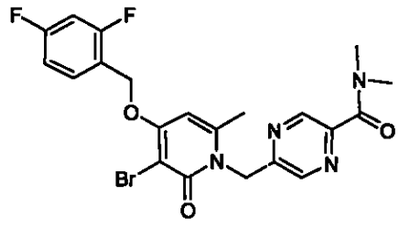

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[(5-hidroximetil)pirazin-2-il]metil}-6- metilpiridin-2(1H)-ona

A una suspensión de 5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}pyrazina-2-carboxilato de etilo (4,0 g, 8,9 mmol)

1.125

en THF t-butanol (1 1) (10 mL) se agrego $NaBH_4$ (0,46 g, 12,4 mmol) La reaccion se agitó a temperatura ambiente bajo argon durante la noche La mezcla de reaccion se enfrio con acido acetico (2 mL) y el disolvente se elimino in vacuo El residuo se trituro con agua y se filtro El sólido se lavo con agua dulce seguido por etanol El solido se purificó mediante cromatografia de columna rapida (acetato de etilo al 100%) Las fracciones apropiadas se combinaron y se corcentraron bajo presión reducida para proporcionar el compuesto deseado (1,58 g, 44%) como un solido de color blanco $^1$H-NMR ($CD_3OD$, 400 MHz) δ 8,59 (s, 1H), 8,56 (s, 1H), 7,52 (m, 1H), 7,01 (m, 2H), 6,55 (m, 1H), 5,45 (s, 2H), 5,29(s,2H), 4,71 (2H), 2,54 (s, 3H), ES-HRMS m/z 408,0940(M+H calculado para $C_{19}H_{17}N_3O_3ClF_2$ requiere 408,0921)

Ejemplo 450



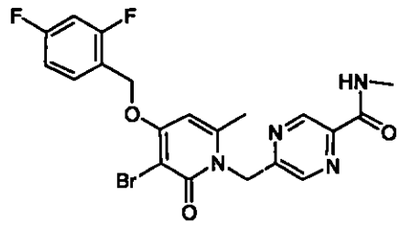
5-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}-N,N-dimetilpirazina-2-carboxamida

A una disolución fria de ácido 5-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}pirazina-2-carboxilico (0,175 g, 0,37 mmol) en DMF (5 mL, -10° C) se agrego IBCF (isobutilcloroformato)(0,046 mL, 0,35 mmol) seguido por NMM (0,041 mL 0,37 mmol) La reaccion se activo durante 20 minutos a -15° C luego de lo cual se agrego dimetilamina (0,375 mL, 0,74 mmol) La reacción se agitó a -10°C a temperatura ambiente durante 45 minutos El disolvente se eliminó in vacuo y el residuo se

1.126

purifico mediante HPLC de fase inversa utilizando $CH_3CN$/agua al 10-90% (gradiente de 30 min) a un caudal de 70 mL/min Las fracciones apropiadas se combinaron y se deshidrataron por congelación para producir el producto deseado (0,140g, 75% ) como un polvo blanco $^1$H-NMR ($CD_3OD$, 400 MHz) δ 8,68 (s, 1H), 8,67 (s, 1H), 7,52 (m, 1H), 7,02 (m, 2H), 6,54 (s, 1H), 5,50 (s, 2H), 5,30 (s,2H), 3,11 (s, 3H), 3,07 (s, 3H), 2,55 (s, 3H), ES-HRMS m/z 493,0680/495,0657 (M+H calculado para $C_{21}H_{20}N_4O_3BrF_2$ requiere 493,0680/495,0657)

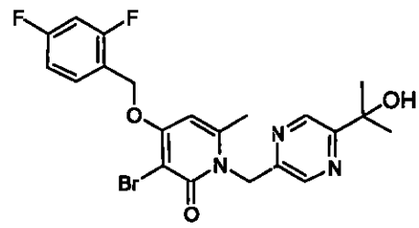
Ejemplo 451



5-{[3-bromo-4-[ 2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}-N-metilpirazina-2-carboxamida

El compuesto del titulo se preparo esencialmente como en el Ej 450, sustituyendo dimetilamina con metilamina $^1$H-NMR ($CD_3OD$, 400 MHz) δ 9,07 (s, 1H), 8,68 (s, 1H), 7,54 (m, 1H), 7,02 (m, 2H), 6,54 (s, 1H), 5,52 (s, 2H), 5,30 (s,2H), 2,94 (s, 3H), 2,54 (s, 3H), ES-HRMS m/z 479,0542/481,0518 (M+H calculado para $C_{20}H_{18}N_4O_3BrF_2$ requiere 479,0525/481,0507)

Ejemplo 452

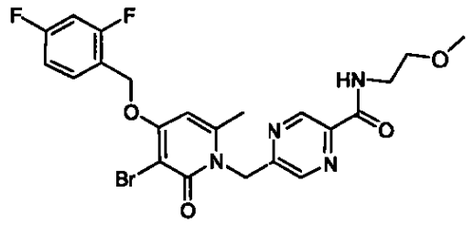


1.172

3-bromo-4-[(2,4-difluorobencil)oxi]-1-{[5-(1-hidroxi-1-metiletil)pirazin-2-il]metil}-6-metilpiridin-2(1H)-ona

A un matraz frio de MeMgBr (1,59 mL, 1,0 mmol) se le agrego una suspension de 5-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}pirazina-2-carboxilato(0,5 g, 1,0 mmol)en THF (20 mL) La reacción se agito a 0 °C durante 1,5 horas y luego a temperatura ambiente durante la noche La reaccion se enfrio rapidamente con acido citrico frio (25 mL,5%) y se extrajo con acetato de etilo (2 x 100 mL) Se lavó los extractos organicos con agua dulce Los extractos organicos se concentraron y purificaron mediante HPLC de fase inversa utilizando $CH_3CN$/agua al 10-90% (gradiente de 30 min) a un caudal de 70 mL/min Las fracciones apropiadas se combinaron y se deshidrataron por congelación para producir el producto deseado (29,9 mg, 6% ) $^1H$ NMR ($CD_3OD$/400 MHz) δ 8,76 (d, 1H, J = 1,6 Hz), 8,54 (d, 1H, J=1,2 Hz), 7,52 (m 1H), 7,02 (m, 2H), 6,52 (s, 1H), 5,45 (s, 2H), 5,29 (s, 2H), 2,55 (s, 3H), 1,52 (s, 6H), ES-HRMS m/z 480,0745/482,0722 (M+H calculado para $C_{21}H_{21}N_3O_3BrF_2$ requiere 480,0729/482,0711)

Ejemplo 453

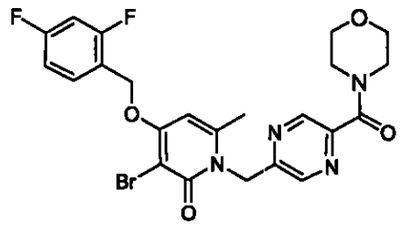



5-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}-N-(2-metoxietil)pirazina-2-carboxamida

9128

El compuesto del título se preparó esencialmente como en el Ej 450, sustituyendo dimetilamina con 2-metoxietilamina $^1$H NMR ($CD_3OD$/400 MHz) δ 9,08 (d, 1H, J = 1,2 Hz), 8,70 (d, 1H, J=1,2 Hz), 7,61 (m, 1H), 7,04 (m, 2H), 6,54 (s, 1H), 5,53 (s, 2H), 5,30 (s, 2H), 3,56 (m, 4H), 3,30 (s, 3H), 2,54 (s, 3H), ES-HRMS m/z 523,0822/525,0810 (M+H calculado para $C_{22}H_{22}N_4O_4BrF_2$ requiere 523,0787/525,0770)

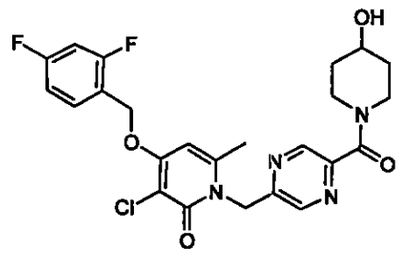
Ejemplo 454



3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-{[5-morfolin-4-ilcarbonil]pirazin-2-il]metil}piridin-2(1H)-ona

El compuesto del título se preparó esencialmente como en el Ej 450, sustituyendo dimetilamina con morfolina $^1$H NMR ($CD_3OD$/400 MHz) δ 8,77 (d, 1H, J = 1,6 Hz), 8,67 (s, 1H), 7,54 (m, 1H), 7,02 (m, 2H), 6,54 (s, 1H), 5,50 (s, 2H), 5,30 (s, 2H), 3,75 (s, 4H), 3,59 (dd, 4H, J= 5,6 Hz, 5,2 Hz), 2,55 (s, 3H), ES-HRMS m/z 535,0816/537,0817 (M+H calculado para $C_{23}H_{22}N_4O_4BrF_2$ requiere 535,0787/537,0770)

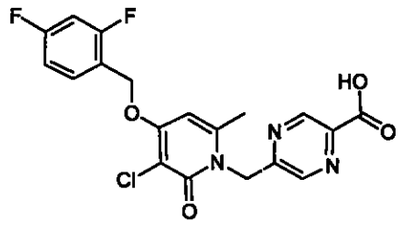
Ejemplo 455



3-cloro-4-[(2,4-difluorobencil)oxi]-1-({5-[(4-hidroxipiperidin-1-il)carbonil]pirazin-2-il}metil)-6-metilpiridin-2(1H)-ona

1.129

Etapa 1 Preparación de acido 5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}pirazina-2-carboxilico



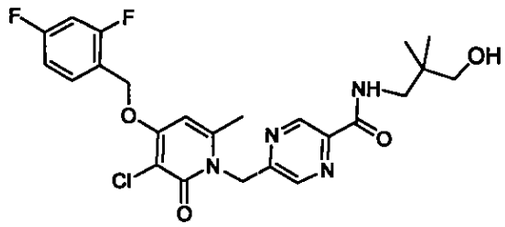
Una mezcla de 5 {[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}pyrazina-2-carboxilato de etilo (1,03g, 2,3 mmol) en 1N NaOH (3,4 ml, 3,45 mmol, EtOH/agua 1 1 vol/vol) se agito a temperatura ambiente durante 2 horas La mezcla de reacción se enfrio rapidamente con acido citrico al 5% y se filtro El solido se lavo con agua y se seco para proporcionar el producto deseado (1,011 g, 100%) como un solido blanco $^1$H-NMR ($CD_3OD$, 400 MHz) δ 9,02 (s, 1H), 8,60 (s, 1H), 7,60 (m, 1H), 7,04 (m, 2H), 6,55 (s, 1H), 5,50 (s, 2H), 5,30(s,2H), 2,52 (s, 3H), ES-HRMS m/z 422,0732(M+H calculado para $C_{19}H_{15}N_3O_4ClF_2$ requiere 422,0714)

Etapa 2 Preparacion de 3-cloro-4-[(2,4-difluorobencil)oxi]-1-({5-[(4-hidroxipiperidin-1-il)carbonil]pirazin-2-il}metil)-6-metilpiridin-2(1H)-ona

El compuesto del título se preparó mediante un procedimiento similar al descrito para el Ejemplo 453(0,1396 g, 47%) $^1$H-NMR ($CD_3OD$, 400 MHz) δ 8,67 (s, 2H), 7,59 (m, 1H), 7,02 (m, 2H), 6,57 (s, 1H), 5,49 (s, 2H), 5,30 (s, 2H), 4,16 (m, 1H), 3,89 (septeto, 1H), 3,72 (m, 1H), 3,38 (m, 2H), 2,56 (s, 3H), 1,93 (m, 1H), 1,83 (m, 1H), 1,45 (m, 2H), ES-HRMS m/z 505,1485/505,1485 (M+H calculado para $C_{24}H_{24}N_4O_4ClF_2$ requiere 505,1149)

Ejemplo 456

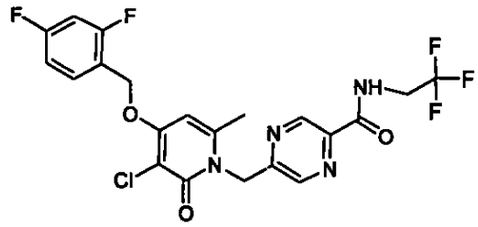
1130



5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}-N-(3-hidroxi-2,2-dimetilpropil)pirazina-2-carboxamida

El compuesto del titulo se preparo mediante un procedimiento similar al descrito para el Ejemplo 455 (0,215 g, 71%) $^1$H NMR ($CD_3OD$/400 MHz) δ 9,08 (d, 1H, J = 1,2 Hz), 8,71 (d, 1H, J=1,6 Hz), 7,58 (m, 1H), 7,02 (m, 2H), 6,57 (s, 1H), 5,52 (s, 1H), 5,30 (s, 1H), 3,31 (s, 4H), 2,55 (s, 3H), 0,912 (s, 6H), ES-HRMS m/z 507,1630(M+H calculado para $C_{24}H_{26}N_4O_4ClF_2$ requiere 507,1605)

Ejemplo 457



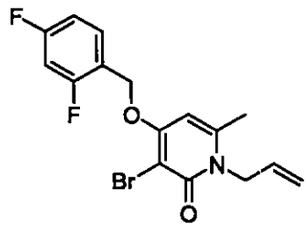
5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}-N-(2,2,2-trifluoroetil)pirazina-2-carboxamida

El compuesto del titulo se preparo mediante un procedimiento similar al descrito para el Ejemplo 455 excepto que no se requirio ninguna purificacion, solamente fue necesaria una extraccion con $NaHCO_3$/acetato de etilo (0,2176 g, 73%) $^1$H NMR ($CD_3OD$/400 MHz) δ 9,11 (d, 1H, J = 1,6 Hz), 8,73 (d, 1H, J=1,3 Hz), 7,59 (m 1H), 7,02 (m, 2H), 6,57 (s, 1H), 5,53 (s, 2H), 5,30 (s, 2H), 4,01 (q, 2H),

1131

2,54 (s, 3H), ES-HRMS m/z 503,0930 (M+H calculado para $C_{21}H_{17}N_4O_3ClF_5$ requiere 503,0904)

Ejemplo 458



1-alil-3-bromo-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona

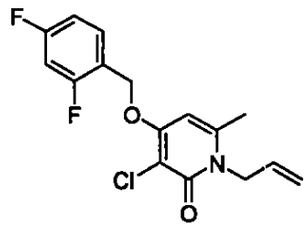
Etapa 1 1-alil-4-hidroxi-6-metilpiridin-2(1H)-ona 4-hidroxi-6-metil-2-pirona (2g, 16 mmol) se agito en agua (25 mL) Se agregó alilamina (1,2 ml, 16 mmol) a la reaccion La reaccion luego se calento a 100 °C punto en el cual la reacción se volvio homogenea La reacción se agito a 100° C durante 2 hs Después se dejo enfriar la reaccion hasta la temperatura ambiente luego de lo cual se formó un precipitado blanco El precipitado se aislo mediante filtracion por aspiracion Luego de lavar adicionalmente con agua, se obtuvo 1,8 g (69%) de un sólido blanquecino

Etapa 2 1-alil-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona A una disolución agitada de la pirona precedente (4,0 g , 24 mmol) en DMF (75 ml) se le agrego $Cs_2CO_3$ (7,8 g, 24 mmol) seguido por el agregado de bromuro de 2,4-difluorobencil (3,4 mmol, 26,4 mmol) La mezcla resultante se agito a temperatura ambiente durante 2 hs Se agregó $Cs_2CO_3$ (1 g) y bromuro (1 ml) adicionales y la reaccion se agito durante dos horas mas El $Cs_2CO_3$ se elimino mediante filtracion por aspiración El DMF se eliminó bajo vacio y el material crudo se purifico mediante cromatografia rapida La elusion con acetato de etilo-hexanos (2 1 a 1 1) proporciono 1,5 g (21%) del compuesto deseado

1132

Etapa 3 1-alil-3-bromo-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona A una suspension agitada de la piridinona precedente (1 g, 3,4 mmol) en $CH_3CN$ (10 ml) se agrego n-bromosuccinimida (670 mg, 3,8 mmol) La mezcla de reacción se agito, a temperatura ambiente, durante 3 hs El producto se obtuvo por filtracion de la mezcla de reacción y lavado del solido con éter de dietilo $^1$H-NMR ($DMSO_{d6}$/400 MHz) δ 7,62 (aprox q, J = 8,8 hz, 1H), 7,31 (ddd, J = 12,0, 9,6, 2,8 hz, 1H), 7,15 (aprox dtd, J = 8,4, 2,4, 0,8 Hz, 1H), 6 50 (s, 1H), 5,87 (ddt, J = 12,4, 10,4, 5,6 Hz, 1H), 5,30 (s, 2H), 5,10 (dd, J = 10, 1,6 Hz, 1H), 4,87 (dd, J = 17,6, 1,6 Hz, 1H), 4,64 (m, 2H), 2,34 (s, 3H), 19F-NMR ($DMSO_{d6}$/282,2 MHz) -109,68 (quin, J = 1H), -113,66(cuar, J = 1H), HRMS m/z 370,0255 (M + H calculado para $C_{16}H_{15}BrF_2NO_2$ = 3'0,0246)

Ejemplo 459




1-alil-3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona

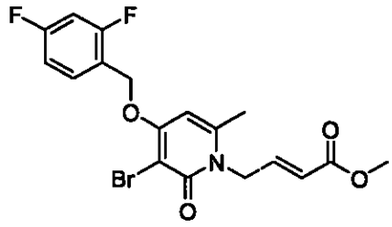
Etapa 1 1-alil-3-cloro-4-hidroxi-6-metilpiridin-2(1H)-ona A una disolucion agitada de 1-alil-4-hidroxi-6-metilpiridin-2(1H)-ora (500 mg, 3,0 mmol) en $CH_3CN$ (10 ml), a temperatura ambiente, se agregó secuencialmente n-bromosuccinimida (440 mg, 3,3 mmol) y acido dicloroacetico (546 µl, 6,62 mmol) La mezcla resultante se agitó durante 2 hs La mezcla heterogenea se filtró y el sólido se lavo con $CH_3CN$ adicional para proporcionar 350 mg (59%) del producto deseado como un solido de color tostado $^1$H-NMR ($DMSO_{d6}$/300 MHz) δ 11,16 (s, 1H), 5,98-5,86 (m, 2H), 5,12

1133

(dd, J = 10,5, 1,5 Hz, 1H), 4,89 (dd, J = 17,1, 1,5 Hz, 1H), 4,63-4,61 (m, 2H), 2,29 (s, 3H) ES-HRMS m/z 200,050 (M + H calculado para $C_9H_{11}ClNO_2$ = 200,0470)

Etapa 2 1-alil-3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona El compuesto del titulo se preparo mediante el esquema de proceso de la sintesis del Ejemplo 458, etapa3 $^1$H-NMR ($DMSO_{d6}$/300 MHz) δ 7,67 (aprox q, J = 8,4 hz, 1H), 7,36 (aprox dt, J = 10,2, 2,7 hz, 1H), 7,15 (m, 1H), 6,58 (s, 1H), 5,93 (ddt, J = 15,3, 9,6, 4,8 Hz, 1H), 5,30 (s, 2H) 5,15 (dd, J = 10,2, 1,2 Hz, 1H), 4,92 (dd, J = 17,4, 1,2 Hz, 1H), 4,69-4,67 (m, 2H), 2,41 (s, 3H) ES-HRMS m/z 326,0760 (M + H calculado para $C_{16}H_{15}F_2NO_2$ = 326,0790)

Ejemplo 460



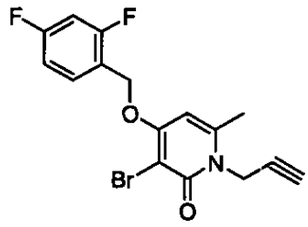

(2E)-4-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]but-2-enoato de metilo

A una suspension agitada de NaH (277 mg, 11 mmol) en THF anhidro (30 ml), la cual se enfrio a 0 °C, se agregó lentamente 3-bromo-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona (3,3 g, 10 mmol) La suspension resultante se agito durante 15 min, luego de lo cual se agrego a la reaccion 4-bromocrotonato (1,4 ml, 12 mmol) Se elimino el baño de hielo y la reaccion se calentó a reflujo durante 16 hs La reaccion se enfrio repentinamente mediante el agregado de 1N $NH_4Cl$ Las capas se separaron y la capa acuosa se extrajo con $CH_2Cl_2$ (5x) Los materiales organicos se combinaron, se secaron y se concentraron in vacuo El material amarillento crudo

1134

luego se trituro con $Et_2O$ para proporcionar, luego de la filtracion y el secado, 1,8 g (43%) de un sólido blanco $^1H$-NMR ($DMSO_{d6}$/300 MHz) δ 7,65 (aprox q, J = 8,7 hz, 1H), 7,36 (aprox dt, J = 12,0, 3,0 hz, 1H), 7,17 (dt, J = 8,4, 1,8 Hz, 1H), 6,94 (dt, J = 15,9, 4,5 Hz, 1H), 6,57 (s, 1H), 5,52 (d, J = 15,9 Hz, 1H), 5,29 (s, 2H), 4,84 (m, 2H), 3,63 (s, 3H), 2,33 (s, 3H) ES-HRMS m/z 428,0301 (M + H calculado para $C_{18}H_{17}F_2NO_4$ = 428,0310)

Ejemplo 461



3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-prop-2-inilpiridin-2(1H)-ona

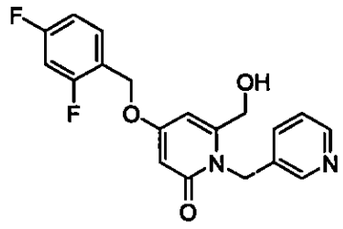
Etapa 1 4-[(2,4-difluorobencil)oxi]-6-metil-1-prop-2-inilpiridin-2(1H)-ona El compuesto del titulo se preparo por alquilación de 4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona (2,5 g, 10 mmol) con bromuro de propargilo (1,3 ml, 11,0 mmol) como se describió en lo precedente para prcporcionar 1,3 g (44%) del producto deseado $^1H$- NMR ($DMSO_{d6}$/300 MHz) δ 7,60 (aprox q, J = 8,4 hz, 1H), 7,35-7,27 (m, 1H), 7,16-7,10 (m, 1H), 5,94 (d, J = 2,1 Hz, 1H), 5,88 (d J = 3,0 Hz, 1H), 5,03 (s, 2H), 4,76 (d, J = 2,4, Hz, 2H), 3,31 (s, 3H), 3,24 (t, J = 2,4 Hz, 1H), 2,39 (s, 3H), LS-HRMS m/z 290,0994 (M + H calculado para $C_{16}H_{14}F_2NO_2$ = 290,0993)

Etapa 2 La bromınación de 4-[(2,4-difluorobencil)oxi]-6-metil-1-prop-2-inilpiridin-2(1H)-ona (500 mg, 1,67 mmol) con NBS (300 mg, 1,67 mmol) se llevo a cabo en la forma descrita en lo precedente para proporcionar 350 mg (57%)

1.135

del compuesto deseado $^1$H-NMR ($DMSO_{d6}$/300 MHz) δ 7,67 (aprox q, J = 9,0 hz, 1H), 7,36 (aprox dt, J = 10,5, 2,4 hz, 1H), 7,23-7,16 (m, 1H), 6,60 (s, 1H), 5,29 (s, 2H), 4,90 (d, J = 2,4, Hz, 1H), 3,35 (s, 3H), 3,32 (s, 1H), 2,53 (s, 3H), ES-HRMS m/z 368,0107 (M + H calculado para $C_{16}H_{13}BrF_2NO_2$ = 368,0098)

Ejemplo 462




4-[(2,4-difluorobencil)oxi]-6-(hidroximetil)-1-(piridin-3-ilmetil)piridin-2(1H)-ona

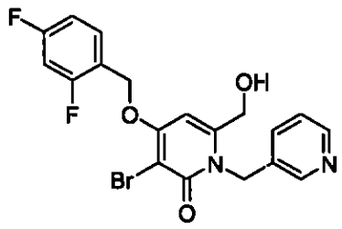
Etapa 1 A una suspension de (4-[(2,4-difluorobencil)oxi]-6-metil-1-(piridin-3-ilmetil)piridin-2(1H)-ona (710 mg, 2 mmol) en dioxano (10 mL) se agrego dióxido de selenio (1,1g, 10 mmol) La mezcla resultante se calento a 160 °C en un tubo sellado de 125 mL durante 1 hora La reacción se filtró a traves de un embudo de vidrio poroso El filtrado se lavo con $CH_2Cl_2$-MeOH (10 1) Los materiales organicos se combinaron y se concentraron in vacuo El material crudo se purifico mediante cromatografía rapida La elucion con hexanos (50 50 □ 0 100) produjo 450 mg (63%) de aldehido $^1$H-NMR ($DMSO_{d6}$/400 MHz) δ9,48 (s, 1H, CHO)

Etapa 2 El aldehido (350 mg, 1 mmol) se disolvió en MeOH (4 mL) y se enfrio a 0 °C A esta mezcla se agrego $NaBH_4$ (28 mg, 1 mmol) en una porcion Despues de 30 minutos, se agregó a la reacción NaBH4 (20 mg) adicional Luego se elimino el MeOH bajo vacio El residuo se diluyo con 1N $NH_4Cl$ y luego se extrajo con $CH_2Cl_2$(4X) Los

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materiales organicos se combinaron, se secaron y se concentraron in vacuo El producto crudo amarillento entonces se absorbió en $CH_2Cl_2$-$Et_2O$ (1 1) Luego de reposar durante un periodo de tiempo se obtuvo un precipitado blanco La filtración y el lavado con $Et_2O$ adicional produjo, luego de secar, 250 mg (55%) del alcohol deseado $^1$H-NMR ($DMSO_{d6}$/400 MHz) δ8,42 (dd, J = 4,4, 1,6 Hz, 1H) 8,37 (d, J = 1,6 Hz, 1H), 7,61 (aprox q, J = 8,0 Hz, 1H), 7,45 (d, J = 8,0 Hz, 1H), 7,32-7,27(M, 2H), 7,12 (dt, J = 8,4, 1,6 Hz, 1H), 6,07 (d, J = 2,8 Hz, 1H), 5,99 (d, J = 12,8 Hz, 1H), 5,63 (br s, 1H), 5,18 (s, 2H), 5,09 (s, 2H), 4,29 (s, 2H) LC/MS, $t_r$ = 1,19 minutos (5 a 95% acetonitrilo/agua durante 5 minutos a 1 ml/min con deteccion de 254 nm, a 50 °C) ES-MS m/z 359,1 (M+H)

Ejemplo 463

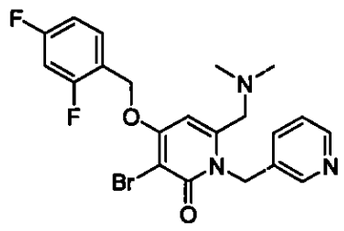



3-bromo-4-[(2,4-difluorobencil)oxi]-6-(hidroximetil)-1-(piridin-3-ilmetil)piridin-2(1H)-ona

El compuesto del titulo se preparo mediante la bromination de 4-[(2,4-difluorobencil)oxi]-6-(hidroximetil)-1-(piridina-3-ilmetil)piridina-2(1H)-ona como se describió en lo precedente para proporcionar un rendimiento del 60% $^1$H-NMR ($DMSO_{d6}$/300 MHz) δ 7,93 (d, J = 7,8 Hz, 1H), 7,73-7,65 (m, 3H), 7,38 (dt, J = 10,2, 2,4 Hz, 1H), 7,21 (aprox t, J = 8,7 Hz, 2H), 6,74 (s, 1H), 5,38 -5,36 (m, 4H), 4,50 (s, 2H) ES-HRMS m/z 437,0311 (M + H calculado para $C_{19}H_{16}BrF_2N_2O_2$ = 437,0313)

1137

Ejemplo 464

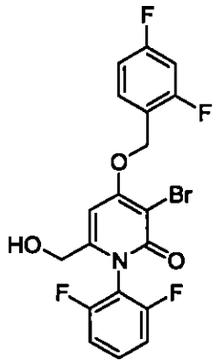


3-bromo-4-[(2,4-difluorobencil)oxi]-6-[dimetilamino)metil]-1-(piridin-3-ilmetil)piridin-2(1H)-ona

El compuesto del titulo se preparó en una forma similar al procedimiento resumido a continuación para 3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorofenil)-6-[(dimetilamino)-metil]piridin-2(1H)-ona utilizando el aldehido (300 mg, 0,85 mmol) descrito en lo precedente y disolución de 2,0 N THF de dimetilamina ( 500 □L, 1 mmol) para proporcionar 110 mg (34%) de un aceite incoloro El aceite luego se disolvió en MeOH (1 mL) y se agito con ácido fumárico (25 mg) durante 1 hora El precipitado resultante se filtro, se lavó con éter de dietilo y se seco para proporcionar el producto puro como su sal de fumurato $^1$H-NMR ($DMSO_{d6}$/400 MH$_z$) δ 8,43-8,41 (m, 1H), 8,35 (s, 1H), 7,67-7,61 (m, 1H), ',44-7,40 (m, 1H), 7,35-7,29 (m, 2H), 7,17-7,12 (m, 1H), 6,62 (s, 1H), 6,60 (s, 1H), 5,41 (s, 2H), 5,32 (s, 2H), 3,13 (s, 2H), 2,12 (s, 6H) LC/MS, $t_r$ = 1,55 minutos (5 a 95% acetonitrilo/agua durante 5 minutos a 1 ml/min con deteccion de 254 nm, a 50 °C) ES-MS m/z 464 (M+H)

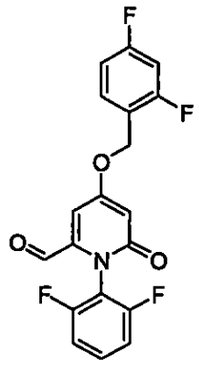
Ejemplo 465

1138



3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorofenil)-6-(hidroximetil)piridin-2(1H)-ona

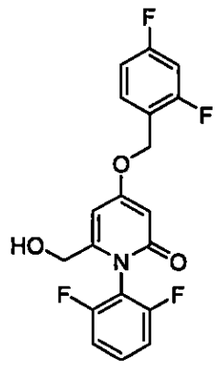
Etapa 1 4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorofenil)-6-oxo-1,6-dihidropiridina-2-carbaldehido



En un recipiente para reacciones de vidrio de alta presión de 300 ml se disolvio (16,3 g, 45 mmol) en 1,4-dioxano (90 mL) El recipiente de reacción se sello y se sumergió en un baño de aceite calentado previamente a 170 °C La reacción se calentó a 170 °C (165-170 °C) durante 1,5 hora y luego se enfrio a temperatura ambiente La reaccion se preparo al filtrar la mezcla de reaccion a traves de un tapon de celite y gel de silice El tapón luego se lavo con 500 ml de una mezcla de $CH_2Cl_2$-metanol (1 5) El filtrado se evaporó para proporcionar 14,2 g del aldehido crudo deseado

1139

Etapa 2 Preparación de 4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorofenil)-6-(hidroximetil)piridin-2(1H)-ona



En un matraz de fondo redondo, de tres cuellos de 500 ml, equipado con una varilla de agitacion, se disolvio 4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorofenil)-6-oxo-1,6-dihidropiridina-2-carbaldehido (14,2 g, 37,7 mmol) en metanol (200 mL) La mezcla de reacción se enfrió a 0 °C y a esto se agregó borohidruro de sodio (2,13 g, 56,30 mmol) en forma lenta y en porciones La reacción se agito a 0 °C durante 2 hs Se agrego una cantidad excedente de borohidruro de sodio para completar la reaccion Luego de agitar durante aproximadamente 2,5 horas, se dejó entibiar la reacción a temperatura ambiente y luego se concentró hasta lograr la sequedad El residuo se absorbio en acetato de etilo (100 mL) y se lavo con HCl diluido (el pH de la capa acuosa era de aproximadamente 4) Los extractos organicos se lavaron con salmuera (1X50 ml), se secaron sobre $MgSO_4$, y se concentraron in vacuo El producto crudo se recristalizo a partir de acetato de etilo y hexano para producir 7,56 g (rendimiento del 44%, comenzando desde la Etapa 1) del alcohol deseado

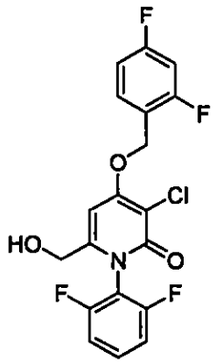
Etapa 3 Preparación del compuesto del titulo

En un matraz de fondo redondo de 100 ml de 4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorofenil)-6-(hidroximetil)piridin-2(1H)-ona (2,49 g, 6,56 mmol), de la

1140

etapa 2, se disolvió en acetonitrilo (35 mL) La mezcla de reaccion se enfrio a 0 °C en un baño de hielo durante 10 min y luego se cargó con N-bromosuccinamida (1,17 g, 6,6 mmol) Se dejo que la mezcla se agitara, a 0 °C, bajo atmósfera de nitrogeno durante 2 horas La reaccion luego se desarrollo removiendo el acetonitrilo bajo vacio El residuo resultante luego se filtro, con el lavado a partir de una pequeña cantidad de acetonitrilo, para proporcionar un sólido amarillo $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7,695 - 7,588 (m, 2H), 7,368-7,314 (m, 3H), 7,175 (dt, J = 8,5, 2,5, Hz, 1H), 6,760 (s, 1H), 5,712 (t, J = 5,674 Hz, 1H), 5,384 (s, 2H), 4,004-3,990 (m, 2H), ES-HRMS m/z 458,0013 (M+H-calculado para $C_{19}H_{13}BrF_4NO_3$ requiere 458,0013)

Ejemplo 466



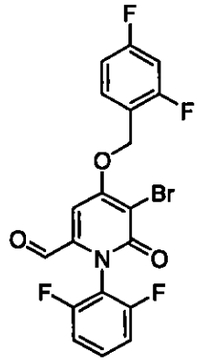

3-cloro-4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorofenil)-6-(hidroximetil)piridin-2(1H)-ona

El compuesto del titulo se preparo poniendo 4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorofenil)-6-(hidroximetil)piridin-2(1H)-ona (1,5 g, 3,9 mmol) en acetonitrilo (15 mL) y agregandole N-clorosuccinimida (580 mg, 4,3 mmol) La reaccion se agitó a temperatura ambiente durante 3 horas luego de lo cual se agregó a la reaccion una pequeña cantidad de N-clorosuccinimida adicional (50 mg, 0,4 mmol) La agitacion continuo durante 1 hora La

1141

mezcla de reaccion se filtro a traves de un embudo de vidrio poroso para ootener el material crudo $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7,69 -7,61 (m, 2H), 7,37-7,31 (m, 3H), 7,17 (dt, J = 8,8, 2,0, Hz, 1H), 6,80 (s, 1H), 5,70 (t, J = 6,0 Hz, 1H), 5,38 (s, 2H), 4,01 (d, J= 6,0 Hz, 2H), ES-HRMS m/z 414,0515 (M+H-calculado para $C_{19}H_{13}ClF_4NO_3$ requiere 414,0520)

Ejemplo 467



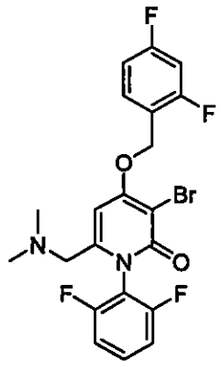
5-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorcfenil)-6-oxo-1,6-dihidropiridina-2-carbaldehido

Preparación del compuesto del titulo En un matraz de fondo redondo, de cuello unico de 50 ml, se disolvió 4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorofenil)-6-oxo-1,6-dihidropiridina-2-carbaldehido (0,36 g, 0,95 mmol) en acetonitrilo (5 mL) La mezcla de reacción se enfrió a 0 °C en un baño de hielo y se cargo con N-bromosuccinamida (0,17 g, 0,95 mmol) Se dejo agitar la mezcla a 0 °C durante 2 horas bajo atmósfera de nitrogeno Luego de 2 horas, el disolvente se evaporo bajo vacio $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9,53 (s, 1H), 7,73 - 7,67 (m, 2H), 7,62-7,54 (m, 1H), 7,35 (dt, J = 10,40, 2,56 Hz, 1H), 7,27 (t, J=8,35 Hz, 2H), 7,19 (dt, J =8,60, 2,44 Hz, 1H), 5,72 (s,

1142

1H), 5,50 (s, 2H), ES-MS m/z 455,9836 (M+H calculado para $C_{19}H_{11}BrF_4NO_3$ requiere 455 9859)

Ejemplo 468



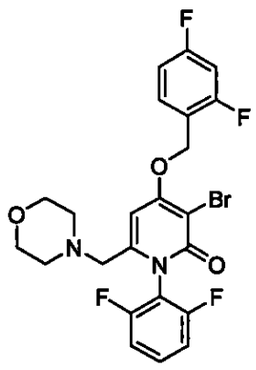
3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorofenil)-6-[(dimetilamino)metil]piridin-2(1H)-ona

En un matraz de fondo redondo de 50 ml, se agito 5-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorofenil)-6-oxo-1,6-dihidropiridina-2-carbaldehido (0,456 g, 1,0 mmol) en diclorometano (5 mL) A esta mezcla se agrego una disolucion de 2M THF de dimetil amina (1,25 ml, 2,5 mmol) Se dejo agitar la mezcla bajo atmosfera de nitrogeno y a temperatura ambiente durante 2 horas Luego se agrego a esta mezcla borohidruro de sodio triacetoxi (0,37 g, 1,75 mmol) seguido por dos a tres gotas de acido acético La mezcla luego se agito a temperatura ambiente durante la noche Los solventes luego se eliminaron por evaporacion y el residuo se absorbió en acetato de etilo (30 ml) y se lavo con bicarbonato de sodio acuoso y salmuera Los materiales organicos luego se combinaron, se secaron sobre $MgSO_4$ y se concentraron in vacuo El producto en crudo se purifico por cromatografia de columna rapida utilizando un gradiente de solvente de acetato de etilo-hexano (3 1) a acetato de etilo (0 100) para proporcionar 0,14 g

1143

(rendimiento del 30%) del producto deseado $^1$H NMR (300 MHz, DMSO-$d_6$) δ 7,73 7,58 (m, 2H), 7,42-7,30 (m, 3H), 7,22 (dt, J=8,73, 2,60 Hz, 1H), 6,81 (s, 1H), 5,44 (s, 2H), 3,04 (s, 2H), 1,96 (s, 6H), ES-MS m/z 485,0 (M+H) ES-HRMS m/z 485,0457 (M+H calculado para $C_{21}H_{18}BrF_4N2O_2$ requiere 485,0489)

Ejemplo 469



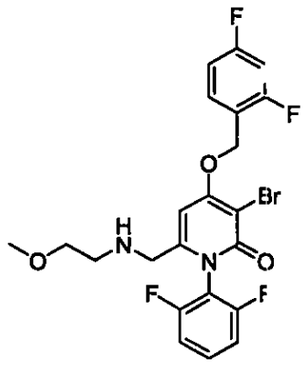
3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorofenil)-6-(morfolin-4-ilmetil)piridin-2(1H)-ona

El compuesto del titulo se preparo haciendo reaccionar 5-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorofenil)-6-oxo-1,6-dihidropiridina-2-carbaldehido (0,456 g, 1mmol) con morfolina (0,13 ml, 1,5 mmol) y borohidruro de sodio triacetoxi (0,42 g, 2,0 mmol) en diclorometano (7 mL) utilizando un procedimiento similar al que se describe en el Ejemplo 468 El producto en crudo se purifico mediante cromatografia de columna rapida La elucion con hexanos-acetato de etilo (50 50 → 0 100) proporcionó 0,15 g (rendimiento del 29%) del producto deseado $^1$H NMR (300 MHz, DMSO-$d_6$) δ 7,75- 7,57 (m, 2H), 7,43-7,31 (m, 3H), 7,20 (dt, J=8,64, 2,48 Hz, 2H), 6,85 (s, 1H), 5,44 (s, 2H), 3,37 (aprox t, J=4,37 Hz, 4H), 3,13 (s, 2H), 2,08 (t, J=

1144

4,19 Hz, 4H), ES-HRMS m/z 527,0600 (M+H calculado para $C_{23}H_{20}BrF_4N_2O_3$ requiere 527 0594)

Ejemplo 470



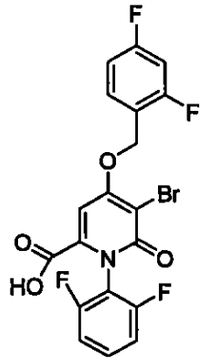
3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorofenil)-6-{[(2-metoxietil)amino]metil}piridin-2(1H)-ona

El compuesto del titulo se preparo haciendo reaccionar 5-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorofenil)-6-oxo-1,6-dihidropiridina-2-carbaldehido (0,319 g, 1mmol) con 2-metoxi etilamina (0,086 ml, 1,0 mmol) y borohidruro de sodio triacetoxi (0,42 g, 2,0 mmol) en diclorometano (4 mL) utilizando un procedimiento similar al que se describe en el Ejemplo 468 El producto crudo se purifico mediante cromatografia de columna rapida La elucion con hexanos-acetato de etilo (50 50 □ 0 100) proporciono 0,13 g del producto deseado

$^1$H NMR (400 MHz, $CDCl_3$) δ 7,54 (q, J=6,89 Hz, 1H), 7,41 - 7,33 (m, 1H), 7,19 (s, 1H), 6,99 (t, J = 7,90 Hz, 2H), 6,90 (dt, J=7,90, 2,78, Hz, 1H), 6,80 (dt, J = 10,60, 2,34 Hz, 1H), 6,51 (s,1H), 5,24 (s,2H), 3,33 (t, J= 4,69 Hz,1H), 3,30 (s, 3H), 2,57(t, J= 4,86 Hz, 2H), 1,53 (s,2H), ES-HRMS m/z 515,0548 (M+H calculado para $C_{22}H_{20}BrF_4N_2O_3$ requiere 515,0594)

1145

Ejemplo 471

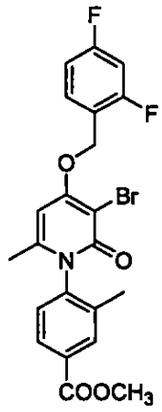


ácido 5-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorofenil)-6-oxo-1,6-dihidropiridina-2-carboxílico

En un matraz de fondo redondo de 100 ml, se disolvió 3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorofenil)-6-(hidroximetil)piridin-2(1H)-ona (1,70 g, 3,7 mmol), en acetona (10 mL) y se enfrió a 0 °C en un baño de hielo A la reacción se agregó disolucion de 1M acetona de Jones (5 ml, cantidad en exceso) Se agregó un reactivo Jones adicional durante un tiempo extra (aproximadamente 6 horas) hasta completar la reaccion La reaccion luego se concentró hasta la sequedad El residuo luego se absorbió en acetato de etilo (10 mL) y se lavo con salmuera El producto en crudo oscuro cuyo color oscilaba entre amarillo y marron se purificó mediante disolucion en 1N NaOH acuoso Las impurezas orgánicas restantes se eliminaron mediante extraccion con éter dietílico Las capas orgánicas se descartaron y la capa acuosa se acidificó con HCl diluido (hasta pH aprox 1) para precipitar el ácido puro el cual luego se filtró y trituró con eter para obtener 1,17 g (65%) del producto deseado $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7,66 (q, J= 9,41 Hz, 1H), 7,57- 7,50 (m, 1H), 7,34 (dt, J= 10,11, 2,78 Hz, 1H), 7,28- 7,23 (m, 3H), 7,18 (dt, 8,90, 2,42 Hz, 1H), 5,47 (s, 2H) ES-HRMS m/z 471,9814 (M+H calculado para $C_{19}H_{11}BrF_4NO_4$ requiere 471,9808)

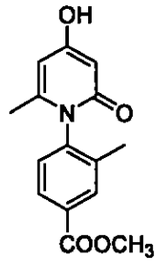
1446

Ejemplo 472



4-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-3-metilbenzoato de metilo

Etapa 1 Preparacion de 4-(4-hidroxi-6-metil-2-oxopiridin-1(2H)-il)-3-metilbenzoato de metilo

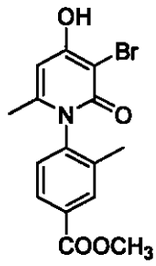


En un matraz de fondo redondo y solo un cuello de 50 ml, equipado con una varilla de agitacion, una trampa Dean Stark, y un condensador se mezclo conjutamente 4-amino -2-metil-metilbenzoato (1,19 g, 11,63 mmol) y 4-hidroxi-6-metil-2H-piran-2-ona (1,611 g, 12,78 mmol) y se disolvio en 1,2-diclorobenzeno (5 mL) La mezcla se agito vigorosamente y luego se colocó en un baño de aceite precalentado a 165 °C La reaccion se mantuvo a 165 °C durante 1,5 hora y se enfrio a temperatura ambiente La reaccion se preparó mediante dilución con tolueno (10 mL) y luego se agitó a temperatura ambiente durante 2 horas Como resultado se obtuvo un precipitado marron claro El producto en crudo

1147

se aisló mediante filtración y luego se trituro con éter $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10,64 (s, 1H), 7,93 (s,1H), 7,85 (dd, 8,46 Hz, 1H), 7,26 (d , J= 8,12 Hz, 1H), 5,91 (d, J= 2,32 Hz, 1H), 5,54 (d, J=2,32 Hz, 1H), 3,84 (s, 3H), 1,99 (s, 3H), 1,73 (s,3H) ES-HRMS m/z 272,0880 (M - H calculado para $C_{15}H_{14}F_2NO_4$ requiere 272,1001)

Etapa 3 Preparación de 4-(3-bromo-4-hidroxi-6-metil-2-oxopiridin-1(2H)-il)-3-metilbenzoato de metilo

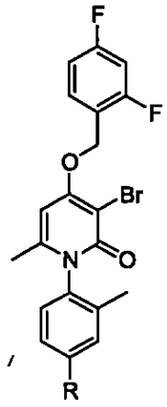



Se preparo 4-(3-bromo-4-hidroxi-6-metil-2-oxopiridin-1(2H)-il)-3-metilbenzoato de metilo haciendo reaccionar 4-(4-hidroxi-6-metil-2-oxopiridin-1(2H)-il)-3-metilbenzoato de metilo con N-bromosuccinamida en acetonitrilo siguiendo un procedimiento, similar al que se describe en el Ejemplo 465 - etapa 3 $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7,95 (s, 1H), 7,87 (dd, J = 7,76, 2,02 Hz, 1H), 7,31 (d, J=8,54, 1H), 6,09 (s,1H), 3,85 (s, 3H), 1,99 (s,3H), 1,74 (s, 1H) ES-HRMS m/z 352,0195 (M+H calculado para $C_{15}H_{14}BrNO_4$ requiere 352,0185)

Etapa 4 El compuesto del titulo se preparó tomando 4-(3-bromo-4-hidroxi-6-metil-2-oxopiridin-1(2H)-il)-3-metilbenzoato de metilo (0,92 g, 2,61 mmol) y disolviéndolo en DMF seco (5 mL) Luego se agrego carbonato de potasio (0,432 g, 3,13 mmol) y bromuro de 2,4 difluorobencilo (0,335 ml, 2,61 mmol) La dejó agitar la mezcla a temperatura ambiente durante 2 horas

La reaccion luego se desarrolló vertiéndola en 100 ml de agua congelada lc cual dio como resultado la formacion de un precipitado que se aislo filtrandolo a traves de un embudo de vidrio porcso El producto en crudo se lavo con eter y se secó en vacio para proporcionar 0,85 g (76,20%) de producto puro $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7,98 (d, J = 1,6 Hz, 1H), 7,88 (cd, J =8,04, 2,0 Hz, 1H), 7,69 (q, J = 8,6 Hz, 1H), 7,36-7,30 (m, 2H), 7,17 (dt, J = 8,7, 2,3 Hz, 1H), 6,71 (s,1H), 5,32 (s,2H), 3,86 (s,3H), 2,00 (s,3H), 1,86 (s, 3H) ES-HRMS m/z 478,0459 (M+H calculado para $C_{22}H_{19}BrF_2NO_4$ requiere 478,0466)

Ejemplos 473-476



Los compuestos de los Ejemplos 473-476 mediante derivatizacion de los compuestos del Ejemplo 472

| Compuesto Nro | R | MF | M+H requiere | ESHRMS m/z |
|---|---|---|---|---|
| Ej 473 | -$CO_2H$ | $C_{21}H_{16}BrF_2NO_4$ | 464 0310 | 464,0324 |
| Ej 474 | -$CH_2OH$ | $C_{21}H_{18}BrF_2NO_3$ | 450,0500 | 450,0517 |
| Ej 475 | $C(O)NH(CH_2)_2OCH_3$ | $C_{24}H_{22}BrF_2N_2O_4$ | 521,0888 | 521,0865 |

1148
1149

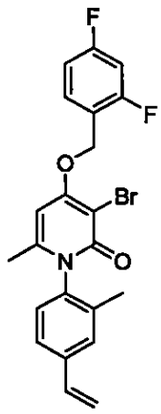
| | | | | |
|---|---|---|---|---|
| Ej 476 | $C(O)NHCH_3$ | $C_{22}H_{20}BrF_2N_2O_3$ | 477,0626 | 477,060 9 |

Caracterizacion por NMR de los compuestos de los Ejemplos 476-476

| Ej N° | Datos de NMR |
|---|---|
| 473 | $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 13,11 (s, 1H), 7 95 (d, J = 1,70 Hz, 1H), 7,86 (dd, J=7,88 1,91 Hz, 1H), 7,67 (dq, J = 8,47 1,89 Hz 1H) 7 36-7 30 (m, 2H), 7,17 (dt, J =8 54 2 48 Hz, 1H), 6 71 (s 1H), 5 32 (s,2H), 1,99 (s, 3H), 1,87 (s 3H) |
| 474 | $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7 67 (q, J =8,5 Hz,1H), 7,34 (dd, J =10,04, 2 77 Hz 1H), 7,32 (s, 1H), 7,24 (dd, J = 8,39,1,47 Hz, 1H), 7,17 (dt J = 8,84,2,6 Hz, 1H), 7,08(d, J = 7,94 Hz, 1 H) 6 66 (s 1H), 5,30 (s, 2H), 5,25 (t, J = 6,01 Hz 1H), 4,5 (d J =6 68 Hz 2H) 1,91 (s, 3H ), 1,86 (s,3H) |
| 475 | $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8,58 (aprox t, J =5,4 Hz,1H), 7 84 (s,1H) 7,76 (dd, J= 8,06, 1,63 Hz, 1H), 7,68 (dq, J= 8 77, 2,04 Hz, 1H), 7,33 (dt, J=9,76, 2,03 Hz, 1H), 7 27 (d J=8,34 Hz,1H), 7,17 (ddt, J=8 51, 2,63, 0,91 Hz 1H), 6,70 (s, 1H), 5,31 (s 2H), 4,50 (t, J=5,6 Hz , 1H), 3,47-3,36 (m 4H), 3,24 (s, 3H), 1,97 (s,3H) 1 87 (s,3H) |
| 476 | $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8,50-8,49 (m, 1H), 7,82 (s, 1H), 7,74 (dd, J=8,2), 1,79 Hz, 1H), 7,69 (q, J= 6,75 Hz, 1H) 7,33 (dt, J= 9,88, 2,57 Hz, 1H), 7,26(d, J=8,52 Hz, 1H) 7,17(dt, J= 8,9., 2,16 Hz, 1H), 6,69 (s, 1H), 5,31 (s 2H) 2,77 (d J= 4,58 Hz, 3H) 1,97 (s, 3H), 1,86 (s, 3H) |

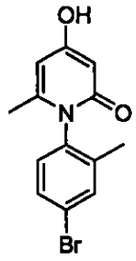
1149
1150

Ejemplo 477



3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-(2-metil-4-vinilfenil)p_ridin-2(1H)-ona

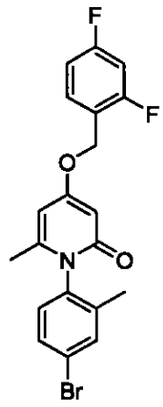
Etapa 1 Preparación de -1-(4-bromo-2-metilfenil)-4-hidroxi-6-metilpirid n-2(1H)-ona



El compuesto cel titulo se preparo en una forma simılar a la del procedimiento delineado en lo precedente para 4-(4-h_droxi-6-metil-2-oxopiridin-1(2H)-il-3-metilbenzoato $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10,61 (s, 1H), 7,59 (d, J= 2,84 Hz, 1H), 7,45 (dd, J= 8,39, 2,44 Hz, 1H), 7,06 (d , J= 7,44, 1H), 5,89 (d, J=2,73 Hz, 1H), 5,53 (d, J=2,30, 1H), 1,91 (s, 3H), 1,75 (s,3H) ES-HRMS m/z 294,0127 (M+H calculado para $C_{13}H_{13}BrNO_3$ requiere 294,0130)

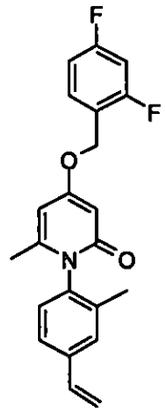
Etapa 2 Prepai ación de -1-(4-bromo-2-metilfenil)-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona

1150
1151



Se disolvió 1-(4-bromo-2-metilfenil)-4-hidroxi-6-metilpiridin-2(1H)-ona (7,35 g, 25,0 mmol) en DMF (15 mL) y se agito con carbonato de potasio (4,14 g, 30,0 mmol) y bromuro de 2,4 difluorobencilo (3,21 ml, 25,0 mmol) a temperatura ambiente durante 2 horas La reacción se desarrolló al vertería en los 300 ml de agua congelada bajo agitación continua Se obtuvo un precipitado blanco que se aisló mediante filtrado y se purifico adicionalmente mediante trituracion con eter para proporcionar 3,06 g (29%) del producto deseado $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7,65- 7,59 (m, 2H), 7,49 (dd, J=8,45, 2,22 Hz, 1H), 7,31 (dt, J= 9,79, 2,22 H-, 1H), 7,16- 7,08 (m, 2H), 6,05 (d, J= 2,58 Hz, 1H) , 5,93 (d, J= 2,66 Hz, 1H), 5,08 (s, 2H), 1,93 (s, 3H), 1,77 (s, 3H) ES-HRMS m/z 420,0390 (M+H calculado para $C_{20}H_{17}BrF_2NO_2$ requiere 420,0411)

Etapa 3 Preparación de 4-[(2,4-difluorobencil)oxi]-6-metil-1-(2-metil-4-vinilfenil)piridin-2(1H)-ona



En un matraz de fondo redondo de 50 ml que previamente se vació y se llenó con nitrogeno, se disolvio 1-(4-bromo-2-metifenil)-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona (0,420 g, 1,0 mmol) en THF seco (10 mL) A esta mezcla se agrego Pd $(PPh_3)_4$ (0,173 g, 0,15 mmol) El matraz de reaccion se sello con un diafragma de caucho, se vació y se llenó con nitrógeno Bajo atmosfera de nitrogeno, se agregó tributil(vinil)estaño (0,35 ml, 1,2 mmol) a la mezcla de reacción sellada y se agito durante la noche a 50 °C

La reaccion se preparo al enfriar rapidamente con agua y extraer el producto con acetato de etilo El producto en crudo se purifico mediante cromatografia de columna rapida La elusion con acetato de etilo-hexanos (50 50→ 0 100) proporcionó 0,32 g (69%) del producto deseado

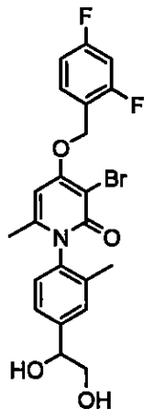
Etapa 4 El compuesto del titulo se preparo haciendo reaccionar

4-[(2,4-difluorobencil)oxi]-6-metil-1-(2-metil-4-vinilfenil)piridin-2(1H)-ona (0,64 g, 1,74 mmol) con N-bromosuccinamida (0,325 g, 1,83 mmol) en acetonitrilo (9 mL) a 0 °C utilizando un procedimiento similar al que se describe en la Etapa 3 del Ejemplo 465, para proporcionar 0,423 g (54,5% luego de la recristalizacion) del producto

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deseado $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7,67(aprox q, J= 7,59 Hz, 1H), 7,48(s,1H), 7,42(dd, J=8,21, 1,98 Hz,1H), 7,33 (dt, J=10,00, 2,27 Hz, 1H), 7,17(dt, J=8,51, 2,44 Hz, 1H), 7,13 (d, J=7,88 Hz, 1H) 6,74(dd, J=11,29, 6,34 Hz, 1H), 6,67 (s,1H), 5,88 (d, J= 17,85, 1H), 5,32-5,30 (m, 2H), 1,92 (s, 3H), 1,88 (s,3H) ES-HRMS m/z 446,0579 (M+H calculado para $C_{22}H_{19}ErF_2NO_2$ requiere 446,0568)

Ejemplo 478



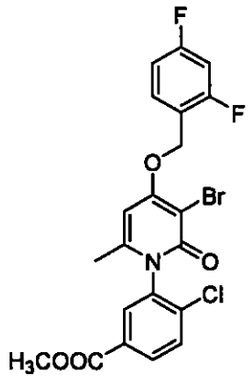

3-bromo-4-[(2,4 difluorobencil)oxi]-1-[4-(1,2-dihidroxietil)-2-metilfenil]-6-metilpiridin-2(1H)-ona

Se disolvio 3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-(2metil-4-vinilfenil)piridin-2(1H)-ona (0,126 g, 0,28 mmol) en una mezcla de acetona (3 mL) y agua (1 mL) A esto se agregó 4-metilmorfolina N-oxido (0,032 g, 0,28 mmol) y una cantidad catalitica (aproximadamente 5 mgs) de tetróxido de osmio, y se agito bajo atmosfera de nitrogeno Luego de aproximadamente 2 horas, la reaccion se preparo mediante la evaporación de la acetona El producto se extrajo en acetato de etilo y se concentró para proporcionar un sólido de color oscuro que se purifico adicionalmente mediante cromatografía de columna para proporcionar 0,049 g (rendimiento del 37%) de solido color carbon $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7,67 (q, J=8,24 Hz, 1H), 7,37-7,23 (m, 3H), 7,17 (dt, J= 8,62, 2,62 Hz, 1H),

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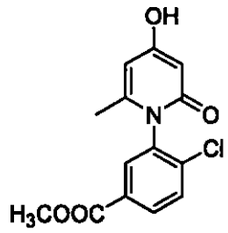
7,07 (dd, J=9,36, 2,24 Hz, 1H), 6,65(s,1H), 5,30 (s, 2H), 4,74(t, J= 6,16Hz, 1H), 4,57- 4,50 (m, 1H), 3,45 (aprox t, J= 6,12 Hz, 2H), 3,41- 3,37 (m, 1H), 1,91(s,3H), 1,85 (s, 3H) ES-HRMS m/z 480,0625 (M+H calculado para $C_{22}H_{21}BrF_2NO_2$ requiere 480,0623)

Ejemplo 479



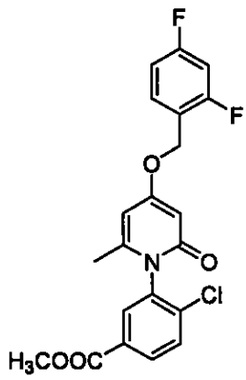

3-[3-bromo-4-[(2,4-difluorobencil) oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-clorobenzoato de metilo

Etapa 1 Preparacion de 4-cloro-3-(4-hidroxi-6-metil-2-oxopiridin-1(2H)-il)benzoato de metilo




Una reaccion de condensación con 3-amino-4-clorobenzoato de metilo (14,5 g, 78,2 mmol) y 4-hidroxi-6-metil piranona bajo una condicion de reaccion similar a la descrita en el Ejemplo 465 - etapa 3 proporciono 12,32 g (53,8%) del producto deseado

Etapa 3- Preparación de 4-cloro-3-[4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]benzoato de metilo

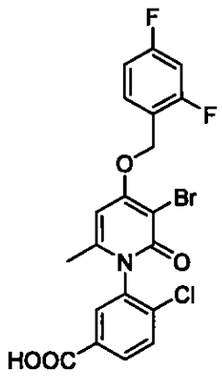


En un matraz de fondo redondo de 250 ml, se hizo reaccionar 4-cloro-3-(4-hidroxi-6-metil-2-oxopiridin-1(2H)-il)benzoato de metilo (5,28 g, 18,0 mmol) de la etapa 1 con bromuro 2,4-difluoro-bencilo (3,72 g, 18,0 mmol) en DMF utilizando un procedimiento similar al del Ejemplo 472 - etapa 3 Luego de la preparacion acuosa y la purificación cromatografica, se obtuvo 2,3 g (30%) de producto puro

Etapa 4 Se preparo 3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-clorobenzoato de metilo haciendo reaccionar 4-cloro-3-[4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]benzoato de metilo (2,3 g, 5,47 mmol) con N-bromosuccinamida (0,97 g, 5,47 mmol) en acetonitrilo (10 mL) a 0 °C, utilizando un procedimiento similar al descrito en la Etapa 3 del Ejemplo 465, para proporcionar 1,80g (66,2%) del productc deseado $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8,06-8,03 (m, 2H), 7,86 (d, J=9,70 Hz, 1H), 7,68 (q, J= 7,62, 1H), 7,34(dt, J=10,07, 2,46 Hz, 1H), 7,17 (dt, J= 8,72, 2,90 Hz, 1H), 6,73 (s, 1H), 5,33 (s, 2H), 3,85 (s, 3H), 1,91 (s, 3H) ES-MS m/z 495,9757 (M - H calculado para $C_{21}H_{14}BrClF_2NO_4$ requiere 495,9795)

1.155
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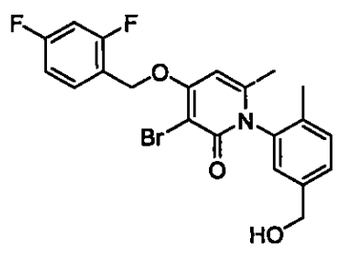
Ejemplo 480



ácido 3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-clorobenzoico

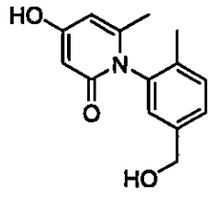
En un matraz de fondo redondo de 50 ml, se agitó 4-cloro-3-[4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]benzoato de metilo (0,450 g, 0,90 mmol) en THF (5 mL) A esta mezcla se agregó NaOH (0,120 g, 3,0 mmol) como una disolución en agua (1,5 mL) La mezcla de reacción se agitó a temperatura ambiente durante la noche El THF se evaporó y el residuo se acidificó con HCl diluido Se obtuvo un precipitado blanco El producto se filtró, se lavó con agua y se secó en vacío para proporcionar 0,375 g (rendimiento del 86 %) del producto deseado $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7,89 (dd, J=7,78, 1,73 Hz, 1H), 7,71-7,65 (m, 2H), 7,53 (d, J= 9,08 Hz, 1H), 7,33 (dt, J=9,95, 2,59 Hz, 1H), 7,17 (dt, J= 8,22, 2,59 Hz, 1H), 6,68 (s, 1H), 5,32 (s, 2H), 1,89 (s, 3H) ES-MS m/z 481,9585 (M - H calculado para $C_{20}H_{12}BrClF_2NO_4$ requiere 481,9601)

Ejemplo 481



3-bromo-4-[(2,4-difluorobencil)oxi]-1-[5-(hidroximetil)-2-metilfenil]-6-metilpiridin-2(1H)-ona

Etapa 1 Preparacion de 4-hidroxi-1-[5-(hidroximetil)-2-metilfenil]-6-metil piridin-2(1H)-ona

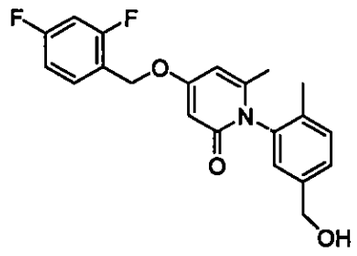


4-hidroxi-6-metil-2-pirona (23,0 g, 182,2 mmol) y 3-amino-4-metilbencil alcohol (25,0 g, 182,2 mmol) se absorvieron en 25 ml de 1,2-diclorobenceno La disolución se calento a 165 °C en un matraz de fondo rendondo de 250 ml equipado con una sonda controladora de temperatura J-Kem y un manto calentador En un matraz de fondo redondo de 250 ml se suspendió 4-hidroxi-6-metil-2-pirona (23,0 g, 182,2 mmol) en 25 ml de 1,2-diclorobenceno y también se calento a 165 °C La disolución de pirona se vertio en un matraz que contenia la anilina y la reacción se agito a 165 °C durante 20 minutos Se dejó enfriar la reaccion a temperatura ambiente El contenido de la reaccion se lavó con $NaHCO_3$ (ac ) Se separaron las capas organicas y acuosas La capa acuosa se convirtió en acidógena con el agregado gota a gota de HCl concentrado El producto se extrajo de la capa acuosa acidógena con n-BuOH Se elimino el N-BuOH in vacuo para producir un aceite marron rojizo (8,5 g, 19%) Los contenidos se llevaron a la siguiente reacción sin ninguna purificación adicional $^1H$ NMR (300 MHz, $CD_3OD$) δ 7,35 (m, 2H), 7,08 (s, 1H), 6,08 (br s, 1H), 5,81 (br s, 1H), 4,60 (s, 2H), 2,01 (s, 3H), 1,87 (s, 3H) LC/MS, $t_r$ = 1,42 minutos (5 a 95% acetonitrilo/agua durante

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5 minutos a 1 ml/min con deteccion de 254 nm, a 50 °C) ES-MS m/z 246,1131 (M+H) ES-HRMS m/z 246,1107 (M+H calculado para $C_{14}H_{16}NO_3$ requiere 246,1125)

Etapa 2 4-[(2,4-difluorobencil)oxi]-1-[5-(hidroximetil)-2-metilfenil]-6-metil-piridin-2(1H)-ona



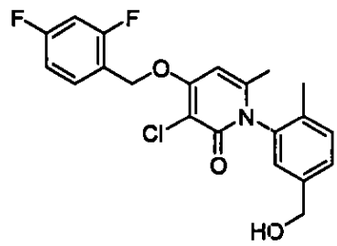
4-hidroxi-1-[5-(hidroximetil)-2-metilfenil]-6-metil piridin-2(1H)-ona de la Etapa 1 (8,0 g, 32,6 mmol) se agito energicamente a temperatura ambiente con bromuro de 2,4-difluorobencilo (4,2 ml, 32,6 mmol) y $K_2CO_3$ (4,5 g, 32,6 mmol) en 50 ml de dimetilformamida Después de agitar durante 8 horas, se agregó $H_2O$ (100 ml) a la mezcla de reaccion El producto se extrajo con acetato de etilo La capa de acetato de etilo se separó y se seco sobre $Na_2SO_4$ El acetato de etilo se eliminó in vacuo Se obtuvo un aceite amarillo El aceite se paso a traves de un tapón de gel de silice eluyendo primero con 500 ml de acetato de etilo/hexano (1 1) Este eluyente se aparto A continuacion, se paso acetato de etilo (100%) a traves del tapón hasta sacar completamente el silice (3 litros) del producto deseado El disolvente se elimino in vacuo Se obtuvo un aceite amarillo claro (7,5 g , 62%) $^1H$ NMR (300 MHz, $CD_3OD$) δ 7,60 (aprox q, J = 6,44 Hz, 1H), 7,42 (d, J = 0,81 Hz, 2H), 7,15 (s, 1H), 7,06 (m, 2H), 6,21 (dd, J = 1,61, 1,00 Hz, 1H), 6,12 (d, J = 2,62 Hz, 1H), 5,16 (s, 2H), 4,65 (s, 2H), 2,07 (s, 3H), 1,93 (s, 3H), LC/MS, $t_r$ =

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2,38 minutos (5 a 95% acetonitrilo/agua durante 5 minutos a 1 ml/min con deteccion de 254 nm, a 50°C) ES-MS m/z 372 (M+H)

Etapa 3 Preparacion del compuesto del titulo 4-[(2,4-difluorobencil)oxi]-1-[5-(hidroximetil)-2-metilfenil]-6-metil-piridin-2(1H)-ona (de la Etapa 2) (4,0 g, 10,8 mmol) se agitó energicamente a temperatura ambiente con bromosuccinimida (2,1 g, 11,9 mmol) en 100 ml de $CH_2Cl_2$ durante 2,0 horas La reaccion se evaporo en un rotavapor y el solido resultante se lavó con acetonitrilo y se secó in vacuo para producir un solido blanco (3,9 g, 80%) $^1H$ NMR (300 MHz, $CDCl_3$) δ 7,67 (app q, J = 6,24 Hz, 1H), 7,35 (d, J = 1,01 Hz, 2H), 7,10 (s, 1H), 7,04 (m, 1H), 6,91 (ddd, J = 11,08, 8,66, 2,42 Hz, 1H), 6,15 (d, J = 0,63 Hz, 2H), 5,29 (s, 2H), 4,66 (s, 2H), 2,08 (s, 3H), 1,97 (s, 3H), ES-MS (Electrospray - Espectrometria de masa) m/z 450 (M+H) ES-HRMS (Electroespray - Espectrometria de masa de alta resolucion) m/z 450,0467 (M+H calculado para $C_{21}H_{19}BrF_2NO_3$ requiere 450,0511)

Ejemplo 482



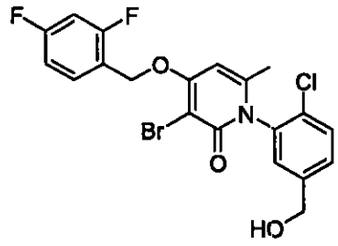

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[5-hidroximetil-2-[(-2-metilfenil]-6-metilpiridin-2(1H)-ona

El compuesto del titulo se preparó mediante un procedimiento similar al descripto para el Ejemplo 481, con excepción del producto de la Etapa 2, Ejemplo 481 que en

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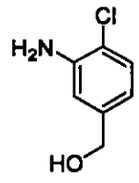
lugar de ser bromado fue clorado El procedimiento es el siguiente 4-[(2,4-difluorobencil)oxi]-1-[5-(hidroximetil)-2-metilfenil]-6-metil-piridin-2(1H)-ona (de la Etapa 2, Ejemplo 481 mas arriba) (7,0 18,8 mmol) se sometio a reflujo con N-clorosuccinimida (2,5 g, 18,8 mmol) en 50 ml de $CH_2Cl_2$ durante la noche La reaccion se evaporó en un rotavapor y el solido resultante se agito en MeOH El precipitado se recolecto en un papel de filtro, se lavo con MeOH y se secó in vacuo para proporcionar un solido blanco (1,6 g 21%) $^1H$ NMR (300 MHz, DMF-$d_7$) δ 7,85 (aprox q, J = 6,44 Hz, 1H), 7,43 (d, J = 0,81, 1H), 7,42 - 7,23 (m, 3H), 6,84 (s, 1H), 5,48 (s, 2H), 4,67 (s, 2H), 2,05 (s, 3H), 2,03 (s, 3H), ES-MS m/z 406 (M+H) ES-HRMS m/z 406,1033 (M+H calculado para $C_{21}H_{19}BrF_2NO_3$ requiere 406,1016)

Ejemplo 483



3-bromo-4-[(2,4-difluorobencil)oxi]-1-[5-hidroximetil-2-[(-2-metilfenil]-6-metilpiridin-2(1H)-ona

Etapa 1 Preparación de alcohol 3-amino-4-cloro-bencil

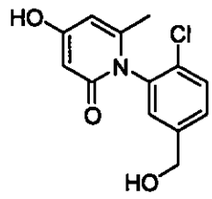


El alcohol 3-Nitro-4-cloro-bencil (23,0 g, 122,6 mmol) se absorbe en alcohol isopropilico (175 ml) y agua (35 ml) Se agrega polvo de hierro (<10 micrones) (68,0 g,

1.160
1161

1,2 mol) y $NH_4Cl$ (66,0 g, 1,2 mol) Se realiza la agitación superior de la suspensión a 70°C en un matraz de tres cuellos con fondo redondo equipado con manta de calentamiento y una sonda controladora de temperatura J-Kem Despues de 4 horas, el alcohol isopropilico se eliminó in vacuo Se agrego a la mezcla el agua (100 ml) y el HCl concentrado (100 ml) El contenido se transfiere a un embudo separador y el acetato de etilo se usa para extraer la capa acuosa de impurezas Luego la capa acuosa se basificó con NaOH acuoso al 50% El producto se extrajo de la capa acuosa ba ica con acetato de etilo La capa de acetato de etilo se seco sobre $Na_2SO_4$ y luego se elimino in vacuo El residuc restante se absorbio en acetato de etilo /hexano al 50% y el precipitado se recolecto en un papel de filtro El precipitado se lavo con acetato de etilo /hexano al 50% para proporcionar un solido marrón floculante (8,4 g, 44%) $^1H$ NMR (300 MHz, $CD_3OD$) δ 7,17 (d, J = 8,26 Hz, 1H), 6,86 (d, J = 2,01 Hz, 1H), 6,66 (dd, J = 2,01, 0,61 Hz, 1H), 4,51 (s, 2H), LC/MS, $t_r$ = 0,32 minutos (5 a 95% de acetonitrilo/ agua durante 5 minutos a 1 ml/min con deteccion 254 nm, a 50°C), ES-MS m/z 158 (M+H)

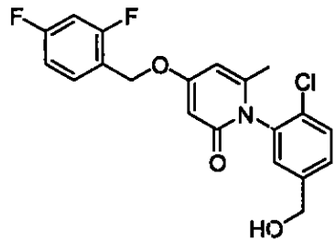
Etapa 2 1-[2-cloro-5-(hidroximetil)fenil]-4-hidroxi-6-metilpiridin-2(1H)-ona




El alcohol 3-amino-4-cloro-bencil (8,0g, 51,0 mmol) y la 4-hidroxi-6-metil-2-pirona (6,4 g, 51,0 mmol) se absorbieron en 1 2-diclorobenceno (50 ml) La mezcla se sumergio en un baño de aceite a 165°C en el cual se agitó

durante 20 minutos La reacción se enfrio a temperatura ambiente y la reaccion se preparó mediante el lavado con $HaHCO_3$ saturado (ac ) y la extraccion de las impurezas con acetato de etilo El producto se mantuvo en la fase acuosa La capa acuosa básica se transformo en acida con HCl concentrado El producto se extrajo de la capa acuosa acida con acetato de etilo La capa de acetato de etilo se secó sobre $Na_2SO_4$ y luego se elimino el disolvente in vacuo El producto se obtuvo como aceite amarillo a un rendimiento del 26% y se transfirió a la etapa siguiente sin ninguna otra purificacion $^1H$ NMR (300 MHz, $CD_3OD$) δ 7,62 (d, J = 8,26 Hz, 2H), 7 51 (dd, J = 8,46, 2,22 Hz, 1H), 7,36 (d, J = 2,01 Hz, 1H), 6,13 (br s, 1H), 5,84 (d, J = 2,42 Hz, 1H), 4,68 (s, 2H), 1,97 (s, 3H), LC/MS, $t_r$ = 0,25 minutos y 1,41 minutos (tautomero), (5 a 95% acetonitrilo/agua durante 5 minutos a 1 ml/min con deteccion 254 nm, a 50°C) ES-MS m/z 266 (M+H)

Etapa 3 1-[2-cloro-5-(hidroximetil)fenil]-4-[(2,4-difluorobencil)oxil]-6-metilpiridin-2(1H)-ona

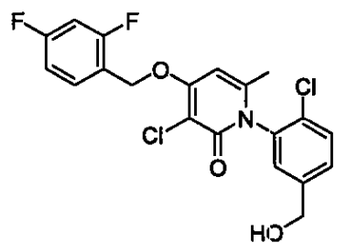



1-[2-cloro-5-(hidroximetil)fenil]-4-hidroxi-6-metilpiridin-2(1H)-ona (de la etapa 2) (3,5g, 13,2 mmol) se absorbio en DMF (10 ml) y se enfrio a 0 °C Se agregó bromuro de 2,4-difluorobencil (1,7 ml, 13,2 mmol) y $K_2CO_3$ (1 8 g, 13,2 mmol) y la reacción se agito durante 6 horas La reaccion se preparo mediante el agregado de $NaHCO_3$ saturado (ac ) y la extraccion con acetato de etilo La extracción de acetato de etilo se lavo con agua, y la capa

acuosa se extrajo con acetato de etilo Las capas organicas se combinaron y secaron sobre $Na_2SO_4$, filtrado, y el disolvente se eliminó in vacuo El producto se obtuvo a un rendimiento del 83% en crudo y se transfirió a la etapa siguiente como aceite marron LC/MS, t = 2,48 minutos (5 a 95% acetonitrilo/agua durante 5 minutos a 1 ml/ min con detección 254 nm, a 50°C) ES-MS m/z 392 (M+H) ES-HRMS m/z 392,0853 (M+H calculado para $C_{20}H_{17}ClF_2NO_3$ requiere 392,0860)

Etapa 4 El compuesto del titulo se preparó a partir de 1-[2-chloro-5-(hidroximetil)fenil]-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona de la etapa 3 (1,8 g, 4,6 mmol) y N-bromosuccinimida (0,82 g, 4,6 mmol) mediante la disolucion de las mismas en $CH_2Cl_2$ (10 ml) y agitacion durante 2 horas a temperatura ambiente El disolvente se elimino in vacuo y el residuo se absorbio en $CH_3CN$ El precipitado se recolectó en un papel de filtro y se enjuago con $CH_3CN$ para proporcionar un solido blanco (370 mg, 17%) $^1H$ NMR (300 MHz, $CDCl_3$) δ 7,65 (app q, J = 6,24 Hz, 1H), 7,52 (d, J = 8,26 Hz, 1H), 7,40 (dd, J = 8,26, 2,01 Hz 1H), 7,26 (d, J = 0,81 Hz, 1H), 7,03 (m, 1H), 6,91 (ddd, J = 11,08, 8,66, 2,42 Hz, 1H), 6,17 (d, J = 0,81 1H), 5,29 (s, 2H), 4,63 (s, 2H), 2,02 (s, 3H), ES-MS m/z 471 (M+H) ES-HRMS m/z 471,9953 (M+H calculado para $C_{20}H_{16}BrClF_2NO_3$ requiere 471,9944)

Ejemplo 484

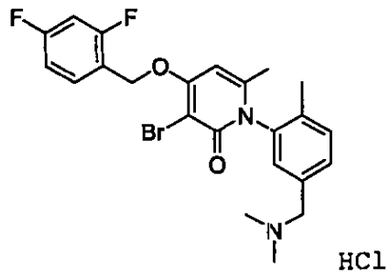


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1164

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[5-hidroximetil-2-[(-2-metilfenil]-6-metilpiridin-2(1H)-ona

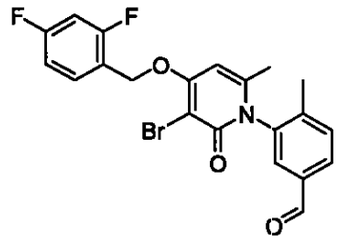
El compuesto de titulo se preparó a partir de 1-[2-cloro-5-(hidroximetil)fenil]-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona (2,4 g, 6,1 mmol) y NCS (815,0 mg, 6,1 mmol) en dicloroetano (20 ml) a 65°C Se agrego una cantidad catalitica de ácido dicloroacetico (2 gotas) Despues de dos horas el disolvente se eliminó in vacuo y el residuo se absorbio en dietileter El precipitado se recolectó en un filtro de papel y luego se absorbió en acetato de etilo/ hexanos al 50% para eliminar la succinimida residual El precipitado se recolecto en un papel de filtro y luego se seco in vacuo para proporcionar un sólido blanco (180 mg, 6,9%) $^1$H NMR (300 MHz, $CDCl_3$) δ 7,61 (app q, J = 6,44 Hz, 1H), 7,52 (d, J = 8,26 Hz, 1H), 7,40 (dd, J = 8,26, 2,01 Hz 1H), 7,27 (d, J = 2,01 Hz, 1H), 7,00 (m, 1H), 6,91 (m,1H), 6,20(s, 1H), 5,29 (s, 2H), 4,65 (s, 2H), 2,03 (s, 3H), ES-MS m/z 426 (M+H) ES-HRMS m/z 426,0453 (M+H calculado para $C_{20}H_{16}Cl2F_2NO_3$ requiere 426,0470)

Ejemplo 485




Hidrocloruro de 3-bromo-4-[(2,4-difluorobencil)oxi]-1-{5-[(dimetilamino)metil]-2-metilfenil}-6-metilpiridin-2(1H)-ona

Etapa 1 Preparación de 3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-metilbenzaldehido

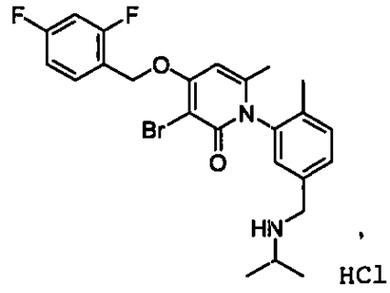


Se disolvio 3-bromo-4-[(2,4-difluorobencil)oxi]-1-[5-(hidroximetil)-2-metilfenil]-6-metilpiridin-2(1H)-ona (1,5 g, 3,33 mmol) en $CH_3CN/CH_2Cl_2$ (20ml) al 75% y se enfrió a 0 °C Se agrego Dess-Martin Periodinane (2,8 g, 6,66 mmol) y la reacción se agitó durante cuatro horas En este momento, la reaccion se enfrio rapidamente con bisulfito de sodio (ac ) al 5% El producto se extrajo con acetato de etilo Luego los extractos organicos combinados se lavaron con $NaHCO_3$ (ac ) saturado La capa acuosa se extrajo con acetato de etilo Los extractos organicos combinados se secaron sobre $Na_2SO_4$, se filtraron y se concentraron El residuo resultante se absorbio en dietileter y el precipitado se recolectó en un filtro de papel y se lavo con más dietiléter para proporcionar un sólido blanco (1,35 g, 91%) $^1H$ NMR (300 MHz, $CDCl_3$) δ 10,00 (s, 1H), 7,91 (dd, J = 7,65, 1,61 Hz, 1H), 7,65 (m, 2H), 7,57 (d, J = 7,85 Hz, 1H), 7,03 (m, 1H), 6,95 (ddd, J = 12,69, 8,86, 2,62 Hz, 1H), 6,19 (s, 1H), 5,31 (s, 2H), 2,20 (s, 3H), 1,96 (s, 3H), ES-MS m/z 448 (M+H) ES-HRMS m/z 448,0347 (M+H calculado para $C_{21}H_{17}BrF_2NO_3$ requiere 448,0354)

Etapa 2 Preparación del compuesto del titulo Se disolvio 3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-metilbenzaldehido (de la Etapa 1) (0,50 g, 1,11 mmol) en $CH_2Cl_2$ (10 ml) Se agrego N,N-

dimetilamina (2,0 M en THF) (1,11 ml, 2,22 mmol) Esta mezcla se agito a temperatura ambiente durante 12 horas A continuacion, se agregó tri-acetoxiborohidruro de sodio (0,47 g, 2,22 mmol) y la reacción se agito durante dos horas adicionales La reaccion se lavo con 1 N NaOH (ac ) y luego se extrajo con $CH_2Cl_2$ Los extractos organicos combinados se lavaron con agua La capa acuosa se separó y se extrajo con $CH_2Cl_2$ Los extractos organicos combinados se secaron sobre $Na_2SO_4$,, se filtraron y se concentraron in vacuo El residuo resultante se absorbio en dietiléter Se agrego 1M HCl en dietileter (5 ml) y el precipitado se recolecto en un filtro de papel Este precipitado fue higroscopico El sólido higroscopico luego se absorbio en acetato de etilo caliente Se agregó hexano hasta que estallo un precipitado El precipitado se recolecto en un papel de filtro para proporcionar un solido blanco (150 mg, 26%) $^1$H NMR (400 MHz, $D_2O$) δ 7,42 (m, 3H), 7,17 (s,1H), 6,86 (m, 2H), 6,53(s, 1H), 5,20(s, 2H), 4,18(s, 1H), 2,72(s, 6H), 1,85(s, 3H), 1,82(s, 3H), ES-MS m/z 477 (M+H) ES-HRMS m/z 477,0955 (M+H calculado para $C_{23}H_{24}BrF_2N_2O2$ requiere 477,0984)

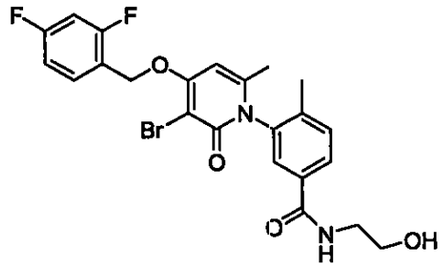
Ejemplo 486



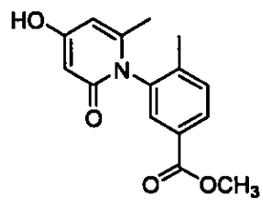

Hidrocloruro de 3-bromo-4-[(2,4-difluorobencil)oxi]-1-{5-[(isopropilamino)metil]-2-metilfenil}-6-metilpiridin-2(1H)-ona

Se preparo el compuesto del titulo mediante la aminacion reductiva de 3-[3-bromo-4-(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1 (2H)-il]-4-metibenzaldehido (de la Etapa 1) (0,50 g, 1,11 mmol) con isopropilamina (0,13 g, 2,22) de acuerdo con el procedimiento descripto mas arriba para el Ejemplo 485 (Etapa 2) para proporcionar el compuesto deseado (0,49 g, 84%) $^1$H NMR (400 MHz, $CD_3OD$) δ 7,64 (cuarteto app, J = 6,58 Hz, 1H), 7,53 (m, 2H), 7,29(br s, 1H), 7,03(m, 1H), 6,68 (s, 1H), 5,36 (s, 2H), 4,22(s, 2H), 3,46(m, 1H), 2,06 (s, 3H), 2,01 (s, 3H), 1,37 (d, J = 6,58 Hz, 6H) , ES-MS m/z 491 (M+H) ES-HRMS m/z 491,1107 (M+H calculado para $C_{24}H_{26}BrF_2N_2O2$ requiere 491,1140)

Ejemplo 487



3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-N-(2-hidroxietil)-4-metilbenzamida

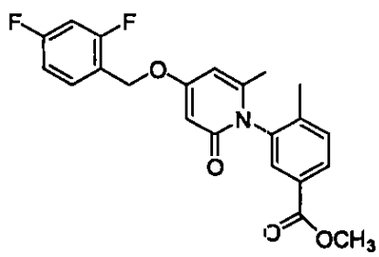


Etapa 1 Preparación de 3-(4-hidroxi-6-metil-2-oxopiridin-1(2H)-il)-4-metilbenzoato de metilo

Se realizó la suspension de 4-hidroxi-6-metil-2-pirona (22,9 g, 181,6 mmol) y -3-amino-2-metilbenzoato de metilo (25 g, 151,3 mmol) en 50 ml de 1,2-diclorobenceno en un

matraz de 250 ml, de tres cuellos, con fondo redondo, equipado con una sonda controladora de temperatura J-Kem, una trampa Dean-Stark y una manta de calentamiento La reaccion se calento a 165°C durante 15 minutos, durante los cuales se recolecto agua y cierta cantidad de 1,2-diclorobenceno en la trampa Dean-Stark La reaccion se dejo enfriar hasta alrededor de 110°C En este punto, se agrego 200 ml de tolueno El matraz se sumergio en un baño de hielo a 0 °C mientras se lo agitaba Se produjo la "salida" de aceite Quiza se agrego demasiado tolueno, de modo que parte del disolvente se elimino in vacuo El aceite volvió a la disolucion y quedo un precipitado de color marron claro Se dejo la mezcla de tolueno en agitacion durante 72 horas a temperatura ambiente Se recolecto un precipitado en un papel de filtro El precipitado se filtro y se lavo 3 veces con tolueno, 3 veces con agua a 50°C para eliminar el exceso de pirona, y se seco in vacuo para proporcionar un solido de color tostado (16,5 g, 40% de rendimiento) $^1$H NMR (300 MHz, $CD_3OD$) δ 8,06 (dd, J = 8,06, 1,61 Hz, 1H), 7,80 (d, J = 1,61 Hz, 1H), 7,56 (d, J = 8,06, Hz, 1H), 6,15 (dd, J = 2,42, 0,81 Hz, 1H), 5,86 (d, J = 2,42 1H), 3,94 (s, 3H), 2,15 (s, 3H), 1,91 (s, 3H), ES-MS m/z 274 (M+H) ES-HRMS m/z 274,1066 (M+H calculado para $C_{15}H_{16}NO_4$ requiere 274,1074)

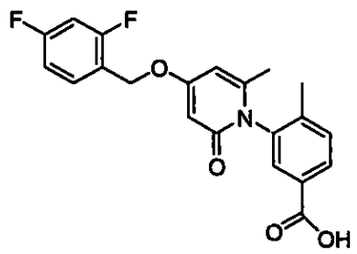
Etapa 2 Preparacion 3-[4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-metilbenzoato de metilo



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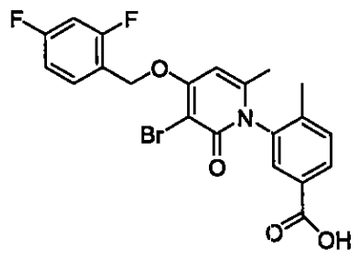
Se realizo la absorción de 3-(4-hidroxi-6-metil-2-oxopiridin-1(2H)-il)-4-metilbenzoato de metilo (de la Etapa 1) (16,5 g, 60,4 mmo ) bromuro de 2,4-difluorobencil (7,8 ml, 60,4 mmol) en 250 ml de N,N-dimetilformamida y la mezcla se enfrió a 0 °C Se agrego $K_2CO_3$ (8,3 g, 60,4 mmol) y la reaccion se agito durante 12 horas, tiempo en el cual se permitio que la reaccion se entibiara a temperatura ambiente LC /MS indico la presencia de material de inicio despues de 12 horas Se agregó un exceso de $K_2CO_3$ a temperatura ambiente junto con 0,50 ml de bromuro de 2,4-difluorobencil La reaccion se agito durante dos horas adicionales Se vertio $NaHCO_3$ (ac ) saturado en el recipiente de reaccion Se extrajo la disolucion con acetato de etilo y se combinaron las capas organicas y luego se lavo con agua Se separo la capa organica y se extrajo la capa acuosa con acetato de etilo Las capas orgánicas se combinaron y secaron sobre $Na_2SO_4$ y se evaporaron El producto se transfirio a la etapa siguiente como aceite en crudo (rendimiento cuantitativo 24,1 g) $^1H$ NMR (300 MHz, $CDCl_3$) δ 8,06 (dd, J = 7,85, 1,61 Hz, 1H), 7,82 (d, J = 1,61, 1H), 7 52-7,44 (m, 2H), 7,01 - 6,88 (m, 2H), 6,05 (d, J = 2,62 Hz, 1H), 5,97 (dd, J = 2,62, 0,81 Hz, 1H), 5,08 (s, 2H), 3,93 (s, 3H), 2,20 (s, 3H), 1,89 (s, 3H), ES-MS m/z 400 (M+H) ES-HRMS m/z 400,1374 (M+H calculado para $C_{22}H_{20}F_2NO_4$ requiere 400,1355)

Etapa 3 Preparacion de acido 3-[4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-metilbenzoico



Se absorbió 3-[4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-metilbenzoato de metilo (14 g, 35,0 mmol) (de la Etapa 2) en THF (25 ml) y $H_2O$ Se agrego N NaOH (ac ) y la reaccion se agito durante 30 minutos a temperatura ambiente La reaccion se transformo en un ácido a través del agregado de HCl concentrado El producto se extrajo con acetato de etilo La extraccion de acetato de etilo se seco sobre $Na_2SO_4$ se filtro y se eliminó el disolvente in vacuo Al eliminar el disolvente en vacio, el producto estallo y salió del acetato de etilo Este precipitado se recolecto en un papel de filtro y se lavó con acetato de etilo / hexanos al 50% para proporcionar un polvo blanco (9 g, 7%) $^1H$ NMR (300 MHz, $CDCl_3$) δ 8,01 (dd, J = , 1,61 Hz, 1H), 7,84 (d, J = 1,61 Hz, 1H), 7,52 - 7,47 (app q, J = 8,26, 1H), 7,43 (d, J = 8,06 Hz, 1H), 7,00 - 6,88 (m, 2H), 6,19 (d, J = 2,62 Hz, 1H), 6,05 (dd, J = 2,62, 1,81 Hz, 1H), 5,17 (s, 2H), 2,19 (s, 3H), 1,90 (s, 3H), ES-HR/MS m/z 386,12 (M+H calculado para $C_{21}H_{18}F_2NO_4$ requiere 386,1198)

Etapa 4 Preparacion de ácido 3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-metilbenzoico

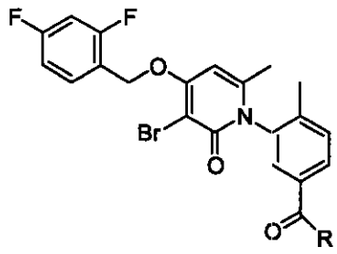


Se absorbió ácido 3-[4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-metilbenzoico (5,9 g, 15,2 mmol) (de la Etapa 3 mas arriba) en diclorometano (25 ml) Se agregó N-Bromosuccinimida y la reacción se agitó durante 14 horas El diclorometano se eliminó in vacuo y el residuo se absorbió en acetonitrilo El precipitado se recolectó en un papel de filtro y se enjuagó con acetonitrilo para proporcionar el producto deseado bajo la forma de un solido blanco (5,2 g, 74%) $^1$H NMR (300 MHz, $CD_3OD$) δ 7,87 (dd, J = 7,85, 1,61,Hz, 1H), 7,82 (d, J = 1,81 Hz, 1H), 7,69 (app q, J = 8,06 Hz 1H), 7,57 (d, J = 8,06 Hz, 1H), 7,09 (dt, J = 8,66, 2,22 Hz, 1H), 6,70 (s, 1H), 5,40 (s, 2H), 2,14 (s, 3H), 2,02 (s, 3H), ES-MS m/z 464 (M+H) ES-HRMS m/z 464,0275 (M+H calculado para $C_{21}H_{17}BrF_2NO_4$ requiere 464,0304)

Etapa 5 Preparación del compuesto del título Se disolvió acido 3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-metilbenzoico (de la Etapa 4 más arriba,) (1,9 g, 4,10 mmol) en 20 ml de $CH_2Cl_2$ Se agregó etanolamina (297 µl, 4,92 mmol) y luego, en orden, se adicionó EDCI (0,764 g, 4,92 mmol), 1-hidroxibenzotriazol (0,665 g, 4,92 mmol) y trietilamina (1,14 ml, 8,20) La reacción se agitó a temperatura ambiente durante toda la noche La reacción se enfrió rapidamente con $NH_4Cl$ y se extrajo 3 veces con acetato de etilo Luego se lavó la capa organica combinada con $NaHCO_3$ (ac ) saturado, y se extrajo 3 veces con acetato de etilo

Las capas organicas ,e combınaron y lavaron con $H_2O$ y se extrajeron 3 veces con acetato de etılo Las capas organıcas se combınaron y secaron sobre $Na_2SO_4$ y se evaporaron El resıduo resultante se trıturo con dıetıléter / hexano para obtener un sólıdo, el cual se seco ın vacuo para proporcıonar un sólıdo blanco (1,5 g, 72%) $^1H$ NMR (300 MHz, $CDCl_3$) δ 7,93 (dd, J = 7,85, 1,61 Hz, 1H), 7,65 (d, J = 1,61 Hz, 1H), 7,62 (app q, J = 8,26 Hz, 1H), 7,40 (d, J = 8,06 Hz, 1H), 7,39 - 7,30 (m, 1H), 7,03 - 6,97 (m, 1H), 6,88 - 6,81 (m, 1H), 6,25 (s, 1H), 5,20 (s, 2H), 3,70 - 3,52 (m, 1H), 3,16 - 3,12 (m, 2H), 2,10 (s, 3H), 1,98 (s, 3H), ES-MS m/z 507 (M+H) ES-HRMS m/z 507,0719 (M+H calculado para $C_{23}H_{22}BrF_2N_2O_4$ requıere 507,0726)

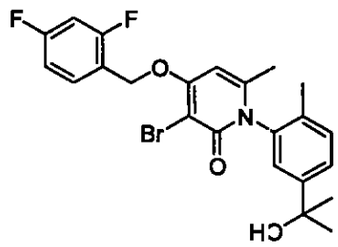
Ejemplos 488-491




Los compuestos de los Ejemplos 488-491-476 se preparan esencıalmente de acuerdo con los procedımıentos establecıdos para el Ejemplo 487

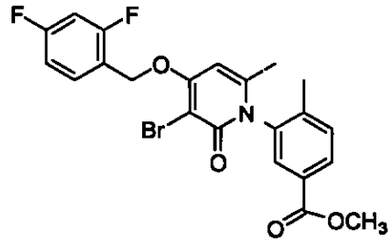
| Compuesto N° | R | Rend % | MF | M+H Requıere | ESHRMS m/z |
|---|---|---|---|---|---|
| Eȷ 488 | -NH(CH$_2$)$_2$OCH$_3$ | 84 | $C_{24}H_{24}BrF_2N_2O_4$ | 528,0882 | 521,0868 |
| Eȷ 489 | -NHCH$_3$ | 79 | $C_{22}H_{20}BrF_2N_2O_3$ | 477,0620 | 477,0602 |
| Eȷ 490 | -N(CH$_3$)$_2$ | 54 | $C_{23}H_{22}BrF_2N_2O_3$ | 491 0776 | 491,0753 |
| Eȷ 491 | -morfolına | 65 | $C_{25}H_{24}BrF_2N_2O_4$ | 533,0858 | 533 0882 |

Ejemplo 492



3-bromo-4-[(2,4-difluorobencil)oxi]-1-[5-hidroxi-1-metiletil)-2-metilfenil]-6-metilpiridin-2(1H)-ona

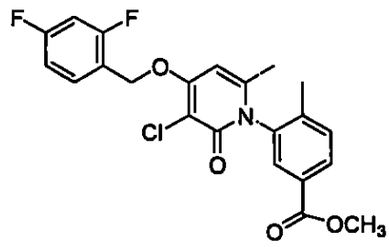
Etapa 1 Preparación de 3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-metilbenzoato de metilo



Se absorbio 3-[4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-metilbenzoato de metilo segun la preparacion anterior) (1,8g, 4,51 mmol) en $CH_2Cl_2$ (10 ml) Se agregó N-bromosuccinimida (0,80 g, 4,51 mmol) y la mezcla se agito a temperatura ambiente durante dos horas El $CH_2Cl_2$ se elimina in vacuo y el residuo se absorbe en $CH_3CN$ El precipitaco resultante se recolecta en un papel de filtro y se lava con $CH_3CN$ para proporcionar un solido blanco (0,30 g, 14%, primera cosecha) $^1H$ NMR (300 MHz, $CDCl_3$) δ 8,06 (dd, J = 8,06, 1,61 Hz, 1H), 7,80 (d, J = 1,61 Hz, 2H), 7,65 (app q, J = 8,46 Hz, 1H), 7,48 (d, J = 8,06, 1H), 7,05 -6,99 (m, 1H), 6,96 - 6,89 (m, 1H), 6,16 (s, 1H), 5,31 (s, 2H), 3,93 (s, 3H), 2,17 (s, 3H), 1,96 (s, 3H) ES-HRMS m/z 478,0476 (M+H calculado para $C_{22}H_{19}BrF_2NO_4$ requiere 478,0476)

Etapa 2 Preparacion del compuesto del titulo Se absorbio 3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-metilbenzoato de metilo (0,22 g, 0,46 mmol) en THF y se enfrio a 0 °C Se agregó lentamente MeMgCl (3,0 M en THF) (0,73 ml, 2,2 mmol) a la disolucion a 0 °C Se dejo que continuara la reacción sin mantener la temperatura del baño a 0°C La reacción se completó en el lapso de dos horas En este momento la mezcla se enfrió rápidamente con $NH_4Cl$ (ac ) y se extrajo con acetato de etilo Las capas orgánicas se combinaron, se lavaron con $H_2O$ y se extrajeron con acetato de etilo Las capas organicas se combinaron y secaron sobre $Na_2SO_4$ se filtraron y evaporaron El residuo se absorbio en acetato de etilo / hexanos al 50% El precipitado se recolectó en un papel de filtro y se lavo con acetato de etilo / hexanos al 50% para proporcionar un polvo blanco (0,10 g, 45%) $^1H$ NMR (300 MHz, $CD_3OD$) δ 7,70 (app q, J = 8,26, Hz, 1H), 7,54 (dd, J = 8,06, 2,01 Hz, 1H), 7,40 (d, J = 1,81 Hz, 1H), 7,12 - 7,06 (m, 2H), 6,68 (s, 1H), 5,40 (s, 2H), 2,05 (s, 3H), 2,02 (s, 3H), 1,57 (s, 6H) ES-HRMS m/z 478,0785 (M+H calculado para $C_{23}H_{23}BrF_2NO_3$ requiere 478,0824)

Ejemplo 493

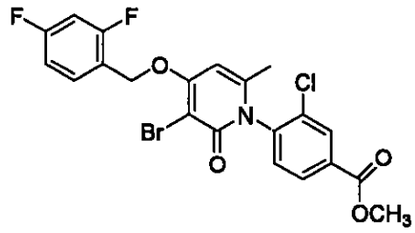



Preparación de 3-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-metilbenzoato de metilo

El compuesto del titulo se preparó mediante la absorcion de 3-[4-[(2,4-difluorobencil)oxi]-6-metil-2-

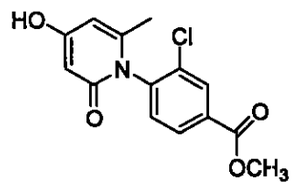
oxopiridin-1(2H)-yl]-4-metilbenzoato de metilo (1,46g, 3,66 mmol) en dicloroetano (25 ml) y el agregado de N-clorosuccinimida (0,49g, 3,66 mmol), acido dicloroacetico (catalitico), y mediante calentamiento a 50°C durante 6 horas En este momento, el disolvente se elimino in vacuo y el residuo se absorbió en éter de dietilo Se recolecto el precipitado en un papel de filtro $^1$H NMR (300 MHz, $CDCl_3$) δ 8,07 (dd, J = 7,85, 1,61 Hz, 1H), 7,80 (d, J = 1,81 Hz, 2H), 7,62 (app q, J = 8,46 Hz, 1H), 7,48 (d, J = 7,85, 1H), 7,05 -6,95 (m, 1H), 6,93 - 6,89 (m, 1H), 6,19 (s, 1H), 5,30 (s, 2H), 3,93 (s, 3H), 2,17 (s, 3H), 1,97 (s, 3H) ES-HRMS m/z 434,0932 (M+H calculado para $C_{22}H_{19}ClF_2NO_4$ requiere 434,0965)

Ejemplo 494




4-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-3-clorobenzoato de metilo

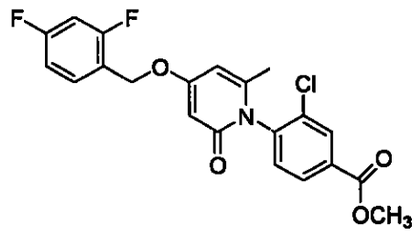
Etapa 1 Preparacion 3-cloro-4-(4-hidroxi-6-metil-2-oxopiridin-1 (2H)-il)-benzoato de metilo




Se realizó la suspensión de 4-hidroxi-6-metil-2-pirona (24,5 g, 193,9 mmol) y metil-3-amino-2-clorobenzoato (30 g,

161,6 mmol) en 75 ml de 1,2-diclorobenceno en un matraz de 250 ml, de tres cuellos, con fondo redondo, equipado con una sonda controladora de temperatura J-Kem, una trampa Dean-Stark y un manto de calentamiento La reacción se calento a 175 °C durante 20 minutos, durante los cuales se recolecto agua y cierta cantidad de 1,2-diclorobenceno en la trampa Dean-Stark La reacción se dejó enfriar hasta alrededor de 110 °C En este punto, se agregó 200 ml de tolueno Se dejo la mezcla de tolueno en agitación durante 72 horas a temperatura ambiente Se recolecto un precipitado en un papel de filtro El precipitado se filtró y se lavo 3 veces con tolueno, 3 veces con agua a 50 °C para eliminar el exceso de pirona, y se seco in vacuo para proporcionar un solido de color tostado (13,0 g, 27% de rendimiento) $^1$H NMR (300 MHz, $CD_3OD$) δ 8,26 (d, J = 1,81 Hz, 1H), 8,14 (dd, J = 8,26, 1,81 Hz, 1H), 7,54 (d, J = 8,26, Hz, 1H), 6,14(dd, J = 2,42, 1,0 Hz, 1H), 5,83 (d, J = 2,42 1H), 4,00 (s, 3H), 1,96 (s, 3H), LC/MS, $t_r$ = 1,81 minutos (5 a 95% de acetonitrilo /agua durante 5 minutos a 1 ml /min con detecc on de 254 nm, a 50 °C) ES-MS m/z 294 (M+H)

Etapa 2 Preparación de 3-cloro-4-[4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-benzoato de metilo



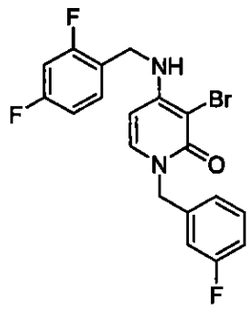

Se absorbió 3-cloro-4-(4-hidroxi-6-metil-2-oxopiridin-1(2H)-il)benzoato de metilo (de la Etapa 1) (2,4g, 8,17 mmol) en DMF (10 ml) Se agrego 2,4-

1127
1276

difluorobencilbromuro (1,05 ml, 8,17 mmol) y $K_2CO_3$ (1,13 g, 8,17 mmol) La reaccion se agito durante 6 horas a temperatura ambiente En este momento, la reaccion se vertio en agua (200 ml) y se extrajo con acetato de etilo La capa de acetato de etilo se seco con $Na_2SO_4$ se filtró y se elimino el disolvente in vacuo para proporcionar un aceite color ambar (2,62 g, 77% de rendimiento en crudo) LC/MS, t = 2,79 minutos (en acetonitrilo/ agua del 5 al 95% durante 5 minutos a 1 ml/ min con detección 254 nm, a 50 °C) ES-MS m/z 294 (M+H)

Etapa 3 Preparacion del compuesto del titulo Se absorbió 3-cloro-4-[4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-benzoato de metilo (de la etapa 2) (2,60g, 6,21mmol) en $CH_2Cl_2$ (20 ml) Se agrego N-bromosuccinimida (1,11g, 6,21 mmol) y la mezcla se agito a temperatura ambiente durante 4 horas El $CH_2Cl_2$ se elimina in vacuo y el residuo se absorbe en $CH_3CN$ El precipitado resultante se recolecta en un papel de filtro y se lava con $CH_3CN$ para proporcionar un solido blanco (0,75 g, 24%) $^1H$ NMR (300 MHz, $CDCl_3$) δ 8,22 (d, J = 1,88 Hz, 1H), 8,06 (dd, J = 8,19, 1,75 Hz, 1H), 7,59 (app q, J = 8,46 Hz, 1H), 7,33 (d, J = 8,19, 1H), 6,96 (dt, J = 8,06, 1,21 Hz, 1H), 6,89 6,84 (m, 1H), 6,13 (s, 1H), 5,26 (s, 2H), 3,95 (s, 3H), 1,95 (s, 3H) ES-HRMS m/z 497,9892 (M+H calculado para $C_{22}H_{16}BrClF_2NO_4$ requiere 497,9914)

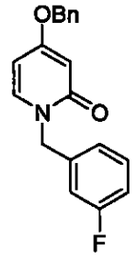
Ejemplo 495



3-bromo-4-[(2,4-difluorobencil)oxi]amino-1-(3-fluorobencil)piridin-2-(1H)-ona

Etapa 1

Preparación de 4-(benciloxi)-1-(3-fluorobenzil)piridin-2(1H)-ona



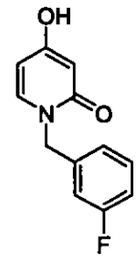
Un matraz de 100 ml, de fondo redondo, equipado con barra de agitacion y entrada de nitrogeno, se cargó con 4-benciloxi-2(1H)-piridinona (20 g, 99,6 mmol) y N,N-dimetil-formamida (50 ml) Se agregó $K_2CO_3$ (13,7 g, 99,6 mmol) y KI ( 1,6 g, 9,6 mmol) y luego bromuro de 3-fluorobencilo (14,6 mL, 119,4 mmol) La mezcla de la reaccion se calento durante 18 horas a 80 °C La mezcla de la reacción se concentro in vacuo y se trato con acetato de etilo caliente Los sólidos se filtraron, el producto del filtrado se vertio en agua y se extrajo con acetato de etilo El extracto organico se lavo con salmuera, se secó con $Na_2SO_4$, anhidro y se concentro in vacuo El residuo se disolvio en acetato de etilo caliente y se precipito con hexanos para proporcionar el compuesto del titulo (10 g,

1179
1278

33%) $^1$H NMR (400 MHz, $CD_3OD$) δ 7,57 (d, J = 8,4 Hz, 1H), 7,37 (m, 5H), 7,07 (d, J = 8,4 Hz, 1H), 7,01 (app d, J = 8,4 Hz, 2H), 6,17 (d, J = 2,68 and 7,6 Hz, 1H), 6,04 (d, J = 2,68 Hz, 1H), 5,10 (s, 2H), 5,08 (s, 2H) ppm $^{19}$ F NMR (400 MHz, $CD_3OD$) □ -114,88 (1 F) ppm ES-HRMS m/z 310,1271 (M+H calculado para $C_{19}H_{17}FNO_2$ requiere 310,1238)

Etapa 2

Preparacion de 1-(3-fluorobencil)-4-hidroxipiridin-2(1H)-ona

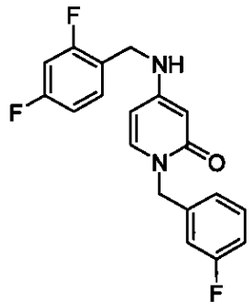



Una botella Parr pequeña se cargó con SC-82484 (10 g, 32,3 mmol), etanol (175 ml) y 10% Pd/C (0,5 g) El sistema se lavo dos veces con nitrogeno y con hidrogeno La mezcla de la reaccion se hidrogeno a 30 lppc hasta que mediante LC-MS no se visualizo mas material de inicio Se realizo una suspension espesa de la mezcla de la reacción con Celite y luego se la filtro a traves de un filtro de celite El producto del filtrado y los lavados subsiguientes con etanol se concentraron in vacuo para proporcionar un sólido beige $^1$H NMR (400 MHz, $CD_3OD$) δ 7,53 (d, J = 7,67 Hz, 1H), 7,32 (m, 1H), 7,06 (d, J = 7,6 Hz, 1H), 6,98 (d, J = 8,4 Hz, 2H), 6,05 (dd, J = 2,58 and 7,67 Hz, 1H), 5,83 (d, J = 2,0 Hz, 2H), 5,10 (s, 2H) ppm $^{19}$ F NMR (400 MHz, $CD_3OD$) δ -115,33 (1 F) ppm ES-HRMS m/z 218,0641 (M+H calculado para $C_{12}H_{11}FNO_2$ requiere 218,0612)

Etapa 3

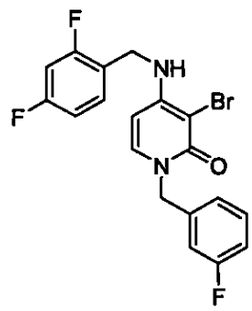
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Preparacion de 4-[(2,4-difluorobencil)amino-1-(3-fluorobencil)piridin-2-(1H)-ona



Se realizo la combinación del producto de la Etapa 2 (0,5 g, 2,28 mmol) y 2,4-difluoro bencilamina (4 ml, 33,6 mmol) en un tubo de cultivo lavado con nitrógeno Se tapo el tubo y se lo ca entó a 180 °C durante 24 horas El exceso de amina se diluyo in vacuo y se realizo la cromatografia del residuo sobre silice (95 5 de acetato de etilo/ metanol) El compuesto final se aisló como solido amarillo claro (0,16 g, 36%) $^{1}$H NMR (400 MHz, $CD_3OD$) δ 7,33 (m, 3H), 7,03 (d, J = 8 Hz, 1H), 6,96 (m, 3H), 6,95 (m, 1H), 5,97 (dd, J = 3,2 y 8,0 Hz, 1 H), 5,48 (d, J = 2,56 Hz, 1H), 5,02 (s, 2H), 4,33 (s, 2H) ppm $^{19}$ F NMR (400 MHz, $CD_3OD$) δ -113,88 (1 F), 115,33 (1F), -116,78 (1F) ppm ES-HRMS m/z 345,1221 (M+H calculado para $C_{19}H_{17}F_3N_2O$ requiere 345,1209)

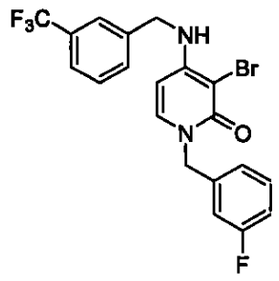
Etapa 4 Preparacion de 3-bromo-4-[(2,4-difluorobencil)amino]-1-(3-fluorobencil)piridin-2-(1H)-ona



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1180

Se agrego N-Bromo succinimida (81 mg, 0,46 mmol) a una disolucion del producto de la Etapa 3 (0,15 g, 0,44 mmol) en cloruro de metileno (10 ml) Despues de agitar la reaccion a 25 °C durante 1 hora, se completo mediante LC-MS La mezcla de la reaccion se vertio en $NaHCO_3$ acuoso saturado La mezcla acuosa se extrajo con acetato de etilo La capa organica se lavó con salmuera, se seco con $Na_2SO_4$, anhidro y se concentro in vacuo $^1H$ NMR (400 MHz, $CDCl_3$) δ 7,3-7,2 (m, 4H), 7,07 (app t, J = 7,6 Hz, 2H), 6,97 (m, 2H), 6,80 (m, 2H), 5,78 (d, J = 7,6 Hz, 1H), 5,30 (br s, 1H), 5,08 (s, 2H), 4,46 (d, J = 6 Hz, 2H) ppm $^{19}$ F NMR (400 MHz, $CDCl_3$) δ -110,64 (1 F), -112,75 (1F), -114,79 (1F) ppm ES-HRMS m/z 423,0275 (M+H calculado para $C_{19}H_{15}BrF_3N_2O$ requiere 423,0314)

Ejemplo 496

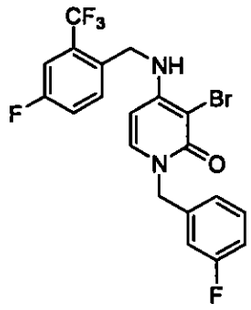



3-bromo-1-(3-fluorobencil)-4-{[3-(trifluorometil)bencil]amino}piridin-2-(1H)-ona

El compuesto del titulo se preparo esencialmente como en el Ejemplo 495 $^1H$ NMR (400 MHz, $CDCl_3$) δ 7,54 (m, 2H), 7,48 (m, 2H), 7,27 (q, J = 3,1, 9,0 Hz, 1H), 6,96 (app t, J = 8,8 Hz, 2H), 5,71 (d, J = 7,6 Hz, 1H), 5,4 (br m, 1H), 5,08 (s, 2H), 4,52 (d, J = 5,6 Hz, 2H) ppm $^{19}$ F NMR (400 MHz, $CDCl_3$) δ -63 (3 F), -112 (1 F) ppm ES-HRMS m/z 455,0388 (M+H calculado para $C_{20}H_{16}BrF_4N_2O$ requiere 455,0377)

1182
1181

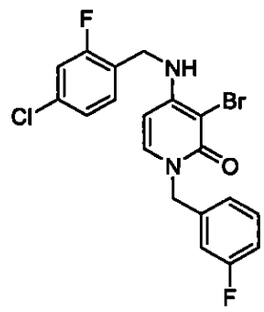
Ejemplo 497



3-bromo-1-(3-fluorobencil)-4-{[4-fluoro-2-(trifluorometil)bencil]amino}piridin-2-(1H)-ona

El compuesto del titulo se preparó esencialmente como en el Ejemplo 495 $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7,43 (m, 2H), 7,27 (m, 3H), 7,07 (m, 2H), 6,99 (m, 2H), 5,65 (d, J = 10Hz, 1H), 5,46 (br s, 1H), 5,09 (s, 2H), 4,64 (s, 2H) ppm $^{19}$ F NMR (400 MHz, $CDCl_3$) δ-61,31 (3 F), -112,69 (1F), 112,97 (1F) ppm ES HRMS m/z 473,0246 (M+H calculado para $C_{20}H_{15}BrF_5N_2O$ requiere 473,0282)

Ejemplo 498

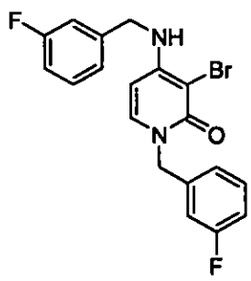


Preparacion de -bromo-4-[(4-cloro-2-fluorobencil)amino]-1-(3-fluorobencil)piridin-2-(1H)-ona

El compuesto del titulo se preparó esencialmente como en el Ejemplo 495 $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7,27 (m, 1H), 7,19 (aprox t, J = 8,8 Hz, 1H), 7,10 (m, 4H), 6,95 (aprox t, J = 8,8 Hz, 2H), 5,74 (d, J = 8 Hz, 1H), 5,40 (br s, 1H), 5,08 (s, 2H), 4,47 (d J = 6 Hz, 2H) ppm $^{19}$ F NMR

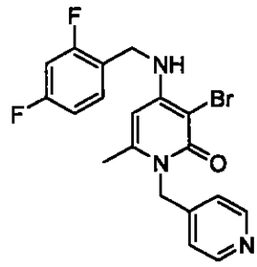
(400 MHz, $CDCl_3$) δ -112,67 (3 F), -116,39 (1 F) ppm ES-HRMS m/z 439,0047 (M+H calculado para $C_{19}H_{15}ClBrF_2N_2O$ requiere 439,0019)

Ejemplo 499




El compuesto del titulo se preparo esencialmente como en el Ejemplo 495 $^1$H NMR (400 MHz, $CDCl_3$) δ 7,35- 7,2 (m, 1H), 7,27 (dd, J = 2,5 y 8 Hz, 1H), 7,05 (aprox d, J = 7,2 Hz, 3H), 6,97 (m, 4H), 5,72 (d, J = 7,6 Hz, 1H), 5,41 (br s, 1H), 5,08 (s, 2H), 4,46 (d, J = 6,4 Hz, 2H) ppm $^{19}$F NMR (400 MHz, $CDCl_3$) δ -112,5 (3 F), -113 (1 F) ppm ES-HRMS m/z 405,0431 (M+H calculado para $C_{19}H_{16}BrF_2N_2O$ requiere 405,0409)

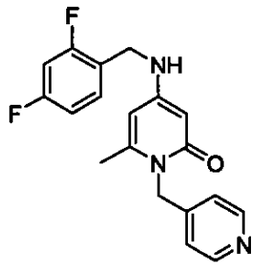
Ejemplo 500




Preparacion de 3-bromo-4-[(2,4-difluorobencil)amino]-6-metil-1-(-piridin-4-ilmetil)piridin-2(1H)-ona

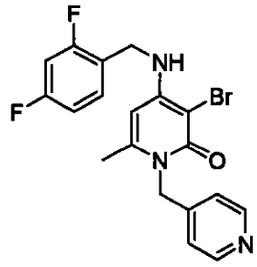
Etapa 1 Preparación de 4-[(2,4-difluorobencil)amino]-6-metil-1-(-piridin-4-ilmetil)piridin-2(1H)-ona

1184
H83



Se realizo la combinación de (0,3 g, 1,39 mmol) y 2,4-difluoro bencilamina (1 ml, 8,4 mmol) en un tubo de cultivo lavado con nitrogeno El tubo se tapo y calento a 180 °C durante 24 horas El exceso de amina se destilo in vacuo $^{1}$H NMR (400 MHz, $CD_3OD$) δ 8,44 (dd, J = 1,7 y 4,8Hz, 2H), 7,38 (q, J = 10 y 15 Hz, 1H), 7,14 (d, J = 4,8 Hz, 2H), 6,95 (m, 2H), 5,90 (dd, J = 1 y 2,5Hz, 1H), 5,47 (d, J = 2, 1H), 5, 28 (s, 2H), 4,33 (s, 2H), 2,27 (s, 3H) ppm $^{19}$ F NMR (400 MHz, $CD_3OD$) δ -113,73 (1 F), -116,66 (1 F) ppm ES-HRMS m/z 342,1422 (M+H calculado para $C_{19}H_{18}F_2N_3O$ requiere 342,1418)

Etapa 2 Preparacion de 3-bromo-4-[(2,4-difluorobencil)amino]-6-metil-1-(-piridin-4-ilmetil)piridin-2(1H)-ona

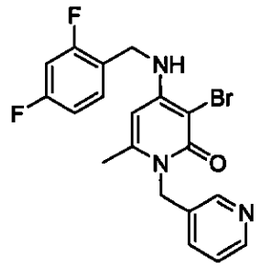


Se agrego N-Bromo succinimida (77 mg, 0,43 mmol) a una disolucion del producto de la Etapa 1 (0,14 g, 0,41 mmol) en cloruro de metileno (10 ml) Despues de agitar la reaccion a 25 °C durante 1 hora, se completó mediante LC-MS La mezcla de la reaccion se vertio en $NaHCO_3$ acuoso saturado La mezcla acuosa se extrajo con acetato de

1105
H84

etilo La capa organica se lavó con salmuera, se seco con $Na_2SO_4$, anhidro, se filtro y se concentro in vacuo El residuo se trituro con hexanos para proporcionar el compuesto del titulo como un sólido amarillo (81 mg, 47%) $^1$H NMR (400 MHz, $CDCl_3$) δ 8,47 (dd, J = 1,6 and 4,8Hz, 2H), 7,24 (q, J = 6,4 and 13,6 Hz, 1H), 7,01 (d, J = 6,4 Hz, 2H), 6,83 (m, 2H), 5,68 (s, 1H), 5,25 (s, 2H), 4,45 (d, J = 6,4Hz, 2H), 2,12 (s, 3H) ppm $^{19}$ F NMR (400 MHz, $CDCl_3$) δ -110,51 (m, 1 F), -114,66 (m, 1 F) ppm ES-HRMS m/z 420,0524 (M+H calculado para $C_{19}H_{17}BrF_2N_3O$ requiere 420,0523)

Ejemplo 501

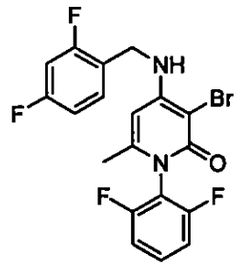



Preparacion de 3-bromo-4-[(2,4-difluorobencil)amino]-6-metil-1-(-piridin-3-ilmetil)piridin-2(1H)-ona

El compuesto del titulo se preparo esencialmente como en el Ejemplo 500 $^1$H NMR (400 MHz, $CDCl_3$) δ 8,45 (d, J = 4,8Hz, 2H), 7,55 (aprox t, J = 6 Hz, 1H), 7,21 (m, 2H), 6,83 (m, 2H), 5,65 (s, 1H), 5,34 (d, J = 5,2Hz, 1H), 5,27 (s, 2H), 4,45 (s, 2H), 2,10 (d, J = 4,8Hz, 3H) ppm $^{19}$ F NMR (400 MHz, $CDCl_3$) δ -110,74 (3 F), -114,86 (1 F) ppm ES-HRMS m/z 420,0513 (M+H calculado para $C_{19}H_{17}BrF_2N_3O$ requiere 420,0523)

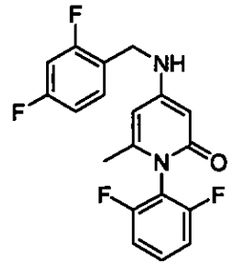
Ejemplo 502

1186



Preparación de 3-bromo-4-[(2,4-difluorobencil)amino]-1-(2,6-difluorofenil)-6-metilpiridin-2(1H)-ona

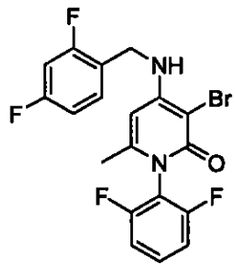
Etapa 1 Preparacion de 4-[(2,4-difluorobencil)amino]-1-(2,6-difluorofenil)-6-metilpiridin-2(1H)-ona



Se combinaron 1-(2,6-difluorofenil)-4-hidroxi-6-metilpiridin-2(1H)-ona (0,3 g, 1,26 mmol) y 2,4-difluoro bencilamina (1ml, 8,4 mmol) en un tubo de cultivo lavado con nitrogeno Se tapo el tubo y se lo calento a 180 °C durante 24 horas El exceso de amina se destiló *in vacuo* y se realizó la cromatografia del residuo sobre silice (1 1 de hexanos/ acetato de etilo) El compuesto fue puro en aproximadamente el 50% y se lo transfirió sin ulterior purificacion (0,633 g) $^1$H NMR (400 MHz, $CD_3OD$) δ 7,53 (m, 1H), 7,41 (m, 1H), 7,16 (t, J = 8,8Hz, 2H), 6,93 (m, 2H), 6,00 (s, 1H), 5,42 (s, 1H), 5,42 (s, 1H), 4,37 (s, 2H), 1,93 (s, 3H) ppm LC/MS, t = 4,65 minutos (en acetonitrilo/ agua del 5 al 95% durante 8 minutos a 1 ml/ min con detección 254 nm, a 50 °C) ES-MS m/z 363 (M+H)

1187
1186

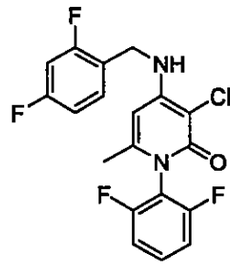
Etapa 2 Preparación de 3-bromo-4-[(2,4-difluorobencil)amino]-1-(2,6-difluorofenil)-6-metilpiridin-2(1H)-ona



Se agrego N-Bromo succinimida (168 mg, 0,945 mmol) a una disolucion del producto de la Etapa 1 (0,633 g) en cloruro de metileno (10 mL) Despues de agitar a 25 °C durante 1 hora, la reacción se completó en un 50% por medio de LC-MS Se agrego N-bromo succinimida adicional (150 mg) y se agito la reaccion a 25 °C durante 12 horas La mezcla de la reaccion se vertió en $NaHCO_3$ acuoso saturado La mezcla acuosa se extrajo con acetato de etilo La capa organica se lavo con salmuera, se seco con $Na_2SO_4$, anhidro y se concentro in vacuo El residuo se purifico mediante cromatografia de fase inversa (60 40 acetonitrilo agua con 0,05% de ácido trifluoroacético) El compuesto del titulo se aislo como sal de TFA (0,161 g, 23%) $^1H$ NMR (400 MHz, $CD_3OD$) δ 7,53 (m, 1H), 7,35 (q, J = 8, 15,6Hz, 1H), 7,16 (t, J = 8 Hz, 2H), 6,96 (app q, J = 8, 16,4Hz, 2H), 6,12 (s, 1H), 4,86 (s, 2H), 1,94 (s, 3H) ppm $^{19}$ F NMR (400 MHz, $CD_3OD$) δ -77,33 (1 F), -113,60 (1 F) -116,63 (1F), -121,50 (1F) ppm ES-HRMS m/z 441,0231 (M+H calculado para $C_{19}H_{14}BrF_4N_2O$ requiere 441,0220)

Ejemplo 503

1188
1187

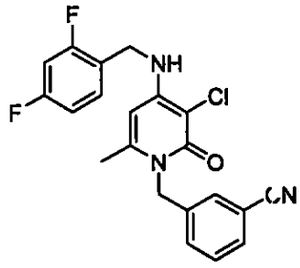


Preparacion de 3-cloro-4-[(2,4-difluorobencil)amino]-1-(2,6-difluorofenil)-6-metilpiridin-2(1H)-ona

Se combinaron 1-(2,6-difluorofenil)-4-hidroxi-6-metilpiridin-2(1H)-ona (0,3 g, 1,26 mmol) y 2,4-difluoro bencilamina (1mL, 84 mmol) en un tubo de cultivo lavado con nitrogeno Se tapó el tubo y se lo calentó a 180 °C durante 24 horas El exceso de amina se destilo in vacuo y el residuo se uso sin ninguna otra purificacion Se agrego N-Cloro succinimida (168 mg, 1,26 mmol) a una disolucion del residuo en cloruro de metileno (10 mL) Despues de agitar a 25 °C durante 1 hora, la mezcla de la reacción se vertio en $NaHCO_3$ saturado acuoso La mezcla acuosa se extrajo con acetato de etilo La capa organica se lavó con salmuera, se seco con $Na_2SO_4$, anhidro y se concentro in vacuo Se sometio el residuo a cromatografia sobre silice (25 75 hexanos acetato de etilo) para proporcionar el compuesto del titulo (32 mg, 6%) $^1H$ NMR (400 MHz, $CD_3OD$) δ 7,55 (m, 1H), 7,36 (q, J = 9,2 y 15,2Hz, 1H), 7,18 (t, J = 7,6Hz, 2H), 6,98 (m, 2H), 6,15 (s, 1H), 4,62 (s, 2H), 1,96 (s, 3H) ppm $^{19}$ F NMR (400 MHz, $CD_3OD$) δ -113,78 (1 F), -116,72 (1 F),-121 57 (1F) ppm ES-HRMS m/z 397,0752 (M+H calculado para $C_{19}H_{14}ClF_4N_2O$ requiere 397,0725)

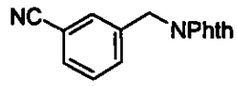
1189
1188

Ejemplo 504



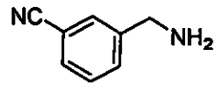

Preparación de 3-{[3-cloro-4-[(2,4-difluorobencil)amino]-6-metil-2-oxopiridin-1(2H)-il]metil}benzonitrilo

Etapa 1 Preparacion de 3-ftalimidometil-benzonitrilo



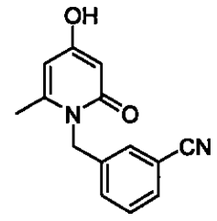

Se preparo 3-ftalimidometil-benzonitrilo segun lo descripto en la literatura (Bookser, B C , Bruice, T C J Am Chem Soc 1991, 113, 4208-18 )

Etapa 2 Preparacion de 3-(aminometil)benzonitrilo




Se preparo 3-(Aminometil)benzonitrilo segun lo descripto en la literatura (Bookser, B C Bruice, T C J Am Chem Soc 1991, 113, 4208-18 )

Etapa 3 Preparación 3-[(4-(hidroxi-6-metil-2-oxopiridin-1 (2H)-il)-metil]benzonitrilo

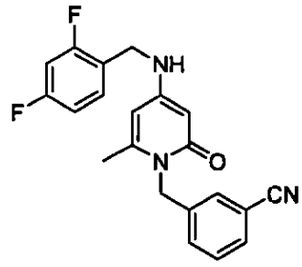



Se cargo un tubo de reaccion Pyrex lavado con nitrógeno, con 3-(aminometil)benzonitrilo (1 g, 7,9 mmol), 4-hidroxi-6-metil-2-pirona (1 g, 7,9 mmol) y agua (20 ml)

1190
H89

El tubo se tapo y se calento hasta el reflujo Despues de 1 ½ hora, el producto se precipitó de la disolucion La mezcla de la reaccion se enfrio a temperatura ambiente, se filtro y se lavo con agua El producto se uso sin ninguna otra purificacion (1,67 g, 88%) $^1$H NMR (400 MHz, dmso-$d_6$) δ 10,53 (s, 1H), 7,61 (d, J = 8Hz, 1H), 7,52 (t, J = 8Hz, 2H), 7,38 (d, J = 8 Hz, 1H), 5,79 (dd, J = 1 y 2,5 Hz, 1H), 5,56 (d, J = 2,7 Hz, 1H), 5,18 (s, 2H), 2,14 (s, 3H) ppm ES-HRMS m/z 241,0968 (M+H calculado para $C_{14}H_{13}N_2O_2$ requiere 241,0972)

Preparación de 3-{[4-[(2,4-difluorobencil)amino]-6-metil-2-oxopiridin-1(2H)-il]metil}benzonitrilo

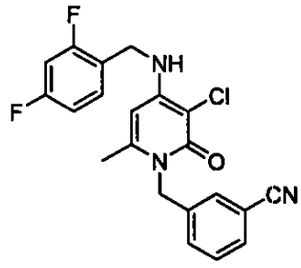



Se realizó la combinacion del producto de la Etapa 4 (0,5 g, 2,08 mmol) y 2,4-difluoro bencilamina (2 mL, 16,8 mmol) en un tubo de cultivo lavado con nitrogeno Se tapo el tubo y se lo calento a 180 °C durante 24 horas El exceso de amina se destilo *in vacuo* y el residuo se trituro con acetato de etilo / hexanos para precipitar los materiales de inicio Se realizó la cromatografia del residuo en fase inversa (1 1 agua acetonitrilo con 0,05% de acido trifluoroacetico) El producto de la Etapa 5 se aislo como un semisólido blanco (0,125 g, 15%) $^1$H NMR (400 MHz, $CD_3OD$) δ 7,61(d, J = 8Hz, 1H), 7,49 (t, J = 8 Hz, 1H), 7,41 (m, 3H), 6,94 (m, 2H), 5,89 (dd, J = 0,8 y 2,7Hz, 1H), 5,47 (d, J = 2,8Hz, 1H), 5,27 (s, 2H), 4,34 (s, 2H), 2,18 (s, 3H) ppm LC/MS, $t_r$ = 4,87 minutos (en

1191
H90

acetonitrilo/ agua del 5 al 95% durante 8 minutos a 1 ml/ min con detección 254 nm, a 50 °C) ES-MS m/z 366 (M+H)

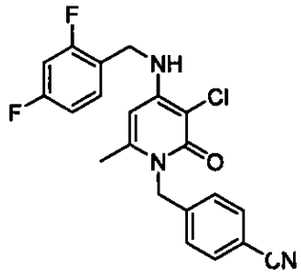
Etapa 6 Preparacion de 3-{[3-cloro-4-[(2,4-difluorobencil)amino]-6-metil-2-oxopiridin-1(2H)-il]metil}benzonitrilo




Se agregó N-Cloro succinimida (36 mg, 0,27 mmol) a una disolucion del producto de la Etapa 5 (0,125 g, 0,26 mmol) en cloruro de metileno (10 mL) Después de agitar la reaccion a 25 °C durante 2 horas, se completó mediante LC-MS La mezcla de la reaccion se vertio en $NaHCO_3$ acuoso saturado La mezcla acuosa se extrajo con acetato de etilo La capa orgánica se lavó con salmuera, se secó con $Na_2SO_4$, anhidro y se concentro in vacuo El residuo se trituro con acetonitrilo para proporcionar el compuesto del titulo como un sólido de color tostado (20 mg, 13%) $^1H$ NMR (400 MHz, $CD_3OD$) δ 7,61 (d, J = 8,4 Hz, 1H), 7,49 (m, 2H), 7,40 (d, J = 8,4 Hz, 1H), 7,33 (q, J = 8,4 and 14,8 Hz, 1H), 6,94 (m, 2H), 6,00 (s, 1H), 5,34 (s, 2H), 4,56 (s, 2H), 2,21 (s, 3H) ppm $^{19}F$ NMR (400 MHz, $CD_3OD$) δ -114,00 (1 F), -116,89 (1 F) ppm LC/MS, t = 5,49 minutos (en acetonitrilo/ agua del 5 al 95% durante 8 minutos a 1 ml/ min con deteccion 254 nm, a 50 °C) ES-MS m/z 400 (M+H)

1191
1192

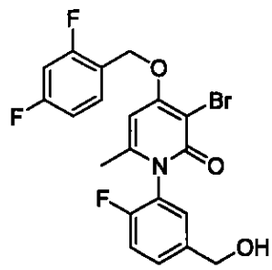
Ejemplo 505



Preparación de 4-{[3-cloro-4-[(2,4-difluorobencil)amino]-6-metil-2-oxopiridin-1(2H)-il]metil}benzonitrilo

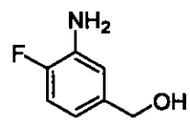
El compuesto del titulo se preparo esencialmente como en el Ejemplo 504 $^{1}$H NMR (400 MHz, $CD_3OD$) δ7,66 (d, J = 8 Hz, 2H), 7,33 (q, J =8 y 15,2 Hz, 1H), 7,25 (d, J = 8 Hz, 2H), 6,94 (m, 2H), 6,01 (s, 1H), 5,36 (s, 2H), 4,55 (s, 2H), 2,19 (s, 3H) ppm $^{19}$ F NMR (400 MHz, $CD_3OD$) δ -77,52 (1 F), -113,89 (1 F), -116,71 (1 F) ppm LC/MS, $t_r$ = 5,49 minutos (en acetonitrilo/ agua del 5 al 95% durante 8 minutos a 1 ml/ min con detección 254 nm, a 50 °C) ES-MS m/z 400 (M+H)

Ejemplo 506



Preparacion de 3-bromo-4-[(2,4-difluorobencil)oxi]-1-[2-fluoro-5-(hidroximetil)fenil]-6-metilpiridin-2(1H)-ona

Etapa 1 Preparación de (3-amino-4-fluorofenil)metanol

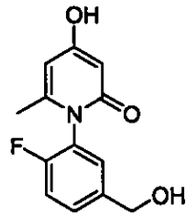


1192
1193

Se cargo un matraz equipado con agitador superior con alcohol 4-fluoro-3-nitrobencilico (20 g, 0,117 mol) y 200 mL de 5 1 isopropanol agua Se agregó cloruro de amoniaco (62 g, 1,17 mol) y luego virutas de hierro (65 g, 1, 17 mol) La mezcla se agito a 70 °C durante 1 ½ hora cuando pareció estar completa mediante LC-MS El liquido decanto y los solidos se lavaron con mas isopropanol agua Se elimino el isopropanol y el residuo se diluyo con 0,5 N HCl y se extrajo con acetato de etilo Se llevo la capa acuosa a un pH igual a 12-14 con 2,5 N NaOH y se extrajo con acetato de etilo La capa organica se seco con $Na_2SO_4$, anhidro y se concentro *in vacuo* Se aislo 3-Amino-4-fluorofenil metanol como un sólido marrón (4,5 g, 27%) y se lo uso sin ninguna otra purificacion LC/MS, $t_r$ = 2,40 minutos (en acetonitrilo/ agua del 5 al 95% durante 8 minutos a 1 ml/ min con detección 254 nm, a 50 °C) ES-MS m/z 142 (M+H)

ES-HRMS m/z 142,0692 (M+H calculado para $C_7H_8FNO$ requiere 142,0663)

Etapa 2 Preparacion de 1-[2-fluoro-5-(hidroximetil)fenil]-4-hidroxi-6-metilpiridin-2(1H)-ona



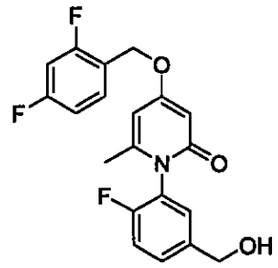

Un matraz de 100 ml, de fondo redondo, equipado con barra de agitación Dean-Stark y condensador de reflujo, se cargó con (3-amino-4-fluorofenil)metanol (4,5 g, 31,9 mmol),

4-hidroxi-6-metil-2-pirona (4 g, 31,9 mmol) y o-diclorobenceno (5 mL) El sistema se sumergió en un baño

1193
1194

de aceite a 170 °C durante 10 minutos El disolvente se elimino in vacuo y el residuo se sometio a cromatografia de fase inversa (75 25 de agua acetonitrilo con TFA al 0,05%) El producto contenia algunos materiales de inicio despues de la purificacion y se lo uso sin ninguna otra purificacion (1,27g, 15%) $^1$H NMR (400 MHz, dmso-$d_6$) δ 7,39 (m, 1H), 7,20 (dd, J = 2,2 and 7,6 Hz, 1H), 6,74 (dd, J = 2,7 y 9,6 Hz, 1H), 5,93 (dd, J = 1,2 and 2,2 Hz, 1H), 5,22 (dd, J = 0,4 y 2,2 Hz, 1H), 2,12 (s, 3H) ppm ES-HRMS m/z 250,0862 (M+H calculado para $C_{13}H_{13}FNO_3$ requiere 250,0874)

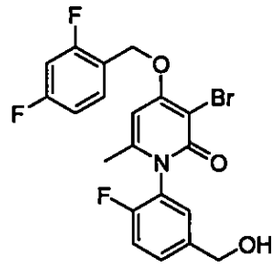
Etapa 3 Preparacion de 4-[(2,4-difluorobencil)oxi]-1-[2-fluoro-5-(hidroximetil)fenil]-6-metilpiridin-2(1H)-ona




Se cargó un matraz de 100 mL, de fondo redondo (purgado con nitrogeno), con 1-[2-fluoro-5-(hidroximetil)fenil]-4-hidroxi-6-metilpiridin-2(1H)-ona (1,2 g, 4,82 mmol) y N,N-dimetil formamida (10 mL) Se agrego carbonato de potasio (0,6 g, 4,4 mmol) y bromuro de 2,4-difluorobencil (0,56 mL, 4,4 mmol) y la mezcla de la reacción se agito a temperatura ambiente durante toda la noche La mezcla de la reaccion se diluyo con $NaHCO_3$ acuoso saturado y se extrajo con acetato de etilo La capa organica se concentró *in vacuo* y el residuo se sometio a cromatografia sobre silice (9 1 cloruro de metileno etanol) El aceite impuro (0,3 g, 17%) se transfirio sin ninguna otra purificación $^1$H NMR (400 MHz, $CD_3OD$) δ 7,54 (m, 2H), 7,30 (m, 2H), 7,02 (m, 2H), 6,17 (dd, J = 1 y 2,8

Hz, 1H), 6,03 (d, J = 2,8 Hz, 1H), 5,14 (s, 2H), 4,62 (s, 2H), 2,14 (s, 3H) ppm $^{19}$F NMR (400 MHz, $CD_3OD$) δ -111,35 (1 F), -115,97 (1 F), -127,31 (1 F) ppm LC/MS, t = 5,05 minutos (en acetonitrilo/ agua del 5 al 95% durante 8 minutos a 1 ml/ min con deteccion 254 nm, a 50 °C) ES-MS m/z 375 (M+H)

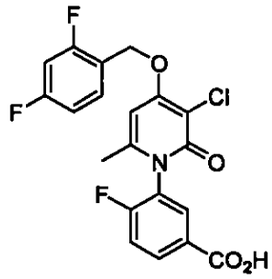
Etapa 4 Preparacion de 3-bromo-4-[(2,4-difluorobencil)oxi]-1-[2-fluoro-5-(hidroximetil)fenil]-6-metilpiridin-2(1H)-ona



Se agregó N-bromo succinimida (50 mg, 0,3 mmol) a una disolucion del producto de la Etapa 3 (0,12 g, 0,32 mmol) en N,N-dimetil formamida (4 mL) Después de agitar a 25°C durante 2 horas, se agrego acido trifluoroacetico (50 □L) Una hora después de agregó más N-bromo succinimida (30 mg) Una hora despues, la reaccion se completo mediante LC-MS La mezcla de la reacción se vertió en salmuera y se extrajo con acetato de etilo La capa organica se lavo con salmuera, se seco con $Na_2SO_4$, anhidro y se concentro in vacuo Se realizó la cromatografía del residuo en fase inversa (95 5 cloruro de metileno etanol) El compuesto del titulo se aisló como sal de TFA (38 mg, 26 %) $^1$H NMR (400 MHz, $CD_3OD$) δ 7,64 (q, J = 7,6 and 14,8 Hz, 1H), 7,51 (m, 1H), 7,31 (app t, J = 8,4 Hz, 1H), 7,04 (t, J = 8,4 Hz, 2H), 6,63 (s, 1H), 5,34 (s, 2H), 4,62 (s, 2H), 2,06 (s, 3H) ppm $^{19}$F NMR (400 MHz, $CD_3OD$) δ -111,48 (1 F), -115,92 (1 F), -127,23 (1 F) ppm ES-HRMS m/z 454,0228 (M+H calculado para $C_{20}H_{16}BrF_3NO_3$ requiere 454,0260)

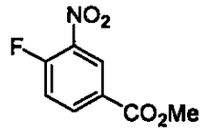
1195
1196

Ejemplo 507



Preparacion de acido 3-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-fluorobenzoico

Etapa 1 Preparación de 4-fluoro-3-nitrobenzoato de metilo

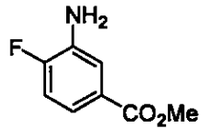


Un matraz de l litro, con tres cuellos y fondo redondo, equipado con entrada de nitrogeno, barra de agitacion, embudo de adicion y termocupla se cargo con ácido 4-fluoro-3-nitrobenzoico (50 g, 0,27 mol) y metanol (300 mL) El sistema se enfrio a 0 °C y se agrego cloruro de acetilo (27 mL, 0,37 mol) en forma de gotas El sistema se entibió a temperatura ambiente, el embudo de adicion se cambio por un condensador de reflujo y se calento a reflujo durante 1 ½ hora La mezcla de la reaccion se enfrio a temperatura ambiente, se enfrio rapidamente con $NaHCO_3$ acuoso saturado, y se extrajo con acetato de etilo El extracto organico se lavo con salmuera, se seco con $Na_2SO_4$ y se concentro in vacuo para proporcionar 4-fluoro-3-nitrobenzoato de metilo como un solido de color anaranjado (40,6 g, 75%) $^1H$ NMR (400 MHz, $CD_3OD$) δ 8,67 ((dd, J = 2,2 y 6,8 Hz, 1H), 8,34 (dddd, J = 2,2, 4,4, 6,4 and 8,8

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1197

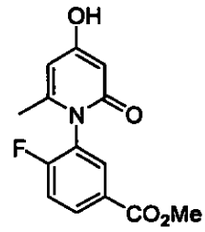
Hz, 1H), 7,55 (dd, J = 8,8 and 10,8 Hz, 1H), 3,94 (s, 3H) ppm ES-HRMS m/z 200,02446 (M+H calculado para $C_8H_7FNO_4$ requiere 200,0354)

Etapa 2 Preparación de 3-amino-4-fluorobenzoato de metilo




Una botella Parr pequeña se cargo con el producto de la Etapa 1 (40 g, 0,2 mmol), etanol (400 ml) y 10% Pd/C (1 g) El sistema se lavo dos veces con nitrogeno y con hidrogeno La mezcla de la reacción se hidrogenó a 40 lppc hasta que mediante LC-MS no se visualizó mas material de inicio Se realizo una suspension espesa de la mezcla de la reaccion con Celite y luego se la filtro a traves de un filtro de celite El producto del filtrado y los lavados subsiguientes con etanol se concentraron *in vacuo* para proporcionar 3-amino-4-fluorobenzoato de metilo bajo la forma de un solido de color anaranjado (30,6 g, 91%) $^1$H NMR (400 MHz, $CD_3OD$) δ 7,54 (d, J = 8,7 Hz, 1H), 7,35 (m, 1H), 7,06 (t, J = 8,' Hz, 1H), 3,09 (s, 3H) ppm $^{19}$ F NMR (400 MHz, $CD_3OD$) δ -131,02 (1 F) ppm ES-HRMS m/z 199,0281 (M+H calculado para $C_8H_7FNO_4$ requiere 199,02)

Etapa 3 Preparación de 4-fluoro-3-(4-hidroxi-6-metil-2-oxopiridin-1 (2H)-il)-benzoato de metilo

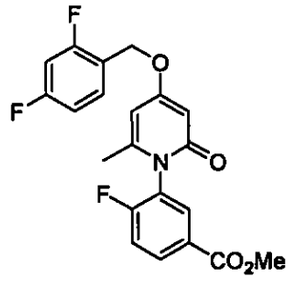



Un matraz de 250 ml, de fondo redondo, equipado con barra de agitacion, trampa Dean-Stark y condensador de

1190
1497

reflujo se cargo con el producto de la Etapa 3 (30 g, 0,18 mol), 4-hidroxi-6-metil-2-pirona (22,6 g, 0,18 mol) y o-diclorobenceno (90 ml) El sistema se sumergió en un baño de aceite a 170°C durante 30 minutos y luego se enfrio a temperatura ambiente La mezcla de la reaccion se lavo con $Na_2CO_3$ acuoso (38 g, 0,36 mol, 300 ml de agua) La capa acuosa se lavo con acetato de etilo y luego se acidificó a un pH 1-2 con HCl concentrado Éste se extrajo con acetato de etilo, el cual luego se seco con $MgSO_4$ y se concentro in vacuo El aceite anaranjado viscoso se uso sin ninguna otra purificacion (14,4 g, 28%) $^1$H NMR (400 MHz, $CD_3OD$) δ 8,18 (dddd, J = 2,3, 5 2, 7,2 y 8,8 Hz, 1H), 7,97 (dd, J = 2 y 7 2 Hz, 1H), 7,44 (t, J = 8,8 Hz, 1H), 6,09 (d, J = 1,8 Hz, 1H), 5,78 (d, J = 2,4 Hz, 1H), 3,9 (s, 3H), 2,14 (s, 3H) ppm $^{19}$ F NMR (400 MHz, $CD_3OD$) δ -117,29 (1 F) ppm ES-HRMS m/z 278,0796 (M+H calculado para $C_{14}H_{13}FNO_4$ requiere 278,0823)

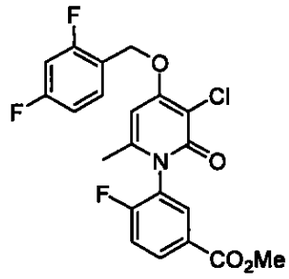
Etapa 4 Preparación de 3-[4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-fluorobenzoato de metilo




Un matraz de 100 ml, de fondo redondo, equipado con barra de agitacion y entrada de nitrogeno, se cargo con el producto de la Etapa 3 (14,4 g, 51,9 mmol) y N,N-dimetil-formamida (40 mL) Se agrego 1 8-diazabiciclo[5,4,0]undec-7-eno(10,9 mL, 72,8 mmol) y luego bromuro de 2,4-difluorobencil (9,3 mL, 72,8 mmol) La mezcla de la reacción se agitó a 65 °C durante 18 horas, se vertio en $NaHCO_3$ acuoso saturado y se extrajo con acetato de etilo

La capa organica se lavo con salmuera, se secó con $Na_2SO_4$ y se concentro in vacuo para proporcionar el producto del título, bajo la forma de aceite de color anaranjando (21,5 g), el cual se transfirió a la reacción siguiente sin ninguna otra purificacion $^1H$ NMR (400 MHz, $CD_3OD$) δ 8,20 (dddd, J = 2,2, 4 8, 7,2 y 8,8 Hz, 1H), 8,00 (dd, J = 2 2 y 7,2 Hz, 1H), 7,56 (td, J = 2,4, 6,4 y 9,2 Hz, 1H), 7,46 (t, J = 9,2 Hz, 1H), 7,02 (m, 2H), 6,18 (dd, J = 0,8 y 2,6 Hz, 1H), 6,04 (d, J = 2,7 Hz, 1H), 5,14 (s, 2H), 3,90 (s, 3H), 1,98 (s, 3H) ppm $^9$ F NMR (400 MHz, $CD_3OD$) δ -111,34 (1 F), -116,00 (1 F), -117,35 (1 F) ppm ES-HRMS m/z 404,1104 (M+H calculado para $C_{21}H_{17}F_3NO_4$ requiere 404,1104)

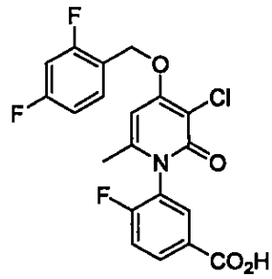
Etapa 5 Preparacion de 3-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-fluorobenzoato de metilo




Un matraz de 250 mL, de fondo redondo, equipado con barra de agitacion y entrada de nitrogeno, se cargo con el producto de la Etapa 4 (21 g, 52 mmol) y N-metil-2-pirrolidina (100 ml) Se agrego N-Cloro succinimida (8,3 g, 62 mmol) y la mezcla de la reacción se agito a 65 °C durante 2 horas La mezcla luego se enfrio a temperatura ambiente, se vertio en $NaHCO_3$ acuoso saturado y se extrajo con acetato de etilo La capa organica se lavo con salmuera, se seco con $Na_2SO_4$, y se concentro *in vacuo* El residuo se trituró con eter dietilico y se filtró para proporcionar el compuesto del titulo, bajo la forma de polvo blanco (5,9 g, 25%) $^1H$ NMR (400 MHz, $CD_3OD$) δ 8,22

(dddd, J = 2, 4,8, 6,8 y 8,8 Hz, 1H), 8,03 (dd, J = 2 y 7,2 Hz, 1H), 7,62 (q, J = 8,4 y 4,8 Hz, 1H), 7,48 (t, J = 14 Hz, 1H), 7,04 (m, 2H), 6,69 (s, 1H), 5,36 (s, 2H), 3,91 (s, 3H), 2,08 (s, 3H) ppm $^{19}$F NMR (400 MHz, $CD_3OD$) δ -111,38 (1 F), -115,97 (1 F), -117,43 (1 F) ppm ES-HRMS m/z 438,0723 (M+H calculado para $C_{21}H_{16}ClF_3NO_4$ requiere 438,0714)

Etapa 6 Preparación de acido 3-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-fluorobenzoico

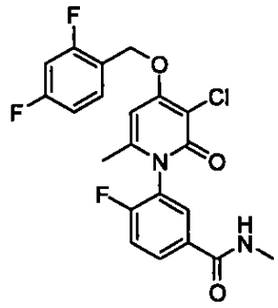



Un matraz de 100 ml, de fondo redondo, se cargo con el producto de la Etapa 5 (2,5 g, 5,72 mmol), tetrahidrofurano (40 mL), metanol (10 mL) y agua (10 mL) A esta suspension se agrego 2,5 N NaOH (4,6 mL, 11,4 mmol) La mezcla de la reaccion se aclaro despues de transcurridos 5 minutos y la reaccion se completo en 35 minutos mediante LC-MS Se eliminaron los elementos organicos en el rotavapor y la disolucion restante se acidifico a un pH 3 con 6N HCl El compuesto deseado se precipito mediante el agregado de eter dietilico y la subsiguiente filtración El compuesto del titulo se aisló como un polvo blanco (2,5 g, 98%) $^1$H NMR (400 MHz, dmso-$d_6$) δ 8,10 (dddd, J = 2,1, 4,8, 7,2 y 8,4 Hz, 1H), 8,0 (dd, J = 2, y 7,6 Hz, 1H), 7,66 (q, J = 9,2 y 15,6 Hz, 1H), 7,57 (t, J = 8,8 Hz, 1H), 7,34 (td, J = 2,4 y 10,4 Hz, 1H), 7,17 (tdd, J = 1, 2,7 y 8,4 Hz, 1H), 6,76 (s, 1H), 5,33 (s, 2H), 1,98 (s, 3H) ppm $^{19}$F NMR (400 MHz, dmso-$d_6$) δ -109,32 (1F), -113,64 (1 F), -117,22 (1 F) ppm

1221

ES-HRMS m/z 424,0575 (M+H calculado para $C_{20}H_{14}ClF_3NO_4$ requiere 424,0558)

Ejemplo 508



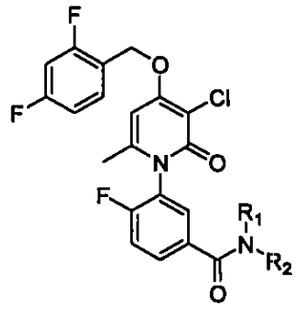
Preparacion de 3-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-fluoro-N-metilbenzamida

A un recipiente de reaccion (tubo de cultivo de borosilicato) se agregó ácido 3-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-fluorobenzoico (0,300 g, 0,708 mmol) y 1-hidroxibenzotriazol (0,048 g, 0,45 mmol) Se agregó N,N-Dimetilformamida (3 mL) al recipiente de reaccion, y luego aproximadamente 1,2 gramos de la resina carbodiimida aglutinada con polimeros (1,38 mmol/g) Luego se agregó al recipiente de reacción N,N-dimetilformamida adicional (2 mL) Luego se sacudió en forma orbital el aparato de reaccion paralela (Agitador Orbital Labline Benchtop) a aproximadamente 200 RPM, a temperatura ambiente, durante 15 minutos Despues se agrego N-Metilamina (1 mL, 2 mmol) al recipiente de reacción y el aparato de reaccion se agito en forma orbital a temperatura ambiente durante toda la noche En este momento la reaccion se diluyó con tetrahidrofurano (20 mL) y se la trato con aproximadamente 2,17 g de resina de poliamina (2,63 mmol/g) y aproximadamente 2,8 g de poliestireno funcionalizado de metilisocianato (1,5 mmol/g) y continuo la agitacion orbital a 200 RPM a temperatura ambiente durante 3 horas Luego se abrio el recipiente de

reaccion y se separó el producto de la fase de disolucion de los subproducto, insolubles enfriados rapidamente mediante filtrado y recoleccion en un frasco pequeño Después de la evaporación parcial, los subproductos insolubles se enjuagaron con tetrahidrofurano (2 x 10 mL) El producto de filtrado se evaporo mediante soplado de $N_2$ sobre el frasco pequeño y el solido resultante se trituró con eter dietilico para proporcionar un solido blanquecino (0,168 g, 59%)

$^1$H NMR (400 MHz, $CD_3OD$) δ 8 02 (dddd, J = 2, 4,4, 7,2 y 8,4 Hz, 1H), 7,80 (dd, J = 2 y 6,8 Hz, 1H), 7,62 (q, J = 8 y 14,4 Hz, 1H), 7,34 (t, J = 8,8 Hz, 1H), 7,04 (m, 2H), 6,69 (s, 1H), 5,36 (s, 2H), 3,29 (s, 3H), 1,98 (s, 3H) ppm $^{19}$ F NMR (400 MHz, $CD_3OD$) δ -108,94 (1 F), -113,55 (1 F), -117,76 (1 F) ppm ES-HRMS m/z 437,0861 (M+H calculado para $C_{21}H_{17}ClF_3N_2O_3$ requiere 437,0874)

Ejemplos 509-518

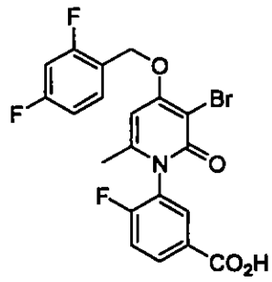


Mediante el método del Ejemplo 508 y el reemplazo de N-metilamine por la amina apropiada, se preparan los compuestos de los Ejemplos 509-518

| Ejemplo N° | R1 | R2 | Rend % | MF | M+H Requiere | ESHRMS m/z |
|---|---|---|---|---|---|---|
| Ej 509 | $CH_3$ | $CH_3$ | 59 | $C_{22}H_{19}ClF_3N_2O_3$ | 451,1031 | 451,1016 |
| Ej 510 | H | $CH_2CH_2OH$ | 70 | $C_{22}H_{19}ClF_3N_2O_4$ | 467 0980 | 467,0985 |
| Ej 511 | $CH_2CH_2N(CH_3)-$ | $CH_2CH_2N(CH_3)-$ | 70 | $C_{25}H_{24}ClF_3N_3O_3$ | 506,1453 | 506,1447 |

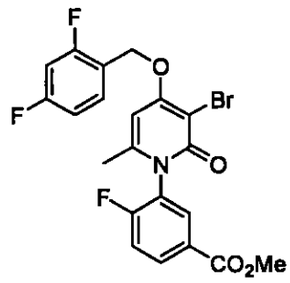
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Ej | 512 | $CH_2CH_2O$- | $CH_2CH_2O$- | 19 | $C_{24}H_{21}ClF_3N_2O_4$ | 493,1101 | 493,1136 |
| Ej | 513 | H | $CH_2CH_2OCH_3$ | 59 | $C_{23}H_{21}ClF_3N_2O_4$ | 481,1136 | 481 1136 |
| Ej | 514 | $CH_3$ | $CH_2CH_2OH$ | 63 | $C_{23}H_{21}ClF_3N_2O_4$ | 481,1136 | 481 1131 |
| Ej | 515 | H | $CH_2CH_2CH_2OH$ | 51 | $C_{23}H_{21}ClF_3N_2O_4$ | 481 1136 | 481,1121 |
| Ej | 516 | H | $CH_2CH(OH)CH_2OH$ | 64 | $C_{23}H_{21}ClF_3N_2O_5$ | 497,1086 | 497,1102 |
| Ej | 517 | H | $C(CH_3)_2CH_2OH$- | 54 | $C_{24}H_{23}ClF_3N_2O_4$ | 495 1293 | 495,1303 |
| Ej | 518 | $CH_2CH_2NH$- | $CH_2CH_2NH$- | 34 | $C_{23}H_{22}ClF_3N_3O_3$ | 491,89 | |

Ejemplo 519



Preparación de acido 3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-fluorobenzoico

Preparacion de 3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-fluorobenzoato de metilo

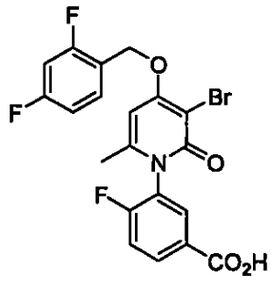


Un matraz de 100 ml, de fondo redondo, equipado con barra de agitacion y entrada de nitrogeno se cargo con 3-[4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-fluorobenzoato de metilo (7,3 g, 18 mmol) y N-metil-2-pirrolidina (20 ml) Se agregó N-Bromosuccinimida (3,5 g, 19,8 mmol) y la mezcla de la reaccion se agito a

1202
1204

temperatura ambiente durante 30 minutos La mezcla se vertio en $NaHCO_3$ y se extrajo con acetato de etilo La capa orgánica se lavo con salmuera, se seco con $Na_2SO_4$, y se concentro *in vacuo* El residuo se trituro con eter dietilico y se filtro para proporcionar el compuesto del titulo, bajo la forma de polvo blanco (3,49 g) $^1H$ NMR (400 MHz, $CD_3OD$) δ 8,16 (qd, J = 3, 6,8 y 15,6 Hz, 1H), 7,84 (d, J = 2,12 Hz, 1H), 7,64 (q, J = 8,4 and14,8 Hz, 1H), 7,29 (d, J = 8,1 Hz, 1H), 7,04 (m, 2H), 6,60 (s, 1H), 5,34 (s, 2H), 3,87 (s, 3H), 2,00 (s, 3H) ppm $^{19}$ F NMR (400 MHz, $CD_3OD$) δ -111,51 (1 F), -115,98 (1F), -117,43 (1F) ppm ES-HRMS m/z 494,0387 (M+H calculado para $C_{22}H_{19}BrF_2NO_5$ requiere 494,0409)

Etapa 2 Preparacion de ácido 3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-fluorobenzoico

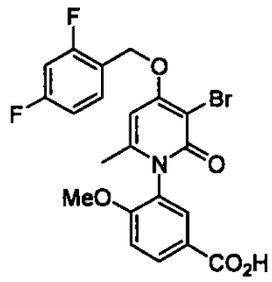



Un matraz de 100 ml, de fondo redondo, se cargo con el producto de la Etapa 2 (3,4 g, 7,05 mmol), tetrahidrofurano (40 mL), metanol (10 mL) y agua (10 mL) A esta suspensión se agrego 2,5N NaOH (5,6 mL, 14,1 mmol) La mezcla de la reaccion se aclaro despues de transcurridos 5 minutos y la reaccion se completo en 1 hora mediante LC-MS Se eliminaron los elementos organicos en el rotavapor y la disolución restante se acidificó a un pH 1-2 con 6N HCl El compuesto deseado se precipitó mediante el agregado de agua y dietileter y la subsiguiente filtracion El

1203
1205

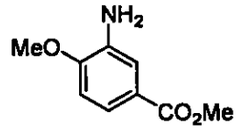
compuesto del título se aisló como un polvo blanco (2,64 g, 80%) $^1$H NMR (400 MHz, $CD_3OD$) δ 8,21 (dddd, J = 2,4, 5,2, 7,2 y 9,2 Hz, 1H), 8,00 (dd, J = 2,0 y 7,2 Hz, 1H), 7,65 (q, J = 8,4 y 14,8 Hz, 1H), 7,45 (t, J = 8,4 Hz, 1H), 7,04 (appt, J = 9,6 Hz, H), 6,65 (s, 1H), 5,36 (s, 2H), 2,07 (s, 3H) ppm $^{19}$ F NMR (400 MHz, $CD_3OD$) δ -111,40 (1 F), -116,00 (1 F), -118,36 (1 F) ppm ES-HRMS m/z 480,0259 (M+H calculado para $C_{21}H_{17}BrF_2NO_5$ requiere 480,0253)

Ejemplo 520




Preparacion de ácido 3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-metoxibenzoico

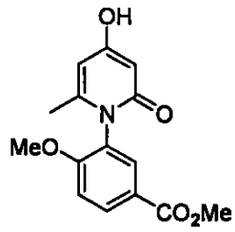
Paso 1 Preparacion de 3-amino-4-metoxibenzoato de metilo




Un matraz de 1 L, 3 cuellos y con la parte inferior redondeada, equipado con una entrada de nitrogeno, una varilla de agitacion, un embudo de agregado y una termocupla se cargo con acido 3-amino-4-metoxy benzoico (50 g, 0,299mol) y metanol (300 mL) El sistema se enfrió hasta 0 °C y se añadió cloruro de acetilo (30 mL, 0,42 mol) en gotas El sistema se llevo a temperatura ambiente, el

embudo de agregado se reemplazo por un condensador de reflujo y se calento hasta llegar a reflujo durante una hora y media La mezcla de reacción se enfrio a temperatura ambiente, se enfrió repentinamente con $NaHCO_3$ acuoso saturado y se extrajo con acetato de etilo El extracto organico se lavó con salmuera, se secó con $Na_2SO_4$ y se concentro in vacuo para dar 3-amino-4-metoxibenzoato de metilo como un sólido oscuro (47,9 g, 88%) $^1H$ NMR (400 MHz, $CD_3OD$) δ 7,40 (t, J = 2 68 Hz, 1H), 7,37 (t, J = 2,0 Hz, 1H), 6,86 (d, J = 8,8 Hz, 1H), 3,98 (s, 3H), 3,81 (s, 3H) ppm ES-HRMS m/z 182,0826 (M+H calculado para $C_9H_{12}ClNO_3$ requiere 182,0812)

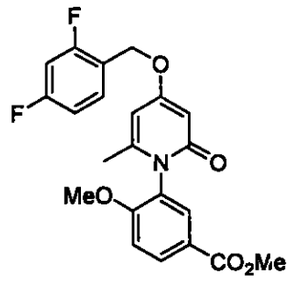
Etapa 2 Preparacion de 3-(4-hidroxi-6-metil-2-oxopiridin-1(2H)-il)-4-metoxibenzoato de metilo




Un matraz de 250 mL con la parte inferior redondeada y equipado con una var lla de agitacion, trampa Dean-Stark y condensador de reflujo se cargo con el producto de la Etapa 1 (23,5 g, 0,129 mol), 4-hidroxi-6-metil-2-pirona (17,8 g, 0,14 mol) y o-diclorobenceno (200 mL) El sistema se sumergio en un baño de aceite a 170 °C durante 2 horas y luego se enfrió a temperatura ambiente La mezcla de la reacción se lavo con $Na_2CO_3$ (28 g, 0,26 mol, 500 mL de agua) La capa acuosa se lavó con acetato de etilo y luego se acidifico a un pH 1-2 con HCl concentrado Esto se extrajo con acetato de etilo, el que luego se secó con $Na_2SO_4$ y se concentro *in vacuo* El aceite anaranjado viscoso se trituró con MeOH para producir el compuesto del titulo como un solido amarillo (1,61g, 4%) $^1H$ NMR (400

MHz, $CD_3OD$) δ 8,14 (dd, J = 2,2 y 8,8 Hz, 1H), 7,79 (d, J = 2,2 Hz, 1H), 7,27 (d, J = 8,8 Hz, 1H), 6,05 (d, J = 2,3 Hz, 1H), 5,77 (d, J = 2,3 Hz, 1H), 3,88 (s, 3H), 3,87 (s, 3H), 1,90 (s, 3H) ppm ES-HRMS m/z 290,0997 (M+H calculado para $C_{15}H_{16}NO_5$ requiere 290,1023)

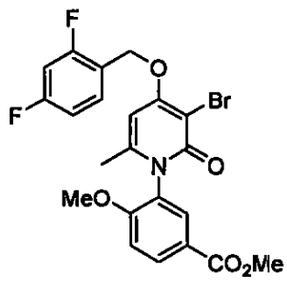
Etapa 3 Preparación de 3-[(4-[2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-metoxibenzoato de metilo




Un matraz de 100 mL y con la parte inferior redondeada, equipado con una entrada de nitrogeno y una varilla de agitacion, se cargó con el producto de la Etapa 2 (1,6 g, 5,5 mmol) y N,N-dimetilformamida (10 mL) Se agregó 1 8-diazabiciclo[5,4,0]undec-7-eno (0,91 mL, 6 mmol) y luego bromuro de 2,4-difluorobencilo (0,77 mL, 6 mmol) La mezcla de la reacción se agito a 60 °C durante 4 horas, se vertió en $NaHCO_3$ acuoso saturado y se extrajo con acetato de etilo La capa organica se lavó con salmuera, se seco con $Na_2SO_4$ y se concentro *in vacuo* para producir el compuesto del titulo en forma de espuma anaranjada (2,13g, 93%), la cual se llevó a la siguiente reacción sin ninguna otra purificación $^1H$ NMR (400 MHz, $CD_3OD$) δ 8,17 (dd, J = 2,64 y 11,6 Hz, 1H), 7,82 (td, J = 2,7 y 6,8 Hz, 1H), 7,57 (m, 1H), 7,29 (d, J = 11,6 Hz, 1H), 7,02 (m, 2H), 6,16 (m, 1H), 6,03 (d, J = 3,5 Hz, 1H), 5,14 (s, 2H), 3,89 (s, 6H), 1,93 (s, 3H) ppm $^{19}$ F NMR (400 MHz, $CD_3OD$) δ -111,43(1F), -116,04 (1 F) ppm ES-HRMS m/z 416,1310 (M+H calculado para $C_{22}H_{20}F_2NO_5$ requiere 416,1304)

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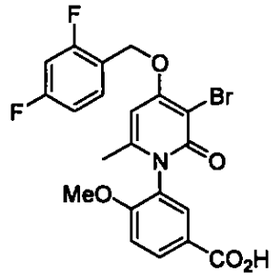
Etapa 4 Preparacion de 3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-metoxibenzoato de metilo




Un matraz de 100 mL y con la parte inferior redondeada, equipado con varilla de agitación y entrada de nitrogeno, se cargó con el producto de la Etapa 3 (2,1 g, 5,06 mmol) y N-metil 2- pirrolidina (10 mL) Se agregó N-Bromosuccinimida (1 g, 5,56 mmol) y la mezcla de reaccion se agitó a temperatura ambiente durante 1 hora La mezcla se vertió en $NaHCO_3$ acuoso saturado y se extrajo con acetato de etilo La capa organica se lavó con salmuera, se secó con $Na_2SO_4$ y se concentro *in vacuo* El residuo se separo por cromatografia sobre silice (1 1 hexanos acetato de etilo) para producir el compuesto del titulo en forma de aceite anaranjado (0,77 g, 31%) $^1H$ NMR (400 MHz, $CD_3OD$) δ 8,16 (aprox qd, J = 2,5 y 7,2 Hz, 1H), 7,84 (d, J = 2,6 Hz, 1H), 7,64 (m, 1H), 7,30 (d, J = 9,2 Hz, 1H), 7,04 (appt, J = 8,4 Hz, 2H), 6,60 (s, 1H), 5,33 (s, 2H), 3,80 (s, 6H), 1,99 (s, 3H) ppm $^{19}$ F NMR (400 MHz, $CD_3OD$) δ -111,56(1F), -116,00 1 F) ppm ES-HRMS m/z 494,0398 (M+H calculado para $C_{22}H_{19}BrF_2NO_5$ requiere 494,0409)

Etapa 5 Preparacion de acido 3-[(3-bromo-4-[2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-metoxibenzoico

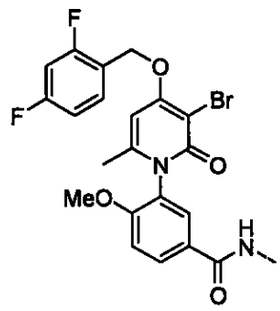
1207
1209




Un matraz con 'a parte ınferıor redondeada se cargo con el producto de la Etapa 4 (0,77 g, 1,55 mmol), tetrahıdrofurano (10 mL), metanol (5 mL) y agua (5 mL) A esta suspensıon se agrego 2,5N NaOH (1,2 mL, 3,1 mmol) La mezcla de reaccıon se volvıó transparente después de 30 mınutos y la reaccıon se completo en una hora por medıo de LC-MS (cromatografıa lıquıda/espectrometrıa de masa) Los elementos orgánıcos se retıraron sobre el rotavapor y la dısolucıon restante se acıdıfıco a un pH 2-3 con 6N HCl El compuesto deseado se precıpıto mediante el agregado de agua y eter dıetílıco, y su posterıor fıltrado El compuesto del tıtulc se aıslo en forma de polvo blanco (0,60 g, 81%) $^1$H NMR (400 MHz, $CD_3OD$) δ 8,17 (dd, J = 2,2 y 8,8 Hz, 1H), 7,82 (d, J = 2,2 Hz, 1H), 7,64 (q, 1H), 7,29 (d, J = 8,8 Hz, 1H), 7,34 (t, J = 8,8 Hz, 2H), 6,60 (s, 1H), 5,34 (s, 2H), 3,87 (s, 3H), 2,01 (s, 3H) ppm ES-HRMS m/z 480,0259 (M+H calculado para $C_{21}H_{17}BrF_2NO_5$ requıere 480,0253)

Ejemplo 521

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Preparacion de 3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-metoxi-N-metilbenzamida

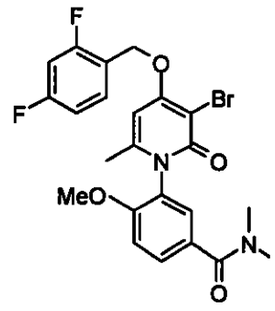
Etapa 1

En un recipiente de reacción (tubo de cultivo de borosilicato) se agrego el Ejemplo 520 (0,300 g, 0,624 mmol) y 1-hidroxiberzotriazol (0,042 g, 0,31 mmol) Se agrego N,N-dimetilformamida (3 mL) al recipiente de reacción, seguido de aproximadamente 1,06 g de la resina carbodiimida aglutinada con polimero (1,38 mmol/g) Despues de ello, se agrego mas N,N-dimetilformamida (2 mL) al recipiente de reacción Luego, el aparato de reacción en paralelo se sacudió en forma orbital (Agitador Orbital Labline Benchtop) a aproximadamente 200 RPM, a temperatura ambiente, durante 15 minutos Luego, se agrego N-metil amina (2 mL, 4 mmol) al recipiente de reaccion, y el aparato de reaccion se sacudio en forma orbital a temperatura ambiente durante toda la noche En este momento, la reacción se diluyó con tetrahidrofurano (20 mL) y se trato con aproximadamente 2g de resina de poliamina (2,63 mmol/g) y aproximadamente 2,5 g de poliestireno funcionalizado con metilisocianato (1,5 mmol/g), y se continuo sacudiendo en forma orbital a 200 RPM a temperatura ambiente durante 3 horas Luego, el recipiente de reaccion se abrio y el producto de la fase de disolución se separo de los subproductos insolubles enfriados repentinamente mediante filtrado y recoleccion en un vial

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Después de una evaporación parcial, los subproductos insolubles se enjuagaron con tetrahidrofurano (2 x 10 mL) El filtrado se evaporo soplando $N_2$ sobre el vial y el sólido resultante se trituró con eter dietílico para generar el producto deseado en forma de solido de color blanquecino (0,094 g, 31%) $^1$H NMR (400 MHz, $CD_3OD$) δ 7,98 (dd, J = 2,2 y 8,8 Hz, 1H), 7,64 (m, 2H), 7,28 (d, J = 9,2 Hz, 1H), 7,04 (t, J = 9,2 Hz, 2H), 6,60 (s, 1H), 5,34 (s, 2H), 3,86 (s, 3H), 2,88 (s, 3H), 2,01 (s, 3H) ppm $^{19}$ F NMR (400 MHz, $CD_3OD$) δ -111,59(1F), -116,01 (1 F) ppm ES-HRMS m/z 493,0593 (M+H calculado para $C_{22}H_{20}BrF_2N_2O_4$ requiere 493,0569)

Ejemplo 522

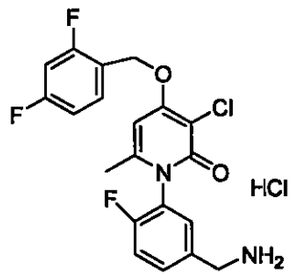



Preparacion de 3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-metoxi-N,N-dimetilbenzamida

El compuesto del titulo se preparó esencialmente como indica el Ejemplo 521 $^1$H NMR (400 MHz, $CD_3OD$) δ 7,64(m, 1H), 7,61 (dd, J = 2 y 8,8 Hz, 1H), 7,33 (d, J = 2,2 Hz, 1H), 7,27 (d, J = 8 Hz, 1H), 7,04 (t, J = 8 Hz, 2H), 6,59 (s, 1H), 5,33 (s, 2H), 3,85 (s, 3H), 3,07 (s, 6H), 2,02 (s, 3H) ppm $^{19}$ F NMR (400 MHz, $CD_3OD$) δ -111,60(1F), -116,01 (1 F) ppm ES-HRMS m/z 507,0716 (M+H calculado para $C_{23}H_{22}BrF_2N_2O_4$ requiere 507,0726)

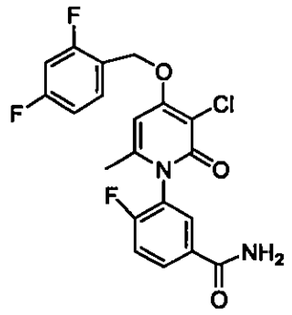
Ejemplo 523

hidrocloruro 1-[5-(aminometil)-2-fluorofenil]-3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona



Etapa 1

Preparacion de 3-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-fluorobenzamida



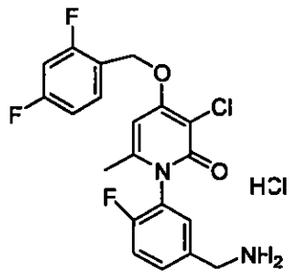
Un matraz de 250 mL con la parte inferior redondeada y equipado con varilla de agitacion y entrada de nitrogeno se cargo con acido 3-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-fluorobenzoico (2,58g, 6,1 mmol), 4-metilmorfolina (2,0 mL, 18,3 mmol), 2-cloro-4,6-dimetoxi-1,3,5-triazina (1,28g, 7,3 mmol) y tetrahidrofurano (30 mL) Despues de agitar la mezcla durante 30 minutos a 25° C, se añadió $NH_4OH$ (15,0 mL) La mezcla se agito durante 30 minutos y se diluyo con agua El producto se precipitó de la disolucion El precipitado se filtró y lavo con agua y eter dietilico para producir el compuesto del titulo (2,55g, 78%) en forma de sólido

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blanco $^1$H NMR (400 MHz, $(CD_3)_2SO$) δ 8,10 (m, 1H), 7,9 (dd, J = 2,1 y 5,2 Hz, 1H), 7 ,5 (q, 6,7 y 8,5 Hz, 1H), 7,56 (t, J = 9,1 Hz, 1H), 7,3ᵇ (td, J = 2,4 y 8,2 Hz, 1H) 7,17 (td, J = 2 y 6,6 Hz, 1H) ᵇ,78 (s, 1H), 5,36 (s, 2H), 2 (s, 3H) ppm ES-HRMS m/z 423, 0719 (M+H calculado para $C_{20}H_{15}ClF_3N_2O_3$ requiere 423,0718)

Etapa 2

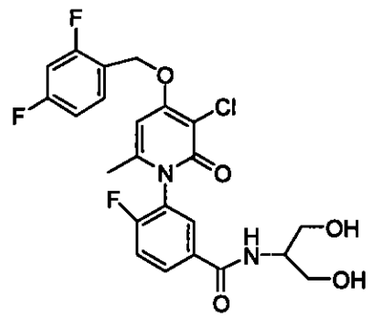
Preparacion de hidrocloruro 1-[5-(aminometil)-2-fluorofenil]-3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona




Un matraz de 100 mL y con la parte inferior redondeada, equipado con varilla de agitación y entrada de nitrogeno, se cargó con el producto de la Etapa 1 (1,5 g, 3,5 mmol), el complejo $BH_3$•THF (7,4 mL, 7,4 mmol) y tetrahidrofurano (15 mL) La mezcla se sometio a reflujo durante 6 horas, se dejo enfriar a temperatura ambiente y se enfrió rápidamente con HCl 6N Los elementos orgánicos se evaporaron, y la disolucion acuosa restante se saturo con NaOH 2,5N y se extrajo con diclorometano La fase organica se seco con $Na_2SO_4$ y se concentró in vacuo Se añadio HCl 6N y se concentro in vacuo $^1$H NMR (400 MHz, $(CD_3)_2SO$) δ 8,2 (m, 1H), 7,6 (m, 1H), 7,5 (m, 1H), 7,3 (t, J = 9,8 Hz, 1H), 7,ᵗ6 (t, J = 8,6 Hz, 1H) 6,78 (s, 1H), 5,36 (s, 2H), 4,05 (d, J = 5,8 Hz, 2H), 2 (s, 3H) ppm ES-HRMS m/z 409, 0940 (M+H calculado para $C_{20}H_{17}ClF_3N_2O2$ requiere 409,0925)

Ejemplo 524

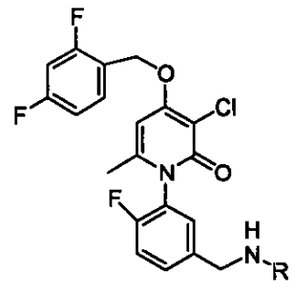
3-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-fluoro-N-[2-hidroxi-1-(-(hidroximetil)etil]benzamida



Preparación de 3-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-fluoro-N-[2-hidroxi-1-(-(hidroximetil)etil]benzamida

El compuesto del título se preparo esencialmente como indica el Ejemplo 521 $^1$H NMR (400 MHz, $CD_3OD$) δ 8,1 (m, 1H), 7,8 (dd, J = 2,3 y 5,1 Hz, 1H), 7,6 (q, J = 7,4 y 7,0 Hz, 1H), 7,41 (t, J = 8,9 Hz, 1H), 7,04 (m, 2H), 6,7 (s, 1H), 5,36 (s, 2H), 4,1 (t, J = 5,8 Hz, 1H), 3,7 (d, J = 5,1 Hz, 4H), 2,1 (s, 3H) ppm ES-HRMS m/z 497, 1045 (M+H calculado para $C_{23}H_{21}ClF_3N_2O_5$ requiere 497,1086)

Ejemplos 525-528



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Los compuestos ce los Ejemplos 525-528 se preparan por derivatizacion del Ejemplo 523 A continuación, se presentan los datos analiticos

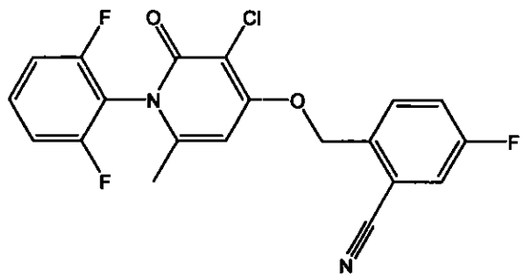
| Ej N° | R | MF | M+H Requiere | ESHRMS m/z |
|---|---|---|---|---|
| Ej 525 | -C(O)$CH_3$ | $C_{22}H_{18}ClF_3N_2O_3$ | 451,1031 | 451,1010 |
| Ej 526 | -C(O)$CH_2OCH_3$ | $C_{23}H_{20}ClF_3N_2O_4$ | 481,1136 | 481,1132 |
| Ej 527 | -$SO_2CH_3$ | $C_{21}H_{18}ClF_3N_2O_4S$ | 487,0701 | 487,0679 |
| Ej 528 | -C(O)$NH_2$ | $C_{21}H_{16}ClF_3N_3O_3$ | 452,0983 | 452,0987 |

Caracterizacion de NMR de los compuestos de los Ejemplos 525-528

| Ej N° | Datos por NMR |
|---|---|
| 525 | $^1$H NMR (400 MHz $CD_3OD$) δ 7,6 (q, J = 7 8 y 7 0 Hz, 1H), 7,5 (m, 1H), 7,3 (t, J = 9,0 Hz 1H) 7 2 (dd, J = 1,9 y 5 1 Hz 1H) 7,05 (m, 2H), 6 65 (s, 1H), 5,36 (s, 2H), 4 39 (s 2H), 2 1 (s 3H), 1,98 (s, 3H) ppm |
| 526 | $^1$H NMR (400 MHz, $CD_3Cl_3$) δ 7,45 (q, J = 8,6 y 6,2 Hz, 1H), 7,3 (m 1H), 7,1 (m, 2H), 6,85 (q J = 6,5 y 1,9 Hz, 1H), 6,78 (td, J = 2,7 y 7 3 Hz 1H), 6,2 (s, 1H), 5,2 (s 2H) 4,39 (d, J = 6,2 Hz, 2H) 4 0 (s 3H) 2,3 (s, 2H), 2,0 (s, 3H) 1 98 (s, 3H) ppm |
| 527 | $^1$H NMR (400 MHz, ( $D_3OD$) δ 7,49 (q, J = 8,2 y 6,3 Hz, 1H), 7,33 (m 1H), 7,23 (m, 1H), 7,1 (t, J = 8 9 1H) 6 9 (td, J = 0,78 y 6,6 1H), 6,8 (td, J = 2 7 y 6 25 Hz, 1H), 6,2 (s, 1H), 5,2 (s, 2H), 4,2 (s,2H) 2,8 (s, 3H), 2,0 (s, 3H) ppm |
| 528 | $^1$H NMR (400 MHz, $(CD_3)_2SO$) δ 7,61 (q, J = 8 9 y 6 6 Hz 1H) 7 38 (d J = 7 8 Hz, 1H), 7,3 (d, J = 10 2 Hz, 1H) 7 21 (d J = 7,4 Hz, 1H), 7,1 (t, J = 8,6 Hz, 1H), 6,71 (s, 1H), 6,5 (t, J = 5,8 Hz, 1H) 5,56 (s, 2H), 5 3 (s, 2H), 4,18 (d, J = 6,25 Hz, 2H), 3,61 (s, 1H), 1,98 (s 3H) ppm |

Ejemplo 529

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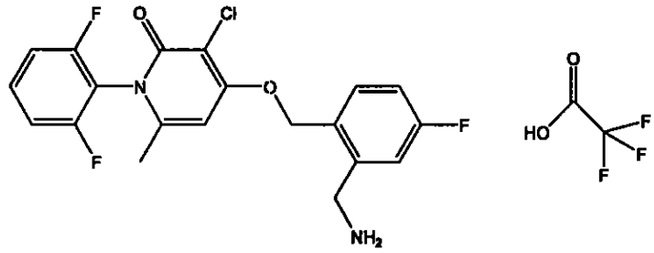


2-({[3-cloro-1-(2,6-difluorofenil)-6-metil-2-oxo-1,2-dihidropiridin-4-il]oxi}methil)-5- fluorobenzonitrilo

2-(bromometil)-5-fluorobenzonitrilo (3,47 g, 16,2 mmol), 3-cloro-1-(2,6-difluorofenil)-4-hidroxi-6-metilpiridin-2(1H)-ona (3,15 g, 11,6 mmol), $K_2CO_3$ (2,56 g, 18,6 mmol), y 18-corona-6 (0,15 g) se disolvieron en N,N-dimetilacetamida (25 mL) La mezcla de la reacción se agitó en un baño de aceite a 60° C durante 4 horas El disolvente se elimino mediante destilacion La reacción se neutralizó con acido citrico al 5% El producto solido se lavo con hexano seguido de 30% de EtOAc/hexano Se filtro un solido marron (5,2 g, rendimiento del 79%)

$^1$H NMR ($CD_3OD$ / 400MHz) δ7,82 (m, 2H), 7,61 (m, 4H), 6,75 (s, 1H), 5,49 (s, 2H), 2,13 (s, 3H) ESHRMS m/z 405,0616 (M+H $C_{20}H_{13}ClF_3N_2O_2$ requiere 405,0612??)

Ejemplo 530

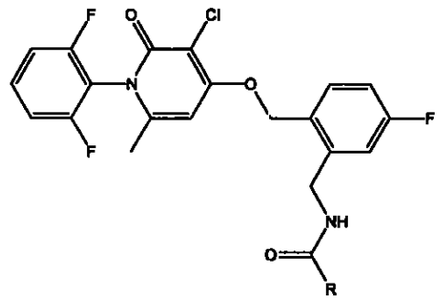


trifluoroacetato 4-{[2-(aminometil)-4-fluorobencil]oxi}-3-cloro-1-(2,6-difluorofenil)-6-metilpiridin-2(1H)-ona

Se agrego $BH_3$THF (17,8 mL, 17,8 mmol) en gotas a una disolucion fria de 2-({[3-cloro-1-(2,6-difluorofenil)-6-

metil-2-oxo-1,2-dihidropiridin-4-il]oxi}metil)-5-fluorobenzonitrilo (3,61 g, 8,92 mol) en THF (30 mL) Luego del agregado, la reacción se calento a 60°C durante una hora y media La reaccion se enfrio repentinamente con MeOH, se evaporo el disolvente, y el producto crudo se purifico mediante preparación de HPLC El producto se aisló mediante secado por congelacion y evaporacion del disolvente para producir un sólido blanco (1,52 g, 32,6%) $^1$H NMR ($CD_3OD$/ 400MHz) δ7,62 (m, 2H), 7,32 (m, 1H), 7,25 (tr, 2H, J = 8,00 Hz), 7,18 (m, 1H), 6,78 (s, 1H), 5,43 (s, 1H), 4,22 (s, 1H), 2,14 (s, 3H) ESHRMS m/z 409,0900 (M+H $C_{20}H_{17}N_2O_2F_3Cl$ requiere 409,0925)

Ejemplos 531-551




Los compuestos de los Ejemplos 531-551 se preparan por derivatizacion del Ejemplo 530 A continuacion, se presentan los datos analiticos

| Compuesto N° | R | MF | M+H Requiere | ESHRMS m/z |
|---|---|---|---|---|
| Ej 531 | $-OCH_3$ | $C_{22}H_{18}ClF_3N_2O_4$ | 467,0980 | 467,0985 |
| Ej 532 | $-CF_3$ | $C_{22}H_{15}ClF_6N_2O_3$ | 505,0748 | 505,0754 |
| Ej 533 | -O-isopropil | $C_{24}H_{22}ClF_3N_2O_4$ | 495,1293 | 495,1304 |
| Ej 534 | $-NH-CH_2CH_3$ | $C_{23}H_{21}ClF_3N_3O_3$ | 480,1296 | 480,1277 |
| Ej 535 | -O-tetrahidrofurano- | $C_{25}H_{22}ClF_3N_2O_5$ | 523,1242 | 523,1282 |

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1218

| | | | | |
|---|---|---|---|---|
| | 3-il | | | |
| Ej 536 | -O-propil | $C_{24}H_{22}ClF_3N_2O_4$ | 495,1293 | 495,1338 |
| Ej 537 | -O-$CH_2CH=CH_2$ | $C_{24}H_{20}ClF_3N_2O_4$ | 493,1136 | 493,1116 |
| Ej 538 | -O-$CH_2C=CH$ | $C_{24}H_{18}ClF_3N_2O_4$ | 491,0980 | 491 0961 |
| Ej 539 | -O-tButil | $C_{25}H_{24}ClF_3N_2O_4$ | 509,1449 | 509,1436 |
| Ej 540 | -NH-tButil | $C_{25}H_{25}ClF_3N_3O_3$ | 508,1609 | 508,1574 |
| EJ 541 | -$SO_2CH_2CH_2CH_3$ | $C_{23}H_{22}ClF_3N_2O_4S$ | 515,1014 | 515,0979 |
| Ej 542 | -$SO_2CH_2CH_3$ | | | |
| Ej 543 | -NH-isopropil | $C_{24}H_{23}ClF_3N_3O_3$ | 494,1453 | 494,1456 |
| Ej 544 | -$CH_2OCH_3$ | $C_{23}H_{20}ClF_3N_2O_4$ | 481,1136 | 481 1174 |
| Ej 545 | -$NHCH_3$ | $C_{22}H_{20}ClF_3N_3O_3$ | 466,1140 | 466,1141 |
| Ej 546 | -$N(CH_3)$(tButil) | $C_{26}H_{27}ClF_3N_3O_3$ | 522,1766 | 522 1737 |
| Ej 547 | -NH(ciclopropil) | $C_{24}H_{21}ClF_3N_3O_3$ | 492 1296 | 492,1285 |
| Ej 548 | -$NHCH_2CF_3$ | $C_{23}H_{17}ClF_6N_3O_3$ | 534,1014 | 534 1005 |
| Ej 549 | $NHCH_2$(ciclopropil) | $C_{25}H_{23}ClF_3N_3O_3$ | 506,1453 | 506 1432 |
| Ej 550 | -$NHCH_2$(tButil) | $C_{26}H_{27}ClF_3N_3O_3$ | 522,1766 | 522,1740 |
| Ej 551 | -$N(CH_3)_2$ | $C_{23}H_{22}ClF_3N_3O_3$ | 480,1296 | 480,1307 |

Caracterización por NMR de los compuestos de los Ejemplos 531-551

| Ej N° | Datos NMR |
|---|---|
| 531 | $^1$H NMR ($CD_3OD$/ 400MHz) δ 7 61 (m 1H) 7 53 (m 1H) 7 24 (t 2H, J = 8,00Hz), 7,14 (m, 1H), 7,05 (m, 1H), 6,74 (s, 1H) 5,40 (s, 2H), 4 42 (s, 2H), 3,63 (s, 3H), 2,12 (s, 3H) |
| 532 | $^1$H NMR ($CD_3OD$ / 400MHz) δ7,59 (m, 2H), 7,24 (t, 2H, J = 8 00 Hz), 7,11 (m, 2H), 6,73 (s, 1H), 5,43 (s, 2H), 4,62 (s, 2H), 2,12 (s, 3H) |
| 533 | $^1$H NMR ($CD_3OD$/ 400MHz) δ 7,61 (m, 1H), 7,53 (m, 1H) 7 24 (t, 2H, J = 7,60 Hz), 7,13 (m, 1H), 7,05 (m, 1H), 6,74 (s, 1H), 5,40 (s, 2H), 4,81 (m, 1H), 4,41 (s, 2H) 2,12 (s 3H), 1,21 (d, 6H, J = 6,0J Hz) |
| 534 | $^1$H NMR ($CD_3OD$/ 400MHz) δ 7,61 (m, 1H), 7,52 (m, 1H), 7,24 (t, |

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| | |
|---|---|
| | 2H J = 0,80 Hz), 7 13 (m, 1H), 7,03 (m, 1H), 6 73 (s 1H) 5 39 (s, 2H), 4,44 (s, 2H), 3,12 (q, 2H, J = 7,20 Hz), 2,12 (s, 3H), 1,08 (t, 3H, J = 7,20 Hz) |
| 535 | $^1$H NMR ($CD_3OD$/ 300MHz) δ 7 62 (m, 1H), 7,54 (m, 1H) 7 25 (t, 2H, J = 8,4 Hz 7,15 (m, 1H), 7,07 (m, 1H), 6,75 (s, 1H), 5,41 (s 2H) 5,15 (s br, 1H) 4 44 (s 2H), 3,82 (m, 4H), 2,13 (s 4H) 2,03 (s br, 1H) |
| 536 | $^1$H NMR ($CD_3OD$/ 300MHz) δ 7,62 (m, 1H), 7,54 (m, 1H), 7,25 (t, 2H, J = 8,1 Hz 7 15 (m, 1H), 7,06 (m, 1H), 6,74 (s, 1H), 5,41 (s 2H), 4,43 (s, 2H), 3 98 (t, 2H, J = 6,6 Hz), 2 13 (s, 3H), 1 63 (m, 2H), 0,94 (t, 3H J = 7,2 Hz) |
| 537 | $^1$H NMR ($CD_3OD$/ 300MHz) δ 7,62 (m, 1H), 7,54 (m, 1H), 7 25 (t 2H, J = 8,4 Hz , 7,14 (m, 1H), 7,07 (m, 1H), 6,74 (s, 1H), 5,41 (s, 2H), 5 92 (m br 1H), 5,41 (s, 2H), 5 29 (d 1H, J = 17,7 Hz), 5, 7 (d, 1H, J = 10,5 Hz), 4,63 (s, 1H), 4,53 (d 2H J = 5,4 Hz), 4,44 (s 2H) 2 13 (s 3H) |
| 538 | $^1$H NMR ($CD_3OD$/ 400MHz) δ 7,61 (m, 1H), 7,53 (m, 1H) 7 24 (t 2H, J = 7 6 Hz$^1$ 7,14 (m, 1H), 7,06 (m, 1H), 6,74 (s, 1H), 5 41 (s, 2H) 4 65 (d, 2H J = 2 4 Hz), 4,44 (s, 2H), 2,86 (t, 1H, J = 2 4 Hz) 2 12 (s 3H) |
| 539 | $^1$H NMR ($CD_3OD$ / 400MHz) δ7,61 (m, 1H), 7,53 (m, 1H), 7,24 (tr 2H, J = 8,40), 7,12 (m 1H) 7 05 (m, 1H), 6,74 (s, 1H), 5,39 (s, 2H), 4,36 (s, 2H), 2 12 (s 3H), 1,43 (s, 9H) |
| 540 | $^1$H NMR ($CD_3OD$ / 400MHz) δ7 61 (m 1H) 7 53 (m, 1H), 7,24 (tr 2H, J = 8,00 Hz), 7,12 (m, 1H), 7,04 (m 1H) 6 73 (s 1H), 5,37 (s, 2H), 4,39 (s 2H) 2 12 (s, 3H), 1,28 (s, 9H) |
| 541 | $^1$H NMR ($CD_3OD$ / 300MHz) δ7,59 (m, 2H), 7,26 (m, 3H), 7,11 (m, 1H), 6,75 (s, 1H), 5,46 (s, 2H), 4,40 (s 2H), 3,02 (m, 2H), 2,12 (s, 3H), 1,80 (m, 2H), 1,03 (tr, 3H, J = 7,50 MHz) |
| 542 | $^1$H NMR ($CD_3OD$ / 400MHz) δ7,58 (m, 2H), 7,26 (m, 3H) 7 10 (m, 1H), 6,74 (s, 1H), 5,45 (s, 2H), 4,39 (s, 2H), 3,06 (q, 2H, J = 7,60 Hz), 2 ,1 (s, 3H), 1,31 (t, 3H, J = 7,2 Hz) |
| 543 | $^1$H NMR ($CD_3OD$ / 400MHz) δ7 61 (m 1H) 7 52 (m 1H) 7 24 (t 2H, J = 8,40 Hz), 7,12 (m, 1H), 7,04 (m, 1H), 6,73 (s, 1H), 5,39 (s, 2H), 4,44 (s, 2H), 3,77 (m, 1H), 2,12 (s, 3H), 1 10 (d, 6H, J = 6,40 Hz) |
| 544 | $^1$H NMR ($CD_3OD$ / 400MHz) δ7,61 (m, 1H), 7,54 (m, 1H), 7,24 (t, |

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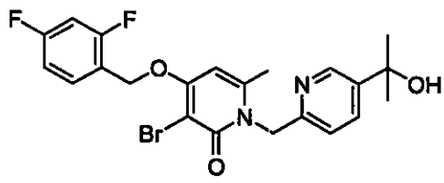
| | |
|---|---|
| | 2H J = 7,6 Hz), 7,15 (m 1H), 7,06 (m, 1H) 6 74 (s, 1H), 5,43 (s, 2H), 4 55 (s, 2H), 3,92 (s, 2H), 3 40 (s, 3H), 2,12 (s, 3H) |
| 545 | $^1$H NMR ($CD_3OD$ / 300MHz) δ7,63 (m 1H), 7,54 (m, 1H), 7 26 (t, 2H, J = 8 7 Hz), 7,15 (m, 1H) 7,05 (m, 1H), 6,75 (s 1H), 5,42 (s, 2H), 4 47 (s, 2H), 2,70 (s, 3H), 2,14 (s, 3H) |
| 546 | $^1$H NNMR ($CD_3OD$ / 300MHz) δ7 63 (m 1H), 7,53 (m 1H) 7 25 (t, 2H, J = 9,0 Hz), 7,14 (m 1H), 7,04 (m, 1H), 6 76 (s, 1H), 5,41 (s, 2H), 4,44 (s, 2H), 2,90 (s, 3H) 2,13 (s, 3H), 1 39 (s, 9H) |
| 547 | $^1$H NNMR ($CD_3OD$ / 400MHz) δ7,61 (m, 1H), 7,52 (m, 1H), 7,24 (t, 2H, J = 7,6 Hz) 7,14 (m, 1H), 7,03 (m, 1H) 6,74 (s, 1H), 5,41 (s, 2H), 4,47 (s, 2H) 2,46 (m, 1H), 2,12 (s, 3H), 0,68 (q, 2H, J = 5,2 Hz), 0 46 (m, 2H) |
| 548 | $^1$H NNMR ($CD_3OD$ / 400MHz) δ7,61 (m 1H), 7,53 (m, 1H), 7 24 (t, 2H, J = 8,0 Hz) 7,12 (m, 1H), 7,04 (m 1H) 6,73 (s, 1H), 5,39 (s, 2H) 4,47 (s, 2H), 3,79 (q, 2H J = 9 6 Hz), 2,12 (s, 3H) |
| 549 | $^1$H NNMR ($CD_3OD$ / 400MHz) δ7 61 (m 1H), 7,52 (m, 1H), 7,24 (t, 2H, J = 8,4 Hz), 7,14 (m, 1H), 7,04 (m, 1H), 6,73 (s, 1H), 5,39 (s, 2H), 4,45 (s, 2H), 2,96 (d 2H, J = 6,8 Hz), 2,12 (s, 3H), C,93 (m, 1H) 0 44 (m, 2H), 0,16 (q, 2H, J = 4 8 Hz) |
| 550 | $^1$H NNMR ($CD_3OD$ / 400MHz) δ7,61 (m, 1H), 7,53 (m, 1H), 7,24 (t, 2H, J = 8,0 Hz) 7,14 (m, 1H), 7,04 (m, 1H), 6,73 (s, 1H) 5 39 (s, 2H), 4,46 (s, 2H), 2,92 (d, 2H, J = 4,8 Hz), 2,12 (s, 3H) 0 87 (s 9H) |
| 551 | $^1$H NNMR ($CD_3OD$ / 300MHz) δ7,62 (m, 1H), 7,52 (m 1H) 7,25 (t, 2H, J = 8,7 Hz), 7,15 (m, 1H), 7,04 (m, 1H), 6,75 (s, 1H), 5,42 (s, 2H), 4,48 (s, 2H), 2,90 (s, 6H), 2,14 (s, 3H) |

$^1$H NMR ($CD_3OD$ / 400MHz) δ7,58 (m, 2H), 7,26 (m, 3H), 7,10 (m, 1H), 6,74 (s, 1H), 5,45 (s, 2H), 4,39 (s, 2H), 3,06 (q, 2H, J = 7,6 Hz), 2,11 (s, 3H), 1,31 (t, 3H, J = 7,2 Hz)$^1$H NMR ($CD_3OD$ / 300MHz) δ7,63 (m, 1H), 7,54 (m, 1H), 7,26 (t, 2H, J = 8,7 Hz), 7,15 (m, 1H), 7,05 (m, 1H), 6,75 (s, 1H), 5,42 (s, 2H), 4,47 (s, 2H), 2,70 (s, 3H), 2,14 (s,

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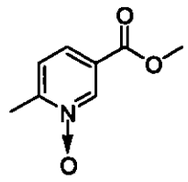
3H) ESHRMS m/z 466,1141 (M+H $C_{22}H_{20}ClF_3N_3O_3$ requiere 466,1140)

Ejemplo 552



3-bromo-4-[(2,4-difluorobencil)oxi]-1-{[5-(1-hidroxi-1-metiletil)piridin-2-il]metil}-6-metilpiridin-2(1H)-ona

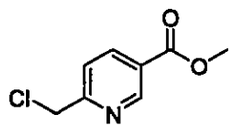
Etapa 1 Preparacion de 6-metilnicotinato 1-oxido de metilo



Se añadió 6-metilnicotinato de metilo (6,0 g, 39,7 mmol) al diclorometano (100 mL) en el matraz de base redondeada bajo nitrógeno Luego, se añadio acido 3-cloroperoxibenzoico (10,0 g, 57,9 mmol) en el matraz y se agito durante 5 horas Se agrego disolucion saturada de bicarbonato de sodio (100 ml) a la reaccion y la mezcla se transfirio al embudo separador Se agrego otros 200 mL de diclorometano en el embudo y se obtuvo la capa orgánica La capa organica se lavo con agua (150 mL) y se seco sobre sulfato de magnesio anhidro La disolución resultante se evaporo para producir un sólido blanco (6 g, 90 %) LC/MS, $t_r$ = 0,33 minutos (5 a 95% acetonitrilo/agua durante 5 minutos a 1 ml/min con deteccion de 254 nm, a 50 °C) ES-MS

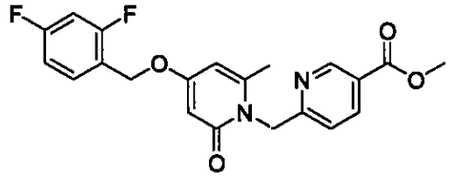
m/z 168 (M+H) ES-HRMS m/z 168,0628 (M+H calculado para $C_8H_{10}NO_3$ requiere 168,0655)

Etapa 2 Preparacion de 6-(clorometil)nicotinato de metilo



Se agregó 6-metilnicotinato 1-oxido de metilo (de la Etapa 1) (6,0 g, 35,9 mmol) al cloruro de p-toluensulfonilo (10 g, 52,4 mmol) en 100 mL de 1,4- dioxano La mezcla se calento a reflujo durante 20 horas Se agregó en la reaccion disolucion saturada de bicarbonato de sodio (200 ml) y la mezcla se transfirio al embudo separador El compuesto se extrajo con acetato de etilo (300ml x 2) y la disolucion combinada de acetato de etilo se seco sobre sulfato de magnesio y se evaporo hasta obtener un solido negro (5,2 g, 78%) LC/MS, $t_r$ = 1,52 minutos (5 a 95% acetonitrilo/agua durante 5 minutos a 1 ml/min con deteccion de 254 nm, a 50 °C) ES-MS m/z 186 (M+H) ES-HRMS m/z 186,0314 (M+H calculado para $C_8H_9ClNO_2$ requiere 186,0316)

Etapa 3 Preparacion de 6-{[(4-[2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-metil}nicotinato de metilo



6-(clorometil)nicotinato de metilo (de la Etapa 2) Se añadieron (2 g, 10,8 mmol) en 4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona en 20 mL de dimetilformamida, seguido del agregado de carbonato de cesio (5g, 15,3 mmol) La mezcla se calentó a 100° C durante 20 horas Se enfrio

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a temperatura ambiente y se le agregaron 400 mL de agua La disolucion produjo un precipitado marron Se filtró y se enjuagó con agua (200 mL x 3) y se seco para obtener 4 g de solido El producto se purifico utilizando cromatografia preparativa Gilson Reversed Phase para obtener un solido blanco (1,4 g, 32%) $^1$H NMR (400 MHz, $CDCl_3$) δ 9,09 (d, J =1,48 Hz, 1H), 8,19 (dd, J = 6,04, 2,15 Hz, 1H), 7,37 (app q, J = 8,32 Hz, 1H), 7,25 (d, J = 8,33 Hz, 1H), 6,84 (m, 2H), 5,94 (d, J = 2,82Hz, 1H), 5,83 (d, J = 2,15Hz, 1H), 5,36 (s, 2H), 4,97 (s, 2H), 3,90 (s, 3H), 2,27(s, 3H), LC/MS, $t_r$ = 2,30 minutos (5 a 95% acetonitrilo/agua durante 5 minutos a 1 ml/min con deteccion de 254 nm, a 50 °C) ES-MS m/z 401 (M+H) ES-HRMS m/z 401,1307 (M+H calculado para $C_{21}H_{19}F_2N_2O_4$ requiere 401,1307)

Etapa 4 Preparacion del compuesto del titulo

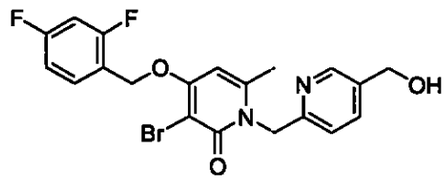
Se agregó una disolucion 3 molar de bromuro de magnesio de metilo en éter (5 mL, 15 mmol) en 5 ml de tetrahidrofurano anhidro en los matraces de base redondeada bajo nitrogeno La mezcla se enfrió a 0 °C Se disolvio 6-{[4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}nicotinato de metilo (de la Etapa 3) (300 mg, 0,75 mmol) en 5 ml de tetrahidrofurano anhidro en el embudo de goteo, y la disolucion se agregó lentamente a la disolucion fria de bromuro de magnesio de metilo en el matraz de base redondeada Después del agregado, la mezcla se agito en forma continua a 0° C durante 30 minutos y se agrego lentamente la disolución fria de cloruro de amonio saturado (100 mL) a la mezcla de reacción La mezcla se transfirió al embudo separador y el producto se extrajo con acetato de etilo (200 ml x 2) La disolucion combinada de acetato de etilo se seco con sulfato de magnesio anhidro y se evaporo hasta secarse El residuo resultante (220 mg) se agrego a

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10 ml de diclorometano seguido por la adicion de N-bromo succinimida (100 mg, 0,56 mmol) La disolucion se agitó a temperatura ambiente durante 3 horas Se agregó una disolución de bicarbonato de sodio saturada (100 ml) en la mezcla de reacción y se la transfirió a un embudo separador El producto se extrajo con acetato de etilo (200 ml x 2) La disolucion de acetato de etilo combinada se seco sobre sulfato de magnesio anhidro y se evaporo hasta lograr la sequedad

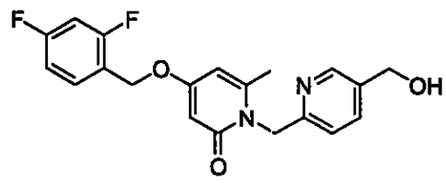
$^1$H NMR (400 MHz, $CDCl_3$) δ 8,61 (d, J =1,88 Hz, 1H), 7,73 (dd, J = 5,77, 2,42 Hz, 1H), 7,55 (aprox q, J = 6,31 Hz, 1H), 7,30 (d, J = 8,19b Hz, 1H), 6,93 (m, 1H), 6,84 (m, 1H), 6,00 (s, 1H), 5,37 (s, 2H), 5,19 (s, 2H), 2,48 (s, 3H), 1,56 (s, 6H), LC/MS, $t_r$ = 2,29 minutos (5 a 95% acetonitrilo/agua durante 5 minutos a 1 ml/min con deteccion a 254 nm, a 50 °C) ES-MS m/z 479 (M+H) ES-HRMS m/z 479,0791 (M+H calculado para $C_{22}H_{22}BrF_2N_2O_3$ requiere 479,0776)

Ejemplo 553



3-bromo-4-[(2,4-difluorobencil)oxi]-1-{[5-(hidroximetil)piridin-2-il]metil}-6-metilpiridin-2(1H)-ona

Etapa 1 Preparacion de 4-[(2,4-difluorobencil)oxi]-1-{[5-(hidroximetil)piridin-2-il]metil}-6-metilpiridin-2(1H)-ona

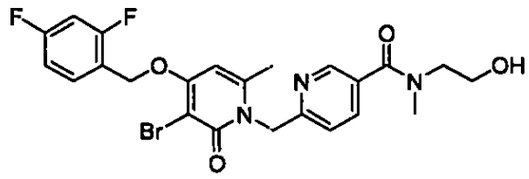


Se agregó 6-{[4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}nicotinato de metilo (de la preparacion de la etapa 3) (350 mg, 0,87 mmol) en el tetrahidrofurano anhidro (15 ml) y la disolucion se enfrio a -78 °C En la disolucion fria se agrego hidruro de aluminio y litio (_00 mg, 2,6 mmol) Despues de la adicion, la mezcla de reacción se entibió a 0 °C y se continuo la agitacion durante una hora adicional Se agrego lentamente sulfato de hidrógeno y potasio (disolucion 1 N, 150 ml) en la mezcla de reaccion para enfriar la reaccion repentinamente La mezcla resultante fue transferida a un embudo separador y el producto se extrajo con acetato de etilo (200 ml x 2) La disolucion de acetato de etilo combinada se secó sobre sulfato de magnesio anhidro y se evaporó hasta lograr la sequedad LC/MS, $t_r$ = 1,88 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con deteccion a 254 nm, a 50 °C) ES-MS m/z 373 (M+H)

Etapa 2 Preparación del compuesto del titulo

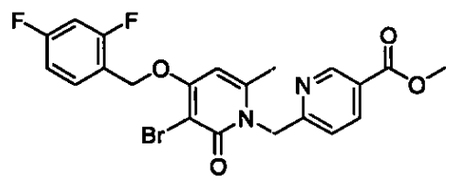
4-[(2,4-difluorobencil)oxi]-1-{[5-(hidroximetil)piridin-2-il]metil}-6-metilpiridin-2(1H)-ona de la etapa 1) Se agrego (230 mg, 0,62 mmol) en 10 ml de diclorometano seguido por la adicion de N-bromo succinimida (110 mg, 0,62 mmol) La disolución se agito a temperatura ambiente durante 3 horas Se agrego una disolucion de bicarbonato de sodio saturada (100 ml) en la mezcla de reacción y se la transfirio a un embudo separador El producto se extrajo con acetato de etilo (200 ml x 2) La disolucion de acetato de etilo combinada se secó sobre sulfato de magnesio anhidro y se evaporo hasta lograr la sequedad $^1$H NMR (400 MHz, $CDCl_3$) δ 8,47 (aprox s, 1H), 7,64 (dd, J = 5,77, 2,29 Hz, 1H), 7,55 (aprox q, J = 6,45 Hz, 1H), 7,33 (d, J = 6,05b Hz, 1H), 6,93 (m, 1H), 6,84 (m, 1H), 6,00 (s, 1H), 5,39 (s, 2H), 5,19 (s, 2H), 4,68 (s, 2H), 2,46 (s, 3H), LC/MS, $t_r$ = 2,01 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con detección a 254 nm, a 50 °C) ES-MS m/z 451 (M+H)

Ejemplo 554



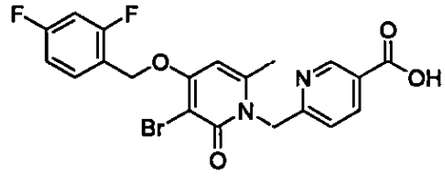
6-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}-N-(2-hidroxietil)-N-metilnicotinamida

Etapa 1 Preparacion de 6-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}nicotinato de metilo



Se agregó 6-{[4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}nicotinato de metilo de la preparacion de la etapa 3(350 mg, 0,87 mmol) (1,0 g, 2,5 mmol) en 150 ml de diclorometano seguido por la adición de N-bromo succinimida (500 mg, 2,8 mmol) La disolución se agitó a temperatura ambiente durante 3 horas Se agregó una disolución de bicarbonato de sodio saturada (300 ml) en la mezcla de reaccion y se la transfirio a un embudo separador El producto se extrajo con acetato de etilo (500ml x 2) La disolucion de acetato de etilo combinada se seco sobre sulfato de magnesio anhidro y se evaporó hasta lograr la sequedad $^1$H NMR (400 MHz, $CDCl_3$) δ 9,08 (aprox d, J =2,15 Hz, 1H), 8,21 (dd, J = 6,04, 2,15 Hz, 1H), 7,55 (aprox qt, J = 6,31 Hz, 1H), 7,41 (d, J = 6,31 Hz, 1H), 6,91 (m, 1H), 6,84 (m, 1H), 6,02 (s, 1H), 5,42 (s, 2H), 5,19 (s, 2H), 3,91 (s, 3H), 2,45 (s, 3H), LC/MS, $t_r$ = 2,85 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min ccn deteccion a 254 nm, a 50 °C) ES-MS m/z 479 (M+H) ES-HRMS m/z 479,0415 (M+H calculado para $C_{21}H_{18}BrF_2N_2O_4$ requiere 479,0413)

Etapa 2 Preparacion de acido 6-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}nicotinico




Se agregó 6-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}nicotinato de metilo de la preparacion de la etapa 1(1,0 g, 2,1 mmol) en la mezcla de 100 ml de tetrahidrofurano y 10 ml de metanol seguido por la adicion de hidroxido de sodio 2,5 N (0,85 ml, 2,1 mmol) La disolucion se calento a 50 °C durante 2 horas

Despues de que la disolucion se enfrio a temperatura ambiente y se evaporó hasta lograr un residuo completamente seco El residuo se agrego en 50 ml de tetrahidrofurano y 4 N HCl en 1,4-dioxano (0,52 ml, 2,1 mmol) y la mezcla se agito durante 30 minutos La mezcla se evaporo hasta lograr la sequedad Se agrego al residuo 20 ml de agua y la disolucion acuosa se neutralizó hasta lograr exactamente un ph 7 mediante la adicion gota a gota de una disolucion de bicarbonato de scdio saturada La mezcla heterogenea resultante se dejo reposar durante 20 horas Se filtro, se enjuago con agua (30 ml x 3) y se secó en horno de alto vacio para lograr un sólido blanco (950 mg, 97%)

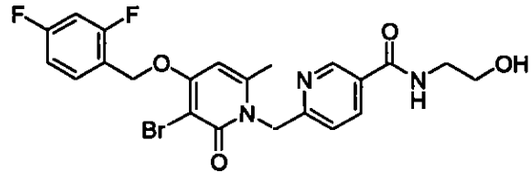
$^1$H NMR (400 MHz $CDCl_3$ y $CD_3OD$) δ 8,98 (aprox br s, 1H), 8,15 (dd, J = 6,17, 2,02 Hz, 1H), 7,45 (aprox q, J = 6,58 Hz, 1H), 7,21 (d, J = 8,19 Hz, 1H), 6,84 (m, 1H), 6,76 (m, 1H), 6,04 (s, 1H), 5,35 (s, 2H), 5,12 (s, 2H), 2,32 (s, 3H), LC/MS, $t_r$ = 2,48 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con detección a 254 nm, a 50 °C) ES-MS m/z 465 (M+H) ES-HRMS m/z 465,0254 (M+H calculado para $C_{20}H_{16}BrF_2N_2O_4$ requiere 465,0256)

Etapa 3 Preparacion del compuesto del titulo

Se agrego acido 6-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}nicotinico ( de la etapa 2) (230 mg, 0,5 mmol) en el hidroxibenzotriazcl (101 mg, 0,75 mmol) en 5 ml de N,N-dimetilformamida Se agrego 4-metil morfolina (0,16 ml, 1,5 mmol) en la mezcla seguido por la adicion de hidrocloruro de 1-(3-(dimetilamino)propil-3-etilcarbodiimida (14[illegible] mg, 0,75 mmol) Se agito la mezcla durante 30 minutos para generar una disolución homogénea A dicha disolución homogénea se adiciono 2-(metilamino)etanol (0,06 ml, 0,75 mmol) y la mezcla se agitó durante 20 horas Se agregó agua (150 ml) en la

mezcla de reaccion y el producto se extrajo empleando acetato de etilo (400 ml x 2) La disolucion de acetato de etilo combinada se seco sobre sulfato de magnesio anhidro y se evaporo hasta lograr la sequedad $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8,47 (aprox br s, 1H), 7,80 (br d, J = 7,92 Hz, 1H), 7,64 (aprox q, J = 6,58 Hz, 1H), 7,30 (m, 2H), 7,15 (m, 1H), 6,56 (s, 1H), 5,39 (s, 2H), 5,28 (s, 2H), 3,46 (m, 2H), 3,23 (m, 2H), 2,93 (m, 3H), 2,36 (s, 3H), LC/MS, $t_r$ = 2,29 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con detección a 254 nm, a 50 °C) ES-HRMS m/z 522,0850 (M+H calculado para $C_{23}H_{23}BrF_2N_3O_4$ requiere 522,0835)

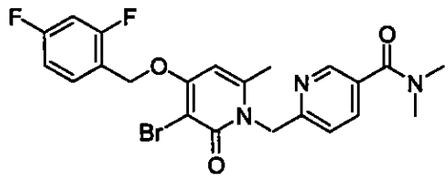
Ejemplo 555




6-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}-N-(2-hidroxietil)nicotinamida

Siguiendo el método del Ejemplo 554 (etapa 3) y sustituyendo 2-(metilamino)etanol por la etanolamina se obtuvo el compuesto del titulo como un solido blanco (rendimiento 79%) $^1$H NMR (400 MHz, $CD_3OD$) δ 8,93 (d, J =2,01 Hz, 1H), 8,21 (dd, J = 6,04, 2,21 Hz, 1H), 7,67 (aprox q, J = 6,44 Hz, 1H), 7,39 (d, J = 8,06 Hz, 1H), 7,08 (m, 2H), 6,58 (s, 1H), 5,55 (s, 2H), 5,37 Hz, 2H), 3,74 (aprox t, J = 5,73Hz, 2H), 3 53 (aprox t, J = 5,73Hz, 2H), 2,49 (s,3H), LC/MS, $t_r$ = 2,26 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con detección a 254 nm, a 50 °C) ES-HRMS m/z 508,0673 (M+H calculado para $C_{22}H_{21}BrF_2N_3O_4$ requiere 508,0678)

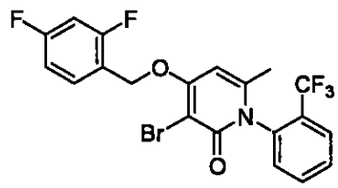
Ejemplo 556



6-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}-N,N-dimetilnicotinamida

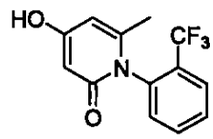
Siguiendo el metodo del Ejemplo 554 (etapa 3) y sustituyendo la etanolamina por dimetilamina se obtuvo el compuesto del titulo como un sólido blanco (rendimiento 75%) $^1$H NMR (400 MHz, $CDCl_3$) δ 8,55 (d, J =1,62 Hz, 1H), 7,68 (dd, J = 5,77, 2,15 Hz, 1H), 7,55 (aprox q, J = 6,45 Hz, 1H), 7,37 (d, J = 8,06 Hz, 1H), 6,93 (m, 1H), 6,84 (m, 1H), 6,02 (s, 1H), 5,40 (s, 2H), 5,20 (s, 2H), 3,09 (s, 3H), 2,97 (s, 3H), 2,45 (s, 3H), LC/MS, $t_r$ = 2,45 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con deteccion a 254 nm, a 50 °C) ES-HRMS m/z 492,0710 (M+H calculado para $C_{22}H_{21}BrF_2N_3O_3$ requiere 492,0729)

Ejemplo 557



3-Bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-[2-(trifluorometil)fenil]piridin-2(1H)-ona

Etapa 1 Preparacion de 4-hidroxi-6-metil-1-[2-trifluorometil)fenil]piridin-2(1H)-ona

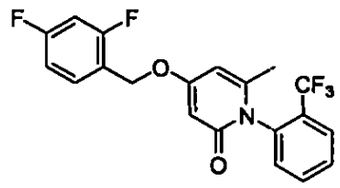


Se adiciono 4-hidroxi-6-metil-2-pirona (10 g, 79,3 mmol) en la 2-(trifluorometil)anilina (14 ml, 111,3 mmol) en 10 ml de 1,2-diclorobenceno en un matraz de fondo

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redondo La mezcla despues se colocó en un baño de aceite precalentado a 165 °C Despues de 30 minutos de calentamiento, la mezcla se enfrió a temperatura ambiente y se agregó 250 ml de disolución de bicarbonato de sodio saturada La mezcla se agito a temperatura ambiente durante 15 minutos y se transfirió a un embudo separador Se agregó acetato de etilo (300 ml) en el embudo separador y se dividieron las capas Se obtuvo la capa acuosa y a la capa organica se agrego 200 ml de disolucion de bicarbonato de sodio saturada La capa acuosa se obtuvo nuevamente y la disolución acuosa combinada fue neutralizada con la disolucion de HCl Despues de la neutralizacion, el solido blanco se precipito de la disolución Se filtro el sólido, se lo enjuago con agua (100 ml x 5) y se lo secó en un horno de alto vacio hasta obtener el solido blanco (7,5 g, 35,5%) LC/MS, $t_r$ = 1,77 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con deteccion a 254 nm, a 50 °C) ES-MS m/z 270 (M+H)

Etapa 2 Preparacion de 4-[(2,4-difluorobencil)oxi]-6-metil-1-[2-(trifluorometil)fenil]piridin-2(1H)-ona




Se agregó 4-hidroxi-6-metil-1-[2-(trifluorometil)fenil]piridin-2(1H)-one ( de la etapa 1) (7,3 g, 27,1 mmol) en bromuro 3,4-difluorobencilico (5,5 g, 26,5 mmol) en 60 ml de dimetil formamida La mezcla se enfrio a 0 °C y se agrego carbonato de cesio (20 g, 61,3 mmol) en la mezcla Despues de la adicion, la mezcla se entibio a temperatura ambiente y se agito durante 4 horas Se agregó agua (500 ml) a la mezcla de reaccion De la disolución surgio un solido de color amarillo Se la

filtró y enjuago con agua (200 ml x 2) para obtener el solido de color amarillo El sólido se disolvió en acetato de etilo (500 ml) y agua (300 ml) y se transfirio a un embudo separador a fin de obtener la capa organica La capa organica se lavo nuevamente con agua (200 ml) y se seco sobre sulfato de magnesio anhidro La disolucion orgánica se evaporo hasta lograr la sequedad $^1$H NMR (400 MHz, $CDCl_3$) δ 7,82 (d, J =7,65 Hz, 1H), 7,7 (t, J = 7,52 Hz, 1H), 7,58 (t, J = 7,65 Hz, 1H), 7,42 (q, J = 6,45 Hz, 1H), 7,27 (s, J= 7,78 Hz, 2H), 6,89 (m, 2H), 5,95 (aprox d, J = 2,42 Hz, 1H), 5,90 (aprox d, J = 2,42 Hz, 1H), 5,01 (aprox d, J = 2,94Hz, 2H), 1,86 (s, 3H), LC/MS, $t_r$ = 2,74 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con detección a 254 nm, a 50 °C) ES-MS m/z 396 (M+H)

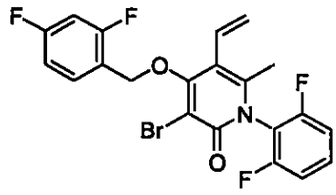
Etapa 3 Preparacion del compuesto del titulo

Se agrego N-bromosuccinimida (0,24g, 1,36 mmol) en 4-[(2,4-difluorobencil)oxi]-6-metil-1-[2-(trifluorometil)fenil]piridin-2(1H)-ona (0,54g, 1,36 mmol) en 20 ml de diclorometano La mezcla se agito a temperatura ambiente durante 2 horas Se añadio una disolucion de bicarbonato de sodio saturada (150 ml) en la mezcla de reaccion y la disolucion combinada se transfirió a un embudo separador El producto se extrajo con acetato de etilo (250ml) La disolucion de acetato de etilo se seco sobre sulfato de magnesio anhidro y se evaporó hasta lograr la sequedad $^1$H NMR (400 MHz, $CDCl_3$) δ 7,82 (d, J =7,25 Hz, 1H), 7,7 (aprox t, J = 7,66 Hz, 1H), 7,60 (m, 2H), 7,26 (s, 1H), 6,97 (m, 1H), 6,87 (m, 1H), 6,09 (s, 1H), 5,25 (aprox t, J = 3,35Hz, 2H), 1,94 (s, 3H), LC/MS, $t_r$ = 2,84 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con deteccion a 254 nm, a 50 °C) ES-

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HRMS m/z 474,0113 (M+H calculado para $C_{20}H_{14}BrF_5NO_4$ requiere 474,0123)

Ejemplo 558

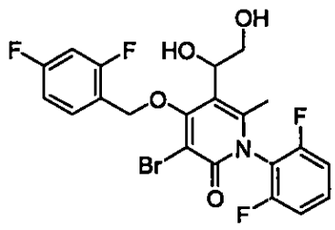


3-bromo-4-[(2,4-difluorobencil)oxi]-1-[2,6-(difluorofenil)-6-metil-5-vinilpiridin-2(1H)-ona

Etapa 1 A una disolución a temperatura ambiente de 3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorofenil)-5-yodo-6-metilpiridin-2(1H)-ona (1,00 g, 1,76 mmol) en THF anhidro (12 ml) se agregó, de manera secuencial, tributil(vinil)tin (1,21 g, 3,81 mmol) y tetrakis(trifenilfosfina)paladio (236 mg, 0,204 mmol) bajo una corriente de argon El recipiente de reaccion después se equipo con un condensador de reflujo y el sistema de reaccion se purgó cor un flujo de argon La disolucion de color amarillo resultante se calento a 68 °C y se agito bajo una presión de argon positiva durante 12,0 horas hasta la desaparicion completa del material de inicio por análisis LC/MS La mezcla de reaccion se concentro *in vacuo* y el residuo de color oscuro oscuro resultante se sometió a cromatografia sobre $SiO_2$ con acetato de etilo/hexanos (3 7) para generar un solido rojizo $^1H$ NMR (400 MHz, $CDCl_3$) δ 7 62 (aprox q, J = 7,8 Hz, 1H), 7,45 (aprox tt, J = 8,4, 6,2, 1H), 7,09 (aprox t, J = 8,8 Hz, 2H), 6,90 (aprox t, J = 8,0 Hz, 1H), 6,83 (aprox dt, J = 6,8, 2,5 Hz, 1H), 6,51 (dd, J = 17,7, 11,4 Hz, 1H), 5,53 (dd, J = 11,4, 1,5 Hz, 1H), 5,41 (dd, J = 17,8, 1,5 Hz, 1H), 5,09 (br s, 2H), 2,09 (s, 3H), LC/MS columna C-18 , $t_r$ = 3,20 minutos (acetonitrilo/agua al 5 a 95% durante 5

minutos a 1 ml/min con detección a 254 nm, a 50 °C) ES-MS m/z 468 (M+H) ES-HRMS m/z 468,0210 (M+H calculado para $C_{21}H_{18}BrF_4NO_2$ requiere 468,0217)

Ejemplo 560

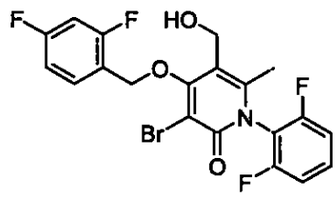


3-bromo-4-[(2,4-difluorobencil)oxi]-1-[2,6-(difluorofenil)-5-(1,2-dihidroxietil)-6-metilpiridin-2(1H)-ona

Etapa 1 A una disolucion a temperatura ambiente de 3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorofenil)-6-metil-5-vinilpiridin-2(1H)-ona (0,970 g, 2,07 mmol) en agua/acetona 1 3 (8,7 ml) se agrego, de manera secuencial, tetróxido de osmio (0,110 g, 0,433 mmol) y óxido de N-metil morfolina (1,32 g, 11,2 mmol) La disolucion resultante se agitó durante una hora hasta la consumición completa del material de inicio por analisis LC/MS, y la reacción se concentró *in vacuo* El residuo de color oscuro resultante se sometio a cromatografia sobre $SiO_2$ con acetato de etilo/hexanos (3 7) para generar un solido $^1H$ NMR (400 MHz, $CDCl_3$) δ 7,59 (aprox q, J = 8,2 Hz, 1H), 7,45 (ddd, J = 14,7, 8,5, 6,8 Hz, 1H), 7,08 (aprox t, J = 8,5 Hz, 2H), 6,94 (aprox t, J = 8,2 Hz, 1H), 6,88 (aprox t, J = 8,5 Hz, 1H), 5,31 (AB-q, J = 10,6 Hz, □= 38,3 Hz, 2H), 5,07 (dd, J = 9,1, 3,8 Hz, 1H), 3,83 (t, J = 10,8 Hz, 1H), 3,60 (dd, J = 11,4, 3,9 Hz, 1H), 2,94 (br s, 1H), 2,16 (s, 3H), LC/MS columna C-18, $t_r$ = 2,26 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con detección a 254 nm, a 50 °C) ES-MS m/z 502 (M+H) ES-HRMS m/z 502,0276 (M+H calculado para $C_{21}H_{17}BrF_4NO_4$ requiere 502,0272)

1234
1235

Ejemplo 561

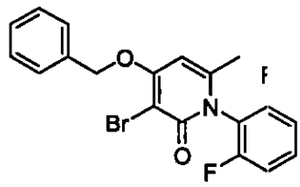


3-bromo-4-[(2,4-difluorobencil)oxi]-1-[2,6-(difluorofenil)-5-(dihidroxietil)-6-metilpiridin-2(1H)-ona

Etapa 1 A una disolucion de 5-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorofenil)-2-metil-6-oxo-1,6-dihidropiridina-3-carbaldehido a -20 °C (0,659 g, 1,40 mmol) en metanol (10 ml) se agregó, por porciones, borohidruro de sodio solido (3,6 g, 96 mmol) durante una hora hasta la consumición completa del material de inicio por analisis LC/MS A continuacion, la mezcla de reacción se diluyo con 500 ml de acetato de etilo y se lavo con 3 X 200 ml de agua El extracto organico resultante fue secado sobre $Na_2SO_4$, filtrado y concentrado *in vacuo* aproximadamente a un volumen de 100 ml El liquido resultante se diluyo con hexanos (100 ml) para formar un sólido amorfo que fue recolectado y secado a un vacio de 1 mm Hg para formar (620 mg, 94 %) del producto deseado $^1H$ NMR (400 MHz, $d_4$-MeOH) δ 7,70 (aprox q, J = 8,3 Hz, 1H), 7,62 (aprox tt, J = 10,4, 6,3 Hz, 1H), 7,25 (aprox t, J = 8,6 Hz, 2H), 7,03 (aprox t, J = 8,6 Hz, 1H), 6,88 (aprox t, J = 8,5 Hz, 1H), 5,31 (s, 2H), 4,58 (s, 2H), 2,17 (s, 3H), LC/MS C-18 columna, $t_r$ = 2,49 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con deteccion a 254 nm, a 50 °C) ES-MS m/z 472 (M+H) ES-HRMS m/z 472,0152 (M+H calculado para $C_{20}H_{15}BrF_4NO_3$ requiere 472,0166)

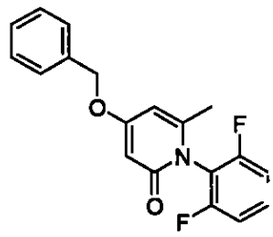
Ejemplo 562

1235
1236




4-(benciloxi)-3-bromo-1-(2,6-difluorofenil)-6-metilpiridin-2(1H)-ona

Etapa 1 Preparación de 4-(benciloxi)-1-(2,6-difluorofenil)-6-metilpiridin-2(1H)-ona

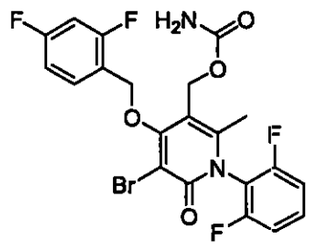



A una disolucion de 1-(2,6-difluorofenil)-4-hidroxi-6-metilpiridin-2(1H)-ona a temperatura ambiente agitada enérgicamente (1,43 g, 6,03 mmol) en dimetilformamida (4,6 ml) se adicionó secuencialmente $K_2CO_3$ (2,01 g, 14,5 mmol) y bromuro de bencilo (2,40 ml, 20,2 mmol) La suspensión resultante se agitó durante 6,5 horas hasta la consumición completa del material de inicio por analisis LC/MS Despues la reacción se diluyo con acetato de etilo (200 ml) y se lavo con salmuera (3 X 200 ml) El extracto organico resultante fue secado sobre $Na_2SO_4$, filtrado y concentrado *in vacuo* aproximadamente a un volumen de 100 ml El licor madre resultante se precipito rapidamente y formó un sólido amorfo que fue recolectado y secado a un vacio de 1 mm Hg para proporcionar un solido (1,62 g, 82%) $^1$H NMR (300 MHz, $d_4$-MeOH) δ 7,62 (aprox tt, J = 8,6, 6,4 Hz, 1H), 7,52-7,32 (m, 4H), 7,30-7,12 (m, 3H), 6,27 (d, J = 1,6 Hz, 1H), 6,04 (d, J = 2,6 Hz, 1H), 5,18 (s, 2H), 2,06 (s, 3H) LC/MS, columna C-18, $t_r$ = 2,51 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con deteccion a 254

nm, a 50 °C) ES-MS m/z 328 (M+H) ES-HRMS m/z 328,1179 (M+H calculado para $C_{19}H_{16}F_2NO_4$ requiere 328,1144)

Etapa 2 A una disolucion de 4-(benciloxi)-1-(2,6-difluorofenil)-6-metilpiridin-2(1H)-ona a temperatura ambiente (1,52 g, 4,64 mmol) en cloruro de metileno (15 ml) se adiciono N-bromosuccinimida solida (2,01 g, 11,3 mmol) y la disolucion rojiza resultante se agitó durante 4,0 horas En este momento la reaccion se diluyó con acetato de etilo (400 ml) y se lavó con sulfito sodico (disolucion acuosa al 5%, 100 ml) y salmuera (3 X 200 ml) Los extractos organicos resultantes fueron secados sobre $Na_2SO_4$, filtrados y concentrados *in vacuo* aproximadamente a un volumen de 60 ml El licor madre resultante se precipito rapidamente y formó un sólido amorfo que fue recolectado y secado a un vacio de 1 mm Hg para proporcionar un solido (1,70 g, 91 %) $^1$H NMR (300 MHz, $d_4$-MeOH) δ 7,64 (aprcx q, J = 8,6, 6,4 Hz, 1H), 7,57 (br d, J = 7,1 Hz, 1H), 7,50-7,34 (m, 4H), 7,27 (aprox t, J = 8,0 Hz, 1H), 7,26-7,21 (m, 1H), 6,66(s, 1H), 5,40(s, 2H), 2,12 (s, 3H), LC/MS columna C-18, $t_r$ = 2,63 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con deteccion a 254 nm, a 50 °C) ES-MS m/z 406 (M+H) ES-HRMS m/z 406,0228 (M+H calculado para $C_{19}H_{15}BrF_2NO_4$ requiere 406,0249)

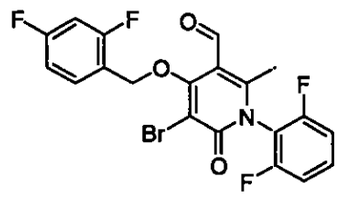
Ejemplo 563



carbamato de 5-bromo-4-[(2,4-difluorobencil)oxi]-1-[2,6-(difluorofenil)-2-metil-6-oxo-1,6-dihidropiridin-3-il]metilo

Etapa 1 A una disolucion de 3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorofenil)-5-(hidroximetil)-6-metilpiridin-2(1H)-ona a temperatura ambiente (76,2 mg, 0,161 mmol) en cloruro de metileno (0,4 ml) se agrego una disolucion de tricloroacetil isocianato (tolueno, 0,60 M, 0,5 ml, 0,30 mmol) La disolución resultante se agitó durante una hora hasta la consumición completa del material de inicio por analisis LC/MS La mezcla de reaccion después se aplicó directamente a $Al_2O_3$ (0,5 g de actividad Broeckman tipo I) y la suspension se maduró durante tres horas En este momento, el tapon de $Al_2O_3$ se lavó con acetato de etilo/metanol (95 5) y el licor madre resultante se concentro a un residuo que se sometio a cromatografia sobre $SiO_2$ usando acetato de etilo/hexanos (1 1) para formar un sólido blanco (71,0 mg, 85%) $^1H$ NMR (400 MHz, $d_4$-MeOH) δ 7,71-7,59 (m, 2H), 7,26 (aprox t, J = 8,5 Hz, 2H), 7,02 (aprox t, J = 9,2 Hz, 2H), 5,32 (s, 2H), 5,02 (s, 2H), 2,15 (s, 3H), LC/MS columna C-18, $t_r$ = 2,35 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con detección a 254 nm, a 50 °C) ES-MS m/z 515 (M+H) ES-HRMS m/z 515,0188 (M+H calculado para $C_{21}H_{16}BrF_4N_2O_4$ requiere 515,0224)

Ejemplo 564

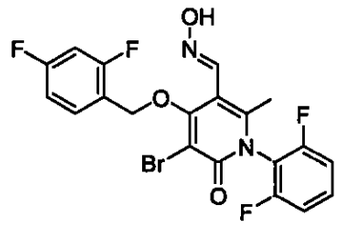


1238
1239

5-bromo-4-[(2,4-difluorobencil)oxi]-1-[2,6-(difluorofenil)-2-metil-6-oxo-1,6-dihidropiridin-3-carbaldehido

Etapa 1 A una disolución de 3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorofenil)-5-(1,2-dihidroxietil)-6-metilpiridin-2(1H)-ona a temperatura ambiente (550 mg, 1,10 mmol) en tolueno (10,0 ml) se agrego acetato de plomo (IV) (810 mg, 1,82 mmol) La disolucion de color marron oscuro resultante se agitó durante dos horas hasta la consumicion completa del material de inicio por analisis LC/MS La mezcla de reaccion despues se diluyo con acetato de etilo (400 ml), se lavó con agua (3 X 100 ml) y se lavó con salmuera (3 X 300 ml) El extracto organico resultante se separo, se secó sobre $Na_2SO_4$ y se concentro El residuo de color oscuro resultante se sometió a cromatografia sobre $SiO_2$ con acetato de etilo/hexanos (1 1) para generar un solido de color amarillo claro (321 mg, 62 %) $^1H$ NMR (400 MHz, $CDCl_3$) δ 10,08 (s, 1H), 7,56-7,48 (m, 2H), 7,12 (aprox t, J = 7,3 Hz, 2H), 6,94 (aprox t, J = 8,5 Hz, 1H), 6,88 (aprox t, J = 8,7 Hz, 1H), 5,33 (s, 2H), 2,45 (s, 3H), LC/MS, columna C-18, $t_r$ = 2,94 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con detección a 254 nm, a 50 °C) ES-MS m/z 470 (M+H) ES-HRMS m/z 469,9996 (M+H calculado para $C_{20}H_{13}BrF_4NO_3$ requiere 470,0009)

Ejemplo 565

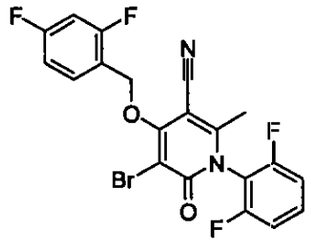


1239
1240

5-bromo-4-[(2,4-difluorobencil)oxi]-1-[2,6-(difluorofenil)-2-metil-6-oxo-1,6-dihidropiridina-3-carbaldehido oxima

Etapa 1 A una disolución de 5-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorofenil)-2-metil-6-oxo-1,6-dihidropiridina-3-carbaldehido a temperatura ambiente (316,5 mg, 0,673 mmol) en metanol (10,0 ml) se agrego $NH_2OH \cdot H_2O$ solido (300,0 mg, 4,32 mmol) y acetato de sodio (480,0 mg, 5,85 mmol) La suspensión resultante se agito durante 1,5 horas hasta la consumicion completa del material de inicio por analisis LC/MS La mezcla de reaccion despues se concentro *in vacuo* y el residuo resultante se diluyo con cloruro de metileno (300 ml) y se lavo con agua (2 X 100 ml) El extracto organico resultante se separo, se seco sobre $Na_2SO_4$, y se concentro hasta formar un solido color amarillo claro (390 mg, 99%) $^1H$ NMR (400 MHz, $d_4$-MeOH con $CDCl_3$) δ 8,06 (s, 1H), 7,51-7,40 (m, 2H), 7,06 (aprox dd, J = 8,6, 7,4 Hz, 2H), 6,88 (aprox dt, J = 8,3, 2,4 Hz, 1H), 6,83 (aprox dt, J = 9,2, 2,4 Hz, 1H), 5,13 (s, 2H), 2,76 (s, 3H), LC/MS, columna C-18, $t_r$ = 2,61 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con deteccion a 254 nm, a 50 °C) ES-MS m/z 485 (M+H) ES-HRMS m/z 485,0093 (M+H calculado para $C_{20}H_{14}BrF_4N_2O_3$ requiere 485,0118)

Ejemplo 566

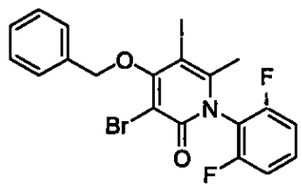


1240
1241

5-bromo-4-[(2,4-difluorobencil)oxi]-1-[2,6-(difluorofenil)-2-metil-6-oxo-1,6-dihidropiridin-3-carbonitrilo

Etapa 1 A una disolución de 5-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorofenil)-2-metil-6-oxo-1,6-dihidropiridina-3-carbaldehído oxima a temperatura ambiente (340,0 mg, 0,701 mmol) en cloruro de metileno (8,0 ml) se agregó 1,1' carbonil diimidazola solida (290,0 mg, 1,79 mmol) y acetato de sodio (480,0 mb, 5,85 mmol) La disolucion resultante se agito durante 1,5 horas hasta la consumición completa del material de inicio por analisis LC/MS La mezcla de reaccion se concentro *in vacuo* y el residuo oscuro resultante se aplicó directamente a cromatografia sobre $SiO_2$ con acetato de etilo/hexanos (3 7) para generar un solido blanco (262 mg, 90%) $^1H$ NMR (400 MHz, $CDCl_3$) δ 7,61 (aprox q, J = 7,4 Hz, 1H), 7,52 (aprox tt, J = 8,4, 6,3 Hz, 1H), 7,14 (aprox t, J = 8,6, 7,4 Hz, 2H), 6,94 (aprox t, J = 8,5, 2,5 Hz, 1H), 6,88 (aprox dt, J = 8,5, 2,4 Hz, 1H), 5,43 (s, 2H), 2,32 (s, 3H), LC/MS columna C-18, $t_r$ = 2,95 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con detección a 254 nm, a 50 °C) IR (puro) 3111, 3067, 3032, 2914, 2840, 2215 (estiramiento del nitrilo), 1678, 1587, 1470 $cm^{-1}$, ES-MS m/z 467 (M+H) ES-HRMS m/z 467,0037 (M+H calculado para $C_{20}H_{12}BrF_4N_2O_2$ requiere 467,0013)

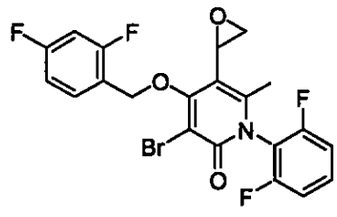
Ejemplo 567




4-(benciloxi)-3-bromo-1-(2,6-difluorofenil)-5-yodo-6-metilpiridin-2(1H)-ona

Etapa 1 Una disolución de 4-(benciloxi)-3-bromo-1-(2,6-difluorofenil)-6-metilpiridina-2(1H)-ona (1,42 g, 3,50 mmol) en 1,2 dicloroetano (18 ml) se trato con N-yodosuccinimida sólida (1,59 g, 7,06 mmol) y ácido dicloroacetico (0,260 g, 2,01 mmol) La disolucion resultante se agitó y se calento a 50 °C durante 2,5 horas hasta la consumición completa del material de inicio por LC/MS En este momento la reacción se diluyo con acetato de etilo (400 ml) y se lavo con sulfito sódico (disolución acuosa al 5%, 100 ml) y salmuera (3 X 200 ml) Los extractos organicos resultantes fueron secados sobre $Na_2SO_4$, filtrados y concentrados *in vacuo* aproximadamente a un volumen de 30 ml El licor madre resultante se precipitó rápidamente y formó un sólido amorfo que fue recolectado y secado a un vacio de 1 mm Hg para proporcionar un solido (1,49 g, 82%) $^1$H NMR (400 MHz, $CDCl_3$) δ 7,62 (aprox d, J = 6,8 Hz, 2H), 7,51-7,38 (m, 4H), 7,09 (aprox t, J = 8,0 Hz, 2H), 5,20 (s, 2H), 2,39 (s, 3H), LC/MS columna C-18, $t_r$ = 3,28 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con deteccion a 254 nm, a 50 °C) ES-MS m/z 532 (M+H) ES-HRMS m/z 531,9196 (M+H calculado para $C_{19}H_{14}BrF_2INO_2$ requiere 531,9215)

Ejemplo 568

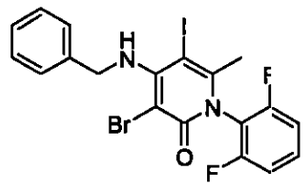



3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorofenil)-6-metil-5-oxiran-2-ilpiridin-2(1H)-ona

Etapa 1 Una muestra de 3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorofenil)-6-metil-5-

vinilpiridin-2(1H)-ona (10,0 mg, 0,0214 mmol) se trato con una disolución de dimetil dioxirano en acetona (aprox 0,1 M, 5 ml, 0,5 mmol) El recipiente de reaccion se tapo y se selló, y la disolucion resultante se agito durante 6,0 horas En este momento, la reaccion se concentro *in vacuo* y el residuo oscuro resultante se sometio a cromatografia sobre $SiO_2$ con acetato de etilo/hexanos (4 6) para generar un semisolido (5,0 mg, 48 %) $^1H$ NMR (400 MHz, $CDCl_3$) δ 7,57 (aprox q, J = 7,4 Hz, 1H), 7,46 (aprox tt, J = 8,5, 6,2, 1H), 7,11 (aprox t, J = 8,0 Hz, 2H), 6,94 (aprox t, J = 8,2 Hz, 1H), 6,83 (aprox t, J = 9,2 Hz, 1H), 5,31 (AB-q, J = 10,9 Hz, □= 29,0 Hz, 2H), 3,63 (aprox t, J = 3,5 Hz, 1H), 3,03 (dd, J = 9,4, 5,0 1H), 2,85 (dd, J = 5,2, 2,7, 1H), 2,14 (s, 3H), LC/MS columna C-18, $t_r$ = 2,26 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con deteccion a 254 nm, a 50 °C) ES-HRMS *m/z* 484 (M+H) y 502 ($M+H_3O$) ES-HRMS m/z 502,0273 ($M+H_3O$ calculado para $C_{21}H_{17}BrF_4NO_4$ requiere 502,0272)

Ejemplo 569

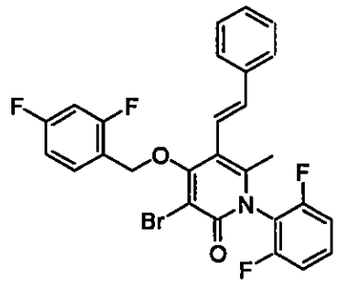


4-(bencilamino)-3-bromo-1-(2,6-difluorofenil)-5-yodo-6-metilpiridin-2(1H)-ona

Etapa 1 Una disolucion de 3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorofenil)-5-yodo-6-metilpiridin-2(1H)-ona (80,0 mg, 0,141 mmol) y bencil amina (300 mg, 2,80 mmol) se calentó a 63 °C y se agito durante 1,0 hora hasta la desaparicion completa del material de inicio por análisis LC/MS Despues la mezcla de reaccion se diluyo con acetato de etilo (300 ml) y se lavo

con salmuera (3 X 200 ml) Los extractos orgánicos resultantes fueron secados sobre $Na_2SO_4$, filtrados y concentrados *in vacuo* a un residuo que después se sometio a cromatografia sobre $SiO_2$ con acetato de etilo/hexanos (3 7) para formar un solido de color marron (60,0 mg, al 81%) $^1H$ NMR (400 MHz, $CDCl_3$) δ 7,43-7,22 (m, 6H), 7,04 (aprox t, J = 8,4 Hz, 2H), 5,02 (br t, J = 1,6 Hz, 1H), 4,86 (d, J = 5,5 Hz, 2H), 2,37 (s, 3H), LC/MS columna C-18, $t_r$ = 3,02 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con deteccion a 254 nm, a 50 °C) ES-MS m/z 531 (M+H) ES-HRMS m/z 530,9344 (M+H calculado para $C_{19}H_{15}BrF_2IN_2O$ requiere 530,9375)

Ejemplo 570



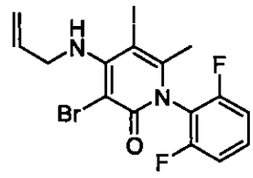

3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorofenil)-6-metil-5-[(E)-2-feniletenil]piridin-2(1H)-ona

Etapa 1 A una disolucion anhidra a -78 °C de □-bromoestireno (1,80 g, 10,0 mmol) en eter (18 ml) se adiciono secuencialmente una disolución de cloruro de zinc (10,0 ml, 1,0 M eter 10,0 mmol) durante 1,0 minuto y una disolucion de litio *terc*-butilico (15,0 ml, 1,6 M pentanos, 24,0 mmol) durante 8,0 minutos La disolución resultante se enturbio y la mezcla de reaccion se dejo entibiar por sí sola a temperatura ambiente (durante 30 minutos) Después de 1 hora adicional, la suspension se transfirio por jeringa directamente a un recipiente separado que contenia

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una disolucion de 3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorofenil)-5-yodo-6-metilpiridin-2(1H)-ona (1,50 g, 2,64 mmol) y tetrakis(trifenilfosfina)paladio (294 mg, 0,254 mmol) en THF anhidro (4 ml) Esta suspension resultante se calento a 55 °C durante 40 minutos y se enfrió a temperatura ambiente, por lo cual se agito bajo una presión de argon positiva durante 4 horas adicionales hasta la desaparicion completa del material de inicio por analisis LC/MS La suspension de reaccion, posteriormente, se trato con $NaHCO_3$ y salmuera (100 y 200 ml), respectivamente) La emulsion resultante se extrajo con acetato de etilo (3 X 300 ml) y los extractos organicos fueron secados sobre $Na_2SO_4$, filtrados y concentrados *in vacuo* hasta lograr un residuo que despues se sometió a cromatografia sobre $SiO_2$ con acetato de etilo/hexanos (3 7) para formar un solido rojizo (1,25 g, al 86%) $^1H$ NMR (400 MHz, $CDCl_3$) δ 7,51-7,39 (m, 2H), 7,38-7,24 (m, 5H), 7,10 (aprox t, J = 8,5 Hz, 2H), 6,84 (d, J = 17,2 Hz, 1H), 6,82-6,75 (m, 1H), 6,74-6,68 (m, 1H), 6,69 (d, J = 17,2, 1H), 5,11 (br s, 2H), 2,15 (s, 3H), LC/MS columna C-18, $t_r$ = 3,74 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con deteccion a 254 nm, a 50 °C) ES-MS m/z 544 (M+H) ES-HRMS m/z 544,0565 (M+H calculado para $C_{27}H_{19}BrF_4NO_2$ requiere 544,0530)

Ejemplo 574



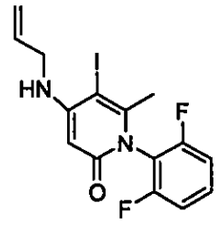

4-(alilamino)-3-bromo-1-(2,6-difluorofenil)-5-yodo-6-metilpiridin-2(1H)-ona

Etapa 1 Una disolución de 3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorofenil)-5-yodo-6-

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metilpiridin-2(1H)-ona (1,40 g, 2,46 mmol) y alil amina (1,98 mg, 34,6 mmol) se calento a 50 °C y se agitó durante 1,0 hora hasta la desaparición completa del material de inicio por análisis LC/MS La mezcla de reaccion despues se concentro *in vacuo* (1,0 mm Hg) durante 2 dias a 50 °C para formar un solido de color marron (1,18 g, al 99%) $^1$H NMR (300 MHz, $CDCl_3$) δ 7,43 (aprox tt, J = 8,4, 6,2, 1H), 7,09 (aprox t, J = 8,4 Hz, 2H), 6,02 (aprox dq, J = 11,0, 6,2 Hz, 1H), 5,39 (dd, J = 16,9, 1,8 Hz, 1H), 5,30 (dd, J = 11,0, 1,8 Hz, 1H), 4,84 (br s, 1H), 4,35 (br s, 2H), 2,42 (s, 3H), IC/MS columna C-18, $t_r$ = 2,71 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con deteccion a 254 nm, a 50 °C) ES-MS m/z 481 (M+H) ES-HRMS m/z 480,9261 (M+H calculado para $C_{15}H_{13}BrF_2IN_2O$ requiere 480,9219)

Ejemplo 575

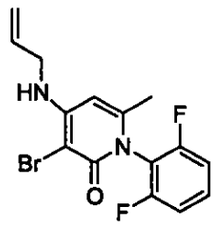



4-(alilamino)-1-(2,6-difluorofenil)-5-yodo-6-metilpiridin-2(1H)-ona

Etapa 1 Una disolucion de 4-(alilamino)-3-bromo-1-[(2,6-difluorofenil)-5-yodo-6-metilpiridin-2(1H)-ona (1,00 g, 2,07 mmol) y tetrakis(trifenilfosfina)paladio (420 mg, 0,363 mmol) en THF anhidro (10 ml) bajo una corriente de argon se calento a 64 °C y se agito durante 12 horas hasta la desaparición completa del material de inicio por analisis LC/MS La suspension de reaccion posteriormente se trato con salmuera (600 ml) La emulsion resultante se extrajo con acetato de etilo (3 X 400 ml) y los extractos orgánicos fueron secados sobre $Na_2SO_4$ anhidro, filtrados y

concentrados *in vacuo* a un residuo que después se sometio a cromatografia sobre $SiO_2$ con acetato de etilo/hexanos (gradiente 3 7) para formar un sólido (376 mg, al 45%) $^1H$ NMR (400 MHz, $d_4$-MeOH) δ 7,55 (aprox tt, J = 8,7, 6,3 1H), 7,18 (aprox t, J = 7,6 Hz, 2H), 5,89 (aprox ddd, J = 15,4, 10,3, 5,1 Hz, 1H), 5,01 (aprox d, J = 17,0 Hz, 1H), 5,50 (s, 1H), 5,22 (aprox d, J = 11,0 Hz, 1H), 4,35 (aprox d, J = 5,0 Hz, 2H), 2,36 (s, 3H), LC/MS columna C-18, $t_r$ = 2,33 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con detección a 254 nm, a 50 °C) ES-MS m/z 403 (M+H) ES-HRMS m/z 403,0133 (M+H calculado para $C_{15}H_{14}F_2IN_2O$ requiere 403,0113)

Ejemplo 576



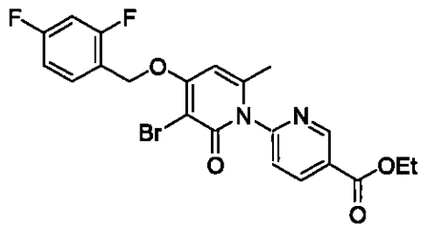

4-(alilamino)-1-(2,6-difluorofenil)-5-yodo-6-metilpiridin-2(1H)-ona

Etapa 1 Una disolución de 3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorofenil)-6-metilpiridin-2(1H)- ona (197 mg, 0,445 mmol) y alil amina (1,32 mg, 23,1 mmol) en THF (6,0 ml) se calento a 68 °C y se agito durante 74,0 horas La mezcla de reacción después se concentro *in vacuo* (30 mm Hg) para formar un residuo que se sometio a cromatografia sobre $SiO_2$ con acetato de etilo/hexanos (3 7) para formar un solido (36,0 mg, al 23%) $^1H$ NMR (400 MHz, $d_4$-MeOH) δ 7,55 (aprox tt, J = 8,5, 6,5 1H), 7,18 (aprox t, J = 8,5 Hz, 2H), 6,14 (s, 1H), 5,91(aprox dq, J = 11,5, 6 4 Hz, 1H), 5,23 (dd, J = 17,0, 1,5 Hz, 1H), 5,19 (dd, J = 11,0, 1,6 Hz, 1H), 4,00

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(aprox d, J = 4,7 Hz, 2H), 1,98 (s, 3H), LC/MS columna C-18, $t_r$ = 2,24 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con deteccion a 254 nm, a 50 °C) ES-MS m/z 355 (M+H) ES-HRMS m/z 355,0257 (M+H calculado para $C_{15}H_{14}F_2BrF_2N_2O$ requiere 355,0252)

Ejemplo 577

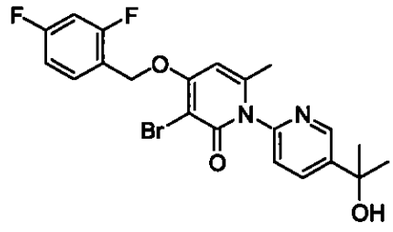



3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxo-2H-1,2'-bipiridina-5'-carboxilato de etilo

Etapa 1 A una suspension de 3-bromo-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona a temperatura ambiente (500,0 mg, 1,51 mmol) y $Cs_2CO_3$ (1,50 g, 4,60 mmol) en 1-metil-2-pirrolidinona (3,0 ml) se adiciono 6-cloronicotinato de etilo (900 mg, 4,85 mmol) La suspension resultante se agito y se calento a 106 °C durante 36 horas hasta la consumicion completa del material de inicio por análisis LC/MS Después la mezcla de reaccion se diluyó con acetato de etilo (400 ml) y se lavo con agua (3 X 200 ml) El extracto organico resultante se separo, se seco sobre $Na_2SO_4$ y se concentró El residuo de color oscuro resultante se sometio a cromatografia sobre $SiO_2$ con acetato de etilo/hexanos (3 7) para generar un solido $^1H$ NMR (400 MHz, $d_4$-MeOH) δ 8,68 (aprox d, J =2,5 Hz, 1H), 8,39 (dd, J = 8,7, 2,3 Hz, 1H), 7,62 (aprox q, J = 8,2 Hz, 1H), 7,15 (d, J = 8,6 Hz, 1H), 7,08-6,99 (m, 2H), 5,31 (s, 2H), 4,37 (q, J = 7,1 Hz, 2H), 2,43 (s, 3H), 1,37 (t, J = 7,1 Hz, 3H), LC/MS columna C-18, $t_r$ = 3,44 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con deteccion de 254 nm, a 50 °C) ES-MS m/z 479 (M+H)

ES-HRMS m/z 479,040_ (M+H calculado para $C_{21}H_{18}BrF_2N_2O_4$ requiere 479,0431)

Ejemplo 578



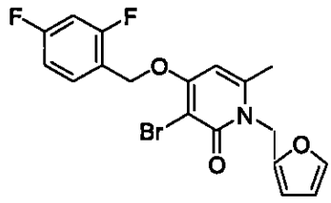
3-bromo-4-[(2,4-difluorobencil)oxi]-5'-(1-hidroxi-1-metiletil)-6-metil-2H-1,2'-bipiridin-2-ona

Etapa 1 A una disolucion de bromuro de metil magnesio a 0 °C (3,0 M, 3,5 ml, 10,5 mmol) se agrego gota a gota durante 15 minutos una disolucion de 3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxo-2H-1,2'-bipiridina-5'-carboxilato de metilo (500,0 mg, 1,05 mmol) en THF (4,0 ml) Nunca se permitió que la temperatura interna de la reaccion superara los 0 °C La disolución resultante se mantuvo durante 30 minutos hasta la consumicion completa del material de inicio por análisis LC/MS A continuacion, se agrego una disolución de cloruro de amonio (acuosa saturada, 160 ml) La mezcla de reaccion se extrajo con acetato de etilo (3 X 100 ml) y los extractos organicos resultantes fueron separados, secados sobre $Na_2SO_4$ y concentrados *in vacuo* hasta lograr un residuo que se sometió a cromatografia sobre $SiO_2$ con acetato de etilo/hexanos (gradiente 3 7 a 6 4) para formar un solido (386 mg, al 79%) $^1H$ NMR (400 MHz, $d_4$-MeOH) δ 8,23 (aprox d, J = 2,8 Hz, 1H), 7,97 (dd, J = 8,6, 2,3 Hz, 1H), 7,61 (aprox q, J = 8,2 Hz, 1H),7,06-7,00 (m, 3H), 7,00 (s, 1H), 5,30(s, 2H), 2,38 (s 3H), 1,54 (s, 6H), LC/MS columna C-18, $t_r$ = 2,75 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con detección a 254 nm, a 50 °C) ES-MS *m/z* 465 (M+H) ES-HRMS m/z 465,0615 (M+H calculado

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para $C_{21}H_{20}BrF_2N_2O_3$ requiere 465,0620) IR(puro) 3366, 3030, 2974, 1600, 1507, 1362, 1232 cm $^{-1}$ $^{13}C$ NMR (400 MHz, $d_4$-MeOH, picos visibles con presencia de fluoruro de carbono) δ 164,4, 160,7, 158,9, 157,6, 143,6, 141,6, 137,5, 131,61, 131,56, 131,51, 131,46, 119,29, 119,25, 119,15, 119,11, 112,23, 111,55, 111,52, 111,33, 111,29, 106,0, 103,9, 103,7, 103,4, 96,8, 70,3, 64,9, 64,8, 30,5, 22,6

Ejemplo 579



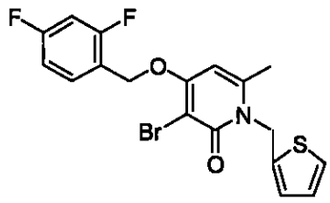

3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2-(furilmetil)-6-metilpiridin-2(1H)-ona

Etapa 1 Preparacion del compuesto del titulo A una suspension de 3-bromo-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona a temperatura ambiente (330,0 mg, 1,00 mmol) y NaH (48,0 mg, 2,00 mmol) en THF (3,0 ml) se adicionó 2-(clorometil)furano (461 mg, 3,97 mmol) La suspensión resultante se agito y se calento a 68 °C durante 9 horas hasta la consumicion completa del material de inicio por analisis LC/MS Despues la mezcla de reaccion se diluyo con acetato de etilo (400 ml) y se lavo con agua (3 X 200 ml) El extracto orgánico resultante se separó, se seco sobre $Na_2SO_4$ y se concentro El residuo de color oscuro resultante se sometio a cromatografia sobre $SiO_2$ con acetato de etilo/hexanos (4 6) para generar un solido $^1H$ NMR (300 MHz, $d_4$-MeOH) δ 7,62 (aprox q, J = 8,4 Hz, 1H), 7,46 (s, 1H), 7,06 (aprox t, J = 8,7 Hz, 2H), 6,51 (s, 1H), 6,41-6,37 (m, 2H), 5,37 (s, 2H), 5,32 (s, 2H), 2,61 (s, 3H), LC/MS columna C-18, $t_r$ = 2,63 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min

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con deteccion a 254 nm, a 50 °C) ES-MS *m/z* 410 (M+H) ES-HRMS m/z 410,0177 (M+H calculado para $C_{18}H_{15}BrF_2NO_3$ requiere 410,0198)

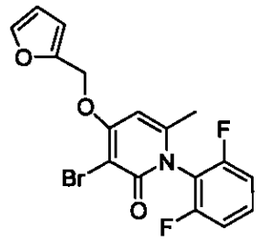
Ejemplo 580



3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-(tien-2-ilmetil)piridin-2(1H)-ona

Etapa 1 A una suspensión de 3-bromo-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona a temperatura ambiente (330,0 mg, 1,00 mmol) y NaH (48,0 mg, 2,00 mmol) en THF (3,0 ml) se adicionó 2-(clorometil)tiofeno (461 mg, 3,97 mmol) La suspensión resultante se agito y se calento a 68 °C durante 12 horas hasta la consumicion completa del material de inicio por análisis LC/MS Después la mezcla de reaccion se diluyo con acetato de etilo (400 ml) y se lavo con agua (3 X 200 ml) El extracto organico resultante se separó, se seco sobre $Na_2SO_4$ y se concentro El residuo de color oscuro resultante se sometio a cromatografia sobre $SiO_2$ con acetato de etilo/hexanos (4 6) para generar un solido $^1H$ NMR (400 MHz, $d_4$-MeOH) δ 7,58 (aprox q, J = 8,2 Hz, 1H), 7,30 (aprox dd, J = 5,1, 1,2 Hz, 1H), 7,05 (d, J = 2,6 Hz, 1H), 7,01 (aprox t, J = 8,1 Hz, 2H), 6,93 (dd, J = 5,1, 3,4 Hz, 1H), 6,43 (s, 1H), 5,49 (s, 2H), 5,25 (s, 2H), 2,51 (s, 3H), LC/MS columna C-18, $t_r$ = 2,74 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con detección a 254 nm, a 50 °C) ES-MS *m/z* 426 (M+H) ES-HRMS m/z 425,9936 (M+H calculado para $C_{18}H_{15}BrF_2NO_2S$ requiere 425,9969)

Ejemplo 581

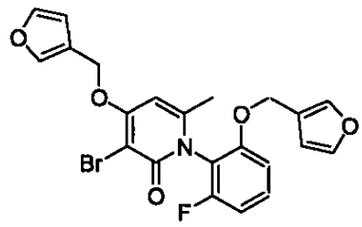


3-bromo-1-[2,6-(difluorofenil)-4-(2-furilmetoxi)-6-metilpiridin-2(1H)-ona

Etapa 1 A una suspensión de 3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorofenil)-6-metilpiridin-2(1H)- ona (250 mg, 0,445 mmol) y alcohol furfurílico (198 mg, 2,0 mmol) en THF (2,5 ml) se adicionó NaH solido (46,0 mg, 1,92 mmol) Después de la evolucion del gas, la suspension resultante se calento a 60 °C y se agitó durante 3,5 horas hasta la consumicion completa del material de inicio por análisis LC/MS Despues la mezcla de reaccion se diluyo con cloruro de amonio (acuoso saturado, 100 ml) y se extrajo con acetato de etilo (3 X 100 ml) Los extractos organicos resultantes fueron separados, secados sobre $Na_2SO_4$ y concentrados para proporcionar un residuo que se sometio a cromatografia sobre $SiO_2$ con acetato de etilo/hexanos (3 7) para formar un solido (110,0 mg, al 49%) $^1H$ NMR (400 MHz, $d_4$-MeOH) δ 7,63 (aprox tt, J = 8,5, 6,2, 1H), 7,62-7,61 (m, 1H), 7,28 (aprox t, J = 8,5 Hz, 2H), 6,77 (s, 1H), 6,68 (d, J = 4,1 Hz, 1H), 6,51(dd, J = 4,2, 3,9 Hz, 1H), 5,34 (s, 2H), 2,15 (s, 3H), LC/MS columna C-18, $t_r$ = 2,43 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con deteccion a 254 nm, a 50°C) ES-MS *m/z* 396 (M+H) ES-HRMS m/z 396,0044 (M+H calculado para $C_{17}H_{13}BrF_2NO_3$ requiere 396,0041)

Ejemplo 582

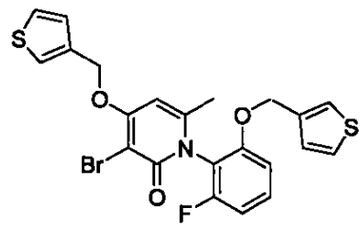
1252
1253



3-bromo-1-[2-fluoro-6-(3-furilmetoxi)fenil]-4-(3-furilmetoxi)-6-metilpiridin-2(1H)-ona

Siguiendo el metodo de preparacion de 3-bromo-1-(2,6-difluorofenil)-4-(2-furilmetoxi)-6-metilpiridin-2(1H)-ona (Ejemplo 581) y sustituyendo alcohol furfurilico por 3-furilmetanol, el compuesto del titulo se preparo con un rendimiento quimico del 55% $^1$H NMR (400 MHz, $d_4$-MeOH) δ 7,64 (s, 1H), 7,55-7,42 (m, 3H), 7,40 (aprox t, J = 1,4 Hz, 1H), 7,12 (d, J = 9,0 Hz, 1H), 6,92 (aprox t, J = 8,4 Hz, 2H), 6,58 (s, 2H), 6,34 (br s, 1H), 5,21 (s, 2H), 5,03 (AB-q, J = 14,0 Hz, □= 58,0 Hz, 2H), 1,99 (s, 3H), LC/MS columna C-18, $t_r$ = 2,67 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con deteccion a 254 nm, a 50 °C) ES-MS *m/z* 474 (M+H) ES-HRMS m/z 474,0346 (M+H calculado para $C_{22}H_{18}BrFNO_5$ requiere 474,0347)

Ejemplo 583

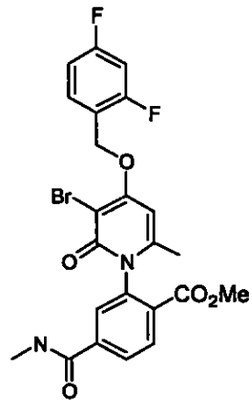


3-bromo-1-[2-fluoro-6-(tien-3-ilmetoxi)fenil]-6-metil-4-(tien-3-ilmetoxi)piridin-2(1H)-ona

Siguiendo el metodo de preparacion de 3-bromo-1-(2,6-difluorofenil)-4-(2-furilmetoxi)-6-metilpiridin-2(1H)-ona (Ejemplo 581) y sust tuyendo alcohol furfurilico por tien-3-ilmetanol, el compuesto del titulo se preparo con un

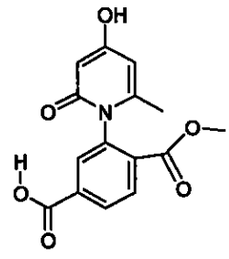
rendimiento químico del 38 % $^1$H NMR (400 MHz, $d_4$-MeOH) δ 7,50 (m, 3H), 7,33 (dd, J = 5,0, 3,0 Hz, 1H), 7,26 (br d, J = 2,0 Hz, 1H), 7,19 (dd, J = 5,0, 1,2 Hz, 1H), 7,09 (d, J = 8,6 Hz, 1H), 6,98 (dd, J = 14,9, 1,3 Hz, 1H), 6,93 (dt, J = 8,7, 1,0 Hz, 1H), 6,53 (br s, 1H), 5,33 (s, 2H), 5,14 (AB-q, J = 12,1 Hz, □= 50,0 Hz, 2H), 1,97 (s, 3H), LC/MS columna C-18, $t_r$ = 2,93 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con detección a 254 nm, a 50 °C) ES-MS *m/z* 506 (M+H) ES-HRMS m/z 505,9881 (M+H calculado para $C_{22}H_{18}BrFNO_3S_2$ requiere 505,9890)

Ejemplo 584




2-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-[(metilamino)carbonil]benzoato de metilo

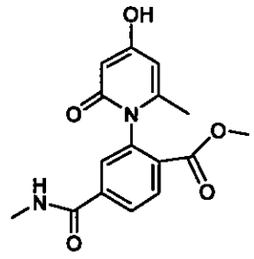
Etapa 1 Preparacion de acido 3-(4-hidroxi-6-metil-2-oxopiridin-1(2H)-il)-4-(metoxicarbonil)benzoico




Se suspendieron 4-hidroxi-6-metil-2-pirona (75,0 g, 595 mmol) y acido 3-amino-4-(metoxicarbonil)benzoico (40,0

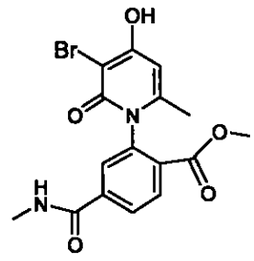
g, 0,205 mmol) en 56 ml de 1,2-diclorobenceno en un matraz de fondo redondo, de tres cuellos de 500 ml, equipado con una sonda controladora de temperatura J-Kem, una trampa Dean-Stark y un manto calentador La reaccion se calento a 180 °C durante un periodo de 26 minutos tiempo durante el cual se disolvieron los solidos Al alcanzar una temperatura interna de 180 °C, se dejó que la reaccion conservara esta termperatura durante 25,0 minutos adicionales tiempo durante el cual la evolucion del agua desde la mezcla de reaccion resulto evidente A continuacion, el aparato para calentamiento se retiró y se dejó que la reacción se enfriara por si sola aproximadamente a 100 °C Después la reacción se diluyo con 160 ml de tolueno y se agitó Despues de alrededor de 10 minutos, la reacción alcanzo la temperatura ambiente y se había formado un solido gomoso El precipitado se filtro, se lavo con EtOAc (400 ml) y agua (200 ml, 55 °C) y se secó *in vacuo* para proporcionar un solido de color tostado (30,5 g, 49%) $^1$H NMR (400 MHz, $d_4$-MeOH) δ 8,20-8,09 (m, 2H), 7,84 (s, 1H), 6,08 (aprox d, J = 1,0 Hz, 1H), 5,76 (aprox d, J = 2,3 Hz, 1H), 3,76 (s, 3H), 1,91 (s, 3H) LC/MS, columna C-18, $t_r$ = 1,96 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con detección a 254 nm, a 50 °C) ES-MS *m/z* 304 (M+H) ES-HRMS m/z 304,0803 (M+H calculado para $C_{15}H_{14}NO_6$ requiere 304,0816)

Etapa 2 Preparación de 2-(4-hidroxi-6-metil-2-oxopiridin-1(2H)-il)-4-[(metilamino)carbonil]benzoato de metilo



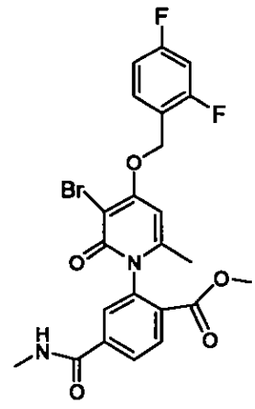
A una disolucion de acido 3-(4-hidroxi-6-metil-2-oxopiridin-1(2H)-il)-4-(metoxicarbonil)benzoico ( de la etapa 1) (1,00 g, 3,30 mmol) en dimetilformamida (10 ml) y THF (10 ml) se agregó gel de silice derivado de ciclohexilcarbodiimida (un producto de la division quimica de Silicycle, Quebec, Canadá) con una carga de 0,60 mmol/g (15,2 g, 9,73 mmol) Después de 30 minutos de agitacion, se agrego una disolución de metilamina (2,9 M, THF, 2,9 ml, 5,8 mmol) seguida por la adicion de 1-hidroxi-benzotriazol (20,0 mg, 0,15 mmol) La suspensión de reaccion se agito durante 24 horas hasta la desaparicion completa del material de inicio por analisis LC/MS La suspension de silice se filtro y se lavó con 300 ml de acetato de etilo/metanol (9 1) y 300 ml de acetato de etilo/metanol (1 1) El licor madre resultante se concentro para formar un semisolido de color marron (898 mg, al 86 %) $^1$H NMR (300 MHz, $d_4$-MeOH) δ 8,22 (d, J = 8,0 Hz, 1H), 8,04 (dd, J = 8,3, 1,9 Hz, 1H), 7,73 (d, J = 1,6 Hz, 1H), 6,13 (d, J = 1,5, Hz, 1H), 5,80 (d, J = 2,2 Hz, 1H), 3,80 (s, 3H), 3,03 (s, 3H), 1,97 (s, 3H) LC/MS, columna C-18, $t_r$ = 1,31 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con deteccion a 254 nm, a 50 °C) ES-MS *m/z* 317 (M+H) ES-HRMS m/z 317,1142 (M+H calculado para $C_{16}H_{17}N_2O_5$ requiere 317,1132)

Etapa 3 Preparacion de 2-(3-bromo-4-hidroxi-6-metil-2-oxopiridin-1(2H)-il)-4-[(metilamino)carbonil]benzoato de metilo



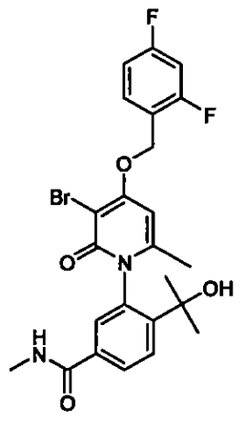
A una suspension de 2-(4-hidroxi-6-metil-2-oxopiridin-1(2H)-il)-4- [(metilamino)carbonil]benzoato de metilo a temperatura ambiente ( de la etapa 2) (406,0 mg, 1,28 mmol) en $CH_2Cl_2$ (8 ml) se agrego N-bromosuccinimida solida (251 mg, 1,41 mmol) y se agito durante 10 minutos hasta la consumición completa del material de inicio por análisis LC/MS La reaccion después se diluyo con $CH_2Cl_2$ (5 ml), acetato de etilo (5 ml) y hexanos (1 ml) Aproximadamente despues de 30 minutos, el precipitado blanco resultante se filtro y se lavo con acetato de etilo (5 ml) para formar un sólido (298 mg, al 62%) $^1$H NMR (400 MHz, $d_4$-MeOH) δ 8,20 (d, J = 8,2 Hz, 1H), 8,01 (d, J = 8,1 Hz, 1H), 7,69 (s, 1H), 6,18 (s 1H), 3,75 (s, 3H), 2,91 (s, 3H), 1,91 (s, 3H), LC/MS, $t_r$ = 1,27 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con deteccion a 254 nm, a 50°C) ES-MS *m/z* 395 (M+H) ES-HRMS m/z 395,0237 (M+H calculado para $C_{16}H_{16}BrN_2O_5$ requiere 395,0237)

Etapa 4 Preparacion del compuesto del titulo



A una disolucion de 2-(3-bromo-4-hidroxi-6-metil-2-oxopiridin-1(2H)-il)-4-[(metilamino)carbonil]benzoato de metilo ( de la etapa 3) (241 mg, 0,610 mmol) en dimetilformamida (0,5 ml) se agrego secuencialmente $K_2CO_3$ (240 mg, 1,73 mmol) y 2,4 bromuro de difluorobencilo (0,085 ml, 0,66 mmol) La suspension resultante se agito durante 6,5 horas hasta la consumicion completa del material de inicio por analisis LC/MS Después la reaccion se diluyo con acetato de etilo (200 ml) y se lavo con salmuera (3 X 200 ml) El extracto organico resultante fue secado sobre $Na_2SO_4$, filtrado y concentrado *in vacuo* aproximadamente a un volumen de 5 ml El licor madre resultante se precipitó rapidamente y formó un solido amorfo que fue recolectado $^1$H NMR (400 MHz, $d_4$-MeOH) δ 8,22 (d, J = 8,2 Hz, 1H), 8,03 (dd, J = 8,2, 1,7 Hz 1H), 7,71 (d, J = 1,8 Hz, 1H), 7,67 (aprox q, J = 8,3, Hz, 1H), 7,05 (aprox t, J = 8,6 Hz, 2H), 6,64 (s, 1H), 5,37 (s, 2H), 3,74 (s, 3H), 2,90 (s, 3H), 2,01 (s, 3H) LC/MS, columna C-18, $t_r$ = 2,87 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con detección a 254 nm, a 50 °C) ES-MS *m/z* 521 (M+H) ES-HRMS m/z 521,0491 (M+H calculado para $C_{23}H_{20}BrF_2N_2O_5$ requiere 521,0518)

Ejemplo 585

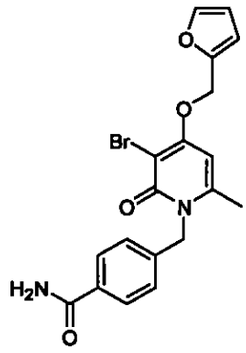


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1291

3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-(1-hidroxi-1-metiletil)-N-metilbenzamida

Etapa 1 A una disolucion de bromuro de metil magnesio a -10 °C (3,0 M, 0,60 ml, 1,8 mmol) se agregó gota a gota durante 10 minutos una disolución 2-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-[(metilamino)carbonil]benzoato de metilo (85,0 mg, 0,163 mmol) en THF (1,0 ml) Nunca se permitió que la temperatura interna de la reacción superara los 0 °C La disolución resultante se mantuvo durante 10 minutos A continuacion, se agregó una disolucion de cloruro de amonio (acuosa saturada, 100 ml) La mezcla de reaccion se quitó del baño y la emulsion resultante se extrajo con acetato de etilo (3 X 100 ml) y los extractos organicos resultantes fueron separados, secados sobre $Na_2SO_4$ y concentrados *in vacuo* hasta lograr un residuo que se sometió a cromatografia sobre $SiO_2$ con acetato de etilo/hexanos (gradiente 3 7 a 6 4) para formar un solido (16 mg, al 19%) $^1H$ NMR (400 MHz, $d_4$-MeOH) δ 7,89 (d, J = 8,5 Hz, 1H), 7,78 (d, J = 8,4, Hz, 1H), 7,61 (aprox q, J = 8,2 Hz, 1H),7,41 (s, 1H), 7,03-6,99 (m, 2H), 6,57 (s, 1H), 5,30 (s, 2H), 2,83 (s, 3H), 2,05 (s, 3H), 1,51 (s, 3H), 1,39 (s, 3H), LC/MS columna C-18, $t_r$ = 2,28 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con deteccion a 254 nm, a 50 °C) ES-MS *m/z* 521 (M+H) ES-HRMS m/z 521,0860 (M+H calculado para $C_{24}H_{24}BrF_2N_2O_4$ requiere 521,0882)

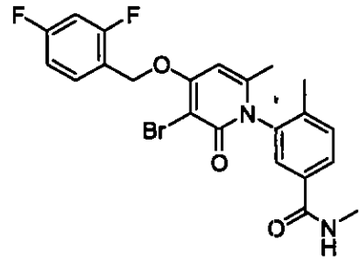
Ejemplo 586



3-bromo-1-[2-fluoro-6-(tien-3-ilmetoxi)fenil]-6-metil-4-(tien-3-ilmetoxi)piridin-2(1H)-ona

Siguiendo el metodo de preparación de 3-bromo-1-(2,6-difluorofenil)-4-(2-furilmetoxi)-6-metilpiridin-2(1H)-ona Example 581 y sustituyendo 3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorofenil)-6-metilpiridin-2(1H)- ona por 4-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)- il]metil}benzamida , se preparó el compuesto del titulo con un rendimiento quimico del 76 % $^1$H NMR (400 MHz, $d_4$-MeOH) δ 7,83 (d, J = 8,1 Hz, 2H), 7,54 (aprox d, J = 1,1 Hz, 1H), 7,19 (d, J = 8,1 Hz, 2H), 6,57 (d, J = 3,2 Hz, 1H), 6,53 (s, 1H), 6,43 (dd, J = 3,1, 1,8 Hz, 1H), 5,45 (br s, 2H), 5,22 (s, 2H), 2,34 (s, 3H), LC/MS columna C-18, $t_r$ = 1,98 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con deteccion a 254 nm, a 50 °C) ES-MS *m/z* 417 (M+H) ES-HRMS *m/z* 417,0469 (M+H calculado para $C_{19}H_{18}BrN_2O_4$ requiere 417,0444)

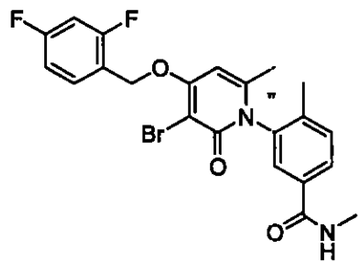
Ejemplo 587



(-)-3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-N,4-dimetilbenzamida

Ejemplo 489 (1,78 g, 4,36 mmol) se separaron usando una columna AD de Chiral Technologies Chiralpak (21 mm x 250 mm, 20 µm) con elusión con etanol al 100% (isocratico, 20 ml/min), y una carga de 10 mg por inyección Fracciones del atropoisomero de elusión temprana se acumularon y concentraron *in vacuo* al compuesto del titulo (718 mg, al 80%) LC quiral analitica (Chiralpak AD, 4,6 mm x 50 mm, tamaño de particulas 10µm, 0,5 ml/min etanol) Tiempo de retencion 1,70 min, ee 94% [□□$_D$ = -23,8° (5 mg/ml DMSO, 22 °C) $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8,42 (br qr, J = 4,51 Hz, 1H), 7,82 (dd, J = 7,92, 1,70 Hz, 1H), 7,68 (dt, J = 8,24, 6,58 Hz, 1H), 7,58 (d, J = 1,59 Hz, 1H), 7,48 (d, J = 7,98 Hz, 1H), 7,34 (dt, J = 9,90, 2,50 Hz, 1H), 7,18 (dt, J = 8,53, 2,57 Hz, 1H), 6,71 (s, 1H), 5,33 (s, 2H), 2,74 (s, 3H), 1,98 (s, 3H), 1,88 (s, 3H) $^{19}$F-NMR (400 MHz, DMSO-$d_6$) δ -109,58 (quinteto, *J* = 7,49 Hz, 1F), -113,65 (cuarteto, J = 9,11 Hz, 1F) ES-HRMS m/z 477,0612 (M+H calculado para $C_{22}H_{20}BrF_2N_2O_3$ requiere 477,0620)

Ejemplo 588

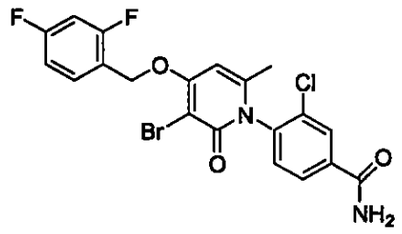



(+)-3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-N,4-dimetilbenzamida

El compuesto del titulo se preparo como en el Ejemplo 587 , y se acumulo el atropisómero de elusion tardia (722 mg, al 81%) LC quiral analitica (Chiralpak AD, 4,6 mm x 50 mm, tamaño de particulas 10µm, 0,5 ml/min etanol) Tiempo

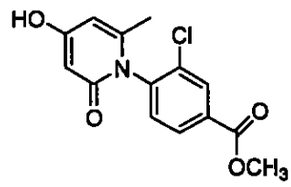
de retención 2,00 min, ee 98% [□□]$_D$ = +28,2° (5 mg/ml DMSO, 22 °C) $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8,42 (br qr, J = 4,51 Hz, 1H), 7,82 (dd, J = 7,92, 1,70 Hz, 1H), 7,68 (dt, J = 8,24, 6,58 Hz, 1H), 7,58 (d, J = 1,59 Hz, 1H), 7,48 (d, J = 7,98 Hz, 1H), 7,34 (dt, J = 9,90, 2,50 Hz, 1H), 7,18 (dt, J = 8,53, 2,57 Hz, 1H), 6,71 (s, 1H), 5,33 (s, 2H), 2,74 (s, 3H), 1,98 (s, 3H), 1,88 (s, 3H) $^{19}$F-NMR (400 MHz, DMSO-$d_6$) δ -109,58 (quinteto, $J$ = 7,49 Hz, 1F), -113,65 (cuarteto, J = 9,11 Hz, 1F) ES-HRMS m/z 477,0614 (M+H calculado para $C_{22}H_{20}BrF_2N_2O_3$ requiere 477,0620)

Ejemplo 589




4-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-3-clorobenzamida

Etapa 1 Preparación de 3-cloro-4-(4-hidroxi-6-metil-2-oxopiridin-1(2H)-il)benzoato de metilo

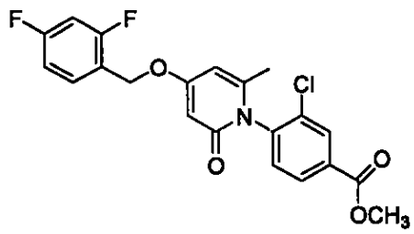



Se suspendieron 4-hidroxi-6-metil-2-pirona (24,5 g, 193,9 mmol) y metil 3-amino-2-clorobenzoato (30 g, 161,6 mmol) en 75 ml de 1,2-diclorobenceno en un matraz de fondo redondo, de tres cuellos de 250 ml, equipado con una sonda controladora de temperatura J-Kem, una trampa Dean-Stark y un manto calentador La reacción se calento a 175 °C durante 20 minutos, durante los cuales se recogio agua y una cantidad de 1,2-diclorobenceno en la trampa Dean-Stark

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Se permitio que la reacción se enfriara hasta aproximadamente 110 °C En este punto, se agregaron 200 ml de tolueno La mezcla de tolueno se agito durante 72 horas a temperatura ambiente Se recolecto un precipitado en una almohadilla de filtro El precipitado se filtró y se lavo 3 veces con tolueno, 3 veces con agua a 50 °C para eliminar el exceso de pirona y se seco *in vacuo* para proporcionar un sólido de color tostado (13,0 g, rendimiento 27%) $^1$H NMR (300 MHz, $CD_3OD$) δ 8,26 (d, J = 1,81 Hz, 1H), 8,14 (dd, J = 8,26, 1,81 Hz, 1H), 7,54 (d, J = 8,26, Hz, 1H), 6,14 (deJ591-DM1, J = 2,42, 1,0 Hz, 1H), 5,83 (d, J = 2,42 1H), 4,00 (s, 3H), 1,96 (s, 3H), LC/MS, $t_r$ = 1,81 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con deteccion a 254 nm, a 50°C) ES-MS *m/z* 294 (M+H)

Etapa 2 Preparacion de 3-cloro-4-[4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]benzoato de metilo

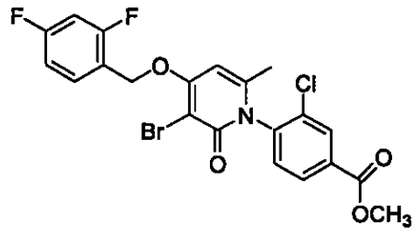



El 3-cloro-4-(4-hidroxi-6-metil-2-oxopiridin-1(2H)-il)benzoato de metilo ( de la etapa 1) (2,4g, 8,17 mmol) fue absorbido en DMF (10 ml) Se agregaron 2,4-difluorobencilbromuro (1,05 ml, 8,17 mmol) y $K_2CO_3$ (1,13 g, 8,17 mmol) La mezcla de reaccion se agitó durante 6 horas a temperatura ambiente En este momento, la reaccion se vertió en agua (200 ml) y se extrajo con acetato de etilo La capa de acetato de etilo se seco sobre $Na_2SO_4$, se filtró y el disolvente se eliminó *in vacuo* para proporcionar aceite de ámbar (2,63 g, rendimiento bruto 77%) LC/MS, $t_r$

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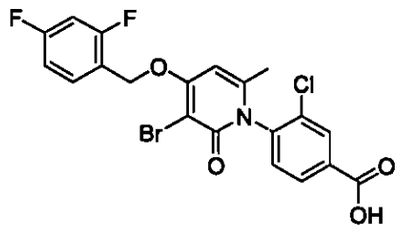
= 2,79 minutos (acetonitrilo/agua al 5 a 95% a lo largo de 5 minutos a 1 ml/min con detección a 254 nm, a 50°C) ES-MS *m/z* 294 (M+H)

Etapa 3 Preparacion de 4-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-3-clorobenzoato de metilo



El 3-cloro-4-[4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]benzoato de metilo ( de la etapa 2) (2,60g, 6,21 mmol) fue absorbido en $CH_2Cl_2$ (20 ml) Se agrego N-bromosuccinimida (1,11g, 6,21 mmol) y se agito la mezcla a temperatura ambiente durante 4 horas El $CH_2Cl_2$ se eliminó *in vacuo* y el residuo se absorbio en $CH_3CN$ El precipitado resultante se recolecto sobre una almohadilla de filtro y se lavó con $CH_3CN$ para proporcionar un solido de color blanco (0,75 g, 24%) $^1H$ NMR (300 MHz, $CDCl_3$) δ 8,22 (d, J = 1,88 Hz, 1H), 8,06 (dd, J = 8,19, 1,75 Hz, 1H), 7,59 (aprox q, J = 8,46 Hz, 1H), 7,33 (d, J = 8,19, 1H), 6,96 (dt, J = 8,06, 1,21 Hz, 1H), 6,89 - 6,84 (m, 1H), 6,13 (s, 1H), 5,26 (s, 2H), 3,95 (s, 3H), 1,95 (s, 3H), ES-MS m/z 478 (M+H) ES-HRMS m/z 497,9892 (M+H calculado para $C_{22}H_{16}BrClF_2NO_4$ requiere 497,9914)

Etapa 4 Preparacion de acido 4-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-3-clorobenzoico

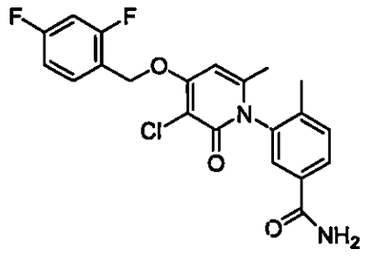


El 4-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-3-clorobenzoato de metilo (2,30g, 4,61 mmol) fue absorbido en THF (20 ml) y $H_2O$ (4 ml) Se agrego 2,5 N NAOH (9,2 ml) al recipiente y la reaccion se agito durante toda la noche hasta completarse Se agrego HCl concentrado gota a gota hasta que la reacción se convirtio en acidogena (pH = 1) Se agregaron $H_2O$ (100 ml) y THF (100 ml) a la mezcla Los contenidos se vertieron en un embudo separador y la capa acuosa se extrajo con acetato de etilo La capa organica se secó sobre $Na_2SO_4$, el disolvente se elimino *in vacuo* y el residuo se absorbio en una mezcla al 50% de acetato de etilo/hexano El precipitado se recolectó sobre una almohadilla de filtro para proporcionar un polvo blanco (1,5 g, al 67%) $^1H$ NMR (300 MHz, DMSO) δ 13,59 (1H), 8,16 (d, J = 1,81 Hz, 1H), 8,06 (dd, J = 6,24, 1,81 Hz, 1H), 7,73 (aprox q, J = 8,46, 1H), 7,68 (d, J = 8,26 Hz, 1H), 7,38 (dt, J = 9,48, 2,62 Hz, 1H), 7,26-7,18 (m, 1H), 6,80 (s, 1H), 5,39 (s, 2H), 3,93 (s, 3H), 1,96 (s, 3H), ES-MS m/z 483 (M+H) ES-HRMS m/z 483,9749 (M+H calculado para $C_{20}H_{14}BrClF_2NO_4$ requiere 483,9757)

Etapa 5 El acido 4-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-3-clorobenzoico (0,5 g, 1,03 mmol) fue absorbido en THF (10 ml) Se agregaron 2-cloro-4,6-dimetoxi-1,3,5-triazina (0,22 g, 1,24 mmol) y N-metil morfolina (0,34 ml, 3,09 mmol) La mezcla se agito a temperatura ambiente durante 1 hora En este momerto, se agregó $NH_4OH$ (2,5 ml) y la

reacción se agito a temperatura ambiente durante una hora mas A la mezcla de reaccion se agrego más THF (50 ml) y agua (200 ml) La mezcla se extrajo con acetato de etilo La extraccion con acetato de etilo se lavo con disolucion de salmuera saturada La capa de salmuera se extrajo con acetato de etilo Las capas organicas se combinaron, se secaron sobre $Na_2SO_4$, se filtraron y el disolvente se elimino *in vacuo* El residuo fue absorbido en acetato de etilo y el precipitado resultante fue recolectado sobre una almohadilla de filtro para propocionar un polvo blanco (0,38 g, 76%) $^1$H NMR (300 MHz, $CD_3OD$) δ 8,18 (d, J = 1,1 Hz, 1H), 8,02 (dd, J = 8,26, 2,01 Hz, 1H), 7,69 (aprox q, J = 8,26 Hz, 1H), 7,55 (d, J = 8,06 Hz, 1 H) 7,12 - 7,06 (m, 2H), 6,71 (s, 1H), 5,40 (s, 2H), 2,07 (s, 3H) ES-MS *m/z* 482 (M+H) ES-HRMS m/z 482,9919 (M+H calculado para $C_{21}H_{15}BrClF_2N_2O_3$ requiere 482,9917)

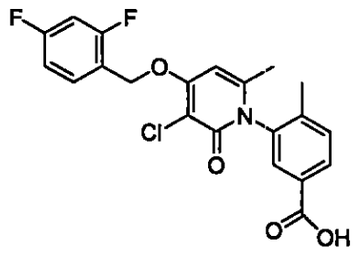
Ejemplo 590




3-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(H)-il]-4-metilbenzamida

Etapa 1 Preparacion de acido 3-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-metilbenzoico

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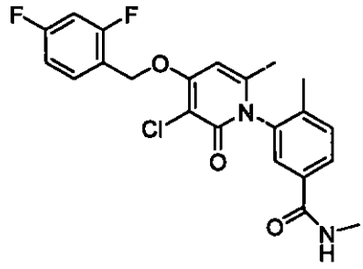
Ácido 3-[4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-metilbenzoico ( precedente) (7,5g, 19,4 mmol) y NCS (2,6 g, 19,4 mmol) fueron absorbidos en dicloroetano a 65 °C (100 ml) Se agrego una cantidad catalitica de acido dicloroacetico (2 gotas) Despues de dos horas, el disolvente fue eliminado *in vacuo* y el residuo fue absorbido en eter dietilico El precipitado fue recolectado sobre una almohadilla de filtro y despues absorbido en acetato de etilo/hexanos al 50% para retirar la succinimida residual El precipitado fue recolectado sobre una almohadilla de filtro y despues secado *in vacuo* para producir un polvo blanco (4,2 g, 52%) $^1$H NMR (300 MHz, $CD_3OD$) δ 8,10 (dd, J = 7,85, 1,81 Hz, 1H), 7,83 (d, J = 8,26, 1,81 Hz, 1H), 7,40 (aprox q, J = 8,26 Hz, 1H), 7,58 (d, J = 7,85, 1H), 7,13-7,06 (m, 2H), 6,74 (s, 1H), 5,40 (s, 2H), 2,14 (s, 3H), 2,04 (s, 3H), ES-MS m/z 420 (M+H) ES-HRMS *m/z* 420,0786 (M+H calculado para $C_{21}H_{17}ClF_2NO_4$ requiere 420,0809)

Etapa 2 El acido 3-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-metilbenzoico (1,5g, 3,57 mmol) fue absorbido en THF (30 ml) Se agregaron 2-cloro-4,6-dimetoxi-1,3,5-triazina (0,75 g, 4,28 mmol) y N-metil morfolina (1,18 ml, 10,72 mmol) La mezcla se agito a temperatura ambiente durante 1 hora En este momento, se agregó $NH_4OH$ (7,5 ml) y la reaccion se agito a temperatura ambiente durante una hora mas A la mezcla de reaccion se agrego mas THF (100 ml) y

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agua (150 ml) La mezcla se extrajo con acetato de etilo La extraccion con acetato de etilo se lavo con disolución de salmuera saturada La capa de salmuera se extrajo con acetato de etilo Las capas organicas se combinaron, se secaron sobre $Na_2SO_4$, se filtraron y el disolvente se elimino *in vacuo* El residuo fue absorbido en acetato de etilo y el precipitado resultante fue recolectado sobre una almohadilla de filtro para producir un polvo blanco (1,32 g, 88%) $^1$H NMR (300 MHz, $CD_3OD$) δ 7,96 (dd, J = 7,85, 1,81 Hz, 1H), 7,71 (d, J = 1,81 Hz, 1H), 7,67 (aprox q, J = 8,06 Hz, 1H), 7,56 (d, J = 8,06 Hz, 1 H) 7,12 - 7,06 (m, 2H), 6,74 (s, 1H), 5,40 (s, 2H), 2,13 (s, 3H), 2,05 (s, 3H) ES-MS *m/z* 419 (M+H) ES-HRMS *m/z* 419,0979 (M+H calculado para $C_{21}H_{18}ClF_2N_2O_3$ requiere 419,0969)

Ejemplo 591

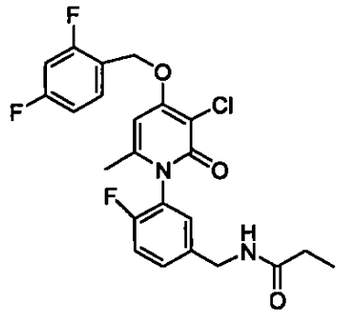


3-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il] N,4-dimetilbenzamida

El compuesto del titulo se preparo acido a partir de ácido 3-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-metilbenzoico ( de la etapa 1 anterior) (1,5 g, 3,57 mmol) en diclorometano (35 ml) A esta mezcla se agrego 2,0 M metil amina en THF (3,6 ml, 7,14 mmol), seguida, en orden, por EDCI (0,67 g, 4,28 mmol), 1-hidroxibenzotriazol (0,58 g, 4,28 mmol) y trietilamina (0,99 ml, 7,14 mmol) La reaccion se agito a temperatura ambiente durante toda la noche La reaccion se enfrio repentinamente con $NH_4Cl$ y se extrajo 3 veces con

acetato de etilo Ia capa organica combinada después se lavo con $NaHCO_3$ (aq ) saturada y se extrajo 3 veces con acetato de etilo Las capas organicas se combinaron y lavaron con $H_2O$ y se extrajeron 3 veces con acetato de etilo Las capas orgánicas fueron combinadas y secadas sobre $Na_2SO_4$ y evaporadas El residuo resultante se trituró con éter dietilico/hexano para obtener un sólido, que se secó *in vacuo* para proporcionar un solido de color blanco (1,5 g, al 7?%) $^1H$ NMR (300 MHz, $CD_3OD$) δ 7,90 (dd, J = 8,06, 1,81 Hz, 1H), 7,67 (aprox q, J = 6,44 Hz, 1H), 7,55 (d, J = 8,06 Hz, 1H), 7,13-7,06 (m, 2H), 6,74 (s, 1H), 5,40 (s, 2H), 2,93 (s, 3H), 2,13 (s, 3H), 2,04 (s, 3H), ES-MS m/z 433 (M+H) ES-HRMS *m/z* 433,1153 (M+H calculado para $C_{22}H_{20}ClF_2N_2O_3$ requiere 433,1125)

Ejemplo 592

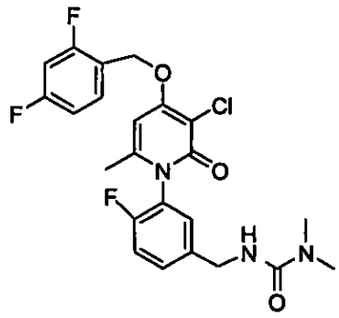


N-{3-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-fluorobenzoato}propanamida

Un matraz de fondo redondo de 10 ml equipado con varilla para agitación y entrada para nitrógeno se cargó con hidrocloruro de 1-[5-(aminometil)-2-fluorofenil]-3-cloro-4-[(2,4 diflucrobencil)oxi]-6-metilpiridin-2(1H)-ona (250 mg, 0,56 mmol), cloruro de propionilo (49 µL, 0,56 mmol), trietilamina (195 µL, 1,4 mmol) y tetrahidrofurano (4,0 ml) Despues de agitar la reacción a 25 °C durante 5 minutos, ésta se completo por LC/MS La mezcla de reacción

se vertio en una disolucion de $NH_4Cl$ acuosa saturada La mezcla acuosa se extrajo con acetato de etilo La fase organica se secó con $Na_2SO_4$ y se concentro *in vacuo* para obtener (240 mg, al 91%) como un sólido de color amarillo $^1H$ NMR (400 MHz, $(CD_3)_2SO$) δ 8,3 (t, J = 5,8 Hz, 1H), 7,6 (q, J = 8,7 y 6,58 Hz, 1H), 7,38 (d, J = 7,78 Hz, 1H), 7,3 (dd, J = 2 6 y 7,6 Hz, 1H), 7,22 (d, J = 7,51 Hz, 1H), 7,12 (td, J = 2 0 y 6,5 Hz, 1H), 6,65 (s, 1H), 5,3 (s, 2H), 4,23 (d, J = 3,6 Hz, 2H), 2,1 (q, J = 7,7 Hz 2H), 1,98 (s, 3H), 0,98 (t, J = 7,5 Hz, 3H) ppm ES-HRMS *m/z* 465,1203 (M+H calculado para $C_{23}H_{21}ClF_3N_2O_3$ requiere 465,1187)

Ejemplo 593

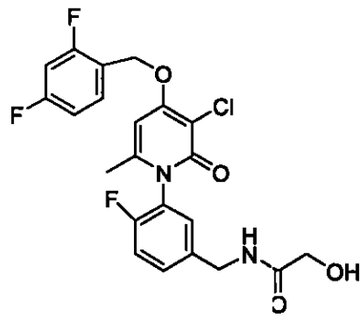


N-{3-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-fluorobenzoato}dimetilurea

Un matraz de fondo redondo de 10 ml equipado con varilla para agitación y entrada para nitrógeno se cargo con hidrocloruro de 1-[5-(aminometil)-2-fluorofenil]-3-cloro-4-[(2,4 difluorobencil)oxi]-6-metilpiridin-2(1H)-ona (250 mg, 0,56 mmol), cloruro de dimetilcarbamilo (52 µL, 0,56 mmol), trietilamina (195 µL, 1,4 mmol) y tetrahidrofurano (4,0 ml) Despues de agitar la reacción a 25 °C durante 5 minutos, ésta se completó por LC/MS La mezcla de reacción se vertio en una disolucion de $NH_4Cl$ acuosa saturada La mezcla acuosa se extrajo con acetato de etilo La fase orgánica se secó con $Na_2SO_4$ y se

concentro *in vacuo* para obtener el producto deseado (245 mg, 86%) como un sólido color blanco $^1$H NMR (400 MHz, ($CD_3OD$) δ 7,61 (q, J = 7,9 y 6,7 Hz, 1H), 7,4(m, 1H), 7,3 (d, J = 9,3 Hz, 1H), 7,21 (m, 1H), 7,1 (m, 2H), 6,65 (s, 1H), 5,35 (s, 2H), 4 38 (s, 2H), 2,9 (s, 6H), 2,1 (s, 3H) ppm ES-HRMS *m/z* 480 1269 (M+H calculado para $C_{23}H_{22}ClF_3N_3O_3$ requiere 480,1296)

Ejemplo 594

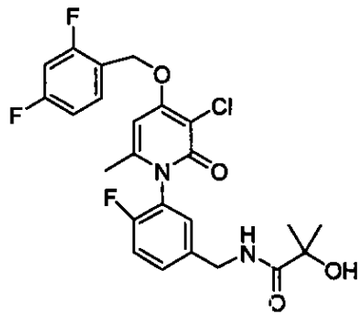


N-{3-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-fluorobencil}-2-hidroxiacetamida

Un matraz de fondo redondo de 10 ml equipado con varilla para agitación y entrada para nitrogeno se cargo con hidrocloruro de 1-[5-(aminometil)-2-fluorofenil]-3-cloro-4-[(2,4 difluorobencil)oxi]-6-metilpiridin-2(1H)-ona (250 mg, 0,56 mmol), cloruro de acetoxiacetilo (66 µL, 0,62 mmol), trietilamina (195 µL, 1,4 mmol) y tetrahidrofurano (4,0 ml) Despues de agitar la reaccion a 25 °C durante 5 minutos, ésta se completo por LC/MS Se agrego NaOH (2,5M, 2,24 mmol, 1,0 ml) y MeOH (2,0mL) y se agitó durante 10 minutos para proporcionar el compuesto del título La mezcla de reacción se acidifico con HCl concentrado y se extrajo con etilo La fase organica se seco con $Na_2SO_4$ y se concentró *in vacuo* para obtener (217 mg, 78%) del producto deseado como un solido color amarillo $^1$H NMR (400 MHz, ($CD_3OD$) δ 7,6 (q, J = 7,6 y 6,9 Hz, 1H), 7,44(m, 1H),

7,34 (m, 2H), 7,22 (m, 2H), 6,63 (s, 1H), 5,35 (s, 2H), 4,41 (s, 2H), 4,0 (s 2H), 2,05 (s, 3H) ppm ES-HRMS *m/z* 467,0957 (M+H calculado para $C_{22}H_{19}ClF_3N_2O_4$ requiere 467,0980)

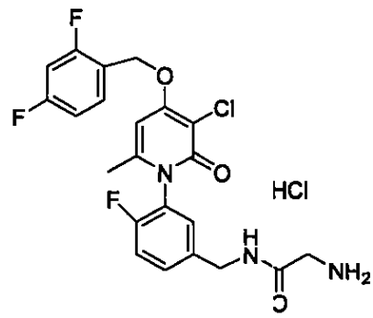
Ejemplo 595



N-{3-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-fluorobencil}-2-hidroxi-2-metilpropanamida

El compuesto del titulo se preparo esencialmente como se describe en el Ejemplo 594 con acetato de 1-clorocarbonil-1-metiletilo sustituyente del cloruro de acetoxiacetilo $^1$H NMR (400 MHz, ($CDCl_3$) δ 9,9 (q, J = 8,2 y 6,5 Hz, 1H), 9,7 (t, J = 2,6 Hz, 1H), 9,5 (t, J = 8,9 Hz, 2H), 9,3 (m, 1H), 9,2 (m, 1H), 8,6 (s, 1H) 7,6 (s, 2H), 6,8 (d, J = 15 Hz, 1H), 6,63 (d, J = 15 Hz, 1H), 4,42 (d, J = 3,2 Hz, 6H), 3,99 (s, 3H) ppm ES-HRMS *m/z* 495,1271 (M+H calculado para $C_{24}H_{23}ClF_3N_2O_4$ requiere 495,1293)

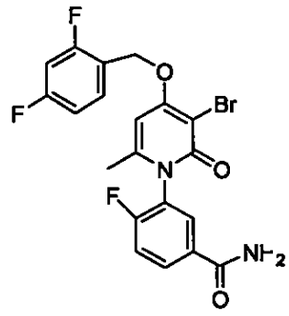
Ejemplo 596



hidrocloruro de N[1]-{3-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-fluorobencil}glicinamida

Un matraz de fondo redondo de 25 ml equipado con varilla para agitación y entrada para nitrogeno se cargo con boc-glicina (105 mg, 0,6 mmol) y 8 ml de DMF La mezcla se enfrio a 0° C y se agregó isboutilcloroformato (77,5 µL, 0,6 mmol) y se agito durante 20 min Se agrego hidrocloruro de 1-[5-(aminometil)-2-fluorofenil]-3-cloro-4-[(2,4 difluorobencil)oxi]-6-metilpiridin-2(1H)-ona (250 mg, 0,6 mmol) y se agito durante 3 horas Después de completar la reaccion por LC/MS, se agregaron HCl concentrado (2 ml) y 2 ml de metanol para eliminar el grupo boc La reaccion se agito durante 24 h, se neutralizó con 2M NaOH y se extrajo con acetato de etilo La fase organica se seco con $Na_2SO_4$ y se concentro *in vacuo* para obtener (196 mg, 66%) del producto deseado como una sal de HCl $^1$H NMR (400 MHz, ($CD_3OD$) δ 7,6 (q, J = 8 y 6,5 Hz, 1H), 7,5(m, 1H), 7,3 (m, 2H), 7,0 (m, 2H), 6,63 (s, 1H), 5,35 (s, 2H), 4,4 (q, J = 15 y 13,6 Hz, 2H), 3,7 (s, 2H), 2,05 (s, 3H) ppm ES-HRMS *m/z* 466,1157 (M+H calculado para $C_{22}H_{20}ClF_3N_2O_3$ requiere 466,1140)

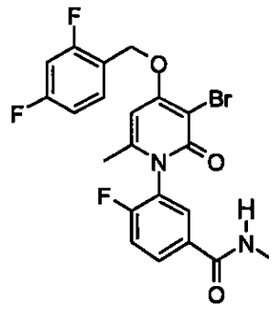
Ejemplo 597




3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-fluorobenzamida

Un matraz de fondo redondo de 250 ml equipado con varilla para agitacion y entrada para nitrogeno se cargo con ácido 3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-fluorobenzoico (3,65g, 7,8 mmol), 4-metilmorfolina (2,6 ml, 23,4 mmol), 2-cloro-4,6-dimetoxi-1,3,5-triazina (1,64 g, 9,36 mmol) y tetrahidrofurano (40 ml) Despues de agitar la mezcla durante 30 minutos a 25 °C, se agrego C, $NH_4OH$ (20,0 ml) La mezcla se agito durante 30 minutos y se diluyo con agua El producto se precipito de la disolución El precipitado se filtro y se lavo con agua y eter dietilico para proporcionar el compuesto del titulo (2,37 g, 65%) como un sólido de color blanco $^1H$ NMR (400 MHz, $(CD_3)_2SO$) δ 7,9 (d, J = 7,3 Hz, 1H), 7,61 (q, J = 8,6 y 6,7 Hz, 1H), 7,5 (m, 2H), 7,3 (t, J = 9,6 Hz, 1H), 7,15 (t, J = 8,7 Hz, 1H), 6,7 (s, 1H), 5,36 (s, 2H), 2 (s, 3H) ppm ES-HRMS m/z 469,0172 (M+H calculado para $C_{20}H_{15}BrF_3N_2O_3$ requiere 469,0195)

Ejemplo 598



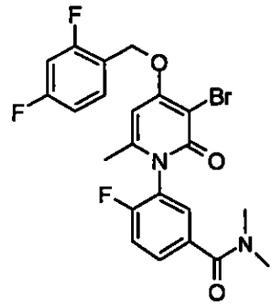

3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-fluoro-N-metilbenzamida

Una disolucion de acido 3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-fluorobenzoico (1 g, 2,1 mmol) en N,N-dimetilformamida (20 ml) se enfrio a -10 °C Se agregaron cloroformato de isobutilo (0,27 ml, 2,1 mmol) y N-metil morfolina (0,23 ml, 2,1 mmol) al recipiente de reaccion Despues de la

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agitacion a -10 °C durante 20 minutos, se agregó una disolución de N-metil amina (2,1 ml, 4,2 mmol, 2 M en THF) y la mezcla de reaccion se entibio a temperatura ambiente mientras se la agitaba durante 18 horas La mezcla de reaccion se concentró *in vacuo*, se suspendio en agua, se filtro y se lavó con agua, acetato de etilo y éter dietilico $^{1}$H NMR (400 MHz, $CD_3OD$) δ 8,03 (dddd, J = 3,0, 6,4, 9,2 y 11,6 Hz, 1H), 7,81 (dd, J = 3,0 y 0,2 Hz, 1H), 7,66 (q, J = 10,4 Hz, 1H), 7,47 (t, J = 12 Hz, 1H), 7,06 (t, J = 12 Hz, 2H), 6,67 (s, 1H), 5,38 (s, 2H), 2,91 (s, 3H), 2,10 (s,3H) ppm $^{19}$ F NMR (400 MHz, $CD_3OD$) δ -111,50 (1F), -115,97 (1 F), -120,16 ppm ES-HRMS *m/z* 481,0346 (M+H calculado para $C_{21}H_{17}BrF_3N_2O_3$ requiere 481,0369)

Ejemplo 599



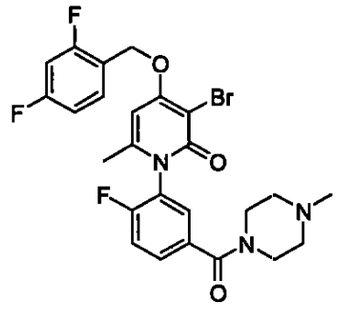

3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-fluoro-N,N-dimetilbenzamida

Una disolución de acido 3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-fluorobenzoico (1 g, 2,1 mmol) en N,N-dimetilformamida (20 ml) se enfrió a -10 °C Se agregaron cloroformato de isobutilo (0,27 ml, 2,1 mmol) y N-metil morfolina (0,23 ml, 2,1 mmol) al recipiente de reacción Despues de la agitacion a -10 °C durante 20 minutos, se agrego una disolucion de N-metil amina (2,1 ml, 4,2 mmol, 2 M en THF) y la mezcla de reaccion se entibio a temperatura ambiente mientras se la agitaba durante 18 horas La mezcla de

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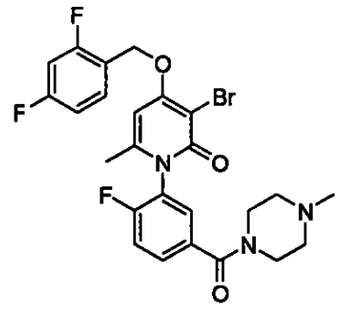
reaccion se concentro *in vacuo* y se dividió entre agua y acetato de etilo La capa organica se lavo con salmuera y se concentro *in vacuo* El sólido se sometio a cromatografia sobre silice (95 5 cloruro de metileno alcohol isopropilico) para proporcionar el producto deseado como un polvo de color blanco (0,31 g, al 30%) $^1$H NMR (400 MHz, $CD_3OD$) δ 7,64 (m, 1H), 7,50 (dd, J = 2,4 y 7,2 Hz, 1H), 7,45 (t, J = 9,6 Hz, 1H), 7,04 (t, J = 9,2 Hz, 2H), 6,65 (s, 1H), 5,36 (s, 2H), 3,09 (s, 3H), 3,05 (s, 3H), 2,10 (s, 3H) ppm $^{19}$ F NMR (400 MHz, $CD_3OD$) δ -111,51 (1F), -115,88 (1 F) -121,90 (1 F) ppm ES-HRMS *m/z* 495,0508 (M+H calculado para $C_{22}H_{19}BrF_3N_2O_3$ requiere 495,0526)

Ejemplo 600




3-bromo-4-[(2,4-difluorobencil)oxi]-1-[2-difluoro-5-[(4-metilpiperazin-1-il)carbonil]fenil}-6-metilpiridin-2(1H)-ona

Etapa 1 Preparación de 3-bromo-4-[(2,4-difluorobencil)oxi]-1-{2-fluoro-5-[(4-metilpiperazin-1-il)carbonil]fenil}-6-metilpiridin-2(1H)-ona

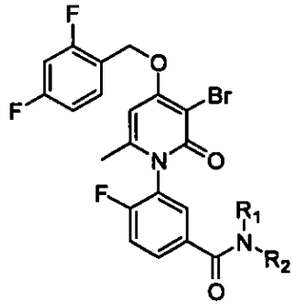


A un recipiente de reaccion (tubo de cultivo borosilicatado) se le agrego acido 3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-fluorobenzoico (0,300 g, 0,623 mmol) y 1-hidroxibenzotriazol (0,042 g, 0,45 mmol) Se agrego N,N-dimetilformamida (3 ml) al recipiente de reaccion seguido por aproximadamente 1,1 g de la resina carbodiimida aglutinada con polimero (1,38 mmol/g) Luego se agregó N,N-dimetilformamida adicional (2 ml) al recipiente de reaccion Luego, se agito orbitalmente el aparato de reacción en paralelo (agitador orbital Labline Benchtop) a aproximadamente 200 rpm a temperatura ambiente durante 15 minutos Luego se agregó N-metilamina (1 ml, 2 mmol) al recipiente de reaccion y se agitó orbitalmente el aparato de reaccion a temperatura ambiente durante toda la noche En este momento se diluyo la reaccion con tetrahidrofurano (20 ml) y se trato con aproximadamente 2,0 g de resina poliamina (2,63 mmol/g) y aproximadamente 2,5 g de poliestireno funcionalizado con metilisocianato (1,5 mmol/g) y se continuó la agitacion orbital a 200 rpm a temperatura ambiente durante 3 horas Luego se abrio el recipiente de reaccion y el producto de fase de disolución se separó de los subproductos enfriados rapidamente insolubles mediante filtración y su recolección en un vial Después de la evaporación parcial, los subproductos insolubles se enjuagaron con tetrahidrofurano (2 x 10 ml)

El filtrado se evaporo soplando $N_2$ sobre el vial y el sólido resultante se trituró con eter dietílico para propocionar un sólidc blanquecino (0,14g, al 41%)

$^1$H NMR (400 MHz, $CD_3OD$) □ 7,63 (m, 1H), 7,51 (dd, J = 2,2 y 7,2 Hz, 1H), 7 45 (t, J = 8,4 Hz, 1H), 7,03 (m, 2H), 6,65 (s, 1H), 5,34 (s, 2H), 3,74 (s, 2H), 3,51 (s, 2H), 2,80 (s, 4H), 2,08 (s, 3H) ppm $^{19}$ F NMR (400 MHz, $CD_3OD$) □ -111,31 (1F), -115,72 (1 F), -121,41 (1 F) ppm ES-HRMS *m/z* 550,0946 (M+H calculado para $C_{25}H_{24}ClF_3N_3O_3$ requiere 550,0948)

Ejemplos 601-603

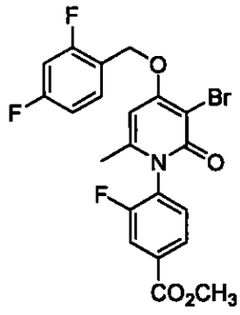


Los compuestos de los Ejemplos 601-603 se preparan siguiendo el metodo del Ejemplo 600 y reemplazando *N*-metilamina con la amina apropiada

| Compuesto N° | $R_1$ | $R_2$ | % Rend | MF | M+H Requiere | ESHRMS m/z |
|---|---|---|---|---|---|---|
| Ej 601 | $CH_2CH_2O$- | $CH_2CH_2$- | 98 | $C_{24}H_{21}BrF_3N_2O_4$ | 537,0631 | 537,0620 |
| Ej 602 | $CH_3$ | $CH_2CH_2OH$ | 43 | $C_{23}H_{21}BrF_3N_2O_4$ | 525,0631 | 525,0618 |
| Ej 603 | H | $CH_2C(CH_3)_2OH$ | 65 | $C_{24}H_{23}BrF_3N_2O_4$ | 539,0783 | 539,0788 |

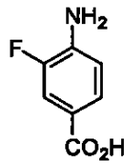
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1279

Ejemplo 604



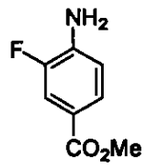
4-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-3-fluorobenzoato de metilo

Etapa 1 Preparacion de acido 4-amino-3-fluorobenzoico



El ácido 3-fluoro-4-aminobenzoico se preparo como se describe en la literatura (Schmelkes, F C , Rubin, M J Am Chem Soc 1944, 66, 1631-2 )

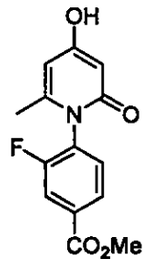
Etapa 2 Preparación de 4-amino-3-fluorobenzoato de metilo



Un matraz de fondo redondo de tres cuellos y de 250 ml equipado con una entrada para nitrogeno, varilla para agitación, embudo de adicion y termocupla se cargo con acido 4-amino-3-fluorobenzoico (11,8 g, 76 mol) y metanol (100 ml) El sistema se enfrió a 0 °C y se agrego cloruro de acetilo (7,6 ml, 107 mol) gota a gota El sistema se entibio a temperatura ambiente, el embudo de adicion se reemplazo con un condensador de reflujo y se calento a reflujo durante 6 horas La mezcla de reacción se enfrio a

temperatura ambiente, se enfrio repentinamente con disolucion $NaHCO_3$ acuosa saturada y se extrajo con acetato de etilo El extracto organico se lavó con salmuera y se concentró *in vacuo* para proporcionar 4-amino-3-fluorobenzoato de metilo como un sólido de color tostado (8,2 g, al 64%) $^1H$ NMR (400 MHz, $CD_3OD$) □ 7,56 (dd, J = 1,6 y 8,0 Hz, 1H), 7,52 (dd, J = 1,9 y 12 Hz, 1H), 6,76 (t, J = 8,4 Hz, 1H), 3,8 (s, 3H) ppm $^{19}F$ NMR (400 MHz, $CD_3OD$) □ -139,05 (1F) ppm ES-HRMS *m/z* 170,0565 (M+H calculado para $C_8H_9FNO_2$ requiere 170,0612)

Etapa 3 Preparacion de 3-fluoro-4-(4-hidroxi-6-metil-2-oxopiridin-1(2H)-il)benzoato de metilo

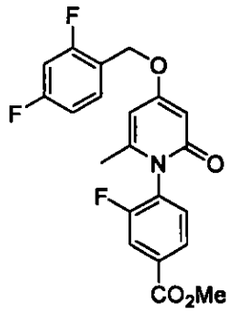



Un matraz de fondo redondo, de 250 ml, equipado con varilla para agitación, una trampa Dean-Stark y condensador de reflujo se cargo con el producto de la Etapa 2 (8 g, 47,3 mmol), 4-hidroxi-6-metil-2-pirona (12 g, 84,6 mmol) y N-metil-2-pirrolidina (8 ml) El sistema se sumergio en un baño de aceite a 150 °C durante 2 horas y despues se enfrio a temperatura ambiente La mezcla de reaccion se lavo con $K_2CO_3$ acuosa (8,5 g, 200 ml agua) La capa acuosa se lavó con acetato de etilo y después se acidifico a pH 4-5 con HOAc glacial Esto se extrajo con acetato de etilo, el cual fue concentrado *in vacuo* El aceite viscoso fue triturado con acetonitrilo y filtrado al compuesto del titulo como un sólido de color tostado (2,3 g, al 17%) $^1H$ NMR (400 MHz, $CD_3OD$) δ 7,98 (dd, J = 1,8 y 8,0 Hz, 1H), 7,91 (dd, J = 1,7 y 10 Hz, 1H), 7,46 (t, J = 8 Hz, 1H),

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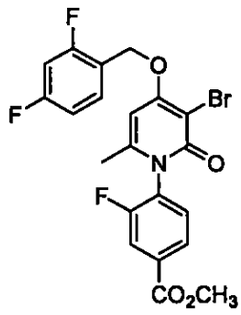
6,09 (dd, J = 0,9 y 2,4 Hz, 1H), 5,77 (d, J = 2,7 Hz, 1H), 3,94 (s, 3H), 1,97 (s, 3H) ppm $^{19}$F NMR (400 MHz, $CD_3OD$) δ -123,00 (1F) ppm ES-HRMS m/z 278,0781 (M+H calculado para $C_{14}H_{13}FNO_4$ requiere 278,0823)

Etapa 4 Preparación de 4-[4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-3-fluorobenzoato de metilo



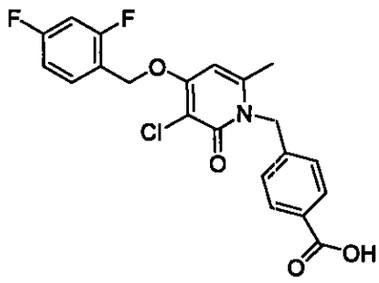

Un matraz de fondo redondo de 10 ml equipado con varilla para agitación y entrada para nitrogeno se cargo con el producto de la Etapa 4 (2,3 g, 8,3 mmol) y N,N-dimetil formamida (20 ml) Se agregó 1,8-diazabiciclo[5 4 0]undec-7-ene (1,4 ml, 9,1 mmol) seguido por bromuro de 2,4-difluorobencilo (1,2 ml, 9,1 mmol) La mezcla de reaccion se agito a 60 °C durante 3 horas, se vertio en $NaHCO_3$ acuosa saturada y se extrajo con acetato de etilo La capa orgánica se lavo con salmuera y se concentro *in vacuo* El solido se trituro con acetonitrilo y se filtró para proporcionar el compuesto del titulo (2,15 g, al 64%) $^1$H NMR (400 MHz, $CD_3OD$) δ 7,99 (dd, J = 1,7 y 8,4 Hz, 1H), 7,93 (dd, J = 1,8 y 10,4 Hz, 1H), 7,55 (m, 1H), 7,48 (t, J = 6,8 Hz, 1H), 7,02 (m, 2H), 6,18 (dd, J = 1,3 y 2,76 Hz, 1H), 5,02 (d, J = 2,7 Hz, 1H), 5,14 (s, 2H), 3,94 (s, 3H), 1,98 (s, 3H) ppm $^{19}$ F NMR (400 MHz, $CD_3OD$) δ -111,34 (1F), -115,97 (1 F), -122,98 (1 F) ppm ES-HRMS *m/z* 404,1133 (M+H calculado para $C_{21}H_{17}F_3NO_4$ requiere 404,1104)

Etapa 5 Preparación de 4-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-3-fluorobenzoato de metilo



Un matraz de fondo redondo de 100 ml equipado con varilla para agitacion y entrada para nitrogeno se cargo con el producto de la Etapa 4 (2,15 g, 5,3 mmol) y N-metil-2-pirrolidina (15 ml) Después del enfriamiento a 0 °C, se agregó una disolución de N-bromo succinimida (1,03 g, 5,8 mmol) en 10 ml de N-metil-2-pirrolidina en un lapso de 15 minutos Después de los 15 minutos adicionales, la mezcla de reacción se entibio a temperatura ambiente y se agitó durante 1 hora Luego la mezcla se vertio en una disolucion $NaHCO_3$ acuosa saturada y se extrajo con acetato de etilo La capa orgánica se lavo con salmuera y se concentro *in vacuo* El residuo fue triturado con acetonitrilo y filtrado para proporcionar el compuesto del titulo como un solido de color blanco (1,5 g, al 59%) $^1H$ NMR (400 MHz, $CD_3OD$) δ 8,00 (dd, J = 2,0 y 8,4 Hz, 1H), 7,95 (dd, J = 1,7 y 10 Hz, 1H), 7,64 (q, J = 8,8 y 14,4 Hz, 1H), 7,51 (t, J = 7,6 Hz, 1H), 7,04 (t, J = 8,4 Hz, 2H), 6,66 (s, 1H), 5,36 (s, 2H), 3,95 (s, 3H), 2,01 (s,3H) ppm $^{19}$ F NMR (400 MHz, $CD_3OD$) δ -111,50 (1F), -115,97 (1 F), -123,01 (1 F) ppm ES-HRMS *m/z* 484,0169 (M+H calculado para $C_{21}H_{16}BrF_3NO_4$ requiere 484,0192)

Ejemplo 605

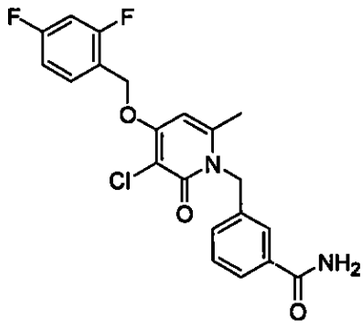


Ácido 4-{[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}benzoico

Preparacion de ácido 4-{[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}benzoico Se suspendio 4-{[3-cloro-4-[2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}benzoato de metilo (30,4 g, 70,1 mmol) en metanol (150 ml) y dioxano (150 ml) Se agrego 2,5N NaOH (30,8 ml, 77,08 mmol) La mezcla resultante se calentó hasta 50°C durante 8,0 horas La reacción se concentró parcialmente y se acidifico (pH 2) la mezcla heterogenea con 1N HCl El precipitado fue recolectado por filtrado lavandolo con $H_2O$ y eter dietilico para proporcionar un solido de color blanco (29,2 g, al 99 %) $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7,88 (d, J = 8,3 Hz, 2H), 7,63 (aprox q, J = 7,9 Hz, 1H), 7,31 (dt, J = 2,4, 9,9 Hz, 1H), 7,18 (aprox d, J = 8,3 Hz, 2H), 7,17-7,12 (m, 1H), 6,60 (s, 1H), 5,35 (s, 2H), 5,27 (s, 2H), 2,28 (s, 3H) ES-HRMS *m/z* 420,0821 (M+H calculado para $C_{21}H_{17}ClF_2NO_4$ requiere 420,0809)

7383
1284

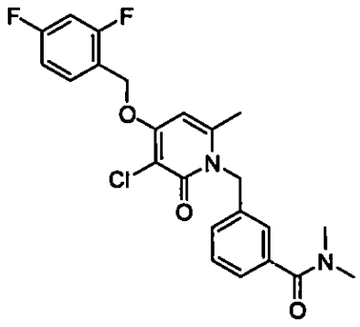
Ejemplo 606



4-{[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}benzamida

Preparación de 4-{[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}benzamida Se suspendió ácido 4-{[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}benzoico (12,0 g, 28,58 mmol) en tetrahidrofurano (100 ml) Se agrego 2-cloro-4,6-dimetoxi-1,3,5-triazina (6,02 g, 34,3 mmol) seguido de 4-metilmorfolina (9,43 ml, 85,74 mmol) La mezcla resultante se agitó a temperatura ambiente durante 1,5 horas, momento en el que se agregó $NH_4OH$ (50,0 ml) La mezcla resultante se agito a temperatura ambiente durante 1 hora y después se concentró parcialmente El precipitado fue recolectado por filtrado lavandolo con $H_2O$ y eter dietilico para proporcionar un solido blanquecino (12,11 g, >100 %) $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 7,91 (br s, 1H), 7,80 (d, J = 8,3 Hz, 2H), 7,63 (aprox q, J = 7,9 Hz, 1H), 7,31 (dt, J = 2,6, 10,5 Hz, 1H), 7,17-7,12 (m, 1H), 7,13 (aprox d, J = 8,3 Hz, 2H), 6,59 (s, 1H), 5,32 (s, 2H), 5,27 (s, 2H), 2,28 (s, 3H) ES-HRMS *m/z* 419,0968 (M+H calculado para $C_{21}H_{18}ClF_2N_2O_3$ requiere 419,0969)

Ejemplo 607



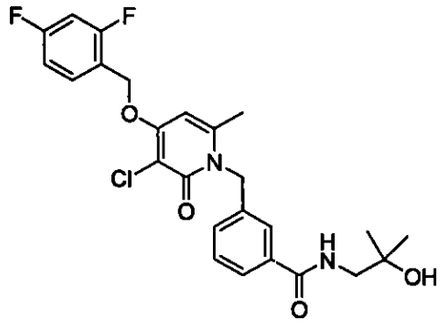
4-{[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}-N,N-dimetilbenzamida

Preparacion de 4-{[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}-N,N-dimetilbenzamida Se suspendió ácido 4-{[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}benzoico (2,00 g, 4,76 mmol) en N,N-dimetilformamida (20 ml) Se agrego 1-hidroxibenzotriazol (0,773 g, 5,72 mmol) seguido por 4-metilmorfolina (1,57ml, 14,28 mmol), dimetlamina (7,14 ml, 2,0 M en tetrahidrofurano, 14,28 mmol) y despues hidrocloruro de 1-[3-(dimetilamino)propil]-3-etilcarbodiimida (1,28 g, 6,66 mmol) La mezcla resultante se agitó a temperatura ambiente durante 3 hcras, momento en el que la reaccion se diluyo con $H_2O$ (75 ml) La mezcla de reaccion despues se extrajo con acetato de etilo Los extractos organicos combinados se lavarcn con $NaHCO_3$ saturada, salmuera, se secaron sobre $Na_2SO_4$, se filtraron y se concentraron El solido resultante se lavo con acetato de etilo para proporcionar el compuesto del titulo como un solido de color blanco (1,67 g, al 78%) $^1H$ NMR (400 MHz, $CDCl_3$) δ 7,53 (aprox q, J = 7,8 Hz, 1H ), 7,33 (d, J = 8,3 Hz, 2H), 7,16 (d, *J* = 8,3 Hz, 2H), 6,95-6,90 (m,1H), 6,84 (aprox dt, J = 2,5, 9,4 Hz, 1H), 6,02 (s, 1H), 5,35 (s, 2H), 5,19 (s, 2H), 2,97-2,93 (br m, 6H), 2,26 (s, 3H) ES-HRMS *m/z*

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447,1246 (M+H calculado para $C_{23}H_{22}ClF_2N_2O_3$ requiere 447,1282)

Ejemplo 608

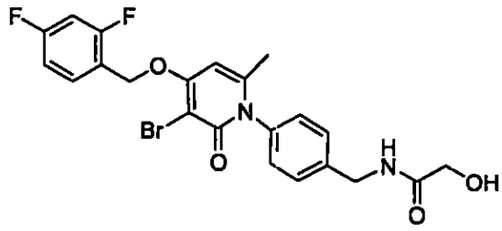


4-{[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}-N-(2-hidroxi-2-metilpropil)benzamida

Preparacion de 4-{[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}-N-(2-hidroxi-2-metilpropil)benzamida Se suspendio acido 4-{[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}benzoico (2,00 g, 4,76 mmol) en N,N-dimetilformamida (10 ml) A continuación se agregó 1-hidroxibenzotriazol 0,772 g, 5,71 mmol) seguido por 4-metilmorfolina (1,57 ml, 14,28 mmol), hidrocloruro de 1-amino-2-metil-2-propanol (1,49 g, 11,90 mmol) y despues hidrocloruro de 1-[3-(dimetilamino)propil]-3-etilcarbodiimida (1,28 g, 6,66 mmol) La mezcla resultante se agito a temperatura ambiente durante 2 dias momento en el que la reaccion se diluyó con $H_2O$ (50 ml) La mezcla de reaccion despues se extrajo con acetato de etilo Los extractos organicos combinados se lavaron con $NaHCO_3$ saturada, salmuera, se secaron sobre $Na_2SO_4$, se filtraron y se concentraron El solido resultante se lavo con eter dietilico para proporcionar el compuesto del titulo como un sólido de color tostado (2,08 g, al 89%) $^1H$ NMR (400 MHz, $CDCl_3$) δ 7,72 (d, J = 8,2 Hz, 2H), 7,51 (aprox q, J =

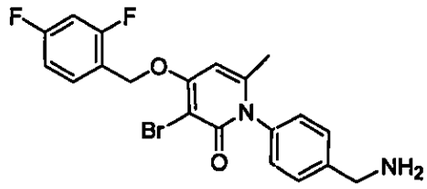
7,7 Hz, 1H), 7,25-7,21 (m, 1H), 710 (d, J = 8,2 Hz, 2H), 6,93 (aprox dt, J = 1,6, 8,3, 9,4 Hz, 1H), 6,87-6,82 (m, 1H), 6,01 (s, 1H), 5,32 (s, 2H), 5,19 (s, 2H), 3,42 (d, J = 5,9 Hz, 2H), 2,26 (s, 3H), 1,23 (s, 6H) ES-HRMS *m/z* 491,1522 (M+H calculado para $C_{25}H_{26}ClF_2N_2O_4$ requiere 491,1544)

Ejemplo 609



N-{4-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]bencil}-2-hidroxiacetamida

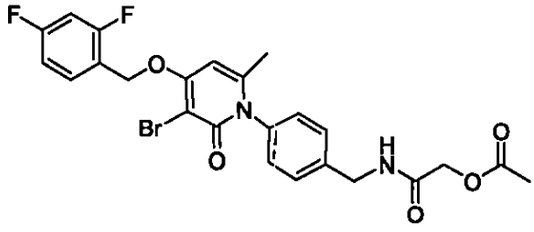
Etapa 1 Preparacion de 1-[4-(aminometil)fenil]-3-bromo-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona



El Ejemplo 244 (0,250 g, 0,556 mmol) se suspendio en tetrahidrofurano (2,0 ml) y se enfrió en un baño de hielo Se agrego borano dimetilsulfuro (0,500 ml, 2,0 M en tetrahidrofurano, 1,00 mmol) La mezcla resultante se calento a reflujo durante toda la noche y despues se enfrio en un baño de hielo La reaccion se enfrio repentinamente por la adicion de 6,C N HCl (5,0 ml) y despues se lavo con acetato de etilo La capa acuosa se alcalinizó con 2,5 N NaOH y se extrajo con acetato de etilo Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $Na_2SO_4$, se filtraron y se concentraron para proporcionar un sólico blanquecino (0,180 g, al 74 %) $^1H$ NMR (400 MHz, $CDCl_3$) δ 7,58 (aprox d, J = 7,8 Hz, 1H),

7,44 (aprox q, J = 8,2 Hz, 2H), 7,10 (d, J = 8,2 Hz, 2H), 6,95 (aprox dt, J = 1,5, 8,5 Hz, 1H), 6,88-6,83 (m, 1H), 6,06 (s, 1H), 5,24 (s, 2H), 3,93 (s, 2H), 1,96, (s, 3H)

Etapa 2 Preparación de 2-({4-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]bencil}amino)-2-oxoetilo

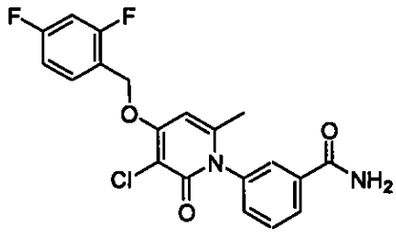


El acido acetoxiacetico (0,037 g, 0,310 mmol) se disolvio en diclorometano (2,0 ml) Se agregó 1-hidroxibenzotriazol (0,021 g, 0,155 mmol) seguido de gel de silice funcionalizado con 3-(1-ciclohexilcarbodiimida)propilo (1,00 g, 0,620 mmol, carga = 0,64 mmol/g) Despues de agitacion a temperatura ambiente durante 15 minutos, se agrego 1-[4-(aminometil)fenil]-3-bromo-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona (Etapa 1) (0,180 g, 0,310 mmol) en diclorometano (2,0 ml) La mezcla resultante se agitó a temperatura ambiente durante toda la noche, momento en el cual la mezcla de reacción se filtró y se concentró La cromatografia (gel de silice, hexanos/acetato de etilo con metanol al 10%) proporciono un sólido de color blanco (0,130 g, al 78%) $^1$H NMR (400 MHz, $CDCl_3$) δ 7,58 (aprox q, J = 7,8 Hz, 1H), 7,33 (d, J = 8,3 Hz, 2H), 7,05 (aprox d, J = 8,3 Hz, 2H), 6,97-6,92 (m, 1H), 6,88-6,83 (m, 1H), 6,08 (s, 1H), 5,24 (s, 2H), 4,58 (s, 2H , 4,44 (d, J = 6,0 Hz, 2H), 2,13 (s, 3H), 1,95 (s, 3H)

Etapa 3 Preparacion de N-{4-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]bencil}-2- hidroxiacetamida Se disolvio 2-({4-[3-bromo-4-[(2,4-

difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]bencil}amino)-2-oxoetilo (Etapa 2) (0,130 g, 0,243 mmol) en metanol (5 ml) y $H_2O$ (1 ml) Se agrego $K_2CO_3$ (0,055 g, 0,398 mmol) y la mezcla resultante se agito a temperatura ambiente durante 2 horas Luego la mezcla se concentro y el residuo se dividió entre $H_2O$ y acetato de etilo La capa organica se eliminó y la capa acuosa se extrajo aun mas con acetato de etilo Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $Na_2SO_4$, se filtraron y se concentraron para proporcionar un solido blanquecino (0,100 g, al 84%) $^1H$ NMR (400 MHz, $CDCl_3$) δ 7,56 (aprox q, J = 7,7 Hz, 1H), 7,43 (d, J = 5,8 Hz, 2H), 7,33 (d, J = 8,2 Hz, 2H), 7,04 (aprox t, J = 8,3 Hz, 2H), 6,98-6,93 (m, 1H), 6,88-6,83 (m, 1H), 6,11 (s, 1H), 5,24 (s, 2H), 4,41 (d, J = 6,0 Hz, 2H), 3,87 (s, 2H), 1,96 (s, 3H) ES-HRMS m/z 493,0575 (M+H calculado para $C_{22}H_{20}BrF_2N_2O_4$ requiere 493,0569)

Ejemplo 610



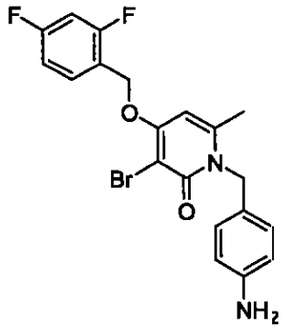
3-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]benzamida

Se suspendieron el compuesto del Ejemplo 291 (2,00 g, 4,93 mmol) y 2-cloro-4,6-dimetoxi-1,3,5-triazina (1,04 g, 5,91 mmol) en tetrahidrofurano (20 ml) Se agrego 4-metilmorfolina (1,6 ml, 14,79 mmol) La mezcla resultante se agitó durante 1,5 horas a temperatura ambiente Se agrego $NH_4OH$ (10 ml, 148,00 mmol), y se agito la reacción durante 0,5 horas a temperatura ambiente Se agregaron $H_2O$

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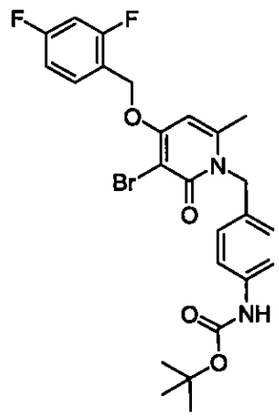
(50 ml) y tetrahidrofurano (50 ml) y se separó la capa orgánica La fase acuosa se extrajo con acetato de etilo (75 ml) y los materiales orgánicos combinados se lavaron con $Na_2CO_3$ saturada (50 ml), 1N HCl (50 ml) y salmuera (50 ml) La fase organica se secó sobre $Na_2SO_4$ y se evaporo El solido resultante se lavo con eter dietilico para proporcionar un solido de color blanco (1,96 g, al 98%) $^1H$ NMR (400 MHz, DMF-$d_6$) δ 8,24 (br s, 1H), 8,10 (dt, J = 1,21, 7,79 Hz, 1H), 7,90 (t, J = 1,88 Hz, 1H), 7,79 (aprox dt, J = 6,58, 8,59 Hz, 1H), 7,66 (t, J = 7,79 Hz, 1H), 7,57-7,55 (m, 1H), 7 46 (br s, 1H), 7,33 (ddd, J = 2,55, 9,26, 11,82 Hz, 1H) 7,24-7,19 (m, 1H), 6,78 (s, 1H), 5,44 (s, 2H), 2,04 (s, 3H) ES-HRMS m/z 405,0835 (M+H calculado para $C_{20}H_{16}BrF_2N_2O_3$ requiere 405,0812)

Ejemplo 611




1-(4-aminobencil)-3-bromo-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona

Etapa 1 Preparacion de 1-terc-butil-4-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}fenilcarbamato

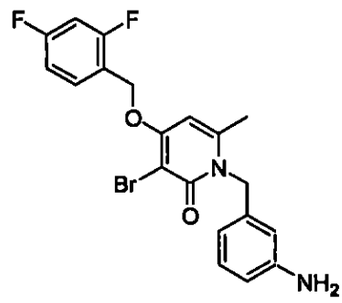


Se suspendio ácido 4-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}benzoico (8,00 g, 17,23 mmol) en 1 1 acetonitrilo t-butanol (172 ml) Se agregaron azida de difenilfosforilo (5,69 g, 20,68 mmol) y trietilamina (2,08 g, 20,68 mmol) La reacción se calentó a reflujo durante 1,5 horas La mezcla de reaccion se enfrió a temperatura ambiente, se concentro y se sometio a cromatografia (sobre silice, acetato de etilo con hexanos/metanol al 10%) para proporcionar un sólido blanquecino (6,14 g, al 66%)

Etapa 2 Se suspendio 1-terc-butil-4-{[3-bromo-4-[2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}fenilcarbamato (Etapa 1) (6,14 g, 11,47 mmol) en 4N HCl en dioxano (5,74 ml, 22,94 mmol) La mezcla de reaccion se agito a temperatura ambiente durante 1 hora y luego se diluyo con eter dietilico El precipitado se recogio mediante filtracion y se lavo con eter dietilico (3 x 30 ml) para proporcionar un solido de color tostado (3,45 g, al 69%) $^1$H NMR (400 MHz, DMSO-$d_6$ ) δ 7,64 (aprox dt, J = 6,58, 8,59 Hz, 1H), 7,31 (ddd, J = 2,55, 9,53, 10,61 Hz, 1H), 7,29-7,12 (m, 5H), 6,56 (s, 1H), 5,28 (s, 2H), 5,27 (s, 2H), 2,28 (s, 3H) ES-HRMS m/z 435,0516 (M+H calculado para $C_{20}H_{18}BrF_2N_2O_2$ requiere 435,0514)

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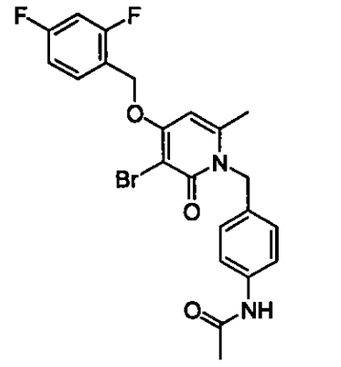
Ejemplo 612



1-(3-aminobencil)-3-bromo-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona

Siguiendo el metodo del Ejemplo 611 y sustituyendo acido 4-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}benzoico por acido 3-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}benzoico , se preparó el compuesto del titulo(2,65 g, al 67%) $^1$H NMR (400 MHz, DMF-$d_6$) δ 7,64 (aprox dt, J = 6,58, 8,59 Hz, 1H), 7,39 (t, J = 7,79 Hz, 1H), 7,32 (ddd, J = 2,55, 9,53, 10,61 Hz, 1H) 7,18-7,08 (m, 3H), 6,96 (s, 1H), 6,58 (s, 1H), 5,30 (s, 2H), 5,27 (s, 2H), 2,29 (s, 3H) ES-HRMS m/z 435,0513 (M+H calculado para $C_{20}H_{18}BrF_2N_2O_2$ requiere 435,0514)

Ejemplo 613

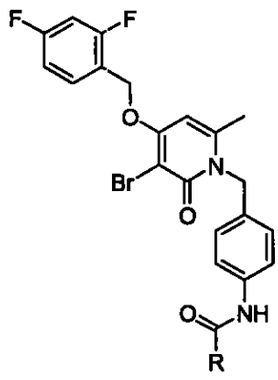


N-(4-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}fenil)acetamida

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A un recipiente de reaccion (tubo de cultivo borosilicatado) se le agrego el compuesto del Ejemplo 611 (0,300 g, 0,689 mmol) y diclorometano (3,0 ml) Se agrego una disolución madre de N-metilmorfolina (0,30 M, 3,0 ml) y el aparato de reaccion en paralelo se agito orbitalmente (Labline Benchtop Orbital Shaker) a aproximadamente 200 rpm a temperatura ambiente durante 10 minutos Luego se agregó cloruro de acetilo (C,074 ml, 1,033 mmol) al recipiente de reaccion y se agitó orbitalmente el aparato de reacción a temperatura ambiente durante 1,5 horas En este momento se diluyo la reaccion con diclorometano (15 ml) y se trato con aproximadamente 2,1 g de resina poliamina (2,63 mmol/g) y aproximadamente 3,8 g de poliestireno funcionalizado con metilisocianato (1,10 mmol/g) y se continuó la agitacion orbital a 200 rpm a temperatura ambiente durante toda la noche Luego se abrio el recipiente de reaccion y los productos de fase de disolucion se separaron de los subproductos enfriados repentinamente insolubles mediante su filtración y recoleccion en un vial Despues de la evaporacion parcial, los subproductos insolubles se enjuagaron con diclorometano (2 x 10 ml) El filtrado se evaporo soplando $N_2$ sobre el vial para proporcionar un solido de color blanco (0,135 g, al 41%) $^1$H NMR (400 MHz, DMF-$d_6$) $\delta$ 7,75 (aprox dt, J = 6,58, 8,59 Hz, 1H), 7,63 (d, J = 8,59 Hz, 1H), 7,30 (ddd, J = 2,55, 9,53, 10,61 Hz, 1H) 7,22-7,14 (m, 3H), 6,60 (s, 1H), 5,37 (s, 4H), 2,40 (s, 3H), 2,06 (s, 3H) ES-HRMS m/z 477,0600 (M+H calculado para $C_{22}H_{21}BrF_2N_2O_3$ requiere 477,0620)

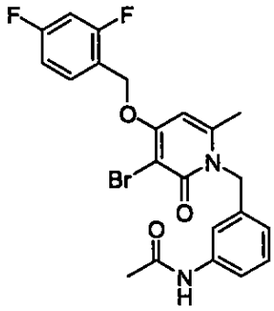
Preparación de los Ejemplos 614-616



Los compuestos de los Ejemplos 614-616 se preparan siguiendo el método del Ejemplo 613 y reemplazando el cloruro de acetilo con el cloruro ácido apropiado o cloruro de sulfamoílo La desprotección del intermedio protegido se llevo a cabo con 1 M $K_2CO_3$ en metanol para proporcionar el compuesto del titulo

| Compuesto N° | R | % Rend | MF | M+H ES-HRMS Requiere | *m/z* |
|---|---|---|---|---|---|
| Ej 614 | $CH_2OH$ | 65 | $C_{22}H_{20}BrF_2N_2O_4$ | 493,0569 | 493,0593 |
| Ej 615 | $CH_2OCOCH_3$ | 43 | $C_{24}H_{22}BrF_2N_2O_5$ | 535,0675 | 535,0702 |
| Ej 616 | $SO_2N(CH_3)_2$ | 43 | $C_{22}H_{23}BrF_2N_3O_4S$ | 542,0555 | 542,0572 |

Ejemplo 617



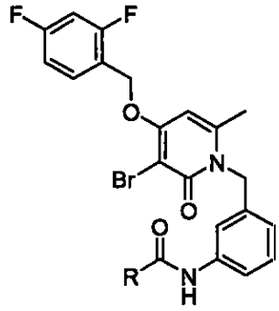
N-(3-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}fenil)acetamida

A un recipiente de reacción (tubo de cultivo borosilicatado) se le agrego el compuesto del Ejemplo 612 (0,300 g, 0,689 mmol) y diclorometano (3,0 ml) Se agregó una disolucion madre de N-metilmorfolina (0,30 M, 3,0 ml) y

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el aparato de reacción en paralelo se agito orbitalmente (Labline Benchtop Orbital Shaker) a aproximadamente 200 rpm a temperatura ambiente durante 10 minutos Luego se agrego cloruro de acetilo (0,074 ml, 1,033 mmol) al recipiente de reaccion y se agitó orbitalmente el aparato de reacción a temperatura ambiente durante 1,5 horas En este momento se diluyo la reaccion con diclorometano (15 ml) y se trató con aproximadamente 2,1 g de resina poliamina (2,63 mmol/g) y aproximadamente 3,8 g de poliestireno funcionalizado con metilisocianato (1,10 mmol/g) y se continuo la agitación orbital a 200 rpm a temperatura ambiente durante toda la noche Luego se abrio el recipiente de reacción y los productos de fase de disolucion se separaron de los subproductos enfriados repentinamente insolubles mediante su filtración y recoleccion en un vial Despues de la evaporación parcial, los subproductos insolubles se enjuagaron con diclorometano (2 x 10 ml) El filtrado se evaporo soplando $N_2$ sobre el vial para proporcionar un solido de color blanco (0,167 g, al 51%) $^1$H NMR (400 MHz, DMF-$d_6$) δ 7,77 (aprox dt, J = 6,58, 8,59 Hz, 1H), 7,69 (d, J = 8,32 Hz, 1H), 7,41 (br s, 1H), 7,34-7,17 (m, 3H), 6,88 (d, J = 7,65 Hz, 1H), 6,63 (s, 1H), 5,39 (s, 3H), 5,38 (s, 2H), 2,40 (s, 3H), 2,06 (s, 3H) ES-HRMS m/z 477,0620 (M+H calculado para $C_{22}H_{21}BrF_2N_2O_3$ requiere 477,0620)

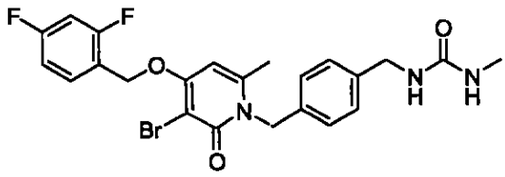
Preparacion de los Ejemplos 618-620



Los compuestos de los Ejemplos 618-620 se preparan siguiendo el metodo del Ejemplo 617 y reemplazando el cloruro de acetilo con el cloruro acido apropiado o cloruro de sulfamoilo La desproteccion del intermedio protegido se llevo a cabo con 1 M $K_2CO_3$ en metanol para proporcionar el compuesto del titulo

| Compuesto N° | R | % Rend | MF | M+H Requiere | ES-HRMS *m/z* |
|---|---|---|---|---|---|
| Ej 618 | $CH_2OH$ | 72 | $C_{22}H_{20}BrF_2N_2O_4$ | 493,0569 | 493,0604 |
| Ej 619 | $CH_2OCOCH_3$ | 53 | $C_{24}H_{22}BrF_2N_2O_5$ | 535,0675 | 535,0692 |
| Ej 620 | $SO_2N(CH_3)_2$ | 21 | $C_{22}H_{23}BrF_2N_3O_4S$ | 542,0555 | 542,0567 |

Ejemplo 621

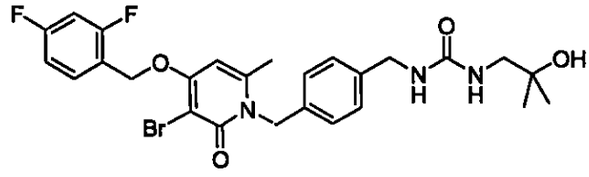


N-(4-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}bencil)-N'-metilurea

Preparación de (4-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}bencil)-N'-metilurea El compuesto del Ejemplo 159 (150 mg, 0,33 mmol) se disolvio en N,N-dimetilacetamida (5 ml) y se enfrió a 0 °C Se agrego 4-nitrofenil cloroformato (100 mg, 0,5 mmol), seguido de N,N-diisopropiletilamina (0,15 ml, 0,85 mmol) y la reaccion se agito a 0 °C durante 5 minutos Se agregó N-metilamina (0,5 ml, 1,0 mmol, 2M en tetrahidrofurano) y se dejó que la reaccion alcanzara la temperatura ambiente y se agito durante 1 hora Luego, se diluyo la reaccion con tetrahidrofurano (40 ml) y resina poliamina (1,3 g, 2,81 mmol/g) y se agregó poliestireno funcionalizado con metilisocianato (1 g, 1,38 mmol/g) Se

agitó la mezcla durante 16 horas a temperatura ambiente, se filtro y el filtrado resultante se concentro hasta lograr un aceite que se trituró con éter Se recogio el solido de color blanco resultante, se lavo con eter y se secó (87 mg, al 52%) $^1$H NMR (400 MHz, $CD_3OD$) δ 7,61 (aprox q, J = 8,4 Hz, 1H), 7,24 (d, J = 8,0 Hz, 2H), 7,07 (d, J = 8,0 Hz, 2H), 7,02 (aprox t, J = 8,4 Hz, 2H), 6,47 (s, 1H), 5,39 (s, 2H), 5,28 (s, 2H), 4,26 (s, 2H), 2,68 (s, 3H), 2,34 (s, 3H) ES-HRMS m/z 506 0862 (M+H calculado para $C_{23}H_{23}BrF_2N_3O_3$ requiere 506,0885)

Ejemplo 622



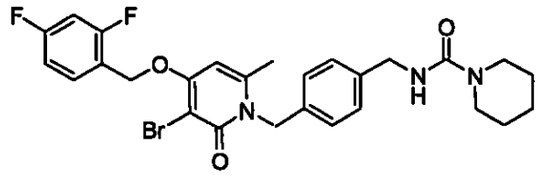
N-(4-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}bencil)-N'-(2-hidroxi-2-metilpropil)urea

Preparacion de N-(4-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}bencil)-N'-(2-hidroxi-2-metilpropil)urea

El compuesto del Ejemplo 159 (300 mg, 0,67 mmol) se disolvió en N,N-dimetilacetamida (5 ml) y se enfrio a 0 °C Se agrego 4-nitrofenil cloroformato (200 mg, 1,0 mmol), seguido de N,N-diisopropiletilamina (0,3 ml, 1,7 mmol) y la reacción se agitó a 0 °C durante 5 minutos Se agregó 3-amino-2-metil-2-propanol (248 mg, 2,0 mmol) y se permitio que la reacción alcanzara la temperatura ambiente y se agito durante 3 horas La reaccion despues se diluyó con tetrahidrofurano (40 ml) y se agregaron resina poliamina (1,3 g, 2,81 mmol/g) y poliestireno funcionalizado con metilisocianato (1 g, 1,38 mmol/g) Se agito la mezcla durante 16 horas a temperatura ambiente, se filtro y el

filtrado resultante se concentró hasta lograr un aceite que se trituró con éter El solido de color blanco resultante se purificó mediante cromatografia (gel de silice, hexano/acetato de etilo/metanol) seguido de cromatografia de fase inversa ($C_{18}$, ácido trifluoroacetico acuoso/acetonitrilo al 0,1%) para producir un sólido blanquecino (43 mg, al 11%) $^1$H NMR (400 MHz, $CDCl_3$) δ 7,56 (aprox q, J = 8,0 Hz, 1H), 7,12 (d, J = 8,4 Hz, 2H), 6,97 (d, J = 8,0 Hz, 2H), 7,02 (aprox dt, J = 1,6, 8,0 Hz, 2H), 6,83-6,88 (m, 1H), 6,06 (s, 1H), 5,26 (s, 2H), 5,21 (s, 2H), 4,22 (s, 2H), 3,09 (s, 2H), 2,30 (s, 3H), 1,14 (s, 6H) ES-HRMS m/z 564,1279 (M+H calculado para $C_{20}H_{20}BrF_2N_3O_4$ requiere 564,1304)

Ejemplo 623

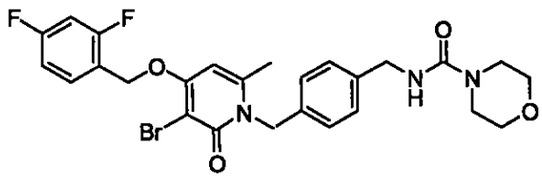


N-(4-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}bencil)piperidina-1-carboxamida

Siguiendo el metodo general para el Ejemplo 622 y sustituyendo 3-amino-2-metil-2-propanol por piperidina (170 mg, 2 0 mmol) se preparó el compuesto del titulo y se purificó por cromatografia (gel de silice, hexano/acetato de etilo/metanol) y asi se proporcionó un aceite que fue triturado con eter para proporcionar un sólido de color blanco (107 mg, al 78%) $^1$H NMR (400 MHz, $CDCl_3$) δ 7,56 (aprox q, J = 8,0 Hz, 1H), 7,23 (d, J = 8,4 Hz, 2H), 7,11 (d, J = 8,0 Hz, 2H), 7,02 (aprox t, J = 8,0 Hz, 2H), 6,81-6,88 (m, 1H), 5,97 (s, 1H), 5,32 (s, 2H), 5,19 (s, 2H), 4,37 (s, 2H), 3,34-3,28 (m, 4H), 2,29 (s, 3H), 1,68-1,50 (m, 6H) ES-HRMS m/z 560,1365 (M+H calculado para $C_{27}H_{29}BrF_2N_3O_3$ requiere 560,1355)

1.298
1299

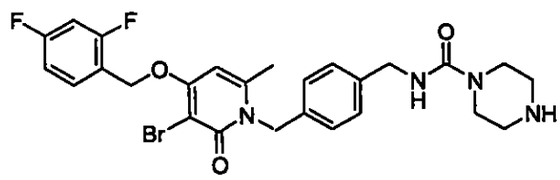
Ejemplo 624



N-(4-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}bencil)morfolina-4-carboxamida

Siguiendo el metodo general para el Ejemplo 622 y sustituyendo 3-amino-2-metil-2-propanol por morfolina (175 mg, 2 0 mmol) se preparó el compuesto del titulo y se purifico por cromatografía (gel de silice, hexano/acetato de etilo/metanol) seguido por cromatografia de fase inversa ($C_{18}$, acido trifluorcacetico acuoso/acetonitrilo al 0,1%) para proporcionar un sólido blanquecino (51 mg, al 13%) $^1$H NMR (400 MHz, $CDCl_3$) δ 7,55 (aprox q, J = 8,0 Hz, 1H), 7,17 (d, J = 8,4 Hz, 2H), 7,01 (d, J = 8,0 Hz, 2H), 6,94 (aprox dt, J = 2,4, 8,0 Hz, 1H), 6,82-6,87 (m, 1H), 6,02 (s, 1H), 5,27 (s, 2H), 5,19 (s, 2H), 4,33 (s, 2H), 3,65-3,62 (m, 4H), 3,34-3,36 (m, 4H), 2,28 (s, 3H) ES-HRMS m/z 562,1152 (M+H calculado para $C_{26}H_{27}BrF_2N_3O_4$ requiere 562,1148)

Ejemplo 625

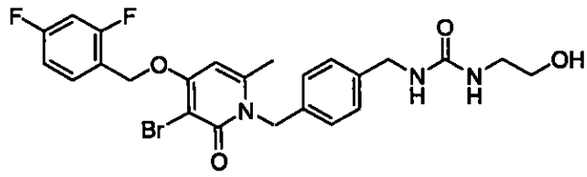


hidrocloruro de N-(4-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}bencil)piperazina-1-carboxamida

Siguiendo el metodo general para el Ejemplo 622 y sustituyendo 3-amino-2-metil-2-propanol por 1-boc-piperazina (372 mg, ?,0 mmol) se preparo el compuesto del titulo a partir de su intermedio protegido N-t-

butoxicarbonilo que fue purificado por cromatografía (gel de sílice, hexano/acetato de etilo/metanol) La desprotección se logro con 4N HCl en dioxano para proporcionar el compuesto del título como su sal de hidrocloruro (78 mg, al 19%) $^1$H NMR (400 MHz, $CD_3OD$) δ 7,61 (aprox q, J = ',6 Hz, 1H), 7,26 (aprox t, J = 8,4, 2H), 7,07 (d, J = 8,4 Hz, 2H), 7,08-7,00 (m, 2H), 6,48 (s, 1H), 5,41 (s, 2H), 5,28 (s, 2H), 4,31 (s, 2H), 3,65-3,62 (m, 4H), 3,21-3,17 (m, 4H), 2,35 (s, 3H) ES-HRMS m/z 561,1318 (M+H calculado para $C_{26}H_{28}BrF_2N_4O_3$ requiere 561,1307)

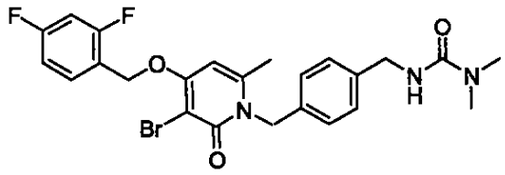
Ejemplo 626




N-(4-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}bencil)-N'-(2-hidroxietil)urea

Siguiendo el metodo general para el Ejemplo 622 y sustituyendo 3-amino-2-metil-2-propanol por etanolamina (121 mg, 2 0 mmol) se preparo el compuesto del título y se purifico por cromatografía (gel de sílice, hexano/acetato de etilo/metanol) para proporcionar un solido blanquecino (130 mg, al 36%) $^1$H NMR (400 MHz, $CDCl_3$) δ 7,54 (aprox q, J = 7,6 Hz, 1H), 7,13 (d, J = 8,4 Hz, 2H), 6,95 (d, J = 8,0 Hz, 2H), 6,96-6,92 (m, 1H), 6,83-6,88 (m, 1H), 6,09 (s, 1H), 5,26 (s, 2H), 5,21 (s, 2H), 4,24 (s, 2H), 3,56 (t, J = 4,8 Hz, 2H), 3,21 (t, J = 4,8 Hz, 2H), 2,31 (s, 3H) ES-HRMS *m/z* 536,0948 (M+H calculado para $C_{24}H_{25}BrF_2N_3O_4$ requiere 536,0991)

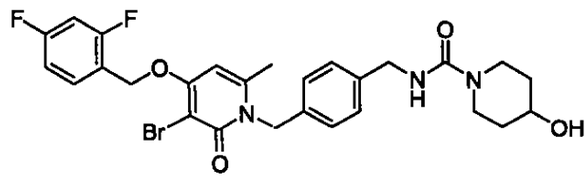
Ejemplo 627



N'-(4-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}bencil)-N,N-dimetilurea

Siguiendo el metodo general para el Ejemplo 622 y sustituyendo 3-amino-2-metil-2-propanol por N,N-dimetilamina (1,0 ml, 2 0 mmol, 2 M en tetrahidrofurano) se preparo el compuesto del titulo y se purifico por cromatografia (gel de silice, hexano/acetato de etilo/metanol) y asi se proporciono un aceite que fue triturado con eter para lograr un solido de color blanco (65 mg, al 19%) $^1$H NMR (400 MHz, $CDCl_3$) δ 7,56 (aprox q, J = 8,0 Hz, 1H ), 7,22 (d, J = 8,0 Hz, 2H), 7,10 (d, J = 8,0 Hz, 2H), 6,93 (aprox dt, J = 2,0, 8,0 Hz, 1H), 6,87-6,81 (m, 1H), 5,97 (s, 1H), 5,31 (s, 2H), 5,19 (s, 2H), 4,36 (s, 3H), 2,89 (s, 6H), 2,28 (s, 3H) ES-HRMS *m/z* 520,1072 (M+H calculado para $C_{24}H_{25}BrF_2N_3O_3$ requiere 520,1042)

Ejemplo 628

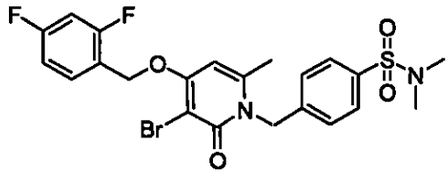


N-(4-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}bencil)-4-hidroxipiperidina-1-carboxamida

Siguiendo el método general para el Ejemplo 622 y sustituyendo 3-amino-2-metil-2-propanol por 4-hidroxipiperidina (202 mg, 2,0 mmol) se preparó el compuesto del titulo y se purifico por cromatografia (gel

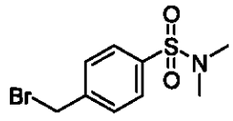
de sılıce, hexano/acetato de etılo/metanol) y ası se proporcıono un aceıte que fue trıturado con eter para proporcıonar un sólıdo de color blanco (41 mg, al 11%) $^1$H NMR (400 MHz, $CDCl_3$) d 7,56 (aprox q, J = 8,0 Hz, 1H), 7,20 (d, J = 7,6 Hz, 2H), 7,06 (d, J = 8,0 Hz, 2H), 6,94 (aprox t, J = 8,0 Hz, 1H), 6,84 (aprox t, J = 8,0 Hz, 1H), 5,99 (s, 1H), 5,29 (s, 2H), 5,19 (s, 2H), 4,34 (s, 2H), 3,84-3,70 (m, 3H) 3,04-2,92 (m, 3H), 2,28 (s, 3H) 1,84-1,81 (m, 2H), 1,47-1,44 (m, 2H) ES-HRMS *m/z* 576,1348 (M+H calculado para $C_{27}H_{29}BrF_2N_3O_4$ requıere 576,1304)

Ejemplo 629



4-{[3-bromo-4-[(2,4-dıfluorobencıl)oxı]-6-metıl-2-oxopırıdın-1(2H)-ıl]metıl}-N,N-dımetılbencenosulfonamıda

Etapa 1 Preparación de 4-bromometıl-N,N-dımetılbencenosulfonamıda

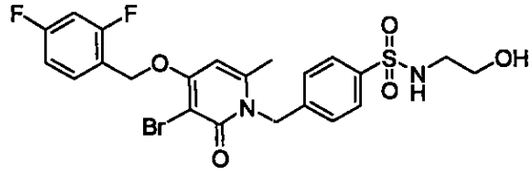


Se dısolvıó cloıuro de 4-(bromometıl)bencenosulfonılo (5,0 g, 18,6 mmol) en tetrahıdrofurano Se agrego N,N-dımetılamına (7,7 ml, 15,5 mmol, 2M en tetrahıdrofurano) y N,N-dıısopropıletılamına (3,5 ml, 20,1 mmol), y la reaccion se agıtó a temperatura ambıente durante 2 horas La reaccion se concentro hasta obtener un aceıte que se dıvıdıó entre agua y acetato de etılo y se extrajo con acetato de etılo Los extractos orgánıcos se combınaron, se lavaron con salmuera, se secaron sobre $Na_2SO_4$, y se fıltraron El fıltrado resultante se concentró hasta obtener un aceıte el cual deposito agujas que eran una

mezcla del compuesto del título y 4-clorometil N,N-dimetilbencenosulfonamida Las agujas resultantes fueron recolectadas y secadas (2,3 g, al 44 %) ES-HRMS *m/z* 534 (M+H) y 578 (M+H)

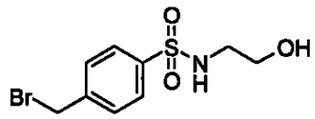
Etapa 2 Preparacion de 4-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}-N,N-dimetilbencenosulfonamida Se suspendio 3-bromo-4-(2,4-difluorofenoxi)-6-metilpiridin-2(1H)-ona (300 mg, 0,91 mmol) en 1,4-dioxano (50 ml) Se agregó 4-(bromometil)-N,N-dimetilbencenosulfonamida ( de la Etapa 1) (300 mg, 1,09 mmol) seguido de hidruro de sodio (45 mg, 1,09 mmol, en aceite mineral al 60%) La reaccion se calento a 80 °C y se agitó durante 16 horas despues de lo cual se agrego mas hidruro de sodio (45 mg, 1,09 mmol, en aceite mineral al 60%) y yoduro de sodio (150 mg, 1,0 mmol) La reacción se agito a 80 °C durante 4 horas más Luego la reaccionse filtro a traves de Celite® y el filtrado se concentro hasta lograr un aceite que se purifico mediante cromatografia (gel de silice, hexanos/acetato de etilo) seguido de cromatografia de fase inversa ($C_{18}$, acido trifluoroacetico acuoso/acetonitrilo al 0,1%) para producir un solido blanquecino (41 mg, al 8%) $^1$H NMR (400 MHz, $CDCl_3$) δ 7,71 (d, J = 8,4 Hz, 1H ), 7,57 (aprox q, J = 7,6 Hz, 1H), 7,29 (d, J = 8,0 Hz, 2H), 6,95 (aprox dt, J = 2,0, 8,0 Hz, 1H), 6,88-6,83 (m, 1H), 6,05 (s, 1H), 5,42 (s, 2H), 5,22 (s, 2H), 2,69 (s, 6H), 2,29 (s, 3H) ES-HRMS m/z 527,0439 (M+H calculado para $C_{22}H_{22}Br_2F_2N_2O_4S$ requiere 527,0446)

Ejemplo 630



4-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}-N-(2-hidroxietil)bencenosulfonamida

Etapa 1 Preparacion de 4-bromometil-N-(2-hidroxietil)bencenosulfonamida



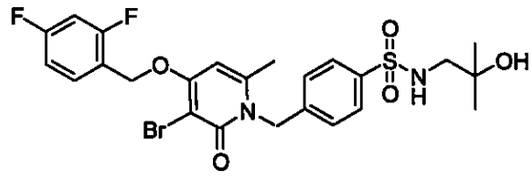
Se disolvió cloruro de 4-(bromometil)bencenosulfonilo (5,0 g, 18,6 mmol) en tetrahidrofurano Se agregó etanolamina (1,1 ml, 18,6 mmol) y N,N-diisopropiletilamina (3,9 ml, 22,3 mmol), y la reaccion se agito a temperatura ambiente durante 30 minutos La reaccion se concentró hasta obtener un aceite que se dividio entre agua y acetato de etilo y se extrajo con acetato de etilo Los extractos organicos se combinaron, se lavaron con salmuera, se secaron sobre $Na_2SO_4$, y se filtraron El filtrado resultante se concentro hasta obtener un aceite que fue una mezcla del compuesto del titulo y 4-clorometil N-(2-hidroxietil)bencenosulfonamida El aceite resultante se seco *in vacuo* (3,7 g, al 68%) ES-HRMS *m/z* 250 (M+H) y 294 (M+H)

Etapa 2 Preparación de 4-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}-N-(2-hidroxietil)bencenosulfonamida

El compuesto del titulo se preparo esencialmente de acuerdo con el procedimiento descrito en la Etapa 2 del Ejemplo 629, usando 4-bromometil-N-(2-hidroxietil)bencenosulfonamida ( de la etapa 1) $^1H$ NMR (400 MHz, $CDCl_3$) d 7,81 (d, J = 8,4 Hz, 2H), 7,61 (aprox q, J = 7,6 Hz, 1H), 7,30 (d, J = 8,4 Hz, 2H), 6,95 (aprox t, J = 8,4 Hz, 2H), 6,53 (s, 1H), 5,49 (s, 2H), 5,30 (s, 2H), 3,50 (t, J = 6,0 Hz, 2H), 2,92 (t, J = 6,0 Hz, 2H),

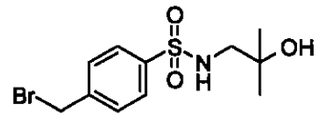
2,36 (s, 3H) ES-HRMS m/z 543,0453 (M+H calculado para $C_{22}H_{22}Br_2F_2N_2O_5S$ requiere 543,0395)

Ejemplo 631



4-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}-N-(2-hidroxi-2-metilpropil)bencenosulfonamida

Etapa 1 Preparacion de 4-bromometil-N-(2-hidroxi-2-metilpropil)bencenosulfonamida

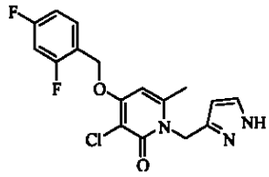


Se disolvió cloruro de 4-(bromometil)bencenosulfonilo (2,0 g, 7,3 mmol) en tetrahidrofurano Se agregó 3-amino-2-metil-2-propanol (1,0 ml, 8 mmol) y N,N-diisopropiletilamina (1,5 ml, 8,8 mmol), y la reaccion se agito a temperatura ambiente durante 30 minutos La reaccion se concentro hasta obtener un aceite que se dividio entre agua y acetato de etilo y se extrajo con acetato de etilo Los extractos organicos se combinaron, se lavaron con salmuera, se secaron sobre $Na_2SO_4$, y se filtraron El filtrado resultante se concentro hasta obtener un aceite que fue una mezcla del compuesto del titulo y 4-clorometil N-(2-hidroxi-2-metilpropil)bencenosulfonamida El aceite resultante se seco *in vacuo* (1,9 g, al 81 %)

Etapa 2 Preparacion de 4-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}-N-(2-hidroxi-2-metilpropil)bencenosulfonamida

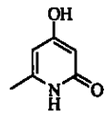
El compuesto del titulo se preparo esencialmente de acuerdo con el procedimiento descrito en la Etapa 2 del Ejemplo 629, usando 4-bromometil-N-(2-hidroxi-2-metilpropil)bencenosulfonamida ( de la etapa 1) $^1$H NMR (400 MHz, $CDCl_3$) d 7,78 (d, J = 8,4 Hz, 2H), 7,56 (aprox q, J = 7,6 Hz, 1H), 7,26 (d, J = 8,4 Hz), 6,95 (aprox t, J = 8,4 Hz, 1H), 6,86-6,83 (m, 1H), 6,07 (s, 1H), 5,41 (s, 2H), 5,22 (s, 2H), 4,98 (t, J = 6,4 Hz, 1H), 2,84 (d, J = 6,4 Hz, 2H), 2,29 (s, 3H), 1,21 (s, 6H) ES-HRMS *m/z* 571,0684 (M+H calculado para $C_{24}H_{26}Br_2F_2N_2O_5S$ requiere 571,0708)

Ejemplo 632



3-Cloro-4-(2,4-difluorobenciloxi)-6-metil-1-(1*H*-pirazol-3-ilmetil)-1*H*-piridin-2-ona

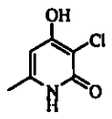
Etapa 1 Preparacion de -4-hidroxi-6-metil-1*H*-piridin-2-ona



Se disolvio 4-hidroxi-6-metil-piran-2-ona (25,8 g, 0,2 mol) en 180 ml de hidroxido de amonio concentrado La reaccion se calento a reflujo durante 4 horas La reacción se enfrio a temperatura ambiente y se evaporo en un rotovapor a un cuarto del volumen original El solido resultante se filtro, se lavo con agua fria, hexanos, y se seco en un horno de vacio durante toda la noche para proporcionar un solido de color blanco (25 g, al 98%) $^1$H NMR (300 MHz, DMSO-$d_6$) d 10,94 (br s, 1H), 10,34 (s, 1H),

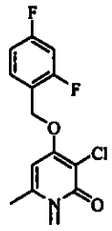
5,59 (d, $J$ = 1,4 Hz, 1H), 5,32 (d, $J$ = 2,0 Hz, 1H), 2,07 (s, 3H)

Etapa 2 Preparación de 3-cloro-4-hidroxi-6-metil-1*H*-piridin-2-ona



Se disolvio 4-hidroxi-6-metil-1*H*-piridin-2-ona (25g, 0,2 mol) y *N*-clorosuccinimida (29,4 g, 0,22 mol) en 200 ml de ácido acético La reaccion se calento a 115 °C durante 6 horas La reacción se enfrió a temperatura ambiente, el sólido se filtro y se lavo con acido acetico y hexanos El sólido se secó en un horno de vacio durante toda la noche para proporcionar un solido de color blanco (19,2 g, al 60%) $^1$H NMR (300 MH , DMSO-$d_6$) d 11,46 (br s, 1H), 11,04 (s, 1H), 5,79 (s, 1H), 2,09 (s, 3H)

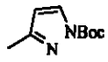
Etapa 3 Preparacion de 3-cloro-4-(2,4-difluorobenciloxi)-6-metil-1*H*-piridin-2-ona



Se disolvio 3-cloro-4-hidroxi-6-metil-1*H*-piridin-2-ona (19,2 g, 0,12 mol) y DBU (19,9 ml, 0,13 mol) en 70 ml de NMP Se agrego 2,4-difluorobencilbromuro (17 ml, 0,13 mol) gota a gota y la reacción se calentó a 80 °C durante 6 horas La reaccion se enfrió a temperatura ambiente, el sólido se filtro y se lavo con NMP y hexanos El solido se seco en un horno de vacio durante toda la noche para proporcionar un solido de color blanco (4,4 g, al 13%) $^1$H NMR (300 MHz, DMSO-$d_6$) d 11,88 (br s, 1H), 7,63 (aprox q,

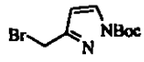
$J$ = 9 Hz, 1H), 7,33 (aprox t, $J$ = 10 Hz, 1H), 7,16 (aprox t, $J$ = 9 Hz, 1H), 6,37 (s, 1H), 5,24 (s, 2H), 2,20 (s, 3H)

Etapa 4 Preparacion de ester *terc*-butılico de acıdo 3-metılpırazol-1-carboxılico



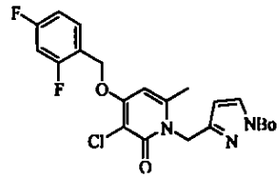

El 3-metıl-1H-pırazol (5,3 g, 65 mmol), DMAP (0,79 g, 6,5 mmol) y el dıcarbonato dı-*terc*-butılico (2,8 g, 13 mmol) estuvıeron a temperatura ambıente en 90 ml de $CH_3CN$ durante 1 hora La reaccıon se evaporó en un rotovapor, y el solıdo resultante se dısolvıo en EtOAc, se lavó con 1 N HCl, agua y salmuera, se secó ($MgSO_4$), se fıltro y se evaporo en un rotovapor para proporcıonar un aceıte de color amarıllo claro (11,4 g, al 96%) $^1$H NMR (300 MHz, $CDCl_3$) d 7,96 (d, $J$ = 2,7 Hz, 1H), 6,17 (d, $J$ = 2,7 Hz, 1H), 2,32 (s, 3H), 1,63 (s, 9H)

Etapa 5 Preparación de ester *terc*-butılico de acıdo 3-bromometılpırazol-1-carboxılico




Se dısolvıo ester *terc*-butılico de acıdo 3-metılpırazol-1-carboxılico (6,0 g, 33 mmol), N-bromosuccınımıda (1,0 g, 5,6 mmol) y peroxıdo de benzoılo (50 mg) en 20 ml de tetracloruro de carbono La reaccıon se calento a reflujo durane 16 horas La reaccıon se enfrıo a temperatura ambıente, se fıltro y se concentro bajo una presión reducıda La purıfıcación por cromatografıa rápıda en columna (sılıce, 1 4 EtOAc/hexanos) proporcıono un aceıte de color amarıllo claro (4,5 g, al 53%) $^1$H NMR (300 MHz, $CDCl_3$) d 8,03 (d, $J$ = 2,6 Hz, 1H), 6,47 (d, $J$ = 2,6 Hz, 1H), 4,48 (s, 2H), 1,64 (s, 9H)

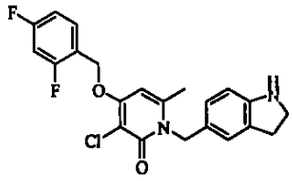
Etapa 6 Preparacion de ester *terc*-butılico de acıdo 3-[3-cloro-4-(2,4-dıfluorobencıloxı)-6-metıl-2-oxo-2*H*-pırıdın-1-ılmetıl]pırazol-1-carboxılico



Se preparó éster *terc*-butílico de ácido 3-[3-cloro-4-(2,4-difluorobenciloxi)-6-metil-2-oxo-2*H*-piridin-1-ilmetil]pirazola-1-carboxílico mediante un procedimiento similar al descrito para el Ejemplo 401 proporciono un solido de color amarillo (1,4 g, al 39%) $^1$H NMR (300 MHz, $CDCl_3$) δ 7,53-7,49 (m, 2H), 6,97-6,81 (m, 2H), 6,35 (d, *J* = 2,0 Hz, 1H), 6,01 (s, 1H), 5,32, (s, 2H), 5,26, (s, 2H), , 2,52 (s, 3H), 1,62 (s, 9H)

Etapa 7 Preparacion del compuesto del titulo del Ejemplo 632 éster *terc*-butílico de acido 3-[3-cloro-4-(2,4-difluorobenciloxi)-6-metil-2-oxo-2*H*-piridin-1-ilmetil]pirazola-1-carboxílico (0,16 g, 0 34 mmol) se calento a 140 °C durante 16 horas La mezcla de reaccion se enfrio a temperatura ambiente La recristalizacion del cloruro de metileno/hexanos proporciono un solido blanquecino (1,0 g, al 91%) $^1$H NMR (300 MHz, DMSO-$d_6$) d 12,67 (br s, 1H), 7,67 - 7,60 (m, 2H), 7,34 (dt, *J* = 10,5, 2,5 Hz, 1H), 7,17 (dt, *J* = 8,5, 1,6 Hz, 1H), 6,52 (s, 1H), 6,10 (d, *J* = 1,9 Hz, 1H), 5,27 (s, 2H), 5,20 (s, 2H), 2,48 (s, 2H)

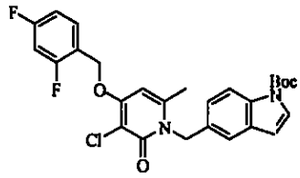
Ejemplo 633



3-Cloro-4-(2,4-difluorobenciloxi)-6-metil-1-(2,3-dihidro-1H-indol-5-ilmetil)-1H-piridin-2-ona

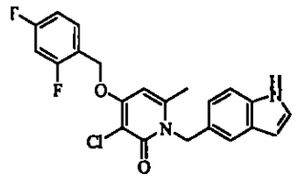
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Etapa 1 Preparacion de éster *terc*-butılico de acido 5-[3-cloro-4-(2,4-dıfluorobencıloxı)-6-metıl-2-oxo-2H-pırıdın-1-ılmetıl]ındol-1-carbamico



Se preparo ester *terc*-butılico de acido 5-[3-cloro-4-(2,4-dıfluorobencıloxı)-2-oxo-2H-pırıdın-1-ılmetıl]ındol-1-carbámico mediante un procedimiento sımılar al descrito para el Ejemplo 632 como un solido blanquecino (2,5 g, al 61%) $^1$H NMR (300 MHz, DMSO-$d_6$) δ 8,00 (d, $J$ = 8,5 Hz, 1H), 7,70-7,62 (m, 2H), 7,39-7,32 (m, 2H), 7,21-7,13 (m, 2H), 6,70 (d, J = 3,8 Hz, 1H), 6,66 (s, 1H), 5,40 (s, 2H), 5,29 (s, 2H), 2,33 (s, 3H), 1,62 (s, 9H)

Etapa 2 Preparación de 3-cloro-4-(2,4-dıfluorobencıloxı)-6-metıl-1-(1H-ındol-5-ılmetıl)-1H-pırıdın-2-ona

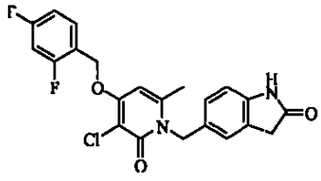


Ester *terc*-butılico de acido 5-[3-cloro-4-(2,4-dıfluorobencıloxı)-6-metıl-2-oxo-2H-pırıdın-1-ılmetıl]ındol-1-carbamico (1,08 g, 2,1 mmol) dısuelto en 40 ml de DMSO se agıto a 120 °C durante 20 horas La reacción se enfrıo a temperatura ambıente, se dıluyo con agua y se lavo 5 veces con acetato de etılo Los materıales organıcos combınados se lavaron 1 vez con salmuera, se secaron ($MgSO_4$), se fıltraron y se concentraron bajo una presion reducıda $^1$H NMR (300 MHz, DMSO-$d_6$) d 11,1 (br s, 1H), 7,67 (d, J = 6,7 Hz, 1H), 7,36 - 7,32 (m, 2H), 7,23 (s, 1H), 7,18 (d, J = 2,3 Hz, 1H), 6,93 (dd, J = 8,4, 1,2

Hz, 1H), 6,57 (s, 1H), 6,38 (s, 1H), 5,37 (s, 2H), 5,29 (s, 2H), 2,35 (s, 3H)

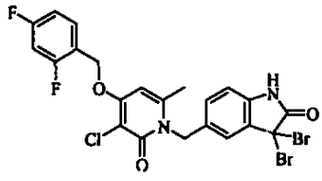
Etapa 3 3-Cloro-4-(2,4-difluorobenciloxi)-6-metil-1-(1H-indol-5-ilmetil)-1H-piridin-2-ona (, de la Etapa 2) (1,7 g, 4,1 mmol) se agito en 26 ml de ácido acetico y se agrego $NaCNBH_3$ (0,27 g, 4,3 mmol) por porciones La reacción se agito durante 1 hora La reaccion se diluyo con agua y se lavo 5 veces con acetato de etilo Los materiales orgánico, combinados se lavaron 1 vez con salmuera, se secaron ($MgSO_4$), se filtraron y se concentraron bajo una presión reducida La purificación por cromatografia rapida en columna (silice, EtOAc al 100%) proporcionó un solido de color blanco (1,2 g, al 71%) $^1H$ NMR (300 MHz, DMSO-$d_6$) d 7,64 (aprox q, J = 8,5 Hz, 1H), 7,34 (dt, J = 9,5, 2,6 Hz, 1H), 7,17 (aprox t, J = 8,5, 1H), 6,82 (s, 1H), 6 72 (d, J = 8,0 Hz, 1H), 6,53 (s, 1H), 6,42 (d, J = 8,0 Hz, 1H), 5,48 (br s, 1H), 5,27 (s, 2H), 5,13 (s, 2H), 3,37 (t, J = 8,3 Hz, 2H), 2,82 (t, J = 8,3 Hz, 2H), 2,35 (s, 3H)

Ejemplo 634



5-[3-Cloro-4-(2,4-difluorobenciloxi)-6-metil-2-oxo-2H-piridin-1-ilmetil]-1,3-dihidro-indol-2-ona

Etapa 1 Preparación de 5-[3-cloro-4-(2,4-difluorobenciloxi)-6-metil-2-oxo-2H-piridin-1-ilmetil]-3,3-dibromo-1H-indol-2-ora



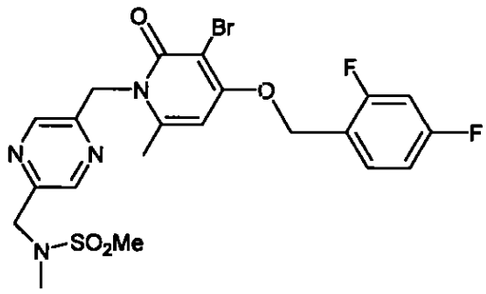
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Se suspendio 3-cloro-4-(2,4-difluorobenciloxi)-6-metil-1-(1H-indol-5-ilmetil)-1H-piridin-2-ona (0,45 mg, 1,1 mmol) (Ejemplo 633, Etapa 2) en 11 ml de *terc*-butanol y se agrego perbromuro de bromuro de piridinio (1,04 g, 3,3 mmol) por porciones La reacción se agito durante 16 horas La reaccion se diluyo con agua y se lavo 4 veces con acetato de etilo Los materiales organicos combinados se lavaron 1 vez con salmuera, se secaron ($MgSO_4$), se filtraron y se concentraron bajo una presion reducida La trituración con cloruro de metileno produjo un sólido blanquecino (0,25 g, al 39%) $^1H$ NMR (300 MHz, DMSO-$d_6$) d 11,26 (br s, 1H), 7,66 (aprox q, J = 8,6 Hz, 1H), 7,48 (s, 1H), 7,35 (dt, J = 10,5, 2,5 Hz, 1H), 7,18 (dt, J = 8,7, 1,9, 1H), 7,05 (dd, J = 8,2, 1,5, 1H), 6,88 (d, J = 8,1 Hz, 1H), 6,61 (s, 1H), 5,29 (s, 4H), 2,36 (s, 3H)

Etapa 2 Se suspendió 5-[3-cloro-4-(2,4-difluorobenciloxi)-6-metil-2-oxo-2H-piridin-1-ilmetil]-3,3-dibromo-1H-indol-2-ona (0,2 g, 0,34 mmol) en 5 ml de ácido acético, y se agrego metal de zinc (0,22 g, 3,4 mmol) La reacción se agito durante 48 horas La reaccion se diluyó con agua y se lavo 2 veces con acetato de etilo Los materiales orgánicos combinados se lavaron 1 vez con salmuera, se secaron ($MgSO_4$), se filtraron y se concentraron bajo una presión reducida La purificación por cromatografia rapida en columna (silice, EtOAc al 100%) proporcionó un solido de color blanco (0,12 g, al 82%) $^1H$ NMR (300 MHz, DMSO-$d_6$) d 10,37 (br s, 1H), 7,65 (aprox q, J = 6,9 Hz, 1H), 7,31 (dt, J = 8,2, 2,5 Hz, 1H), 7,18 (dt, J = 7,1, 1,9, 1H), 6,98 (br s, 2H), 6,77 (d, J = 8,4 Hz, 1H), 6,57 (s, 1H), 5,28 (s, 2H), 5,23 (s, 2H), 3,44 (s, 2H), 2,34 (s, 3H)

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Ejemplo 635

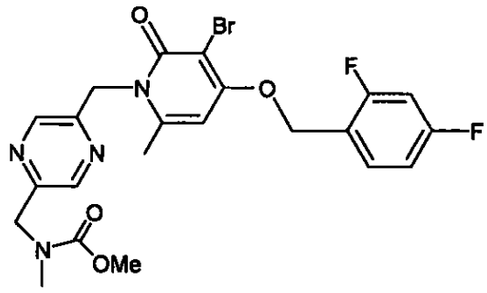



N-[5-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}pirazin-2-il)metil]-N-metilmetanosulfonamida

A una suspensión de 3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-({5-[(metilamino)metil]pirazin-2-il}metil)piridin-2(1H)-ona (0,16 g, 0,34 mmol) en acetonitrilo a 0 °C se agregó trietilamina (0,043 g, 0,42 mmol), seguida de la adición de sulfonilcloruro de metano (0,047 g, 0,41 mmol) y se agito a temperatura ambiente durante 1 h bajo atmósfera de argon Los disolventes fueron retirados *in vacuo* y el residuo fue triturado con agua y filtrado Se lavo con agua y acetonitrilo, y se seco *in vacuo* para proporcionar 0,11 g de material $^1$H NMR ($CD_3OD$/400 MHz) δ 8,62 (s, 1H), 8,55 (s, 1H), 7,61 (m, 1H), 7,0 (m, 2H), 6,53 (s, 1H), 5,47 (s, 2H), 5,29 (s, 2H), 4,49 (s, 2H), 5,95 (s, 3H), 2,85 (s,3H) y 2,55 (s, 3H), $^{19}$F NMR ($CD_3OD$/400 MHz) ) -111 70(m) and –116 07 (m), ES-HRMS m/z 543,0515 (M+H calculado para $C_{21}H_{22}BrF_2N_4O_4S$ requiere 543,0508)

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1314

Ejemplo 636



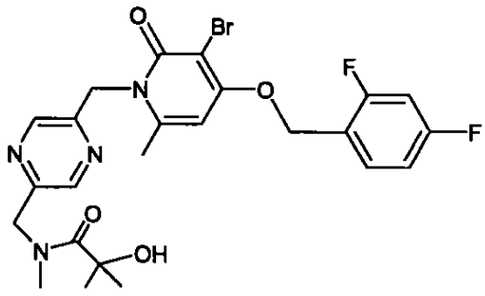
5-{[3-Bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}pirazin-2-il)metil (metil) carbamato de metilo

A una disolucion fría (5 °C) de 3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-({5-[(metilamino)metil]pirazin-2-il}metil)piridin-2(1H)-ona (0,20 g, 0,4 mmol) en DMF (2,0 ml), se agregó metilcloroformato (0,049 g, 0,52 mmol), seguido de la adición de trietilamina (0,072 g, 0,71 mmol) La mezcla se agito a 5 °C durante 30 minutos y a temperatura ambiente durante 30 minutos adicionales y se concentro *in vacuo* El residuo se dividio entre agua (5,0 ml) y EtOAc (10,0 ml) El extracto orgánico se lavo con agua, se seco ($Na_2SO_4$), y se concentro hasta lograr la sequedad El material resultante se purificó mediante HPLC de fase inversa utilizando $CH_3CN$/Agua al 10-90 % en gradiente (60 min) a un caudal de 70 ml/min Las fracciones apropiadas (m/z = 523 M+H) se combinaron y se deshidrataron por congelacion para producir un polvo de color blanco Esto se dividio entre $NaHCO_3$ al 5% (10 ml) y EtOAc (15 ml) La capa organica se lavó con agua, se secó ($Na_2SO_4$) y se concentro hasta alcanzar la sequedad para producir el compuesto del titulo (0,12 g, al 53%) como un polvo de color blanco $^1H$ NMR ($CD_3OD$/400 MHz) □ □ □□ s, 1H), 8,41 (m, 1H), 7,60 (m, 1H), 7,05 (m, 2H), 6,52 (s, 1H), 5,45 (s, 2H), 5,29 (s,

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1315

2H), 4,58 (s, 2H), 3,69 y 3,64 (s, 3H), 2,97 (s, 3H), 2,85 (s,3H) y 2,55 (s, 3H), $^{19}F$ NMR ($CD_3OD$/400 MHz) ) -111,69(m) y -116, 09 (m), ES-HRMS m/z 523,0775 (M+H calculado para $C_{22}H_{22}BrF_2N_4O_4$ requiere 523,0787)

Ejemplo 637



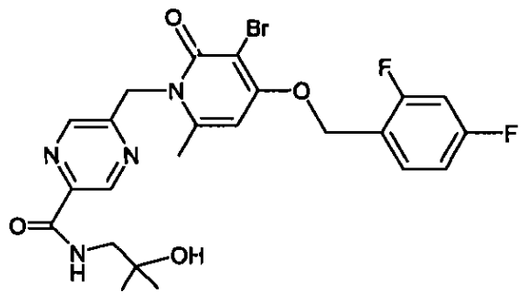
N-[(5-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}pirazin-2-il)metil]-2-hidroxi-N,2-dimetilpropanamida

A una disolucion fria (5 °C) de 3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-({5-[(metilamino)metil]pirazin-2-il}metil)piridin-2(1H)-ona (0,24 g, 0,52 mmol) en DMF (2,0 ml), se agrego cloruro de 2-acetoxiisobutirilo (0,093g, 0,56 mmol), seguido de la adición de trietilamina (0,072 g, 0,71 mmol) La mezcla se agito a temperatura ambiente durante 2 horas adicionales y se concentro *in vacuo* El residuo se dividió entre agua (5,0 ml) y EtOAc (15,0 ml) El extracto de EtOAc se lavo con agua, se seco ($Na_2SO_4$), y se concentro hasta lograr la sequedad El material resultante (0,2 g) se agitó con 1 M LiOH (0,5 ml, MeOH,/Agua1 1vol/vol) a temperatura ambiente durante 3 horas, se enfrio, se acidifico con ácido trifluoroacetico y el producto se purifico por HPLC de fase inversa utilizando $CH_3CN$/ Agua al 10 -90 % en gradiente (60 min ) a un caudal de 70 ml/min Las fracciones apropiadas (m/z = 551 M+H) se combinaron y se deshidrataron por congelación para producir un polvo de color blanco Esto

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se dividio entre $NaHCO_3$ al 5% (10 ml) y EtOAc (15 ml) La capa organica se lavó con agua, se seco ($Na_2SO_4$) y se concentró hasta alcanzar la sequedad para producir el compuesto del titulo (0,075 g) como un polvo de color blanco $^1H$ NMR ($CD_3OD$/400 MHz) δ 8,59 (s, 1H), 8,41 (br, 1H), 7,60 (m, 2H), 7,01 (m, 2H), 6,52 (s, 1H), 5,45 (s, 2H), 5,29 (s, 2H)

Ejemplo 638



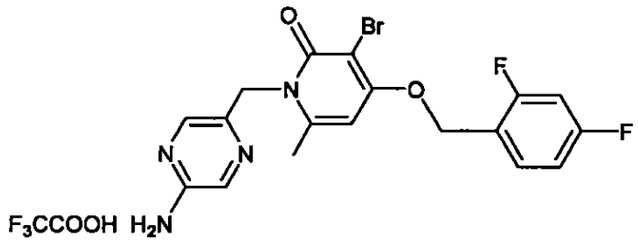

5-{[3-Bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}-N-(2-hidroxi-2-metilpropil)pirazina-2-carboxamida

A una disolución de acido 5-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopyridin-1(2H)-il]metil}pirazina-2-carboxilico (0,42 g, 0,9 mmol) en DMF (3,0 ml) se agrego isobutilcloroformato (0,126 g, 0,13 mmol) seguido de la adicion de N-metilmorfolina (0,11 g, 1,1 mmol ) y se agito a -10 °C, bajo atmosfera de argón Despues de 20 minutos, se agrego una disolucion de hidrocloruro de 1,1 dimetil-2-aminoetanol (0,135 g, 1,1 mmol) en DMF (2,0 ml) que contenia N-metilmorfolina (0,11 g, 1,1 mmol) La mezcla se agito a temperatura ambiente durante 1 hora y se concentro *in vacuo* hasta lograr la sequedad El residuo resultante se purifico mediante HPLC de fase inversa utilizando $CH_3CN$/Agua al 10-90% (60 min) a un caudal de 70 ml/min Las fracciones apropiadas (m/z = 537 M+H) se combinaron y se deshidrataron por congelacion

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para producir un polvo de color blanco Esto se dividio entre $NaHCO_3$ al 5% (10 ml) y EtOAc (15 ml) La capa organica se lavó con agua, se seco ($Na_2SO_4$) y se concentro hasta alcanzar la sequedad para producir el compuesto del titulo (0,35 g, al 75%) como un polvo de color blanco $^1H$ NMR ($CD_3OD$/ 400 MHz) δ 9,1 (d, 1H, J = 1,6 Hz), 8,71 (d, 1H, J = 1,6 Hz), 7,61 (m 1H), 7,02 (m, 2H), 6,54 (s, 1H), 5,54 (s, 2H), 5,30 (s, 2h) 3,30 (s, 2h), 2,55 (s, 3H) y 1,21 (s, 6H), $^{19}F$ NMR($CD_3OD$/ 400 MHz) -111,67(m) y -116,05 (m), ES-HRMS m/z 537,0948 (M+H calculado para $C_{23}H_{24}BrF_2N_4O_4$ requiere 537,0943)

Ejemplo 639




Trifluoroacetatc de 1-[(5-aminopirazin-2-il)-metil]-3-bromo-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona

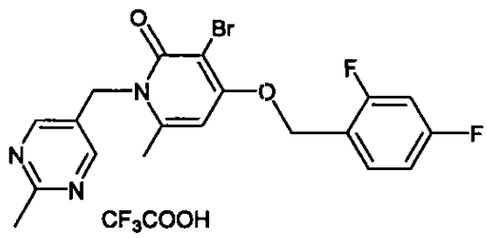
Una mezcla de ácido 5-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopyridin-1(2H)-il]metil}pirazina-2-carboxilico (0,70g, 1,5 mmol) azuro difenilfosforilo (0,51 g, 1,8 mmol) en dimetilacetamida (15,0 ml) y t-butanol (5,0 ml) que contenia trietilamina (0,18 g, 1,8 mmol) se calento a 90 °C durante 6 horas, bajo atmósfera de argon La mezcla de reaccion se enfrió y se filtro el precipitado Se lavo con acetonitrilo y se seco para obtener 0,22 g del acido no reaccionado El filtrado combinado y los lavados se concentraron *in vacuo* y el material resultante se purificó mediante HPLC de fase inversa utilizando $CH_3CN$/Agua al 10-90 % en gradiente (60 min) a un caudal de 70 ml/min Las fracciones apropiadas

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(m/z = 437 M+H) se combinaron y se deshidrataron por congelacion para producir el compuesto del titulo (0,21g, 37%) como un polvo de color blanco $^1$H NMR (DMSO-$d_6$/ 400 MHz) □ 7 ,8 (d, 1H, J = 1,2 Hz), 7,75 (d, 1H, J = 1,2 Hz), 7,61 (m 1H), 7,34 (m, 1H), 7,18 (m,1H), 6,49 (s, 1H), 5,25 (s, 2H), 5,10 (s, 2H), y 2,49 (s, 3H), $^{19}$F NMR($CD_3OD$/ 400 MHz)

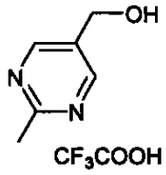
-111,72(m) y -116,11 (m), ES-HRMS m/z 437,0402(M+H calculado para $C_{18}H_{16}BrF_2N_4O_2$ requiere 437,0419)

Ejemplo 640




Trifluoroacetato de 3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-[(3-(metil-1,2,4-triazin-6-il)metil]piridin-2(1H)-ona

Etapa 1 Preparacion de trifluoroacetato de (2-metilpirimidin-5-il)metanol




A una disolucion de 2-metilpirimidinacarboxilato de metilo (2,6 g, 17,1 mmol) en THF se agrego gota a gota diisobutilaluminiohidruro (39,5 ml, disolución 1 M en THF) y se agito a -20 °C bajo atmosfera de argon durante 1,5 horas, y a temperatura ambiente durante 2 horas La reaccion se enfrió lepentinamente mediante la adición de decahidrato de sodio sulfato en polvo (25 g), se agrego THF (25 ml) y se agitó a temperatura ambiente durante 1 hora

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Esta mezcla se dejo reposar en el refrigerador durante toda la noche y se filtro a través de una almohadilla de celite El precipitado se lavo por completo con THF (100 ml) tibio que contenia etanol al 10% Los lavados combinados y el filtrado se concentraron para producir un jarabe de color amarillo, el cual se purifico mediante HPLC de fase inversa utilizando $CH_3CN$/ Agua al 10-90% en gradiente (60 minutos) a un caudal de 70 ml/min Las fracciones apropiadas (m/z = 125 M+H) se combinaron y liofilizaron para producir el compuesto del titulo (0,67 g, al 32%) como su sal de trifluoroacetato $^1H$ NMR ($CD_3OD$/ 400 MHz) δ 8,65 (s, 2H) 4,62 (s, 2H) y 2,66 (s, 3H), ES-HRMS m/z 125,0678 (M+H calculado para $C_6H_9N_2O$ requiere 125,0709)

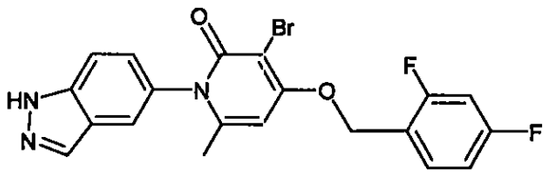
Etapa 2 Preparación de trifluoroacetato de 3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-[(3-(metil-1,2,4-triazin-6-il)metil]piridin-2(1H)-ona

A una disolución de trifluoroacetato de (2-metilpirimidin-5-il)metanol (0,9 g, 3,76 mmol) en diclorometaneo (10 ml) a 0 °C, se agrego trietilamina (0,95 g, 9,41 mmol), seguido de la adicion de cloruro de metanosulfonilo (0,59 g, 5,17 mmol) y se agitó a 0 °C durante 1 hora Despues de la agitacion durante 1 h a temperatura ambiente, se agrego trietilamina ( 0,22 g) y cloruro de metanosulfonilo (0,15 g) adicionales y la mezcla se agitó a temperatura ambiente durante otra hora bajo atmósfera de argón La reaccion se enfrió repentinamente mediante la adicion de agua fría (15 ml) y se agitó durante 15 minutos La capa orgánica se lavo con agua, seguida de bicarbonato de sodio al 5% (2 x 15 ml), agua y se seco ($Na_2SO_4$) Despues de la eliminacion del disolvente bajo una presion reducida, el residuo se seco en una secadora bajo vacio durante 4 horas Este material se suspendió en THF (10 ml) y DMF (5,0 ml), se agrego 3-bromo-4-(2,4-

difluorofenoxi)-6-metilpiridin-2(1H)-ona (0,5 g, 1,52 mmol) y NaH (0,04 g) La mezcla resultante se calentó a 65 °C durante 16 horas bajo atmósfera de argón Los disolventes fueron destilados bajo vacio y el residuo se purificó mediante HPLC de fase inversa utilizando $CH_3CN$/ Agua al 10-90% en gradiente (60 minutos) a un caudal de 70 ml/min Las fracciones apropiadas (m/z = 436 M+H) se combinaron y deshidrataron por congelacion para producir el compuesto del titulo (0,045 g) como su sal de trifluoroacetato $^1H$ NMR ($CD_3OD$/ 400 MHz) δ 8,58 (s, 2H) 7,61 (m, 1H), 7,01 (m, 2H), 6,53 (s, 1H), 5,37 (s, 2h), 5,29 (s, 2H), 2,65 (s, 3H) y 2,46 (s, 3H), $^{19}F$ NMR($CD_3OD$/ 400 MHz)

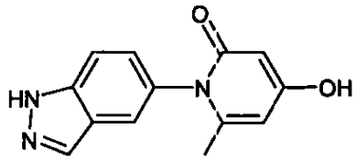
-111,62 (m) y -116,08 (m), ES-HRMS m/z 436,0433(M+H calculado para $C_{19}H_{17}BrF_2N_3O_2$ requiere 436,0467)

Ejemplo 641




3-Bromo-4-[(2,4-difluorobencil)oxi]-1-(1H-indazol-5-il)-6-metilpiridin-2(1H)-ona

Etapa 1 Preparación de 4-hidroxi-1-(1H-indazol-5-il)-6-metilpiridin-2(1H)-ona




Una mezcla de 4- hidroxi-6-metil-2-pirone (3,75 g, 0,029 mol) y 5-aminoindazol (4,0 g, 0,03 mol) en agua (70 ml) se calentó a 90 °C bajo argon durante 1 h La mezcla se enfrio, se decanto el sobrenadante y el residuo se trituro con etanol, se enfrio y se filtró el solido Se

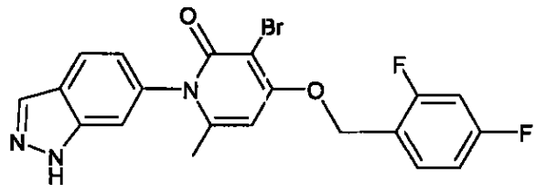
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lavo con etanol frio y se seco $^1$H NMR ($CD_3OD$/ 400 MHz) δ 8,11 (s, 1H), 7,64 (m, 2H), 7,18 (d, 1H, J = 2,0 Hz), 7,16 (d, 1H, J = 2,0 Hz) 6,07 (m, 1H), 5,81 (d, 1H, J = 2,8 Hz) y 1,94 (s, 3H), ES-HRMS m/z 242,0962(M+H calculado para $C_{13}H_{12}N_3O_2$ requiere 242,0924)

Etapa 2

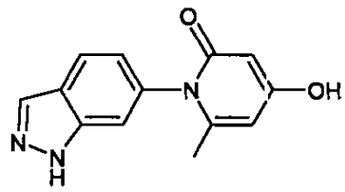
Una mezcla de 4-hidroxi-1-(1H-indazol-5-il)-6-metilpiridin-2(1H)-ona (0,2g, 0,83 mmol), N-bromosuccinmida (0,15 g, 0,84 mmol) en diclorometano (4,0 ml) y acido acético (1,0 ml) se agitó a temperatura ambiente bajo atmósfera de argon durante 2,5 horas Despues de retirar los disolventes, el residuo se seco *in vacuo* durante 4 horas en una secadora Se suspendio en DMF (3,0 ml), se agrego carbonato de potasio (0,1 g) y bromuro de 2,4 difluorobencilo y la mezcla se agitó a temperatura ambiente durante 3 horas Se destiló DMF *in vacuo* y el residuo se purificó mediante HPLC de fase inversa utilizando $CH_3CN$/ Agua al 10-90% en gradiente (60 min ) a un caudal de 70 ml/min Las fracciones apropiadas (m/z = 537 M+H) se combinaron y se deshidrataron por congelacion para producir un polvo de color blanco Esto se dividio entre $NaHCO_3$ al 5% (10 ml) y EtOAc (15 ml) La capa orgánica se lavo con agua, se seco ($Na_2SO_4$) y se concentró hasta alcanzar la sequedad para producir el compuesto del titulo (0,075 g) como un polvo de color blanco $^1$H NMR ($CD_3OD$/ 400 MHz) δ 8,13 (s, 1H ), 7,68 (m, 3H), 7,20 (2d, 1H, J = 1,2 Hz), 7,05 (m, 2H), 6,61 (s, 1H), 5,35 (s, 2H) y 2,05 (s, 3H), $^{19}$F NMR($CD_3OD$/ 400 MHz) -111,62 (m) y -116,02 (m), ES-HRMS m/z 446,0305(M+H calculado para $C_{20}H_{15}BrF_2N_3O_2$ requiere 446,0310) \

Ejemplo 642



3-Bromo-4-[(2,4-difluorobencil)oxi]-1-(1H-indazol-6-il)-6-metilpiridin-2(1H)-ona

Etapa 1 Preparacion de 4-hidroxi-1-(1H-indazol-6-il)-6-metilpiridin-2(1H)-ona

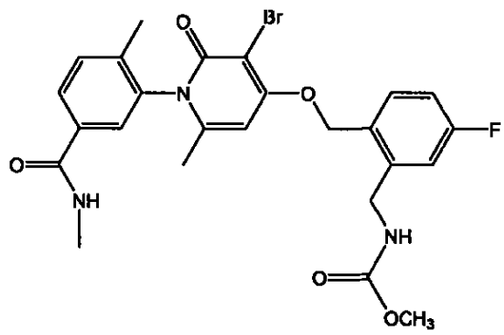


El compuesto del titulo se preparó mediante un procedimiento similar al descrito para 4-hidroxi-1-(1H-indazol-5-il)-6-metilpiridin-2(1H)-ona Rendimiento = 12%, $^1$H NMR ($CD_3OD$/ 400 MHz) δ 8,12 (s, 1H), 7,90 (d, 1H, J = 8,0 Hz), 7,42 (s, 1H), 6,94 (d, 1H, J = 8,8 Hz) 6,08 (br s, 1H), 5,81 (d, 1H, J = 2,4 Hz) y 1,96 (s, 3H), ES-HRMS m/z 242,0946(M+H calculaco para $C_{13}H_{12}N_3O_2$ requiere 242,0924)

Etapa 2

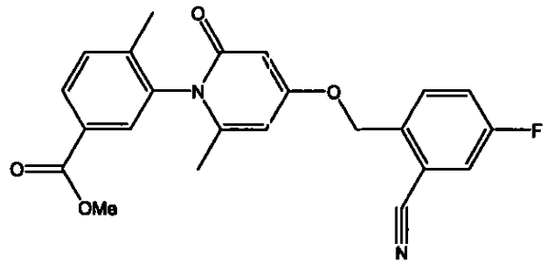
El compuesto del titulo se preparo mediante un procedimiento similar al descrito para 3-bromo-4-[(2,4-difluorobencil)oxi]-1-(1H-indazol-5-il)-6-metilpiridin-2(1H)-ona $^1$H NMR ($CD_3OD$/ 400 MHz) δ 8,14 (s, 1H), 7,93 (d, 1H, J = 8 4Hz), 7,61 (m 1H), 7,46 (s, 1H), 7,04 (m, 2H), 6,98 (m, 1H) 6,62 (s, 1H), 5,36 (s, 2H) y 2,06 (s, 3H), $^{19}$F NMR($CD_3OD$/ 400 MHz) -111,62 (m) y -116,03 (m), ES-HRMS m/z 446,0302(M+H calculado para $C_{13}H_{12}N_3O_2$ requiere 446,0310)

Ejemplo 643



2-{[(3-bromo-6-metil-1-{2-metil-5-[(metilamino)carbonil]fenil}-2-oxo-1,2-dihidropiridin-4-il)oxi]metil}-5-fluorobencilcarbamato de metilo

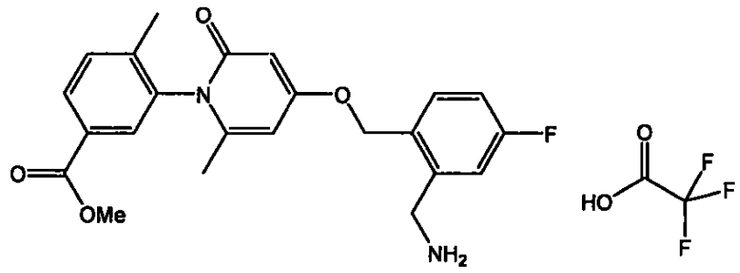
Etapa 1 Preparación de 3-[4-[(2-ciano-4-fluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-metilbenzoato de metilo



A una disolución enfriada (0 °C) de 2-(bromometil)-5-fluorobenzonitrilo (4,31 g, 20,1 mmol) y 3-(4-hidroxi-6-metil-2-oxopiridin-1(2H)-il)-4-metilbenzoato de metilo (5,00 g, 18,3 mmol) en DMF (20 ml) se agregó $K_2CO_3$ (3,00 g, 22,0 mmol) La reaccion se dejo entibiar a temperatura ambiente y se agito durante toda la noche Se agrego 2-(bromometil)-5-fluorcbenzonitrilo (0,39 g, 1,83 mmol) y $K_2CO_3$ (0,25 g, 1,83 mmol) adicionales y la reaccion se calento a 60 °C durante 2 horas El disolvente se elimino por destilacion La reaccion se neutralizo con acido citrico al 5% (50 ml) Los productos orgánicos fueron extraidos en DCM (3 x 25 ml), secados sobre $Na_2SO_4$,

filtrados y concentrados hasta obtener un aceite espeso de color marrón oscuro Se purificó mediante cromatografía rapida en columna de gel de sílice utilizando EtOAc como eluyente para generar el producto como un sólido de color marron, y se secó *in vacuo* (6,18 g, al 76%) $^1$H NMR ($CD_3OD$/ 400MHz) δ 8,03 (m, 1H), 7,76 (m, 2H), 7,66 (m, 1H), 7,52 (m, 2H), 6,24 (s, 1H), 6,09 (s, 1H), 5,27 (s, 2H), 3,89 (s, 3H), 2,12 (s, 3H), 1,90 (s, 3H) ESHRMS m/z 407,1408 (M+H calculado para $C_{23}H_{20}FN_2O_4$ requiere 407,1402)

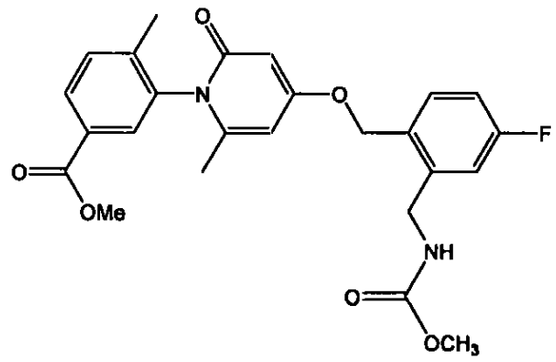
Etapa 2 Preparacion de trifluoroacetato 3-[4-{[2-(aminometil)-4-fluorcbencil]oxi}-6-metil-2-oxopiridin-1(2H)-il]-4-metilbenzoato de metilo




A una disolucion enfriada (0 °C) de 3-[4-[(2-ciano-4-fluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-metilbenzoato de metilo ( de la Etapa 1) (0,510 g, 1,25 mmol) en THF (5 ml) se agrego gota a gota $BH_3$THF (2,51 ml, 2,51 mmol) La reaccion luego se agitó a temperatura ambiente durante 2,5 horas La reaccion se enfrio (0 °C), se enfrio repentinamente por la adicion lenta de MeOH, se concentró y se purifico mediante HPLC preparatoria El producto se aisló mediante deshidratacion por congelacion y evaporación del disolvente para proporcionar un solido de color blanco, secado *in vacuo* (0,39 g, al 76%) $^1$H NMR ($CD_3OD$/ 400MHz) δ 8,04 (m, 1H), 7,75 (s, 1H), 7,63 (m, 1H), 7,55 (d, 1H, J = 8,4 Hz), 7,32 (m, 1H), 7,24 (m, 1H), 6,25 (s, 1H), 6,12 (s, 1H), 5,23 (s, 2H), 4,25 (s, 2H), 3,90 (s,

3H), 2,11 (s, 3H), 1,90 (s, 3H) ESHRMS m/z 411,1691 (M+H calculado para $C_{23}H_{24}FN_2O_4$ requiere 411,1715)

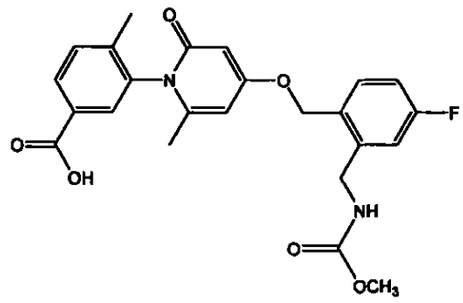
Etapa 3 Preparacion de 3-[4-[(4-fluoro-2-{[(metoxicarbonil)amino]metil}bencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-metilbenzoato de metilo




A una disolucion enfriada (0 °C) de trifluoroacetato de 3-[4-{[2-(aminometil)-4-fluorobencil]oxi}-6-metil-2-oxopiridin-1(2H)-il]-4-metilbenzoato de metilo ( de la Etapa 2) (0,50 g, 0,95 mmol) en DMA (4 ml) se agrego 4-metilmorfolina (0,21 ml, 1,9 mmol) y cloroformato de metilo (0,08 ml, 1,0 mmol) La reaccion se agitó a temperatura ambiente durante 1 hora El disolvente se elimino por destilacion El producto en crudo se purifico mediante HPLC preparatoria El acetonitrilo se evaporo y la disolucion se lavo con $NaHCO_3$ al 5% (30 ml) y se extrajo en DCM (3 x 25 ml) Los extractos organicos se secaron sobre $Na_2SO_4$, se filtraron y se concentraron hasta obtener un sólido de color blanco, secado *in vacuo* (0,36 g, al 81%) $^1H$ NMR ($CD_3OD$/ 400MHz) δ8,03 (m, 1H), 7,77 (s, 1H), 7,53 (d, 1H, J = 7,6 Hz), 7,47 (m, 1H), 7,12 (m, 1H), 7,03 (m, 1H), 6,21 (s, 1H), 6,08 (s, 1H), 5,18 (s, 2H), 4,38 (s, 2H), 3,89 (s, 3H), 3,65 (s, 3H), 2,12 (s, 3H), 1,89 (s, 3H) ESHRMS m/z 469,1767 (M+H calculado para $C_{25}H_{26}FN_2O_6$ requiere 469,1769)

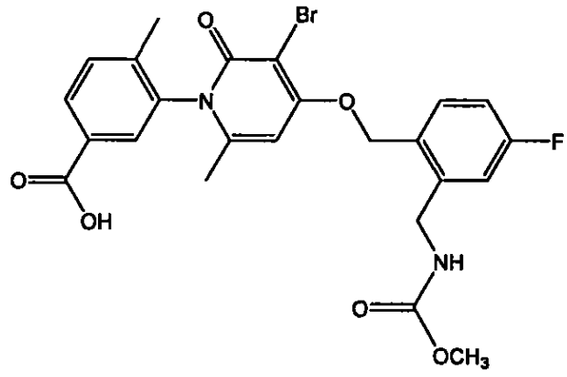
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Etapa 4 Preparacion de ácido 3-[4-[(4-fluoro-2-{[(metoxicarbonil)amino]metil}bencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-metilbenzoico



Al 3-[4-[(4-fluoro-2-{[(metoxicarbonil)amino]metil}bencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-metilbenzoato de metilo ( de la Etapa 3) (0,17 g, 0,36 mmol) se agrego disolución NaOH 1,5 N en 1 1 MeOH agua (0,39 ml, 0,59 mmol) La mezcla de reaccion se agito a 60°C durante 2,5 horas La disolución se enfrio a (0 °C), se neutralizó por la adicion lenta de ácido citrico al 5% y los productos orgánicos se extrajeron en DCM Un sólido de color blanco suspendido en la capa orgánica se filtro, se lavo con DCM y agua, se seco *in vacuo* y se convirtio en el producto deseado (0,090 g, al 55%) $^1$H NMR ($CD_3OD$/ 400MHz) δ8,03 (m, 1H), 7,75 (s, 1H), 7,52 (d, 1H, J = 8,0 Hz), 7,47 (m, 1H), 7,12 (m, 1H), 7,03 (m, 1H), 6,21 (s, 1H), 6,08 (s, 1H), 5,18 (s, 2H), 4,38 (s, 2H), 3,65 (s, 3H), 2,12 (s, 3H), 1,90 (s, 3H) ESHRMS m/z 455,1632 (M+H calculado para $C_{24}H_{24}FN_2O_6$ requiere 455,1613)

Etapa 5 Preparacion de ácido 3-[3-bromo-4-[(4-fluoro-2-{[(metoxicarbonil)amino]metil}bencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-metilbenzoico



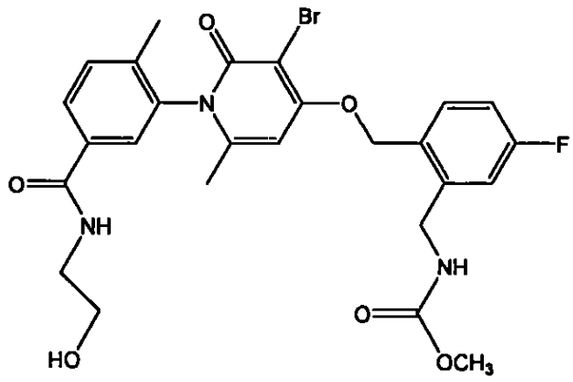
Se agrego NBS (0,69 g, 3,85 mmol) a una disolución de acido 3-[4-[(4-fluoro-2-{[(metoxicarbonil)amino]metil}bencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-metilbenzoico ( de la Etapa 4) (1,75 g, 3,85 mmol) en DCM (45 ml) Después de 1,5 horas, el disolvente se eliminó en un rotovapor Se agregaron el solido disuelto en EtOAc y hexano, lo que produjo un precipitado solido Se filtro el sólido Posteriormente, el solido se disolvio en DCM y se lavó con agua La capa orgánica se seco sobre $Na_2SO_4$, se filtró y se concentro El solido de color amarillo palido se seco *in vacuo* (1,47 g, al 72%) $^1$H NMR ($CD_3OD$/ 400MHz) δ8,04 (m, 1H), 7,77 (s, 1H), 7,54 (m, 2H), 7,13 (m, 1H), 7,05 (m, 1H), 6,68 (s, 1H), 5,40 (s, 2H), 4,44 (s, 2H), 3,64 (s, 3H), 2,09 (s, 3H), 1,99 (s, 3H) ESHRMS m/z 533,0700 y 535,0677 (M+H calculado para $C_{24}H_{23}BrFN_2O_6$ requiere 533,0718 y 535,0701)

Etapa 6 Preparacion del compuesto del titulo

A una disolución enfriada (-10 °C) de acido 3-[3-bromo-4-[(4-fluoro-2-{[(metoxicarbonil)amino]metil}bencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-metilbenzoico (0,07 g, 0,13 mmol) en DMF (2,0 ml) se agrego cloroformato de isobutilo (0,02 ml, 0,16 mmol) y 4-metilmorfolina (0,02 ml, 0,16 mmol) Despues de 15 minutos, se agrego 2,0 M metilamina en THF

(0,01 ml, 0,20 mmol) El disolvente se eliminó por destilacion despues de 30 minutos El producto en crudo se purifico mediante HPLC preparatoria El acetonitrilo se evaporó y la disolucion se lavo con $NaHCO_3$ al 5% (30 ml) y se extrajo en DCM (3 x 25 ml) Los extractos orgánicos se secaron sobre $Na_2SO_4$, se filtraron, se concentraron y se secaron *in vacuo* para proporcionar una espuma de color blanco, (0,061 g, al 86%) $^1H$ NMR ($CD_3OD$/ 400MHz) δ7,85 (m, 1H), 7,54 (m, 3H), 7,14 (m, 1H), 7,05 (m, 1H), 6,68 (s, 1H), 5,40 (s, 2H), 4,43 (s, 2H), 3,64 (s, 3H), 2,89 (s, 3H), 2,08 (s, 3H), 1,99 (s, 3H) ESHRMS m/z 546,0987 y 548,1018 (M+H calculado para $C_{25}H_{26}BrFN_3O_5$ requiere 546,1034 y 548,1018)

Ejemplo 644

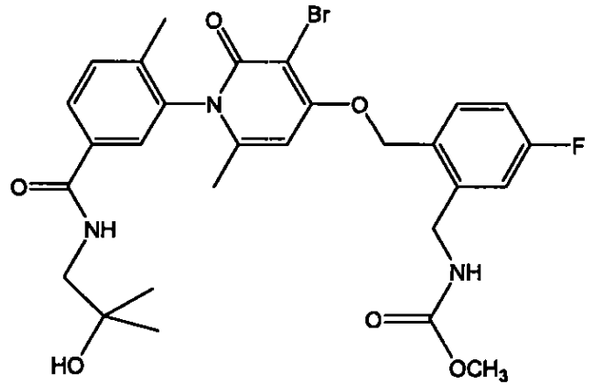



2-({[3-bromo-1-(5-{[(2-hidroxietil)amino]carbonil}-2-metilfenil)-6-metil-2-oxo-1,2-dihidropiridin-4-il]oxi}metil)-5-fluorobencilcarbamato de metilo

El compuesto del titulo se preparo utilizando un procedimiento similar al empleado en la preparacion del compuesto del Ejemplo 643 $^1H$ NMR ($CD_3OD$/ 400MHz) δ7,88 (m, 1H), 7,61 (s, 1H), 7,53 (m, 2H), 7,13 (m, 1H), 7,04 (m, 1H), 6,68 (s, 1H), 5,41 (s, 2H), 4,43 (s, 2H), 3,68 (t, 2H, J = 5,6 Hz), 3,64 (s, 3H), 3,48 (t, 2H, J = 5,6Hz), 2,08

(s, 3H), 2,00 (s, 3H) ESHRMS m/z 576,1101 y 578,1072 (M+H calculado para $C_{26}H_{28}BrFN_3O_6$ requiere 576,1140 y 578,1124)

Ejemplo 645

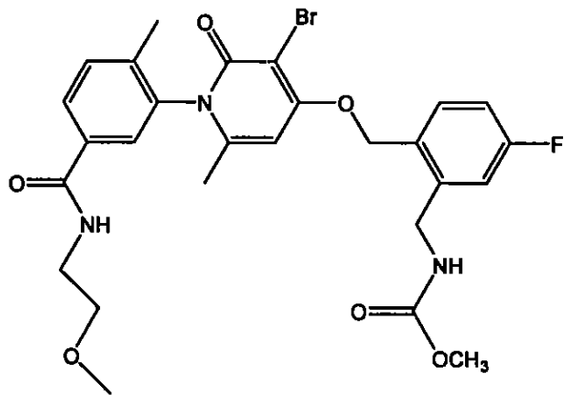



2-({[3-bromo-1-(5-{[(2-hidroxi-2-metilpropil)amino]carbonil}-2-metilfenil)-6-metil-2-oxo-1,2-dihidropiridin-4-il]oxi}metil)-5-fluorobencilcarbamato de metilo

El compuesto del titulo se preparó utilizando un procedimiento similar al empleado en la preparacion del compuesto del Ejemplo 643 $^1$H NMR ($CD_3OD$/ 400MHz) δ7,89 (m, 1H), 7,63 (s, 1H), 7,54 (m, 2H), 7,13 (m, 1H), 7,04 (m, 1H), 6,69 (s, 1H), ɔ,41 (s, 2H), 4,43 (s, 2H), 3,64 (s, 3H), 3,38 (s, 2H, 2,09 (s, 3H), 2,01 (d, 6H, J = 3,2 Hz), 1,21 (s, 3H) ESHRMS m/z 604,1412 y 606,1418 (M+H calculado para $C_{28}H_{32}BrFN_3O_6$ requiere 604,1453 y 606,1438)

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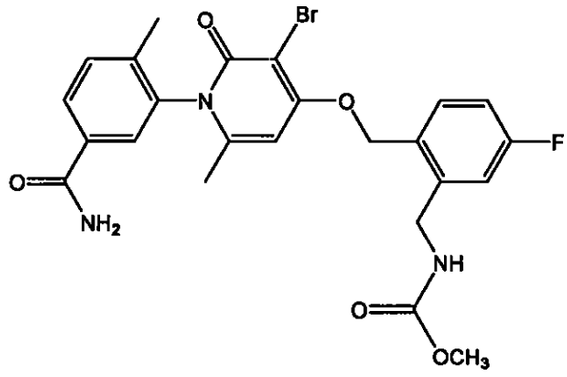
Ejemplo 646



2-({[3-bromo-1-(5-{[(2-metoxietil)amino]carbonil}-2-metilfenil)-6-metil-2-oxo-1,2-dihidropiridin-4-il]oxi}metil)-5-fluorobencilcarbamato de metilo

El compuesto del titulo se preparó utilizando un procedimiento similar al empleado en la preparacion del compuesto del Ejemplo 643 $^1$H NMR ($CD_3OD$/ 400MHz) δ7,87 (m, 1H), 7,59 (s, 1H), 7,53 (m, 2H), 7,14 (m, 1H), 7,05 (m, 1H), 6,68 (s, 1H), 5,41 (s, 2H), 4,44 (s, 2H), 3,64 (s, 3H), 3,54 (s, 4H, 3,25 (s, 3H), 2,08 (s, 3H), 2,00 (s, 3H) ESHRMS m/z 590,1267 y 592,1219 (M+H calculado para $C_{27}H_{30}BrFN_3O_6$ requiere 590,1297 y 592,1281)

Ejemplo 647

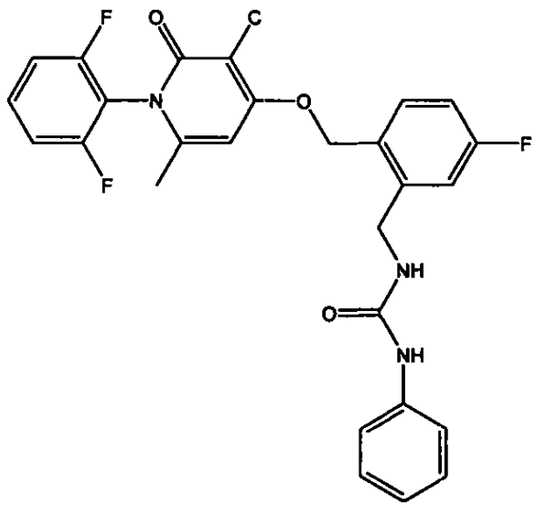


2-[({1-[5-(aminocarbonil)-2-metilfenil]-3-bromo-6-metil-2-oxo-1,2-dihidropiridin-4-il}oxi)metil]-5-fluorobencilcarbamatc de metilo

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El compuesto del titulo se preparó utilizando un procedimiento similar al empleado en la preparación del compuesto del Ejemplo 643 $^1$H NMR ($CD_3OD$/ 400MHz) δ7,91 (m, 1H), 7,64 (s, 1H), 7,54 (m, 2H), 7,14 (m, 1H), 7,05 (m, 1H), 6,68 (s, 1H), 5,40 (s, 2H), 4,44 (s, 2H), 3,64 (s, 3H), 2,09 (s, 3H, 2,00 (s, 3H) ESHRMS m/z 532,0836 y 534,0787 (M+H calculado para $C_{24}H_{24}BrFN_3O_5$ requiere 532,0878 y 534,0861)

Ejemplo 648

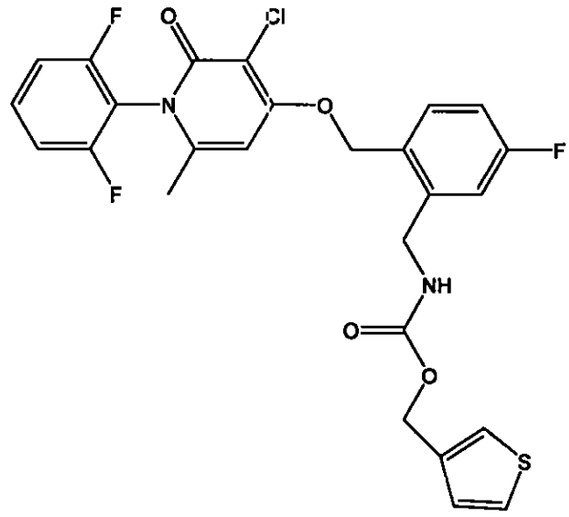



N-[2-({[3-cloro-1-(2,6-difluorofenil)-6-metil-2-oxo-1,2-dihidropiridin-4-il]oxi}metil)-5- fluorobencil]-N'-fenilurea

A una disolucion enfriada (0 °C) de trifluoroacetato de 4-{[2-(aminometil)-4-fluorobencil]oxi}-3-cloro-1-(2,6-difluorofenil)-6-metilpiridin-2(1H)-ona (0,25 g, 0,48 mol) en DMA (2,0 ml), se agregó 4-metilmorfolina (0,06 ml, 0,53 mmol) y fenil isocianato(0,06 ml, 0,53 mmol) La reacción se agito a temperatura ambiente durante 1,5 horas El disolvente se destilo y el producto en crudo se purifico mediante HPLC preparatoria El acetonitrilo se evaporo y la disolución se lavo con $NaHCO_3$ al 5% (30 ml) y se extrajo en DCM (3 x 25 ml) Los extractos organicos se secaron

sobre $Na_2SO_4$, se filtraron y se concentraron hasta obtener un solido de color blanco, secado *in vacuo* (0,18 g, al 71%) $^1H$ NMR ($CD_3OD$, 400MHz) δ7,60 (m, 1H), 7,54 (m, 1H), 7,33 (d, 2H, J = 7,6 Hz), 7,22 (m, 5H), 7,06 (m, 1H), 6,95 (t, 1H, J = 7,2 Hz), 6,73 (s, 1H), 5,44 (s, 2H), 4,53 (s, 2H), 2,07 (s, 3H) FSHRMS m/z 528,1304 (M+H calculado para $C_{27}H_{22}ClF_3N_3O_3$ requiere 528,1296)

Ejemplo 649



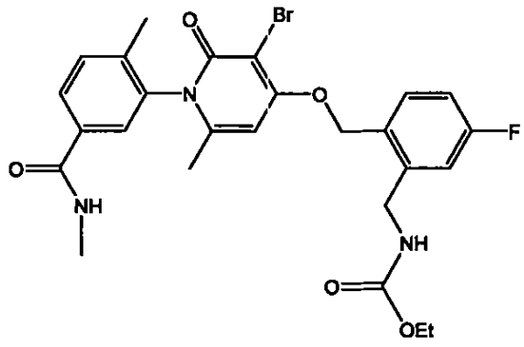

Tien-3-ilmetil 2-({[3-cloro-1-(2,6-difluorofenil)-6-metil-2-oxo-1,2-dihidropiridin-4-il]oxi}metil)-5-fluorobencilcarbamatc

A una disolucion enfriada (0 °C) de trifluoroacetato de 4-{[2-(aminometil)-4-fluorobencil]oxi}-3-cloro-1-(2,6-difluorofenil)-6-metilpiridin-2(1H)-ona (0,26 g, 0,50 mmol) y 1,1-carbonildiimidazola (0,10 g, 0,60 mmol) en DMA (2,0 ml), se agrego 4-metilmorfolina (0,06 ml, 0,55 mmol) Despues de 1 hora a temperatura ambiente, se agrego 3-tiofenometanol (0,09 ml, 0,99 mmol) No se observaron productos despues de 2 horas a temperatura ambiente Se agrego NaH (0,01 g, 0,50 mmol) y la reaccion se agito a 60 °C La reacción se completo despues de 20 minutos La

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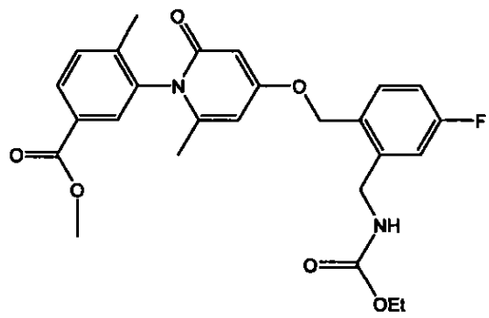
mezcla de reaccion se enfrio (0 °C) y se agrego acido acetico para enfriar repentinamente la reaccion El disolvente se elimino por destilación El producto en crudo se purifico mediante HPLC preparatoria El acetonitrilo se evaporo y la disolución se lavo con $NaHCO_3$ al 5% (30 ml) y se extrajo en DCM (3 x 25 ml) Los extractos organicos se secaron sobre $Na_2SO_4$, se filtraron y se concentraron hasta obtener una espuma de color blanco, secada *in vacuo* (0,20 g, al 73%) $^1H$ NMR ($CD_3OD$/ 400MHz) δ7,61 (m, 1H), 7,52 (m, 1H), 7,34 (s, 2H), 7,23 (t, 3H, J = 8,4 Hz), 7,10 (m, 2H), 6,71 (s, 1H), 5,40 (s, 2H), 5,07 (s, 2H), 4,43 (s, 2H), 2,10 (s, 3H) ESHRMS m/z 549,0858 (M+H calculado para $C_{26}H_{21}ClF_3N_2O_4S$ requiere 549,0857)

Ejemplo 650



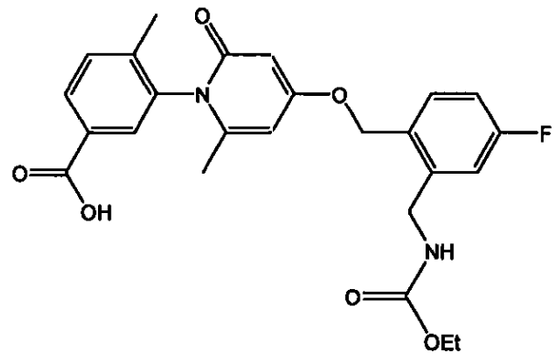

2-{[(3-bromo-6-metil-1-{2-metil-5-[(metilamino)carbonil]fenil}-2-oxo-1,2-dihidropiridin-4-il)oxi]metil}-5-fluorobencilcarbamato de etilo

Etapa 1 Preparacion de 3-[4-[(2-{[(etoxicarbonil)amino]metil}-4-fluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-metilbenzoato de metilo



Se preparó utilizando un procedimiento similar al empleado en la preparación del 3-[4-[(4-fluoro-2-{[(metoxicarbonil)amino]metil}bencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-metilbenzoato de metilo $^1$H NMR ($CD_3OD$/ 400MHz) δ8,03 (m, 1H), 7,76 (s, 1H), 7,53 (d, 1H, J = 8,0 Hz), 7,47 (m, 1H), 7,12 (m, 1H), 7,03 (m, 1H), 6,21 (s, 1H), 6,08 (s, 1H), 5,18 (s, 2H), 4,38 (s, 2H), 4,08 (q, 2H, J = 6,8 Hz), 3,89 (s, 3H), 2,12 (s, 3H), 1,89 (s, 3H), 1,23 (t, 3H, J = 6,8 Hz) ESHRMS m/z 483,1900 (M+H calculado para $C_{26}H_{28}FN_2O_6$ requiere 483,1926)

Etapa 2 Preparación de ácido 3-[4-[(2-{[(etoxicarbonil)amino]metil}-4-fluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-metilbenzoico

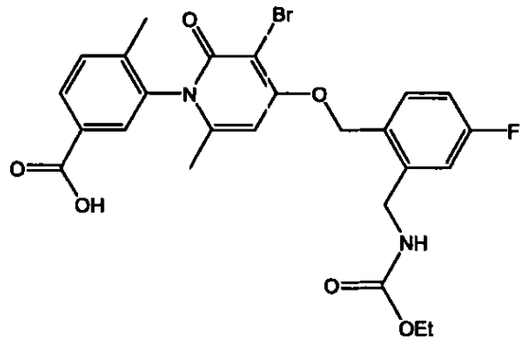


Se preparó utilizando un procedimiento similar al empleado en la preparacion del ácido 3-[4-[(4-fluoro-2-{[(metoxicarbonil)amino]metil}bencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-metilbenzoico $^1$H NMR ($CD_3OD$/ 400MHz) δ8,03 (m, 1H), 7,74 (s, 1H), 7,48 (m, 2H), 7,11 (m,

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1H), 7,03 (m, 1H), 6,21 (s, 1H), 6,08 (s, 1H), 5,18 (s, 2H), 4,38 (s, 2H), 4 08 (q, 2H, J = 7,2 Hz), 2,11 (s, 3H), 1,90 (s, 3H), 1,23 (t, 3H, J = 7,2 Hz) ESHRMS m/z 469,1738 (M+H calculado para $C_{25}H_{26}FN_2O_6$ requiere 469,1769)

Etapa 3 Preparacion de acido 3-[3-bromo-4-[(2-{[(etoxicarbonil)amino]metil}-4-fluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-metilbenzoico



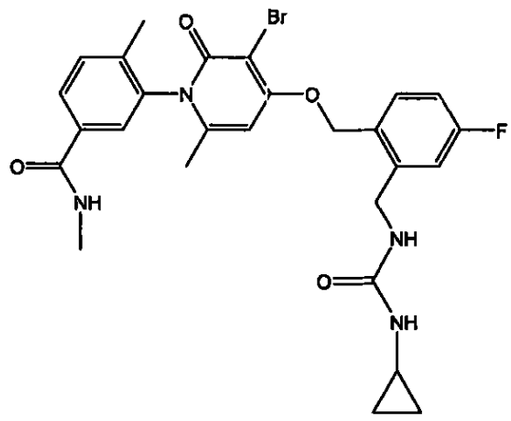

Se preparo utilizando un procedimiento similar al empleado en la Etapa 5 de la sintesis del Ejemplo 643 $^1$H NMR ($CD_3OD$/ 400MHz) δ8,04 (m, 1H), 7,76 (s, 1H), 7,55 (m, 2H), 7,13 (m, 1H), 7,05 (m, 1H), 6,68 (s, 1H), 5,40 (s, 2H), 4,43 (s, 2H), 4,07 (m, 2H), 2,09 (s, 3H),1,99 (s, 3H), 1,22 (t, 3H, J = 7,2 Hz) ESHRMS m/z 547,0842 y 549,0818 (M+H calculado para $C_{25}H_{25}BrFN_2O_6$ requiere 547,0875 y 549,0858)

Etapa 4

Se preparo utilizando un procedimiento similar al empleado en la preparación del Ejemplo 643 $^1$H NMR ($CD_3OD$/ 400MHz) δ7,85 (m, 1H), 7,54 (m, 3H), 7,13 (m, 1H), 7,04 (m, 1H), 6,68 (s, 1H), 5,40 (s, 2H), 4,43 (s, 2H), 4,07 (q, 2H), 2,89 (s, 3H), 2,08 (s, 3H), 1,99 (s, 3H), 1,23 (t, 3H, J = 7,2 Hz) ESHRMS m/z 560,1215 y 562,1193 (M+H calculado para $C_{26}H_{28}BrFN_3O_5$ requiere 560,1191 y 562,1175)

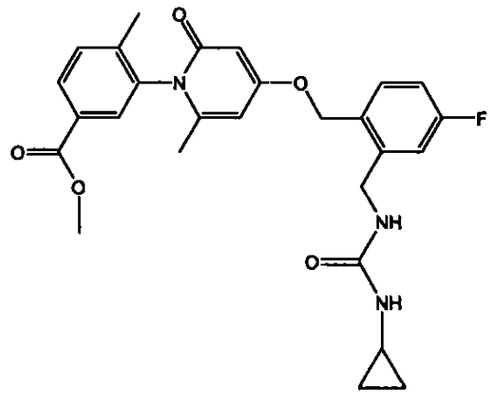
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Ejemplo 651



3-[3-bromo-4-{[2-({[(ciclopropilamino)carbonil]amino}metil)-4-fluorobencil]oxi}-6-metil-2-oxopiridin-1(2H)-il]-N,4-dimetilbenzamida

Etapa 1 Preparacion de 3-[4-{[2-({[(ciclopropilamino)carbonil]amino}metil)-4-fluorobencil]oxi}-6-metil-2-oxopiridin-1(2H)-il]-4-metilbenzoato de metilo

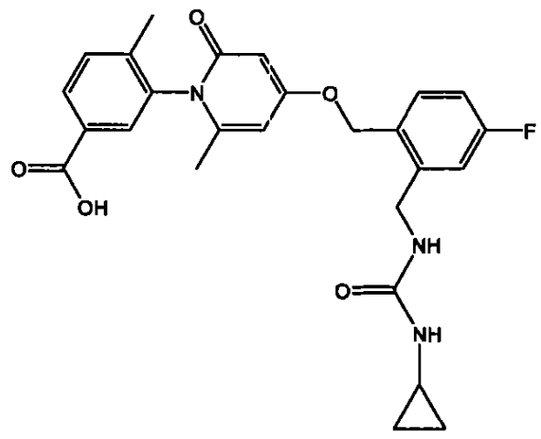


A una disolucion enfriada (0 °C) de trifluoroacetato de 3-[4-{[2-(aminometil)-4-fluorobencil]oxi}-6-metil-2-oxopiridin-1(2H)-il]-4-metilbenzoato de metilo (1,13 g, 2,16 mmol) y 1,1-carbonildiimidazola (0,42 g, 2,59 mmol) en DMA (8,0 ml) se agrego 4-metilmorfolina (0,36 ml, 3,2 mmol) La reacción se agito a temperatura ambiente durante

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2 horas El DMA se eliminó por destilación El producto en crudo se purificó mediante HPLC preparatoria El acetonitrilo se evaporó y la disolución se lavó con $NaHCO_3$ al 5% (30 ml) y se extrajo en DCM (3 x 25 ml) Los extractos orgánicos se secaron sobre $Na_2SO_4$, se filtraron, se concentraron y se secaron *in vacuo* (0,78 g, al 73%) $^1H$ NMR ($CD_3OD$/ 400MHz) δ8,03 (m, 1H), 7,76 (s, 1H), 7,53 (d, 1H, J = 8,0 Hz), 7,45 (m, 1H), 7,12 (m, 1H), 7,01 (m, 1H), 6,22 (s, 1H), 6,08 (s, 1H), 5,19 (s, 2H), 4,44 (s, 2H), 3,89 (s, 3H), 2,48 (m, 1H), 2,12 (s, 3H), 1,89 (s, 3H), 0,70 (m, 2H), 0,47 (m, 2H) ESHRMS m/z 494,2076 (M+H calculado para $C_{27}H_{29}FN_3O_5$ requiere 494,2086)

Etapa 2 Preparación de ácido 3-[4-{[2-({[(ciclopropilamino)carbonil]amino}metil)-4-fluorobencil]oxi}-6-metil-2-oxopiridin-1(2H)-il]-4-metilbenzoico

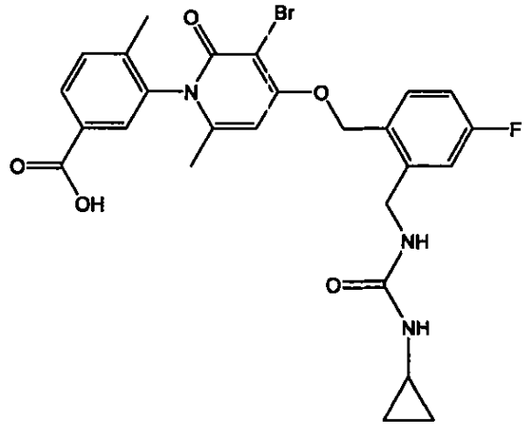


Se preparó utilizando un procedimiento similar al empleado en la preparación del ácido 3-[4-[(4-fluoro-2-{[(metoxicarbonil)amino]metil}bencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-metilbenzoico $^1H$ NMR ($CD_3OD$/ 400MHz) δ8,02 (m, 1H), 7,74 (s, 1H), 7,48 (m, 2H), 7,12 (m, 1H), 7,01 (m, 1H), 6,22 (s, 1H), 6,08 (s, 1H), 5,19 (s, 2H), 4,44 (s, 2H), 2,48 (m, 1H), 2,11 (s, 3H), 1,90 (s,

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3H), 0,69 (m, 2H), 0,47 (m, 2H) ESHRMS m/z 480,1921 (M+H calculado para $C_{26}H_{27}FN_3O_5$ requiere 480,1929)

Etapa 3 Preparacion de acido 3-[3-bromo-4-{[2-({[(ciclopropilamino)carbonil]amino}metil)-4-fluorobencil]oxi}-6-metil-2-oxopiridin-1(2H)-il]-4-metilbenzoico

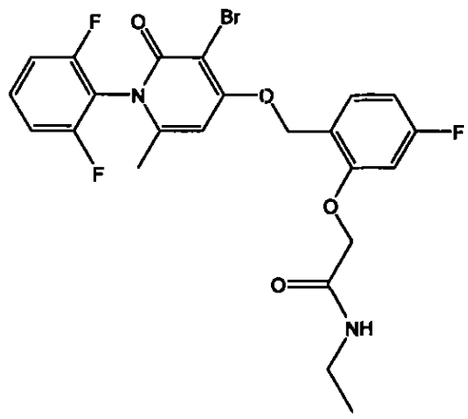



Se preparo utilizando un procedimiento similar al empleado en la Etapa 5 de la sintesis del Ejemplo 643 $^1$H NMR (DMSO-$d_6$/ 400MHz) δ7,92 (m, 1H), 7,67 (s, 1H), 7,54 (m, 2H), 7,12 (m, 2H), 6,71 (s, 1H), 5,37 (s, 2H), 4,31 (d, 2H, J = 6,4 Hz), 2,40 (m, 1H), 2,00 (s, 3H), 1,88 (s, 3H), 0,56 (m, 2H), 0,33 (m, 2H) ESHRMS m/z 558,0988 y 560,0981 (M+H calculado para $C_{26}H_{26}BrFN_3O_5$ requiere 558,1034 y 560,1018)

Etapa 4

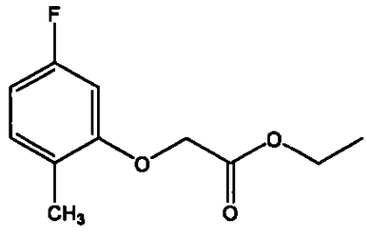
Se preparó utilizando un procedimiento similar al empleado en la preparacion del Ejemplo 643 $^1$H NMR ($CD_3OD$/ 400MHz) δ7,85 (m, 1H), 7,54 (m, 3H), 7,14 (m, 1H), 7,03 (m, 1H), 6,69 (s, 1H), 5,41 (s, 2H), 4,48 (s, 2H), 2,89 (s, 3H), 2,48 (m, 1H), 2,08 (s, 3H), 1,99 (s, 2H), 0,70 (m, 2H), 0,47 (m, 2H) ESHRMS m/z 571,1348 y 573,1355 (M+H calculado para $C_{27}H_{29}BrFN_4O_4$ requiere 571,1351 y 573,1335)

Ejemplo 652



Ácido 3-[3-bromo-4-{[2-({[(ciclopropilamino)carbonil]amino}metil)-4-fluorobencil]oxi}-6-metil-2-oxopiridin-1(2H)-il]-4-metilbenzoico

Etapa 1 Preparación de (5-fluoro-2-metilfenoxi)acetato de etilo

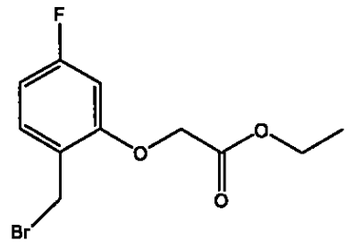


A una disolucion de 5-fluoro-2-metilfenol (1,00 g, 7,93 mmol) y etilbromoacetato (1,59 g, 9,51 mmol) en DMF (15 ml) se agrego $K_2CO_3$ (1,10 g, 7,93 mmol) Después de 30 minutos a temperatura ambiente, el DMF se elimino por destilacion El producto en crudo se lavo con acido citrico al 5% (30 ml y agua (30 ml), se extrajo en DCM (3 x 20 ml), se seco sobre $Na_2SO_4$, se filtro, se concentro y se secó *in vacuo* El producto deseado se obtuvo como un aceite de color amarillo (1,30 g, al 77%) $^1H$ NMR ($CD_3OD$/ 400MHz) δ7,09 (t, 1H, J = 8,8 Hz), 6,58 (m, 1H), 6,56 (m, 1H), 4,71 (s, 2H), 4,23 (q, 2H, J = 7,2 Hz), 2,18 (s, 3H),

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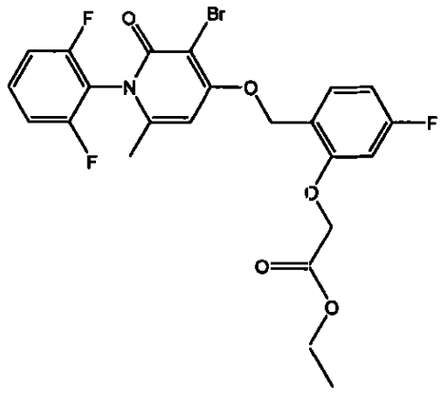
1,27 (t, 3H, J = 7,2 Hz) ESHRMS m/z 212,0847 (M+H calculado para $C_{11}H_{13}FO_3$ requiere 212,0849)

Etapa 2 Preparación de etil [2-(bromometil)-5-fluorofenoxi]acetato




Una disolucion de (5-fluoro-2-metilfenoxi)acetato de etilo (de la Etapa 1) (0,65 g, 3,06 mmol), NBS (0,65 g, 3,68 mmol) y peroxido de benzoilo (0,05 g, 0,21 mmol) en CCl4 (7,0 ml) se sometió a reflujo a 90 °C durante 2,5 horas Se agregó NBS (0,16 g, 0,92 mmol) adicional y la raccion continuo durante toda la noche El solido se filtró y el filtrado se concentro sobre gel de sílice Se purificó mediante cromatografia rapida en columna utilizando hexano y EtOAc/hexano al 2,5% como eluyente El producto se obtuvo como un liquido de color amarillo (0,27 g, al 30%) $^1$H NMR ($CD_3OD$/ 400MHz) δ7,37 (m, 1H), 6,69 (m, 2H), 4,80 (s, 2H), 4 60 (s, 2H), 4,23 (q, 2H, J = 7,2 Hz), 1,27 (t, 3H, J = 7,2 Hz)

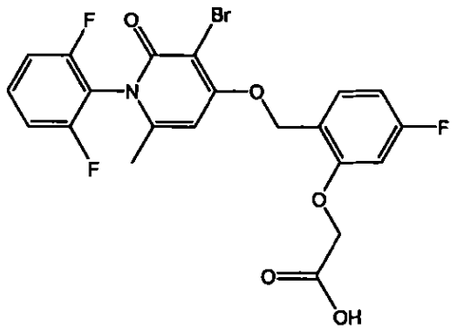
Etapa 3 Preparacion de [2-({[3-bromo-1-(2,6-difluorofenil)-6-metil-2-oxo-1,2-dihidropiridin-4-il]oxi}metil)-5- fluorofenoxi]acetato de etilo



A una disolucion de [2-(bromometil)-5-fluorofenoxi]acetato de etilo (de la Etapa 2) (0,59 g, 2,03 mmol) y 3-bromo-1-(2,6-difluorofenil)-4-hidroxi-6-metilpiridin-2(1H)-ona (0,61 g, 1,93 mmol) en DMF (3,0 ml) se agregó $K_2CO_3$ (0,34 g, 2,43 mmol) Después de 2 horas a temperatura ambiente, el DMF se eliminó por destilacion El producto en crudo se lavo con ácido cítrico al 5%, se extrajo en DCM, se secó sobre $Na_2SO_4$, se filtró y se concentro sobre gel de sıice Se purificó mediante cromatografia rápida en columna utilizando EtOAc/hexano al 50% como eluyente El producto se obtuvo como un solido de color amarillo palido (0,45 g, al 42%) $^1H$ NMR ($CD_3OD$/ 400MHz) δ7,21 (q, 3H, J = 8,4 Hz), 6,80 (m, 2H), 6,69 (s, 1H), 6,15 (s, 1H), 5,40 (s, 2H), 4,84 (s, 2H), 4,23 (q, 2H, J = 6,8 Hz), 2,08 (s, 3H), 1,26 (t, 3H, J = 6,8 Hz) ESHRMS m/z 526,0446 y 528,0414 (M+H calculado para $C_{23}H_{20}BrF_3NO_5$ requiere 526,0471 y 528,0454)

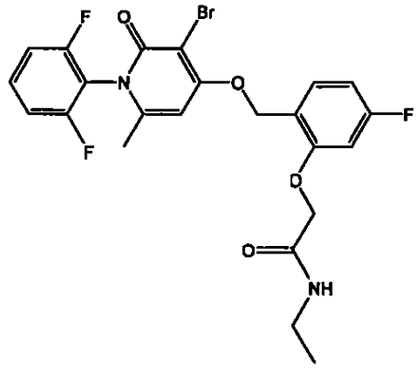
Etapa 4 Preparación de ácido [2-({[3-bromo-1-(2,6-difluorofenil)-6-metil-2-oxo-1,2-dihidropiridin-4-il]oxi}metil)-5- fluorofenoxi]acetico

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Una disolucion de 2-({[3-bromo-1-(2,6-difluorofenil)-6-metil-2-oxo-1,2-dihidropiridin-4-il]oxi}metil)-5-fluorofenoxi]acetato de etilo (de la Etapa 3) (0,62 g, 1,18 mmol), disolucion 1,5 N NaOH en 1 1 MeOH agua (1,2 ml, 1,77 mmol), y THF (1,2 ml) se sometieron a reflujo a 60 °C durante 1 hora La disolución se concentró en un rotovapor, se enfrio y se le agrego acido citrico al 5% El precipitado solido se filtro y se seco *in vacuo* El producto se obtuvo como un solido de color amarillo pálido (0,35 g, al 60%) $^1$H NMR ($CD_3OD$/ 400MHz) δ7,59 (m, 1H), 7,49 (m, 2H), 7,22 (m, 2H), 6,75 (m, 2H), 6,72 (s, 1H), 5,43 (s, 2H), 4,66 (s, 2H), 2,07 (s, 3H) ESHRMS m/z 498,0143 y 500,0186 (M+H calculado para $C_{21}H_{16}BrF_3NO_5$ requiere 498,0158 y 500,0141)

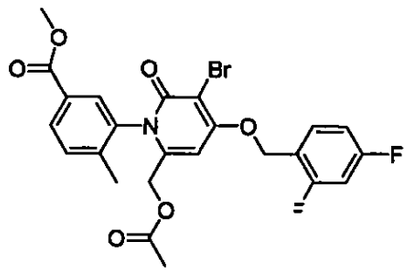
Etapa 5 Preparacion de 2-[2-({[3-bromo-1-(2,6-difluorofenil)-6-metil 2-oxo-1,2-dihidropiridin-4-il]oxi}metil)-5- fluorofenoxi]-N-etilacetamida



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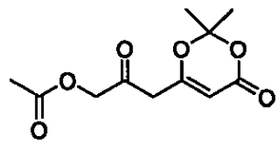
A una disolución enfriada (-10 °C) de acido [2-({[3-bromo-1-(2,6-difluorofenil)-6-metil-2-oxo-1,2-dihidropiridin-4-il]oxi}metil)-5-fluorofenoxi]acetico (de la Etapa 4) (0,15 g, 0 30 mmol) en DMA (2,0 ml) se agrego 4-metilmorfolina (0,04 ml, 0,36 mmol) y cloroformato de isobutilo (0,05 ml, 0,36 mmol) Se agrego etilamina (0,04 ml, 0,45 mmol) después de 20 minutos El DMF se eliminó por destilación despues de 1 hora El producto en crudo se purificó mediante HPLC preparatoria El acetonitrilo se evaporo y la disolucion se lavo con $NaHCO_3$ al 5% (30 ml) y se extrajo en DCM (3 x 25 ml) Los extractos orgánicos se secaron sobre $Na_2SO_4$, se filtraron, se concentraron y se secaron *in vacuo* para proporcionar un sólido de color blanco (0,080 g, al 51%) $^1H$ NMR ($CD_3OD$/ 400MHz) δ7,60 (m, 1H), 7,53 (t, 1H, J = 8,0 Hz), 7,23 (t, 2H, J = 8,4 Hz), 6,82 (m, 2H), 6,71 (s, 1H), 5,42 (s, 2H), 4,61 (s, 2H), 3,31 (q, 2H, J = 6,4 Hz), 2,10 (s, 3H), 1,09 (t, 3H, J = 7,2 Hz) ESHRMS m/z 525,0616 y 527,0568 (M+H calculado para $C_{23}H_{21}BrF_3N_2O_4$ requiere 525,0631 y 527,0614)

Ejemplo 653



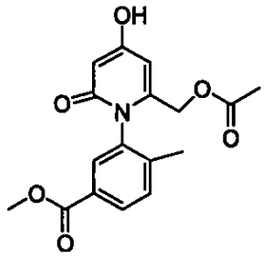
3-[6-[(acetiloxi)metil]-3-bromo-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2H)-il]-4-metilbenzoato de metilo

Etapa 1 Preparacion de 3-(2,2-dimetil-4-oxo-4H-1,3-dioxin-6-il)-2-oxopropil acetato



Una disolucion de 2,2,6-trimetil-4H-1,3-dioxin-4-ona (20g, 141 mmol) en THF seco (400 ml) se enfrió a -78 °C A esta disolución se agrego lentamente un LiHMDS (1M-THF, 160 ml, 160 mmol) La disolucion resultante se mantuvo a -78 °C con agitación durante 30 min A la mezcla de reacción se agregó acetoxi acetilcloruro (17 ml, 160 mmol) y la mezcla resultante se mantuvo a -78 °C durante 1 hora Luego se dejó que la reacción se entibiara lentamente a temperatura ambiente y se agitara durante 1 hora adicional A continuación, la reaccion se enfrio repentinamente con la adición de una disolución 1N de cloruro de amonio Se separaron las capas y la capa acuosa se extrajo con acetato de etilo (5x) Los materiales orgánicos se combinaron, se secaron y se concentraron *in vacuo* El producto en crudo fue purificado utilizando un sistema biotage de cromatografia liquida con presión media La elucion con hexanos-acetato de etilo (3 1) proporcionó 13,1 g (al 38%) de un aceite de color rojo-marron El producto se ve limpio por NMR $^1$H NMP (300 MHz, $CDCl_3$) δ 5,42 (s, 1H), 4,75 (s, 2H), 3,41 (s, 2H), 2,22 (s, 3H), 1,75 (s, 6H)

Etapa 2 Preparacion de 3-[6-[(acetiloxi)metil]-4-hidroxi-2-oxopiridin-1(2H)-il]-4-metilbenzoato de metilo

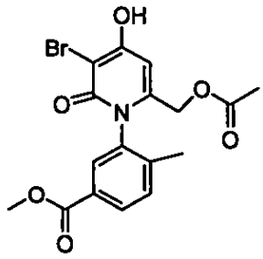


A 100 ml de RBF que contenia 3-amino,4-metilbenzoato de metilo (1,65 g, 10 mmol) se agregó la enona de la Etapa

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1 (2,6 g, 10,7 mmol) La mezcla luego se disolvio en tolueno (40 ml), se equipó con un condensador de reflujo y se coloco en un baño de aceite previamente configurado a 115 °C La mezcla se calento a reflujo durante 1,5 horas El matraz de reacción se retiro del baño de aceite y se agrego una cantidad catalitica de TFA (5-6 gotas) La reacción volvio a colocarse en el baño de aceite y se calento a reflujo durante 2 horas adicionales Luego se dejo que la reaccion se enfriara a 0 °C El toluene despues se eliminó bajo vacio para proporcionar un residuo espeso de color marron El residuo luego se disolvio en acetonitrilo (10-15 ml) y se lo dejo reposar Después de 20-30 minutos se produce un precipitado que se filtra y se lava con éter dietilico Despues del secado, se obtuvo un solido blanquecino (1,9 g, rendimiento 57%) $^1$H NMR (300 MHz, DMSO-$_{d6}$) δ 7,94 (dd, J = 7,8, 1,5 Hz, 1H), 7,73 (s, 1H), 7,54 (d, J = 8,1 Hz, 1H), 6,19 (s, 1H), 5,73-5,71 (m, 1H), 4,47 (AB quar, J = 10,5 Hz, 2H), 3,87 (s, 3H), 2,09 (s, 3H), 1,91 (s, 3H) ES-HRMS m/z 332,1096 (M+H calculado para $C_{17}H_{18}NO_6$ requiere 332,1129)

Etapa 3 Preparacion de metil 3-[6-[(acetiloxi)metil]-3-bromo-4-hidroxi-2-oxopiridin-1(2H)-il]-4-metilbenzoato



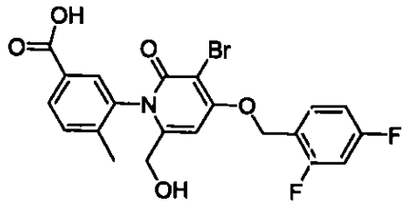

A una suspensión de fenol (2,5 g, 7,5 mmol) en acetonitrilo seco (50 ml), a temperatura ambiente, se agrego n-bromosuccinimida (1,33 g, 7,5 mmol) La mezcla homogénea resultante se agitó a temperatura ambiente

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durante 3 horas El precipitado resultante se filtró y se lavo secuencialmente con acetonitrilo y el eter dietilico El producto se seco en un horno de vacio para producir un solido blanquecino (2,5 g, al 81%) $^1$H NMR (300 MHz, DMSO-$_{d6}$) δ 11,82 (s, 1H), 7,97 (dd, J = 7,8,1,5 Hz, 1H), 7,80 (d, J = 1,5 Hz, 1H), 7,57 (d, J = 8,1 Hz, 1H), 6,38 (s, 1H), 4,49 (AB quar, J = 13,8 Hz, 2H), 3,87 (s, 3H), 2,08 (s, 3H), 1,92 (s, 3H) ES-HRMS m/z 410,0225 (M+H calculado para $C_{17}H_{17}NBrO_6$ requiere 410,0234)

Etapa 4 Preparación del compuesto del titulo A una disolución del fenol precedente (2,5 g, 6,0 mmol) en DMF seco (25 ml) se agregó carbonato potasico solido (804 mg, 6,0 mmol) A esta mezcla despues se agrego, via jeringa, bromuro de 2,4-difluorobencilo (783 □L, 6,0 mmol) La mezcla resultante se agito a temperatura ambiente durante toda la noche Luego la reaccion se vertio en agua helada y se agito enérgicamente El precipitado resultante se filtró y se lavo secuencialmente con agua y eter dietilico El solido se seco en un horno de vacio para producir un solido blanquecino (3,3 g, al 99%) $^1$H NMR (400 MHz, DMSO-$_{d6}$) δ 7,97 (dd, J = 7,6,1,2 Hz, 1H), 7,83 (d, J = 1,6 Hz, 1H), 7,71 (q, J = 8,8 Hz, 1H), 7,57 (d, J = 8,0 Hz, 1H), 7,37 (dt, J = 10,4, 2,4 Hz, 1H), 7,21 (dt, J = 8,4, 2,0 Hz, 1H), 6,90 (s, 1H), 5,40 (s, 2H), 4,57 (AB quar, J = 13,6 Hz, 2H), 3,86 (s, 3H), 2,07 (s, 3H), 1,90 (s, 3H) ES-HRMS m/z 536,0484 (M+H calculado para $C_{24}H_{21}NF_2BrO_6$ requiere 536,0515)

Ejemplo 654

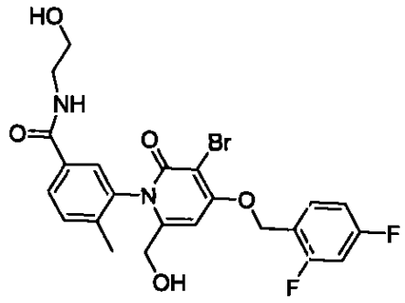


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Acido 3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-(hidroximetil)-2-oxopiridin-1(2H)-il]-4-metilbenzoico

A una suspensión agitada, a temperatura ambiente, del Ejemplo 643 (20 g, 3,7 mmol) en THF (10 ml) se agrego una disolucion de 2,5N NaOH (3 ml, 7,5 mmol) La disolucion homogenea resultante se agito durante 2 horas La reaccion se consideró completa y se agrego gota a gota 1N HCl hasta obtener un pH ~ 4 Luego se diluyo la reacción con $CH_2Cl_2$ (10 ml) El precipitado resultante se filtro con lavado adicional de $CH_2Cl_2$ El solido se secó en un horno de vacio para producir un sólido de color blanco puro (1,8 g, al 99%) $^1H$ NMR (300 MHz, $DMSO_{-d6}$) δ 7,95 (dd, J = 7,8, 1,8 Hz, 1H), 7,74-7,66 (m, 2H), 7,54 (d, J = 8,1 Hz, 1H), 7,37 (dq, J = 7,8, 2,7 Hz, 1H), 7,24-7,17 (m, 1H), 6,72 (s, 1H), 5,39 (s, 2H), 3,83 (AB quar, J = 15,6 Hz, 2H), 2,02 (s, 3H) ES-HRMS *m/z* 480,0253 (M+H calculado para $C_{21}H_{17}NF_2BrO_5$ requiere 480,0253)

Ejemplo 655



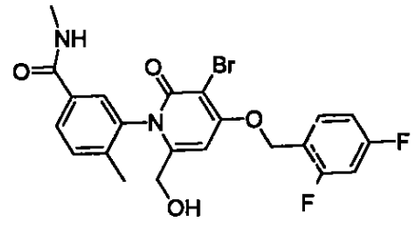

3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-(hidroximetil)-2-oxopiridin-1(2H)-il]-N-(2-hidroxietil)-4-metilbenzamida

A una suspension del Ejemplo 654 (500 mg, 1,04 mmol) en $CH_2Cl_2$ anhidro se agrego $Et_3N$ (218 µL, 1,56 mmol) y la mezcla homogenea resultante se agitó a temperatura ambiente A esta mezcla luego se agregó etanolamina (70 µL, 1,14 mmol) via jer nga Luego se agregó HOBt (155mg,

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1,14 mmol) mediante la adicion de EDC (217 mg, 1,14 mmol) La reacción se agito a temperatura ambiente durante toda la noche La reacción se enfrio repentinamente por la adicion de una disolucion de 1N $NH_4Cl$ La mezcla bifásica se separó y la capa acuosa se extrajo con $CH_2Cl_2$ (4X) Los materiales orgánicos se combinaron, se secaron y se concentraron *in vacuo* El residuo resultante fue purificado por cromatografia rápida sobre una columna Michele-Miller de 16 g La elusión con $CH_2Cl_2$-MeOH (10 1 → 12 1) dio por resultado la obtencion del producto deseado como un aceite viscoso El aceite despues se disolvio en una combinación $CH_3CN$-$Et_2O$ Despues de 5-10 minutos, se produjo un precipitado que, después de la filtración y el secado, produjo un solido de color blanco puro (210 mg, al 40%) $^1H$ NMR (300 MHz, $DMSO_{-d6}$) δ 8,46 (t, J = 5,2 Hz, 1H), 7,88 (dd, J = 8,0, 2,0 Hz, 1H), 7,72-7,65 (m, 2H), 7,50 (d, J = 8,4 Hz, 1H), 7,37 (dq, J = 9,6, 2,4 Hz, 1H), 7,20 (dq, J = 7,6, 1,6 Hz, 1H), 6,71 (s, 1H), 5,68 (t, J = 5,6 Hz, -OH), 5,40 (s, 2H), 4,73 (t, J = 5,6 Hz, -OH), 4,02 (dd, J = 16,4, 5,6 Hz, 1H), 3,7C (dd, J = 16,4, 5,6 Hz, 1H), 3,52-3,48 (m, 2H), 3,39-3,25 (m, 2H), 2,00 (s, 3H) ES-HRMS m/z 523,0674 (M+H calculado para $C_{23}H_{22}N_2F_2BrO_5$ requiere 523,0675)

Ejemplo 656



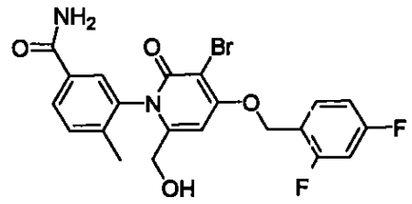

3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-(hidroximetil)-2-oxopiridin-1(2H)-il]-N,4-dimetilbenzamida

El compuesto del titulo se preparó a partir del acido del Ejemplo 654 (550 mg, 1,07 mmol) de manera similar a la

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amida descrita en lo precedente utilizando EDC (245 mg, 1,28 mmol), HOBt (171 µL, 1,28 mmol), $Et_3N$ (225 ml, 1,6 mmol), y 2,0M $MeNH_2$-THF (1,2 µL, 2,48 mmol) Despues de la preparacion con 1N $NH_4Cl$, el producto se precipito de la mezcla bifasica después de la dilución con $CH_2Cl_2$ adicional para producir un solido de color blanco (250 mg, rendimiento 51%) %) $^1H$ NMR (300 MHz, $DMSO_{-d6}$) δ 8,48 (quar, J = 4,5 Hz, 1H), 7,88 (dd, J = 8,1, 1,8 Hz, 1H), 7,72 (aprox quar, J = 6,6 Hz, 1H), 7,63 (d, J = 1,8 Hz, 1H), 7,52 (d, J = 8,1 Hz, 1H), 7,37 (dt, J = 10,2, 2,4 Hz, 1H), 7,20 (aprox dt, J = 8,4, 1,8 Hz, 1H), 6,74 (s, 1H), 5,71 (t, J = 5,4 Hz, 1H), 5,42 (s, 2H), 4,03 (dd, J = 13,8, 5,1 Hz, 1H), 3,72 (dd, J = 16,4, 5,1 Hz, 1H), 2,78 (d, J = 4,5 Hz, 3H), 2,02 (s, 3H) ES-HRMS m/z 493,0575 (M+H calculado para $C_{22}H_{20}N_2F_2BrO_4$ requiere 493,0569)

Ejemplo 657



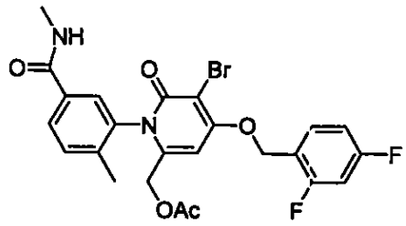

3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-(hidroximetil)-2-oxopiridin-1(2H)-il]-4-metilbenzamida

A una suspension agitada, a temperatura ambiente, del acido carboxilico del Ejemplo 654 (400 mg, 0,80 mmol) en THF anhidro (4 ml) se agrego 4-metilmorfolina (274 µL, 2,5 mmol) A la disolucion heterogenea resultante luego se agrego 2-cloro-4,6-dimetiltriazina (170 mg, 1,0 mmol) y la mezcla se agito durante 1 hora a temperatura ambiente Luego se agrego una disolucion de hidroxido de amonio (28-32%, 2 ml) a la reaccion y se la agito a temperatura ambiente durante toda la noche La reaccion se preparo luego diluyendo con $H_2O$ (2-3 ml) y se la agito

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enérgicamente El precipitado resultante se filtro y se lavó con H2O y despues con eter dietílico Despues del secado con un horno de vacio se obtuvo un solido blanquecino (140 mg, al 32%) %) $^1$H NMR (300 MHz, DMSO-$_{d6}$) δ 7,99-7,80 (m, 2H), 7,76 (m, 3H), 7,52 (d, J = 8,1 Hz, 1H), 7,43-7,39 (m, 2H), 7,52 (d, J = 8,1 Hz, 1H), 7,43-7,36 (m, 2H), 7,20 (dt, J = 8,7, 1,8 Hz, 1H), 6,74 (s, 1H), 5,41 (s, 2H), 4,02-3,62 (m, 2H), 2,03 (s, 3H) ES-HRMS m/z 479,0411 (M+H calculado para $C_{21}H_{18}N_2F_2BrO_4$ requiere 479,0413)

Ejemplo 658



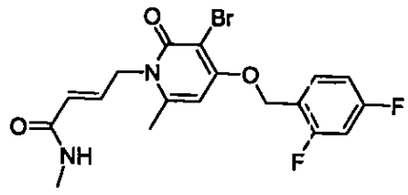

(5-bromo-4-[(2,4-d_fluorobencil)oxi]-1-{2-metil-5-[(metilamino)carbonil]fenil}-6-oxo-1,6-dihidropiridin-2-il)acetato de metilo

A una disolucion de 3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-(hidroximetil)-2-oxopiridin-1(2H)-il]-N,4-dimetilbenzamida, (225 mg, 0,50 mmol) agitada en $CH_2Cl_2$ se agrego piridina (55 µL, 0,69 mmol) A la disolucion homogenea resultante luego se agrego anhidrido acetico (47 µL, 0,51 mmol) La mezcla se agito a temperatura ambiente durante 3 horas Luego se agregaron piridina (150 µL, 1,8 mmol) y anhidrido acetico (100 µL, 1,05 mmol) y la reaccicn se agitó durante toda la noche a temperatura ambiente Despues la reaccion se enfrió repentinamente con 1N $NHCl_4$ y se la diluyo con $CH_2Cl_2$ Las capas se separaron y la capa organica luego se extrajo con $CH_2Cl_2$ (3X) Los materiales organicos luego se combinaron,

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se secaron y se concentraron *in vacuo* El residuo se trituró con $Et_2O$ y se filtro para producir un sólido blanquecino (150 mg, a' 61%) $^1H$ NMR (300 MHz, $DMSO_{-d6}$) δ 8,48 (br s, 1H), 7,87 (aprox d, J = 7,8 Hz, 1H), 7,74-7,69 (m, 2H), 7,52 (d, J = 7,5 Hz, 1H), 7,40 (aprox t, J = 8,1 Hz, 1H), 7,28-7,19 (m, 1H), 6,91 (s, 1H), 5,43 (s, 2H), 4,60 (s, 2H), 2,79 (s, 3H), 2,06 (s, 3H), 1,94 (s, 3H) ES-HRMS m/z 535,0676 (M+H calculado para $C_{24}H_{22}N_2F_2BrO_5$ requiere 535,0675)

Ejemplo 659




(2E)-4-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-N-metilbut-2-enamida

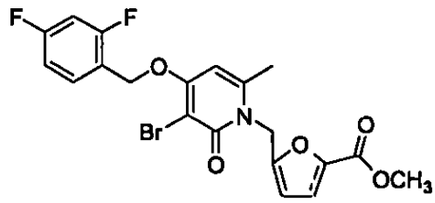
Etapa 1, ácido (2E)-4-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]but-2-enoico, La composición de acido carboxilico se preparo agitando el éster (900 mg, 2,1 mmol) en THF (10 ml) A esta disolución se agrego 1N NaOH (1 ml) y la mezcla resultante se agito a temperatura ambiente Después de 2 horas, se agrego NaOH (1 ml) adicional a la reacción y se la agito a temperatura ambiente durante toda la noche El THF despues se concentro bajo vacio La capa acuosa remanente luego se acidificó a un pH ~ 4 despues de lo cual se produjo un precipitado de color blanco La filtracion y el secado bajo vacio dieron origen a un sólido de color blanco (900 mg) que se utilizo como en la etapa siguiente

El compuesto del titulo se preparo agitando el ácido precedente (480 mg, 1,16 mmol) en $CH_2Cl_2$ a temperatura ambiente A esta mezcla se agrego secuencialmente $Et_3N$ (244

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µL), HOBt (188 mg, 1,4 mmol), $MeNH_2$ (2 0M-THF, 700 ml, 1,4 mmol) y, por ultimo, EDC (266 mg, 1,4 mmol) La mezcla homogénea se agito a temperatura ambiente durante toda la noche La reaccion se enfrio repentinamente con 1N HCl Las capas se separaron y la capa acuosa se extrajo con $CH_2Cl_2$ (4X) Los materiales organicos se combinaron, se secaron y se concentraron *in vacuo* El residuo en crudo se trituro en una combinacion $CH_3CN$-$Et_2O$ y se filtró para producir un sólido de color blanco puro (330 mg, al 67%) $^1$H-NMR ($DMSO_{d6}$/300 MHz) δ 8,20-7,90 (m, 1H), 7,68 (q, J = 8,4 hz, 1H), 7,37 (dt, J = 10,2, 2,4 Hz, 1H), 7,20 (dt, J = 15,6, 4,2 Hz, 1H), 6,60 (s, 1H), 5,63 (d, J = 15,6 Hz, 1H), 5,31 (s, 2H), 4,81 (d, J = 2,7 Hz, 2H), 3,33 (d, J = 6,9 Hz, 1H), 2,61 (d, J = 4,8 Hz, 3H), 2,37 (s, 3H) ES-HRMS m/z 427,0493 (M+H calculado para $C_{18}H_{18}BrF_2N_2O_3$ = 427,0463)

Ejemplo 660



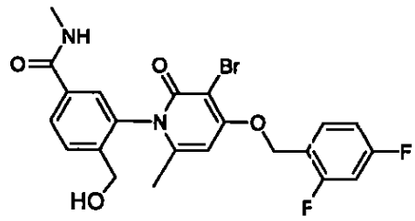

5-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}-2-fluorato de metilo

Etapa 1 A una suspension de 3-bromo-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona a temperatura ambiente (330,1 mg, 1,00 mmol) y NaH (48,0 mg, 2,00 mmol) en THF (1,6 ml) se adicionó metil-5-clorometil-2-furato (400 mg, 2,30 mmol) La suspensión resultante se agito y se calento a 68 °C durante 8 horas hasta la consumicion completa del material de inicio por analisis LC/MS La mezcla de reaccion lueço se diluyó con cloruro de amonio (disolucion acuosa saturada, 10 ml) y agua (100 ml) Esta emulsión resultante despues se extrajo con acetato de etilo

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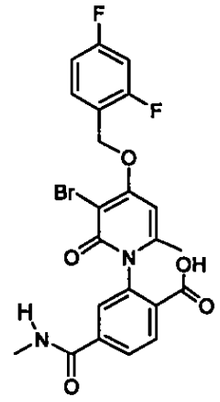
(3 X 300 ml) El extracto organico resultante se separó, se seco sobre $Na_2SO_4$ y se concentro El residuo de color oscuro resultante se sometió a cromatografia sobre $SiO_2$ con acetato de etilo/hexanos (3 7) para generar un sólido $^1H$ NMR (400 MHz, $CDCl_3$) δ 7 53 (aprox q, J = 8,2 Hz, 1H), 7,07 (d, J = 3,5 Hz, 1H), 6,93 (aprox dt, J = 8,4, 1,5 Hz, 1H), 6,84 (aprox ddd, J = 10,2, 8,7, 2,4 Hz, 1H), 6,53 (d, J = 3,4 Hz, 1H), 6,00 (s, 1H), 5,27 (s, 2H), 5,18 (s, 2H), 3,85 (s, 3H), 2,54 (s, 3H), LC/MS columna C-18, $t_r$ = 2,64 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con deteccion a 254 nm, a 50 °C) ES-MS *m/z* 468 (M+H) ES-HRMS m/z 468,0276 (M+H calculado para $C_{20}H_{17}BrF_2NO_5$ requiere 468,0253)

Ejemplo 661




3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4- hidroximetil)-N-metilbenzamida

Etapa 1 Preparacion de acido 2-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-[(metilamino)carbonil]benzoico



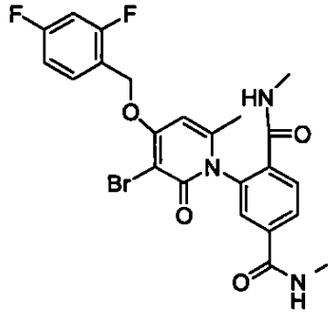
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A una disolución de 2-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-[(metilamino)carbonil]benzoato de metilo (1,05 g, 2,02 mmol) en THF (10,0 ml) se agregó gota a gota una disolucion acuosa de hidroxido de sodio (3,0 M, 3,5 ml, 10 mmol) La reacción luego se calentó a 60 °C durante 8,0 horas La suspension resultante despues se diluyo con 500 ml de acetato de etilo y se neutralizó con una disolucion acuosa de ácido clorhídrico (2,0 N, 5,0 ml, 10 mmol) La disolucion bifásica resultante se separo y la capa acuosa resultante se extrajo adicionalmente con acetato de etilo (2 X 200 ml) Los extractos organicos combinados resultantes fueron secados sobre $Na_2SO_4$, filtrados y concentrados *in vacuo* a un volumen de 50 ml En este momento comenzo a formarse un solido de color blanco y la suspension sólida resultante se dejo reposar hasta que pareciera detenerse la precipitacion (aproximadamente 1,0 hora) El precipitado se recolectó y se seco *in vacuo* (1,0 mm Hg) para formar el acido solido como un intermedio (806 mg, al 78%) $^1$H NMR (400 MHz, $d_7$-DMF) δ 13,19 (s, 1H), 8,63 (aprox d, J = 4,5 Hz, 1H), 8,09 (d, J = 8,0 Hz, 1H), 8,00 (dd, J = 8,0, 1,6 Hz, 1H), 7,71-7,67 (m, 2H), 7,34 (aprox dt, J = 9,6, 1,6 Hz, 1H), 7,16 (aprox dt, J = 8,7, 1,8 Hz, 1H), 6,66 (s, 1H), 5,33 (s, 2H), 3,29 (s, 3H), 1,92 (s, 3H), LC/MS columna C-18, $t_r$ = 2,15 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con deteccion a 254 nm, a 50 °C) ES-MS *m/z* 507 (M+H) ES-HRMS m/z 507,0344 (M+H calculado para $C_{22}H_{18}BrF_2N_2O_5$ requiere 507,0362)

Etapa 2 Preparación del compuesto del título A una disolucion de acido 2-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-[(metilamino)carbonil]benzoico (500 mg, 0,986 mmol) en THF

(6,8 ml) se agrego gota a gota una disolucion de complejo borano-dimetil sulfuro (disolución THF, 2,0 M, 2,0 ml, 4,0 mmol) No se permitio que la temperatura interna de la reacción superara los 0 °C La disolucion resultante se conservo durante 4,0 horas, en cuyo momento se quito el baño refrigerante y la reaccion se mantuvo a temperatura ambiente durante dos horas adicionales A continuación, se agrego una disoluciór de cloruro de amonio (acuosa saturada, 300 ml) La emulsión resultante se extrajo con acetato de etilo (3 X 300 ml) y los extractos orgánicos resultantes fueron separados, secados sobre $Na_2SO_4$ y concentrados *in vacuo* hasta lograr un residuo que después se sometió a cromatografia sobre $SiO_2$ con acetato de etilo/hexanos (6 4) para formar un solido (392 mg, al 81%) $^1H$ NMR (400 MHz, $d_4$-MeOH) δ 7,96 (dd, J = 8,0, 1,9 Hz, 1H), 7,75 (d, J = 8,1 Hz, 1H), 7,65 (aprox q, J = 8,0 Hz, 1H), 7,58 (d, J = 1,7 Hz, 1H), 7,05 (aprox t, J = 8,5 Hz, 2H), 6,64 (s, 1H), 5,36 (s, 2H), 4,35 (AB-q, J = 14,1 Hz, Δ= 60,8 Hz, 2H), 2,90 (s, 3H), 2,03 (s, 3H), LC/MS columna C-18, $t_r$ = 2,16 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con deteccion a 254 nm, a 50 °C) ES-MS *m/z* 493 (M+H) ES-HRMS m/z 493,0590 (M+H calculado para $C_{22}H_{20}BrF_2N_2O_4$ requiere 493,0596)

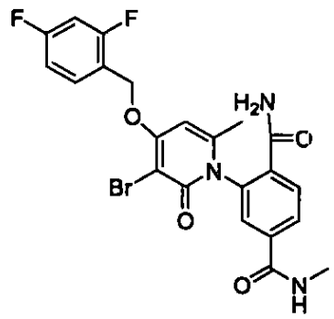
Ejemplo 662



2-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-N,N'-dimetiltereftalamida

Etapa 1 A una disolucion de acido 2-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-[(metilamino)carbonil]benzoico a temperature ambiente (500 mg, 0,986 mmol) en DMF (5,0 ml) se agrego secuencialmente hidrocloruro de 1-(3-dimetilaminopropil)-etilcarbodiimida (EDC-HCl, 350,0 mg, 1,83 mmol) y 1-hidroxi-benzotriazola (HOBT, 100,0 mg, 0,74 mmol) A esta suspensión resultante luego se agregó una disolucion de metilamina (2,0 M THF, 1,0 ml, 2,0 mmol) La reacción se agito durante 16,0 horas, en cuyo momento la reacción se diluyo con acetato de etilo (600 ml) La mezcla se lavó con (3 x 200 ml) de agua y el extracto orgánico se separó, se secó sobre $Na_2SO_4$ y se concentró *in vacuo* hasta obtener un volumen de aproximadamente 60 ml En este momento se formó un precipitado solido y se recolecto para formar (289 mg, al 56%) $^1$H NMR (300 MHz, $d_4$-MeOH) δ 8,06 (br d, J = 8,0 Hz, 1H), 7,81 (d, J = 8,1 Hz, 1H), 7,73 (s, 1H), 7,70 (aprox q, J = 7,4 Hz, 1H), 7,09 (aprox t, J = 8,0 Hz, 2H), 6,65 (s, 1H), 5,39 (s, 2H), 2,96 (s, 3H), 2,79 (s, 3H), 2,13 (s, 3H), LC/MS columna C-18, $t_r$ = 2,13 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con deteccion a 254 nm, a 50 °C) ES-MS *m/z* 520 (M+H) ES-HRMS m/z 520,0700 (M+H calculado para $C_{23}H_{21}BrF_2N_3O_4$ requiere 520,0678)

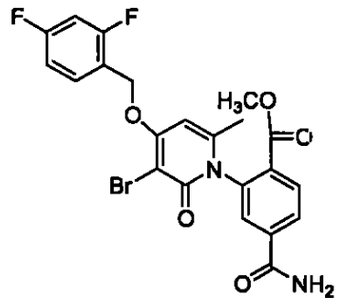
Ejemplo 663



2-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-N-4-metiltereftalamida

Etapa 1 A una suspensión de acido 2-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-[(metilamino)carbonil]benzoico a temperatura ambiente (302 mg, 0,595 mmol) en THF(1,8 ml) se agregó secuencialmente 2-cloro-4,6-dimetoxi-1,3,5 triazina (140,5 mg, 0,800 mmol) y N-metil morfolina (NMM, 184 mg, 1,824 mmol) La disolucion resultante se maduro durante 2 horas y luego se le agregó una disolución acuosa saturada de hidroxido de amonio (0,60 ml) La reacción se dejo continuar durante 1 hora adicional en cuyo momento se formó un precipitado que fue recolectado, lavado con 20 ml de eter dietilico y secado *in vacuo* para formar un sólido (201 mg, al 66%) $^1$H NMR (400 MHz, $d_6$-DMSO) δ 8,59 (br d, J = 8,0, 1H), 7,96 (d, J = 8,0 Hz, 1H), 7,83 (s, 1H), ',72 (d, J = 9,0, 1H), 7,69-7,64 (m, 2H), 7,39-7,31 (m, 1H), 7,19 (aprox t, J = 8,0 Hz, 1H), 6,60 (s, 1H), 5,31(s, 2H), 3,85 (s, 1H), 2,78 (br d, J = 8,0 Hz, 3H), 1,96 (s, 3H), LC/MS columna C-18, $t_r$ = 2,20 minutos (acetonitrilo/aqua al 5 a 95% durante 5 minutos a 1 ml/min con detección a 254 nm, a 50 °C) ES-MS *m/z* 506 (M+H) ES-HRMS m/z 506,0550 (M+H calculado para $C_{22}H_{19}BrF_2N_3O_4$ requiere 506,0522)

Ejemplo 664

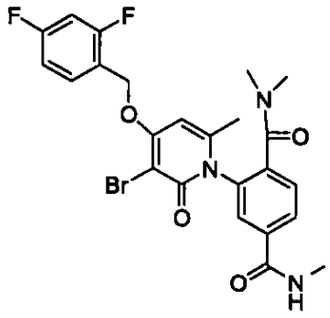


4-(aminocarbonil)-2-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]benzoato de metilo

Etapa 1 A una disolución de acido 3-(4-hidroxi-6-metil-2-oxopiridin-1(2H)-il)-4-(metoxicarbonil)benzoico a temperatura ambiente (3,01 g, 9,93 mmol) en DMF (20 ml) se agrego secuencialmente hidrocloruro de 1-(3-dimetilaminopropil)-etilcarbodiimida (EDC-HCl, 2,00 g, 10,4 mmol) y 1-hidroxi-benzotriazola (HOBT, 50,0 mg, 0,367 mmol) A esta suspension resultante luego se agrego una disolucion de amoniaco (0,5 M 1,4 dioxano, 30,0 ml, 15,0 mmol) La reaccion resultante se agitó durante 16,0 horas hasta que se observó la consumicion completa del material de inicio por análisis LC/MS En este momento, el recipiente de reaccion se colocó sobre un rotovapor a un vacio de 30 mm Hg y se mantuvo a 30 °C durante 30 minutos para quitar todo los residuos de amoniaco de la mezcla de reaccion El recipiente de reaccion se retiro del rotovapor y, posteriormente, se lo cargo con N-bromosuccinimida solida (1,790 g, 10,06 mmol) y la disolucion de color rojizo resultante se agito durante 3,0 horas En este momento la reaccion se cargo con $K_2CO_3$ (3,00 g, 21,7 mmol) y 2,4 difluorobencil bromuro (1,95 ml, 15,2 mmol) La suspensión resultante se agitó durante 16,0 horas En este momento la suspensión de reaccion se diluyo con agua (400 ml) y se extrajo con acetato de etilo (3 X 300 ml) Los

extractos organicos resultantes fueron separados, secados sobre $Na_2SO_4$ y concentrados para proporcionar un residuo que se sometio a cromatografia sobre $SiO_2$ usando acetato de etilo/hexanos/metanol (6 3,5 0,5) para formar un solido blanquecino (1,09 g, al 21%) $^1H$ NMR (400 MHz, $d_4$-MeOH) δ 8,21 (dd, J = 8,5, 1,5 Hz, 1H), 8,09 (dd, J = 7,6, 2,0 Hz, 1H), 7,78 (br s, 1H), 7 65 (aprox q, J = 7,9 Hz, 1H), 7,03 (aprox t, J = 8,0 Hz, 2H), 6,63 (s, 1H), 5,37 (s, 2H), 3,75 (s, 3H), 2,02 (s, 3H), LC/MS columna C-18, $t_r$ = 2,28 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con detección a 254 nm, a 50 °C) ES-MS *m/z* 507 (M+H) ES-HRMS m/. 507,0385 (M+H calculado para $C_{22}H_{18}BrF_2N_2O_5$ requiere 507,0362)

Ejemplo 665



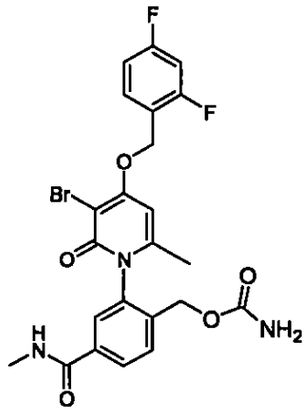
2-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-$N^1$,$N^1$,$N^4$-trimetiltereftalamida

Etapa 1 A una disolución de acido 2-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-[(metilamino)carbonil]benzoico a temperature ambiente (300 mg, 0,591 mmol) en DMF (1,8 ml) se agrego secuencialmente hidrocloruro de 1-(3-dimetilaminopropil)-etilcarbodiimida (EDC-HCl, 190,0 mg, 1,0 mmol) y 1-hidroxi-benzotriazola (HOBT, 26,0 mg, 0,191 mmol) A esta suspensión resultante luego se agregó una disolucion de dimetilamina (2,0 M THF, 0,50 ml, 1,0 mmol) La reaccion se agitó durante 16,0 horas, en cuyo momento la mezcla de reaccion se aplico

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directamente a cromatografía sobre $SiO_2$ con acetato de etilo/hexanos (6 4) para formar un sólido (206 mg, al 65%) $^1H$ NMR (400 MHz, $d_4$-MeOH) δ 8,01 (dd, J = 8,2, 1,5 Hz, 1H), 7,73 (aprox d J = 8,1 Hz, 1H), 7,61 (aprox q, J = 7,2 Hz, 1H), 7,60 (aprox d, J = 9,5 Hz, 1H), 7,04 (aprox t, J = 8,0 Hz, 2H), 6,65 (s, 1H), 5,32 (s, 2H), 3,64 (s, 3H), 2,92 (s, 6H), 2,13 (s, 3H), LC/MS columna C-18, $t_r$ = 2,20 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con detección a 254 nm, a 50 °C) ES-MS *m/z* 534 (M+H) ES-HRMS *m/z* 534,0820 (M+H calculado para $C_{24}H_{23}BrF_2N_3O_4$ requiere 534,0835)

Ejemplo 666

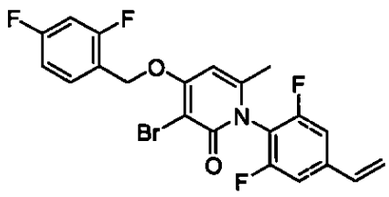



2-[3-bromo-4-[(2,4 difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-[(metilamino)carbonil]bencil carbamato

Etapa 1 A una disolución de 3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-(hidroximetil)-N-metilbenzamida a temperatura ambiente (493 mg, 1,00 mmol) en cloruro de metileno (5,0 ml) se agregó una disolución de tricloroacetil isocianato (tolueno, 0,53 M, 1,9 ml, 1,0 mmol) La suspensión resultante se agitó durante una hora hasta la consumición completa del material de inicio por análisis LC/MS La

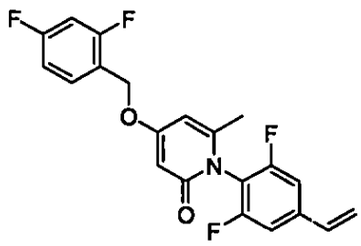
mezcla de reaccion después se aplico directamente a $Al_2O_3$ (0,5 g de actividad tipo I) y la suspension se maduró durante tres horas En este momento, el tapon de $Al_2O_3$ se lavo con acetato de etilo/metanol (95 5) y el licor madre resultante se concentró a un residuo que se sometio a cromatografia sobre $SiO_2$ usando acetato de etilo/hexanos/metanol (6 3,5 0,5) para formar un sólido de color blanco (396 mg, al 74%) $^1H$ NMR (300 MHz, $d_4$-MeOH) δ 8,00 (dd, J = 8,0, 1,7 Hz, 1H), 7,75 (d, J = 8,2 Hz, 1H), 7,72-7,64 (m, 2H), 7,09 (aprox t, J = 8,5 Hz, 2H), 6,69 (s, 1H), 5,40 (s, 2H), 1,85 (m, 2H), 2,90 (s, 3H), 2,10 (s, 3H), LC/MS columna C-18, $t_r$ = 2,15 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con detección a 254 nm, a 50 °C) ES-MS *m/z* 536 (M+H) ES-HRMS m/z 536,0617 (M+H calculado para $C_{23}H_{21}BrF_2N_3O_5$ requiere 536,0627)

Ejemplo 667



3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-(difluoro-4-vinilfenil)-6-metilpiridin-2(1H)-ona

Etapa 1 Preparacion de 4-[(2,4-difluorobencil)oxi]-1-(2,6-difluoro-4-vinilfenil)-6-metilpiridin-2(1H)-ona



A una disolucion a temperatura ambiente de 1-(4-bromo-2,6-difluorofenil)-4-[(2,4-difluorobencil)oxi]-6-

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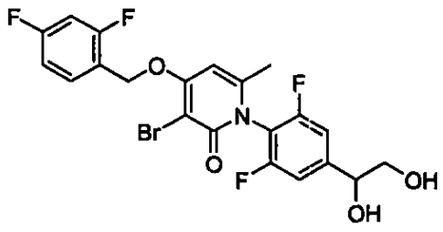
metilpiridin-2(1H)-ona (4,01 g, 9,06 mmol) en THF anhidro (30 ml) se agregó, de manera secuencial, tributil(vinil)tin (5,00 g, 15,7 mmol) y tetrakis(trifenilfosfina)paladio (1,00 g, 0,865 mmol) bajo una corriente de argon El recipiente de reaccion después se equipó con un condensador de reflujo y el sistema de reaccion se purgo con un flujo de argón La disolucion de color amarillo resultante se calento a 68 °C y se agito bajo una presion de argón positiva durante 12,0 horas hasta la desaparicion completa del material de inicio por analisis LC/MS La mezcla de reacción se diluyo con 300 ml de salmuera y se extrajo con acetato de etilo (3 X 300 ml) Los extractos organicos fueron separados, secados sobre $Na_2SO_4$ y concentrados *in vacuo* y el residuo oscuro resultante se sometió a cromatografia sobre SiO con acetato de etilo/hexanos (1 1) para formar un solido de color amarillo (3,18 g, al 90 %) $^1H$ NMR (400 MHz, $CDCl_3$) δ 7 41 (aprox q, J = 8,0 Hz, 1H), 7,08 (aprox d, J = 8,3 Hz, 2H), 6,90 (aprox t, J =7,2 Hz, 1H), 6,85 (aprox t, J = 7,4 Hz, 1H), 6,63 (dd, J = 17,5, 10,9 Hz, 1H), 5,96 (aprox d, 15,8 Hz, 1H), 5,94 (aprox d, J = 15,8 Hz, 1H), 5,79 (d, J = 17,4 Hz, 1H), 5,43 (d, J = 10,9 Hz, 1H), 5,01 (br s, 2H), 1,99 (s, 3H), LC/MS columna C-18, $t_r$ = 2,93 minuts (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con detección a 254 nm, a 50 °C) ES-MS *m/z* 390 (M+H) ES-HRMS m/z 390,1095 (M+H calculado para $C_{21}H_{16}F_4NO$, requiere 390,1112)

Etapa 2 A una disolucion a temperatura ambiente agitada enérgicamente de 4-[(2,4-difluorobencil)oxi]-1-(2,6-difluoro-4-vinilfenil)-6-metilpiridin-2(1H)- ona (721 mg, 1,85 mmol) en cloruro de metileno (10 ml) se agrego N-bromosuccinimida solida (330 mg, 1,86 mmol) y la disolución de color rojizo resultante se agito durante 10 minutos En este momento la reacción se diluyo con acetato de etilo

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(100 ml) y se lavo con sulfuro sodico (disolucion acuosa al 5%, 50 ml) Los extractos organicos resultantes se secaron sobre $Na_2SO_4$ se filtraron y se concentraron *in vacuo* a un volumen de aproximadamente 50 ml El licor madre resultante se precipitó rápidamente y formo un solido amorfo que fue recolectado y secado a un vacio de 1 mm Hg para proporcionar un solido (610 mg, 70 %) $^1$H NMR (400 MHz, $CDCl_3$) δ 7,59 (aprox q, J = 8,0 Hz, 1H), 7,09 (aprox d, J = 8,3 Hz, 2H), 6,95 (aprox t, J =7,2 Hz, 1H), 6,87 (aprox t, J = 7,4 Hz, 1H), 6,62 (dd, J = 17,5, 10,9 Hz, 1H), 6,12 (s, 1H), 5,81 (d, J = 17,4 Hz, 1H), 5,43 (d, J = 10,9 Hz, 1H), 5,25 (br s, 2H), 2,07 (s, 3H), LC/MS columna C-18, $t_r$ = 3,17 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con detección a 254 nm, a 50 °C) ES-MS *m/z* 468 (M+H) ES-HRMS m/z 468,0249 (M+H calculado para $C_{21}H_{18}BrF_4NO_2$ requiere 468,0217)

Ejemplo 668



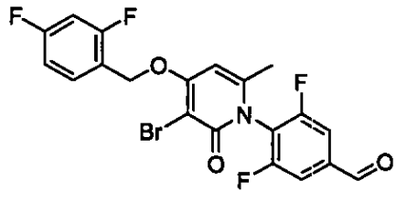

3-bromo-4-[(2,4-difluorobencil)oxi]-1-[4-(1,2-dihidroxietil)-2,6-difluorofenil]-6-metilpiridin-2(1H)-ona

Etapa 1 Preparacion del compuesto del titulo A una disolucion a temperatura ambiente de 3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-difluoro-4-vinilfenil)-6-metilpiridin-2(1H)-ona (408,0 mg, 0,871 mmol) en agua/acetona 1 3 (8,0 ml) se agrego, de manera secuencial, óxido de N-metil morfolina (268,0 g, 2,29 mmol) y tetróxido de osmio (disolución acuosa al 4%, 0,25 ml o aproximadamente 10 mg, 0,039 mmol) La disolucion resultante se agito durante 8 horas hasta la consumición

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completa del material de inicio por analisis LC/MS, y la reacción se concentro *in vacuo* a un cuarto del volumen original La disolucion resultante se diluyo con acetato de etilo (300 ml) y se lavo con agua (2 X 100 ml) El extracto organico se separó, se seco sobre $Na_2SO_4$ y se concentro *in vacuo* y el residuo de color oscuro resultante se sometio a cromatografia sobre $SiO_2$ con acetato de etilo/hexanos/metanol (6 3,5 0,5) para formar un solido (389 mg, al 88%) $^1H$ NMR (400 MHz, $d_4$-MeOH) δ 7,62 (aprox q, J = 8,0, Hz, 1H), 7,26 (dd, J = 9,6, 4,5 Hz, 2H), 7,04 (aprox t, J = 8,6 Hz, 2H), 6,67 (s, 1H), 5,36 (s, 2H), 4,75 (aprox t, J = 5,6 Hz, 1H), 3,68-3,61 (m, 2H), 2,11 (s, 3H), LC/MS columna C-18, $t_r$ = 2,26 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con deteccion a 254 nm, a 50 °C) ES-MS *m/z* 502 (M+H) ES-HRMS m/z 502,0247 (M+H calculado para $C_{21}H_{17}BrF_4NO_4$ requiere 502,0272)

Ejemplo 669

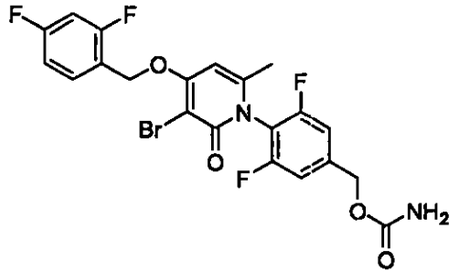


4-[3-bromo-4-[(2,4 difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-3,5-difluorobenzaldehido

Etapa 1 Preparacion del compuesto del titulo A una disolucion de 3-bromo-4-[(2,4-difluorobencil)oxi]-1-(4-(1,2-dihidroxietil)-2,6-difluorofenil]-6-metilpiridin-2(1H)-ona a temperatura ambiente (310 mg, 0,615 mmol) en tolueno (3,0 ml) se agrego acetato de plomo (IV) (443 mg, 1,63 mmol) La disolucion de color marrón oscuro resultante se agito durante una hora hasta la consumición completa del material de inicio por analisis LC/MS La mezcla de

reaccion después se diluyó con acetato de etilo (100 ml), se lavó con agua (3 X 100 ml) y se lavo con salmuera (3 X 30 ml) El extracto organico resultante se separo, se seco sobre $Na_2SO_4$ y se concentró El residuo de color oscuro resultante se sometió a cromatografia sobre $SiO_2$ con acetato de etilo/hexanos (1 1) para generar un solido de color amarillo claro (269 mg, 93%) Precaucion, el producto se oxida facilmente al contacto con el aire $^1H$ NMR (300 MHz, $d_4$-MeOH) δ 10,05 (s, 1H), 7,68 (aprox q, J = 7,2 Hz, 1H), 7,38 (d, J = 8,9 Hz, 2H), 7,05 (aprox t, J = 8,2 Hz, 2H), 6,73 (s, 1H), 5,40 (s, 2H), 2,15 (s, 3H), LC/MS columna C-18, $t_r$ = 2,72 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con deteccion a 254 nm, a 50 °C) ES-MS *m/z* 470 (M+H) ES-HRMS m/z 470,0049 (M+H calculado para $C_{20}H_{13}BrF_4NO_3$ requiere 470,0009)

Ejemplo 670




4-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-3,5-difluorobencil carbamato

Etapa 1 A una disolución de 4-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-3,5-difluorobenzaldehido a temperatura ambiente (220 mg, 0,468 mmol) en metanol (10 ml) se agrego borohidruro de sodio solido (60,0 mg, 1,58 mmol) La disolucion resultante emanó gas durante aproximadamente 0,5 minutos y se agitó durante 10 minutos adicionales hasta la consumición completa del material de inicio por análisis LC/MS Despues la reacción

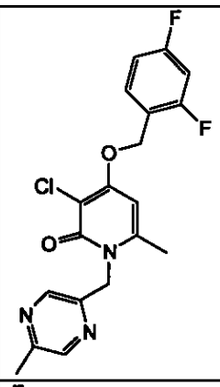
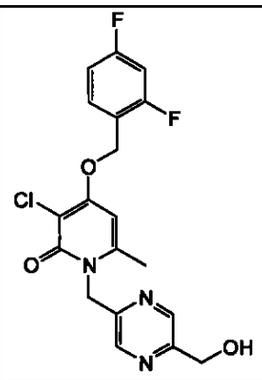
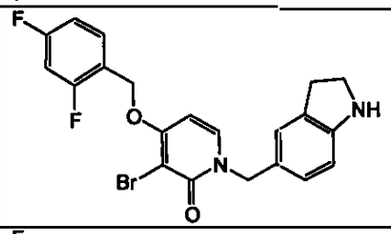
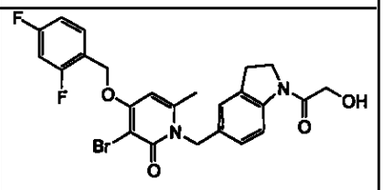
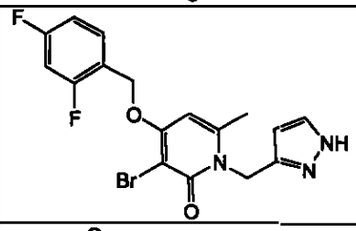
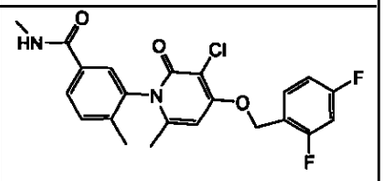
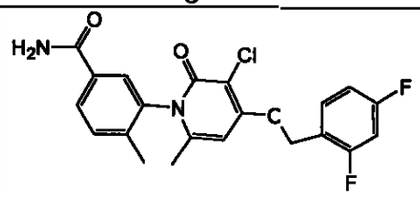
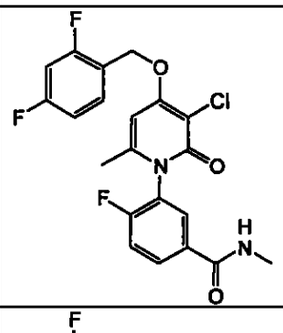
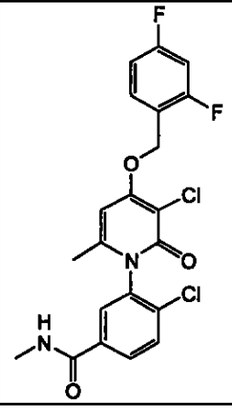
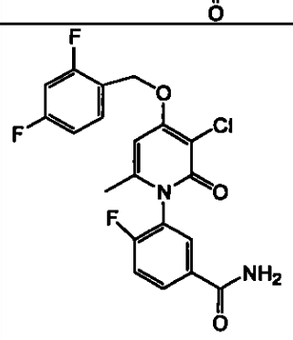
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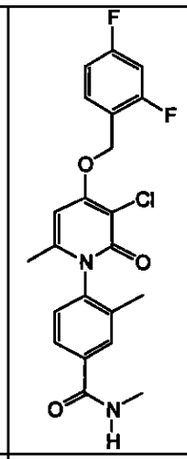
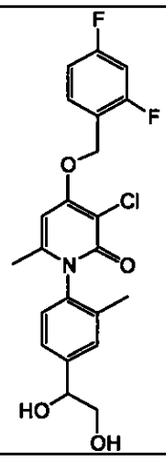
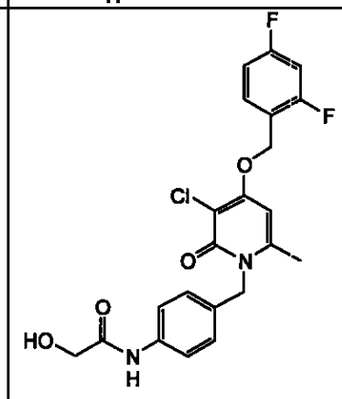
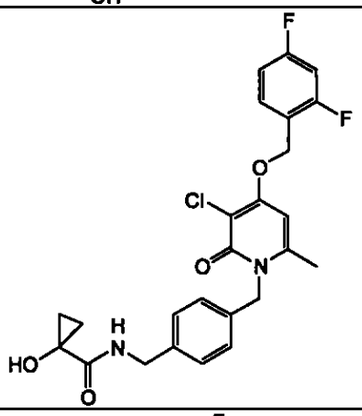
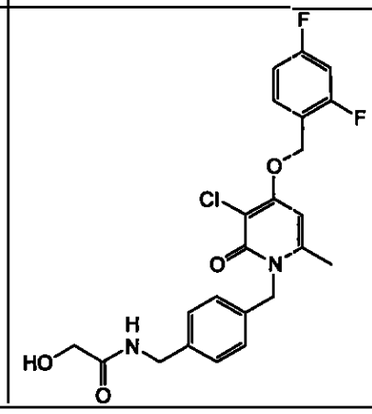
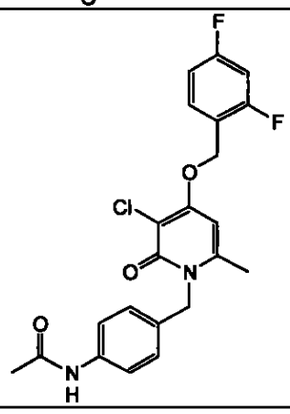
se diluyó con disolución acuosa saturada de cloruro de amonio (10 ml) y se extrajo con acetato de etilo (4 X 50 ml) El extracto organico se separo, se secó sobre $Na_2SO_4$ y se concentró hasta lograr un residuo Este residuo resultante luego se diluyó con cloruro de metileno (5,0 ml) y se agregó una disolución de tricloroacetil isocianato (tolueno, 0,53 M, 1,0 ml, 0,53 mmol) La disolucion resultante se agito durante una hora hasta la consumicion completa del material de inicio por analisis LC/MS La mezcla de reacción despues se aplico directamente a $Al_2O_3$ (0,5 g de actividad tipo I) y la suspension se maduró durante tres horas En este momento, el tapon de $Al_2O_3$ se lavo con acetato de etilo/metanol (95 5) y el licor madre resultante se concentro a un residuo que se sometio a cromatografia sobre $SiO_2$ usando acetato de etilo/hexanos/metanol (5 3,8 0,2) para formar un solido de color blanco (181 mg, al 75%) $^1H$ NMR (400 MHz, $d_4$-MeOH) δ 7,63 (aprox q, J = 8,0, Hz, 1H), 7,43 (d, J = 8,2, Hz, 2H), 7,04 (aprox t, J = 8,1 Hz, 2H), 6,68 (s, 1H), 5,37 (s, 2H), 5,12 (m, 2H), 3,11 (s, 3H), LC/MS columna C-18, $t_r$ = 2,54 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con deteccion a 254 nm, a 50 °C) ES-MS *m/z* 515 (M+H) ES-HRMS m/z 515,0232 (M+H calculado para $C_{21}H_{16}BrF_4N_2O_4$ requiere 515,0234)

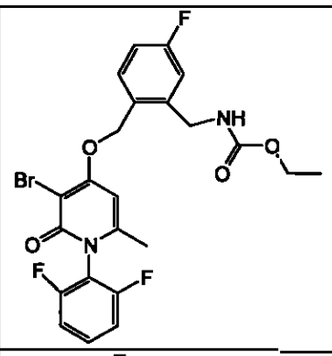
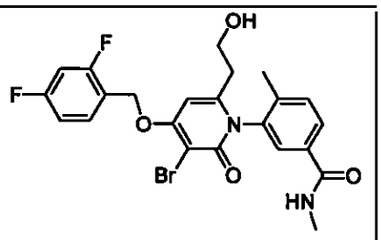
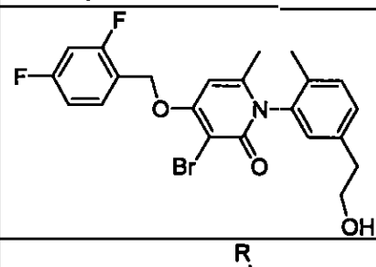
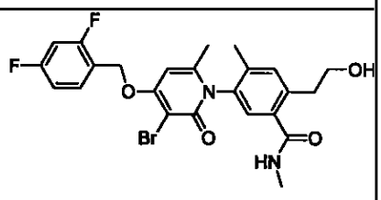
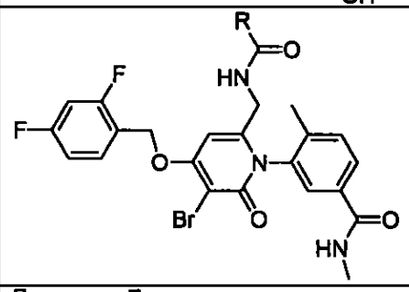
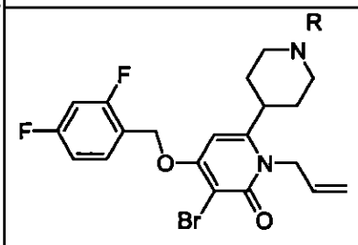
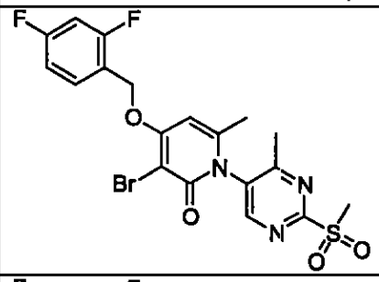
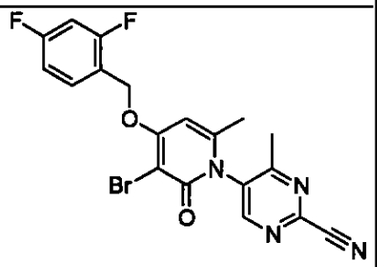
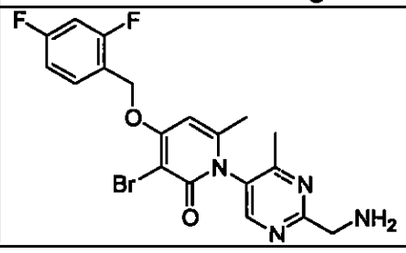
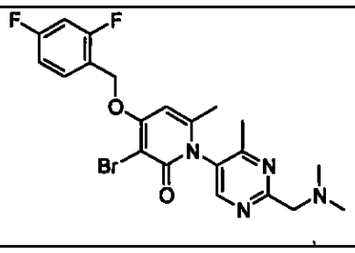
Ejemplos 671-687

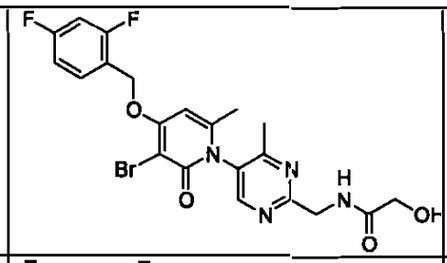
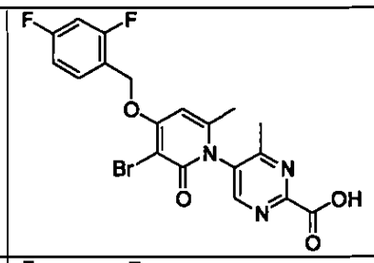
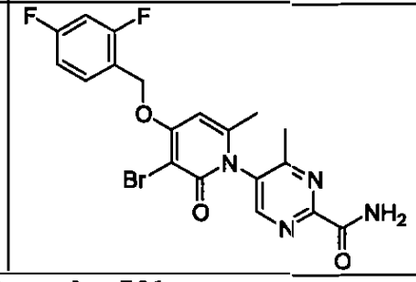
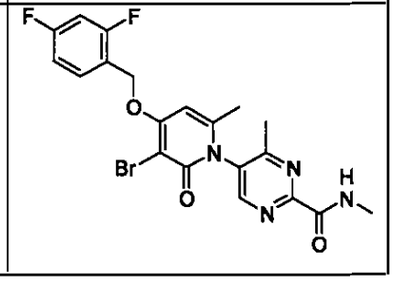
Los siguientes compuestos se preparan esencialmente de acuerdo con los procedimientos desarrollados en los esquemas y en los ejemplos precedentes

| Ejemplo N° | Ejemplo N° |
|---|---|

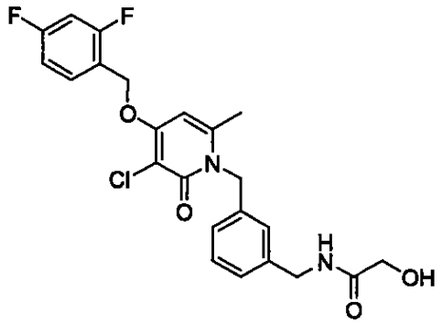
| | | | |
|---|---|---|---|
| Ejemplo 671 |  | 672 |  |
| 673 |  | 674 |  |
| 675 |  | 676 |  |
| 677 |  | 678 |  |
| 679 |  | 680 |  |

| | | | |
|---|---|---|---|
| 681 |  | 682 |  |
| 683 |  | 684 |  |
| 685 |  | 686 |  |

| | | | |
|---|---|---|---|
| 687 |  | 688 |  |
| 689 |  | 690 |  |
| 691 |  | 692 |  |
| 693 |  | 694 |  |
| 695 |  | 696 |  |

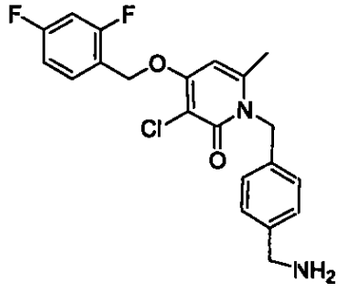
| | | | |
|---|---|---|---|
| 697 |  | 698 |  |
| 699 |  | 700 |  |

Ejemplo 701



N-(4-{[3-cloro-4-[ 2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}bencil)-2-hidroxiacetamida

Etapa 1 Preparación de 1-[4-(aminometil)bencil]-3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona ()



El compuesto del Ejemplo 606 (10,0 g, 23,38 mmol) se suspendio en tetrahidrofurano (100 ml) y se enfrio en un

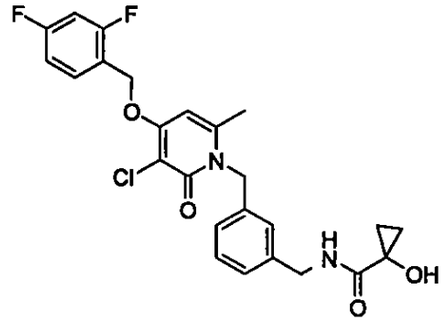
baño de hielo Se agregó borano dimetil sulfuro (29,9 ml, 2,0 *M* en tetrahidrofurano, 59,7 mmol) La mezcla resultante se calento a reflujo durante toda la noche y despues se enfrio en un baño de hielo Se agrego borano dimetil sulfuro adicional (5,85 ml, 2,0 *M* en tetrahidrofurano, 11,7 mmol) La mezcla resultante se calentó a reflujo durante toda la noche y se enfrio a temperatura ambiente El matraz se equipó con un cabezal de destilación y la reaccion se concentró parcialmente Se agrego borano dimetil sulfuro adicional (5,85 ml, 2,0 *M* en tetrahidrofurano, 11,7 mmol) La mezcla se calentó a reflujo durante toda la noche y se enfrio en un baño de hielo La reaccion se enfrió repentinamente por la adición de 1,0 *N* HCl (75,0 ml) y después se concentro parcialmente La capa acuosa se alcalinizó con 2,5 *N* NaOH y se desarrolló un precipitado El sólido se recogio mediante filtración del lavado con eter dietílico para proporcionar un sólido de color violeta pálido (3,00 g, al 32%) $^1$H NMR (400 MHz, DMSO-$d_6$) d 7 64 (*aprox* q, *J* = 7,9 Hz, 1H), 7,44 (d, *J* = 7,9 Hz, 2H), 7,32 (*aprox* dt, *J* = 2,4, 9,9 Hz, 1H), 7 14 (*aprox* dt, *J* = 1,9, 8,5 Hz, 1H), 7,13 (d, *J* = 7,9 Hz, 2H), 6,61 (s, 1H), 5,27 (s, 4H), 3,90 (s, 2H), 2,29 (s, 3H)

Etapa 2 Preparación de N-(4-{[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]metil}bencil)-2-hidroxiacetamida

Se disolvió acido acetoxiacetico (1,46 g, 12,35 mmol) en *N*,*N*-dimetilformamica (30 ml) y se agrego 1-hidroxibenzotriazol (1,84 g, 13,59 mmol) seguido de 4-metilmorfolina (2,04 ml, 18,53 mmol), 1-[4-(aminometil)bencil]-3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona (compuesto de la etapa 1) (2,50 g, 6,18 mmol) y después 1-[3-(dimetilamino)propil]-3-etilcarbodiimida hidrocloruro (2,84 g, 14,83 mmol) La

mezcla resultante se agitó a temperatura ambiente durante 1 hora, momento en el que la reaccion se diluyó con $H_2O$ (100 ml) La mezcla de reaccion despues se extrajo con acetato de etilo Los extractos organicos combinados se lavaron con $NaHCO_3$ saturada, salmuera, se secaron sobre $Na_2SO_4$, se filtraron y se concentraron La cromatografia (gel de silice, hexanos/acetato de etilo con metanol al 10%) proporciono una espuma de color blanco La espuma resultante se disolvió en metanol acuoso al 10% (20 ml) Se agregó $K_2CO_3$ (0,653 g, 4,73 mmol) y la mezcla se agito a temperatura ambiente duiante 2 horas La mezcla de reaccion se concentro y se agregó $H_2O$ (50 ml) El precipitado resultante fue recolectado mediante filtracion de lavado con eter dietilico para proporcionar un solido blanquecino (1,34 g, al 47%) $^1H$ NMR (400 MHz, $CDCl_3$) d 7,50 (*aprox* q, *J* = 7,7 Hz, 1H), 7,27 (aprox t, *J* = 5,8 Hz, 1H), 7,12 (d, *J* = 8,1 Hz, 2H), 6,97 (d, *J* = 8,1 Hz, 2H), 6,94-6,89 (m, 1H), 6,86-6,81 (m, 1H), 6,09 (s, 2H), 5,23 (s, 2H), 5,18 (s, 2H), 4,53 (t, *J* = 5,8 Hz, 1H), 4,33 (d, *J* = 5,9 Hz, 2H), 3,85 (d, *J* = 5,6 Hz, 2H), 2,30 (s, 3H) ES-HRMS *m/z* 463,1256 (M+H calculado para $C_{23}H_{22}ClF_2N_2O_4$ requiere 463,1231)

Ejemplo 702

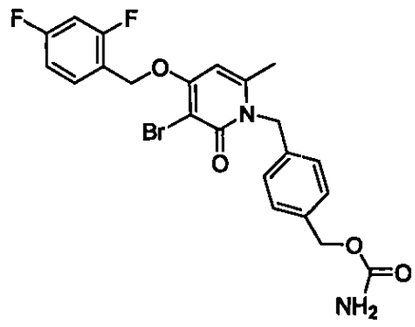



N-(4-{[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}bencil)-1-hidroxiciclopropanocarboxamida

Preparación de N-(4-{[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]metil}bencil)-1-hidroxiciclopropanocarboxamida Se disolvió acido 1-hidroxi-1-ciclopropane-carboxilico (1,26 g, 12,35 mmol) en *N,N*-dimetilformamida (30 ml) Se agregó 1-hidroxibenzotriazol (1,84 g, 13,59 mmol) seguido de 4-metilmorfolina (2,04 ml, 18,53 mmol), 1-[4-(aminometil)bencil]-3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona (Ejemplo 701 , etapa 1) (2,50 g, 6,18 mmol) y despues 1-[3-(dimetilamino)propil]-3-etilcarbodiimida hidrocloruro (2,84 g, 14,83 mmol) La mezcla resultante se agito a temperatura ambiente durante 24 horas, momento en el que la reacción se diluyo con $H_2O$ (100 ml) La mezcla de reaccion después se extrajo con acetato de etilo Los extractos organicos combinados se lavaron con $NaHCO_3$ saturada, salmuera, se secaron sobre $Na_2SO_4$, se filtraron y se concentraron La cromatografia (gel de silice, hexanos/acetato de etilo con metanol al 10%) proporcionó una espuma de color blanco La espuma resultante se disolvio en metanol acuoso al 10% (20 ml) para proporcionar una espuma de color blanco (1,45 g, al 48%) $^1H$ NMR (400 MHz, $CDCl_3$) d 7,52-7,46 (m, 1H), 7,34 (t, *J* = 5,9 Hz, 1H), 7,08 (d, *J* = 8,2 Hz, 2H), 6,92 (*aprox* d, *J* = 8,2 Hz, 2H), 6,92-6,89 (m, 1H), 6,86-6,81 (m, 1H), 6,11 (s, 1H), 5,22 (s, 2H), 5,18 (s, 2H), 4,30 (d, *J* = 5,9 Hz, 2H), 2,28 (s, 3H), 1,11 (*aprox* q, *J* = 4,1 Hz, 2H), 0,90 (*aprox* q, *J* = 4,1 Hz, 2H) ES-HRMS *m/z* 489,1420 (M+H calculado para $C_{25}H_{24}ClF_2N_2O_4$ requiere 489,1387)

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Ejemplo 703



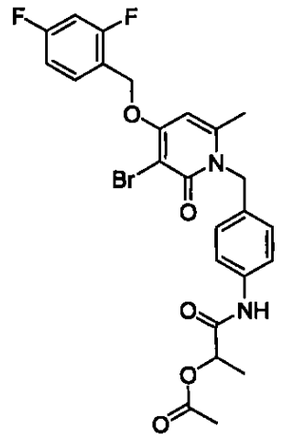
4-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]metil}bencil carbamato

Preparacion de 4-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]metil}bencil carbamato

El compuesto del Ejemplo 206 (0,868 g, 1,93 mmol) se suspendio en diclorometano (7,0 ml) Se agregó tricloroacetil isocianato (4,00 ml, 0,53 *M* en tolueno, 2,12 mmol) La mezcla resultante se agito a temperatura ambiente durante 3 horas y despues se diluyó con tetrahidrofurano (50 ml) y se agregó Al2O3 (5,0 g) y la mezcla se agito a temperatura ambiente durante toda la noche La mezcla de reaccion se filtro a través de una almohadilla de Celite® y se lavo con metanol El filtrado se concentro y el residuo se redisolvió en tetrahidrofurano (30 ml) Se agregó $Al_2O_3$ (5,0 g) y la mezcla se calentó a 40 °C durante 3 horas Despues de enfriarse a temperatura ambiente, la reaccion se filtro a traves de una almohadilla de Celite® y se lavo con metanol El filtrado se concentró y el solido resultante se lavo con eter dietilico para producir un solido blanquecino (0,831 g, al 87%) $^1$H NMR (400 MHz, $CDCl_3$) δ 7,54 (*aprox* q, *J* = 7,7 Hz, 1H), 7,25 (d, *J* = 8,2 Hz, 2H), 7,13 (d, *J* = 8,2 Hz, 2H), 6,25 (*aprox* dt, *J* = 2,0, 8,3 Hz, 1H), 6,86-6,30 (m, 1H), 5,97 (s, 1H), 5,32 (s, 2H), 5,18 (s, 2H), 5,02 (s, 2H), 4,81 (br s, 2H),

2,25 (s, 3H) ES-HRMS m/z 493,0580 (M+H calculado para $C_{22}H_{20}BrF_2N_2O_4$ requiere 493,0569)

Ejemplo 704



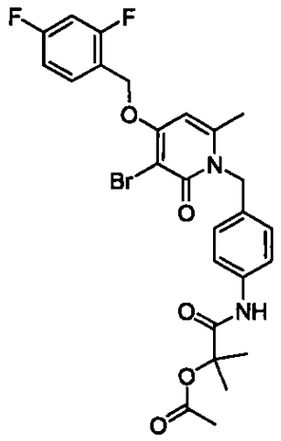
2-[(4-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]metil}fenil)amino]-1-metil-2-oxoetil acetato

A un recipiente de reaccion (tubo de cultivo borosilicatado) se le agregó el compuesto del Ejemplo 611 PHA-797266 (0,300 g, 0,69 mmol) y diclorometano (3,0 ml) Se agrego una disolución madre de *N*-metilmorfolina (0,30 M, 3,0 ml) y el aparato de reaccion en paralelo se agito orbitalmente (Labline Benchtop Orbital Shaker) a aproximadamente 200 rpm a temperatura ambiente durante 10 minutos Luego se agrego (S)-(-)-2-acetoxipropionil cloruro (0,131 ml, 1,04 mmol) al recipiente de reaccion y se agitó orbitalmente el aparato de reaccion a temperatura ambiente durante 1,5 horas En este momento se diluyó la reaccion con diclorometano (20 ml) y se trato con aproximadamente 2,1 g de resina poliamina (2,63 mmol/g) y aproximadamente 3,8 g de poliestireno funcionalizado con metilisocianato (1,10 mmol/g) y se continuo la agitacion orbital a 200 rpm a temperatura ambiente durante toda la noche Luego se abrio el recipiente de reaccion y los

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productos de fase de disolución se separaron de los subproductos enfriados repentinamente insolubles mediante su filtracion y recoleccion en un vial Después de la evaporacion parcial, los subproductos insolubles se enjuagaron con diclorometano (2 x 10 ml) El filtrado se evaporo soplando $N_2$ sobre el vial para proporcionar un solido blanquecino (0,375 g, al 99%) $^1$H NMR (400 MHz, DMF-$d_6$) δ 10,14 (s, 1H), 7,75 (*aprox* dt, *J* = 6,98, 8,59 Hz, 1H), 7,67-7,64 (m, 2H), 7,30 (ddd, *J* = 2,55, 9,26, 11,81 Hz, 1H), 7,21-7,17 (m, 3H), 6,61 (s, 1H), 5,37 (s, 4H), 5,11 (q, *J* = 6,85 Hz, 1H), 2,40 (s, 3H), 2,10 (s, 3H), 1,46 (d, *J* = 6,85 Hz 3H) ES-HRMS m/z 549,0790 (M+H calculado para $C_{25}H_{23}BrF_2N_2O_5$ requiere 549,0831)

Ejemplo 705

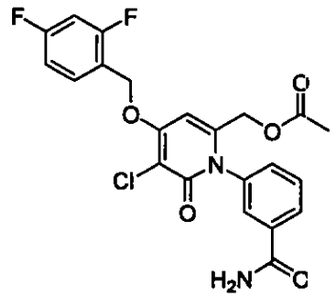



2-[(4-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}fenil)amino]-1,1-dimetil-2-oxoetil acetato

Por el metodo del Ejemplo 704 y sustituyendo (S)-(-)-2-acetoxipropionil cloruro con 2-acetoxi-2-metilpropionil cloruro, se preparó el compuesto del titulo (0,380 g, al 98%) $^1$H NMR (400 MHz, DMF-$d_6$) δ 9,68 (s, 1H), 7,75 (*aprox* dt, *J* = 6,72, 8,60 Hz, 1H), 7,71-7,68 (m, 2H), 7,30 (ddd, *J* = 2,55, 9,40, 11,95 Hz, 1H), 7,21-7,15 (m, 3H),

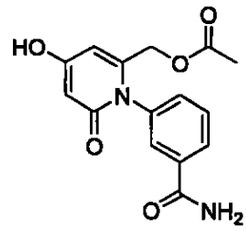
6,61 (s, 1H), 5,37 (s, 4H), 2,41 (s, 3H), 2,04 (s, 3H),1,59 (s, 6H) ES-HRMS m/z 563,1027 (M+H calculado para $C_{26}H_{25}BrF_2N_2O_5$ requiere 563,0988)

Ejemplo 706



{1-[3-(aminocarbonil)fenil]-5-cloro-4-[(2,4-difluorobencil)oxi]-6-oxo-1,6-dihidropiridin-2-il}metil acetato

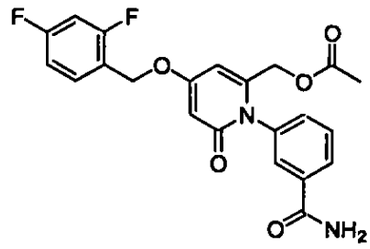
Etapa 1 Preparación de {1-[3-(aminocarbonil)fenil]-4-hidroxi-6-oxo-1,6-dihidropiridin-2-il}metil acetato



3-(2,2-dimetil-4-oxo-4H-1,3-dioxin-6-il)-2-oxopropil acetato (4,00 g, 16,52 mmol) se disolvio en 1,4-dioxano (160 ml) y se agrego 3-aminobenzamida (1,73 g, 12,71 mmol) La reaccion se calentó a reflujo durante 1 hora y despues se enfrio a 70 °C Se agrego acido metanosulfonico (1,22 g, 12,71 mmol) y la reaccion se volvio a reflujo durante 1 hora La reacción se enfrio a temperatura ambiente, se concentró y se utilizo como producto en crudo para la etapa siguiente

Etapa 2 Preparacion de {1-[3-(aminocarbonil)fenil]-4-[(2,4-difluorobencil)oxi]-6-oxo-1,6-dihidropiridin-2-il}metil acetato

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{1-[3-(aminocarbonil)fenil]-4-hidroxi-6-oxo-1,6-dihidropiridin-2-il}metil acetato (crudo de la etapa 1) (3,61 g, 11,94 mmol) se disolvio en *N,N*-dimetilformamida (40 ml) Se agregó $K_2CO_3$ (3,80 g, 27,46 mmol), seguido de bromuro 2,4-difluorobencílico (5,44 g, 26,27 mmol) La mezcla de reaccion se agito durante 48 horas a temperatura ambiente La mezcla de reaccion luego se concentro parcialmente y el residuo se absorbio en diclorometano/tetrahidrofurano 1 1 y se filtro El filtrado fue recolectado, concentrado y el residuo triturado con diclorometano para producir un sólido de color tostado (1,64 g, al 32%) $^1$H NMR (400 MHz, DMF-$d_6$) δ 8,19 (br s, 1H), 8,07 (*aprox* dt, *J* = 1,35, 7,66 Hz, 1H), 7,91 (*aprox* t, *J* = 1 81 Hz, 1H), 7,76 (*aprox* dt, *J* = 6,58, 8,59 Hz, 1H) 7,62 (t, *J* = 7,79 Hz, 1H), 7,55 (ddd, *J* = 1,21, 2,01, 7,79 Hz, 1H), 7,46 (br s, 1H), 7,34 (ddd, *J* = 2,55, 9,40, 10,47 Hz, 1H), 7,23-7,18 (m, 1H), 6,26 (d, *J* = 2,55 Hz, 1H), 6,11 (d, *J* = 2,69 Hz, 1H), 5,23 (s, 2H), 4,62 (AB q, $J_{AB}$ = 14,97 Hz, 2H), 1,96 (s, 3H) ES-HRMS m/z 429,1280 (M+H calculado para $C_{22}H_{18}F_2N_2O_5$ requiere 429,1257)

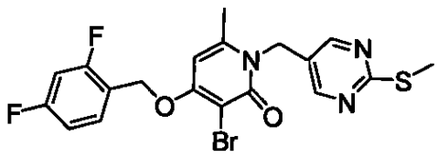
Etapa 3 Preparacion del compuesto del titulo

Se suspendio {1-[3-(aminocarbonil)fenil]-4-[(2,4-difluorobencil)oxi]-6-oxo-1,6-dihidropiridin-2-il}metil acetato (de la etapa 2) (1,02 g, 2,39 mmol) en diclorometano (15 ml) y se agrego *N*-clorosuccinimida (0,37 g, 2,75 mmol) Se agregó acido dicloroacetico (0,10 ml, 1,22 mmol) y la mezcla de reaccion se agito a 40 °C durante

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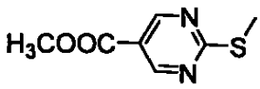
1,5 horas La reaccion se enfrio a temperatura ambiente y se formo un precipitado La mezcla de reacción se diluyo con eter dietilico y el precipitado se recolectó por filtracion y se lavo con eter dietilico (3 x 15 ml) para producir un solido de color de tostado (0,940 g, 85%) $^1$H NMR (400 MHz, DMF-$d_6$) δ 8,21 (*br* s, 1H), 8,11 (*aprox* dt, *J* = 1,48, 7,52 Hz, 1H), 7,95 (*aprox* t, *J* = 1,61 Hz, 1H), 7,80 (*aprox* dt, *J* = 6,72, 8,59 Hz, 1H) 7,69-7,60 (m, 2H), 7,48 (*br* s, 1H), 7,35 (ddd, *J* = 2,55, 9,53, 10,61 Hz, 1H), 7,24-7,19 (m, 1H), 6,97 (s, 1H), 5,49 (s, 2H), 4,71 (AB q, $J_{AB}$ = 15,04 Hz, 2H), 1,98 (s, 3H) ES-HRMS *m/z* 463,0883 (M+H calculado para $C_{22}H_{17}ClF_2N_2O_5$ requiere 463,0867)

Ejemplo 707



3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-{[2-(metiltio)pirimidin-5-il]metil}piridin-2(1*H*)-ona

Etapa 1 Preparacion de metil 2-(metiltio)pirimidina-5-carboxilato

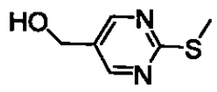


Una disolucion de sal de sodio de 3,3-dimetoxi-2-metoxicarbonilpropen-1-ol (5,0 g, 25 mmol), 2-metil-2-tiopseudourea sulfato (3,5g, 25 mmol) en metanol anhidro (25 ml) fue sometida a reflujo durante 3 horas bajo condiciones anhidras La mezcla de reaccion después se enfrio y se diluyó con acetato de etilo La mezcla de reaccion se filtró y el residuo se lavo con acetato de etilo El filtrado se concentro y el residuo se purifico por cromatografia rapida (gel de silice) utilizando acetato de etilo al 25% en hexano para proporcionar el producto

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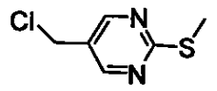
deseado (3,5 g, al 75%) como un polvo de color blanco $^1$H-NMR ($d_6$-DMSO, 400 MHz) δ 9,0 (s, 2H), 3,92 (s, 3H), 2,58 (s, 3H), ES-HRMS *m/z* 185,041 (M+H $C_7H_8N_2O_2S$ requiere 185,0379)

Etapa 2 Preparacion de [2-(metiltio)pirimidin-5-il]metanol



A una suspension fria de 2-(metilito)pirimidina-5-carboxilato de metilo (1,74 g, 9,4 mmol) en diclorometano (20 ml, -70°C) se agrego DIBAL (20,8 ml, 20 mmol) gota a gota a traves de un embudo de adición La mezcla se agito bajo nitrogeno a -70 °C durante 1 hora y después a -50 °C durante 3 horas La reacción se diluyo con diclorometano (50 ml) y se enfrió repentinamente con una suspension de sulfato sodico decahidrato (10 g) en agua (50 ml) La suspension se filtró a traves de celite y el filtrado se concentro El residuo se purifico por cromatografia rápida (gel de sílice) utilizando acetato de etilo al 100% para proporcionar el compuesto deseado (0,7813 g, al 39%) como un solido de color amarillo $^1$H-NMR ((CD$_3$OD, 400 MHz) δ 8,53 (s, 2H), 4,56 (s, 2H), 2,54 (s, 3H), ES-HRMS *m/z* 157,0409 (M+H $C_6H_8N_2OS$ requiere 157,0430)

Etapa 3 Preparacion de 5-(clorometil)-2-(metiltio)pirimidina



A una disolucion fria de [2-(metiltio)pirimidin-5-il]metanol (0,7813 g, 5,0 mmol) en diclorometane anihdro (10 ml, 0 °C) se agrego trietilamina (0,836 ml, 8,2 mmol) seguida de la adicion de metanosulfonil cloruro (0,465 ml, 6,0 mmol) La mezcla de reaccion se agito a 0° C bajo una atmosfera de nitrógeno durante 30 minutos y despues a

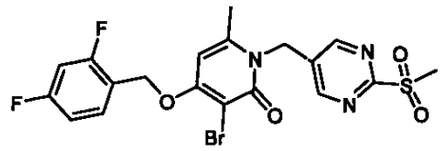
temperatura ambiente durante 3,5 horas La reaccion se enfrió repentinamente con bicarbonato de sodio (100 ml, al 5%) y se extrajo con diclorometano (50 ml) Los extractos organicos se concentraron y el residuo se purifico por cromatografia rápida (gel de silice) utilizando acetato de etilo al 15% en hexano para proporcionar el compuesto deseado (0,720 g, al 8?%) como un solido de color blanco $^1$H-NMR ((CD$_3$OD, 400 MHz) δ 8,60 (s, 2H), 4,64 (s, 2H), 2,54 (s, 3H), ES-HRMS *m/z* 175,0106 (M+H $C_6H_7N_2ClS$ requiere 175,0091)

Etapa 4 Preparacion de 3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-{[2-(metiltio)pirimidin-5-il]metil}piridin-2(1*H*)-ona

A una disclución de 5-(clorometil)-2-(metiltio)pirimidina (0,62g, 3,56 mmol) en DMF anhidro (10 ml) se agrego KBr (0,424, 3,56 mmol) Despues de que la suspension se agito a temperatura ambiente durante 30 minutos, se agregó 3-bromo-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona (1,05g, 3,19 mmol) seguida de NaH (0,102 g, 4,25 mmol) La mezcla de reaccion se agitó a 70 °C bajo una atmósfera de nitrogeno durante 3,5 horas El disolvente se destilo y el residuo se lavó con agua y se extrajo con acetato de etilo Los extractos orgánicos se concentraron y el residuo se purifico mediante HPLC de fase inversa utilizando acetonitrilo/agua al 10-90% (gradiente en 30 minutos) a un caudal de 70 ml/min para producir la sal TFA deseada (0,32 g, al 15%) como un polvo de color blanco El compuesto TFA se lavó con bicarbonato de sodio (al 5%) y se extrajo con diclorometano El extracto organico se concentro para producir el compuesto deseado (0,295 g, 18%) como un sólido de color amarillo $^1$H-NMR (CD$_3$OD, 400 MHz) δ 8,47 (s, 2H), 7,62 (q, 1H, J= 8Hz), 7,03 (m, 2H), 6,51 (s, 1H), 5,31 (s, 2H), 5,29 (s, 2H), 2,52 (s,

3H), 2,47 (s, 2H), ES-HRMS *m/z* 468,0174/470,0156 (M+H $C_{19}H_{16}N_3O_2F_2BrS$ requiere 168,0187/470,0168)

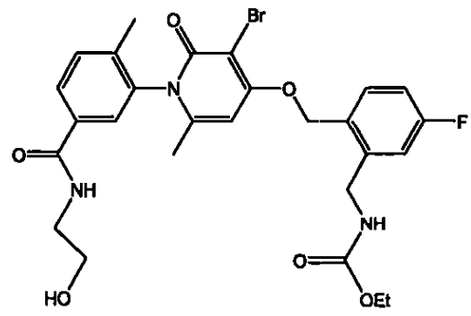
Ejemplo 708



3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-{[2-(metilsulfonil)pirimidin-5-il]metil}piridin-2(1*H*)-ona

A una disolucion de 3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-{[2-(metiltio)pirimidin-5-il]metil}piridin-2(1H)-ona (Ejemplo 707 ) (0,26 g, 0,55 mmol) en acetonitrilo se agregó agua (4 1 vol/vol, 10 ml) MMPP (0,549 g, 1,1 mmol) La reaccion se agitó a temperatura ambiente durante 30 horas La mezcla de reaccion se diluyó con acetato de etilo y se filtro El filtrado se concentro y el residuo se purifico mediante HPLC de fase inversa utilizando acetonitrilo/agua al 10-90% (gradiente en 30 minutos) a un caudal de 70 ml/min para producir la sal TFA deseada del compuesto del titulo (0,13 g, al 38%) como un polvo de color blanco $^1$H-NMR ($CD_3OD$, 400 MHz) δ 8,86 (s, 2H), 7,62 (q, 1H, J= 8Hz), 7,02 (m, 2H), 6,56 (s, 1H), 5,48 (s, 2H), 5,31 (s, 2H), 3,34 (s, 3H), 2,47 (s, 2H), ES-HRMS *m/z* 500,0109/502,0066 (M+H $C_{19}H_{16}N_3O_4F_2BrS$ requiere 500,0086/502,0067)

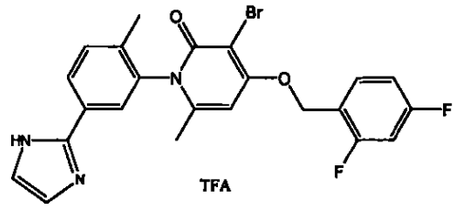
Ejemplo 709



2-({[3-bromo-1-(5-{[(2-hidroxietil)amino]carbonil}-2-metilfenil)-6-metil-2-oxo-1,2-dihidropiridin-4-il]oxi}metil)-5-fluorobencilcarbamato de etilo

A una disolucion enfriada (-10 °C) de acido 3-[3-bromo-4-[(2-{[(etoxicarbonil)amino]metil}-4-fluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-4-metilbenzoico (0,25 g, 0,46 mmol) y 4-metilmorfolina (0,06 ml, 0,55 mmol) en DMF se agregó cloroformato de isobutilo (0,07 ml, 0,55 mmol) La disolución incolora gradualmente se torno de color marron oscuro Después de 30 minutos, se agrego etanolamina (0,04 ml, 0,69 mmol) y la disolucion se entibió a temperatura ambiente Después de 1 hora, el disolvente fue retirado y el producto en crudo se purifico mediante HPLC preparatoria El acetonitrilo se evaporó y la disolución se lavo con $NaHCO_3$ al 5% (20 ml) y se extrajo en DCM (3 x 15 ml) Los extractos organicos se secaron sobre $Na_2SO_4$, se filtraron y se concentraron hasta obtener un solido de color blanco, secado *in vacuo* (0,09 g, al 33%) $^1H$ NMR ($CD_3OD$/ 400MHz) δ 7,88 (m, 1H), 7,61 (s, 1H), 7,53 (m, 2H), 7,13 (m, 1H), 7,05 (m, 1H), 6,68 (s, 1H), 5,40 (s, 2H), 4,43 (s, 2H), 4,07 (q, 2H, *J* = 7,2 Hz), 3,68 (t, 2H, *J* = 5,6 Hz), 3,48 (t, 2H, *J* = 5,6 Hz), 2,09 (s, 3H), 2,0 (s, 3H), 1,2 (t, 3H , *J* = 7, Hz) ESHRMS m/z 590,1266 y 592,1254 (M+H calculado para $C_{27}H_{30}BrFN_3O_6$ requiere 590,1297 y 592,1281)

Ejemplo 710

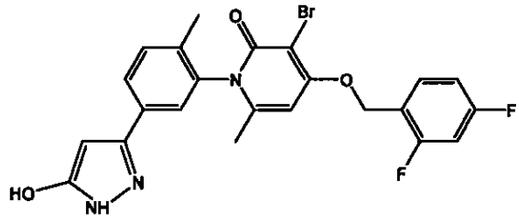


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trifluoroacetato de 3-bromo-4-[(2,4-difluorobencil)oxi]-1-[5-(1H-imidazol-2-il)-2-metilfenil]-6-metilpiridin-2(1*H*)-ona

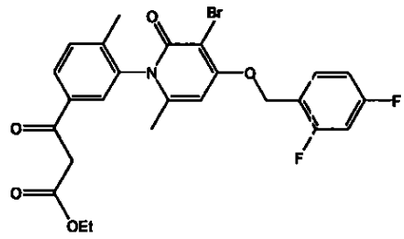
Un matraz secado en horno se evacuo alternativamente y se lavó con argon Se agregaron secuencialmente toluene (2,18 ml) y trimetil aluminio (1,25 ml, 2,51 mmol) y la disolución se enfrió a -5 °C Se agrego gota a gota etilen diamina (0,17 ml, 2,51 mmol) Se agrego 3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]4-metilbenzoato de metilo (PHA-797274)(0,75 g, 1,57 mmol) por porciones a la disolución enfriada Luego, la mezcla de reacción se calento a reflujo a 110 °C durante 4 horas La disolucion se enfrio y se agrego agua (0,7 ml), DCM (2,2 ml) y MeOH (2,2 ml) La disolucion se sometio a reflujo durante 15 minutos despues de esta adición y luego se secó sobre $Na_2SO_4$, se filtro y se concentro El residuo se disolvió en EtOAc (20 m_), se sometio a reflujo 15 minutos, se seco sobre $Na_2SO_4$, se filtro y se concentro El producto en crudo se purifico mediante HPLC preparatoria El producto se aislo mediante deshidratación por congelación y evaporación del disolvente para proporcionar un sólido de color blanco, secado *in vacuo* (0,30 g, al 31%) $^1$H NMR ($CD_3OD$/ 400MHz) δ 7,88 (m, 1H), 7,71 (d, 1H, *J* = 8,0 Hz), 7,64 (m, 2H), 7,05 (m, 2H), 6,70 (s, 1H), 5,37 (s, 2H), 4,09 (s, 4H), 2,16 (s, 3H), 2,01 (s, 3H) ESHRMS m/z 488,0750 y 490,0774 (M+H calculado para $C_{23}H_{21}BrF_2N_3O_2$ requiere 488,0780 y 490,0762)

Ejemplo 711



3-bromo-4-[(2,4-difluorobencil)oxi]-1-[5-(5-hidroxi-1H-pirazol-3-il)-2-metilfenil]-6-metilpiridin-2(1*H*)-ona

Etapa 1 Preparacion de 3-{3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-4-metilfenil}-3-oxopropanoato de etilo



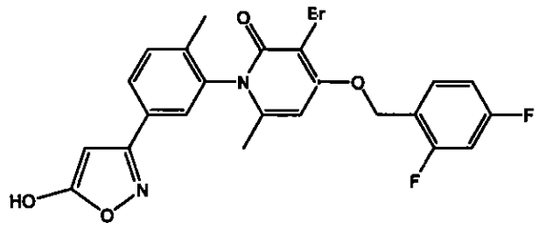
En un matraz de fondo redondo secado en horno se combinaron bajo argon ácido 3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-4-metilbenzoico (vease Ejemplo 487) (0,75 g, 1,62 mmol), DCM (2,00 ml), y cloruro de oxalilo (0,97 ml, 1,94 mmol) Se agrego DMF (3-5 gotas) para colaborar en la disolucion Se agito a temperatura ambiente durante toda la noche El disolvente se quito y el cloruro de ácido en crudo se coevaporo con DCM (3-5 ml x 3) y se secó *in vacuo* para proporcionar un sólido de color anaranjado En un matraz secado en horno separado, en una atmosfera de argon, una disolucion de monoetil malonato (0,38 ml, 3,23 mmol) en THF (3,00 ml) se enfrio a -78 °C Se agregó gota a gota cloruro de isopropil magnesio (3,23 ml, 6,46 mmol) La disolucion se agitó durante 30 minutos a -78 °C El cloruro acido preparado como se describio en lo precedente se agrego gota a gota como una disolucion en THF La reaccion se entibió a temperatura ambiente Despues de 30 min , la reacción se enfrio (0 °C) y se agrego acido citrico al 10% (5,0 ml) El producto en crudo se extrajo en EtOAc, se lavo con $NaHCO_3$ al 5%, se seco sobre $Na_2SO_4$, se filtro y se concentro hasta obtener un aceite de color marron en crudo Recristalización de DCM y hexano Un sólido de color beis

se filtro y se seco *in vacuo* (0,41 g, al 47%) $^1$H NMR ($CD_3OD$/ 400MHz) δ 8,02 (m, 1H), 7,79 (s, 1H), 7,65 (m, 2H), 7,05 (t, 2H, *J* = 9,2 Hz), 6,66 (s, 1H), 5,36 (s, 2H), 4,16 (q, 2H, *J* = 7,2 Hz), 2,11 (s, 3H), 2,07 (s, 2H), 1,99 (s, 3H), 1,23 (t, 3H, *J* = 7,2 Hz) ESHRMS m/z 534,0744 y 536,0746 (M+H calculado para $C_{25}H_{23}BrF_2NO_5$ requiere 534,0722 y 536,0706)

Etapa 2 Preparacion del compuesto del titulo

A una mezcla de 3-{3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-4-metilfenil}-3-oxopropanoato de etilo (de la Etapa 1) (0,20 g, 0,37 mmol) en EtOH (5,00 ml) se agrego hidrato de hidracina (0,01 ml, 0,11 mmol) La mezcla de reaccion se calentó a 60 °C con un condensador Despues de 1 hora, se agrego hidrato de hidracina adicional (0,01 ml) Despues de 2 horas, se agrego ácido acetico (2 gotas) Después de 4 horas, se agregó hidracina adicional (0,1 ml) A las 5 horas, la reacción parecia estar completa Se guardo en el refrigerador durante toda la noche El precipitado se filtró, se lavó con hexano, se halló que el producto era un solido de color blanco (0,10 g, al 54%) $^1$H NMR ($CD_3OD$/ 400MHz) δ 7,66 (m, 2H), 7,45 (m, 2H), 7,05 (t, 2H, *J* = 9,6 Hz), 6,65 (s, 1H), 5,36 (s, 2H), 2,04 (s, 3H), 2,02 (s, 3H) ESHRMS m/z 502,0552 y 504,0569 (M+H calculado para $C_{23}H_{19}BrF_2N_3O_3$ requiere 502,0572 y 504,0555)

Ejemplo 712

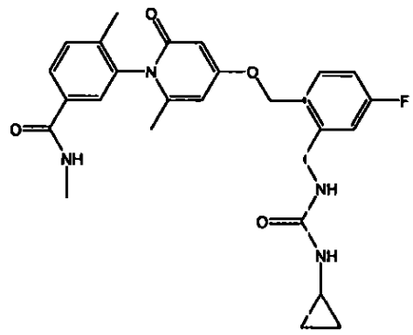


3-bromo-4-[(2,4-difluorobencil)oxi]-1-[5-(5-hidroxiisoxazol-3-il)-2-metilfenil]-6-metilpiridin-2(1*H*)-ona

Una disolucion de 3-{3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-4-metilfenil}-3-oxopropanoato de etilo (0,20 g, 0,37 mmol), trietilamina (0,06 ml, 0,41 mmol), e hidrocloruro de hidroxilamina (0,03 g, 0,41 mmol) en EtOH (3,00 ml) se calento durante toda la noche a 60 °C con un condensador Se agregaron trietilamina adicional (0,06 ml) e hidrocloruro de hidroxilamina (0,03 g) Despues de 2,5 horas, se reiteraron las adiciones de trietilamina y de hidrocloruro de hidroxilamina Despues de 1 hora, la reaccion se concentró y se purifico mediante HPLC preparatoria El producto se aisló mediante deshidratacion por congelación y evaporacion del disolvente para proporcionar un solido de color blanco El solido se disolvió en DCM Después de la adición de $NaHCO_3$ al 5%, la disolucion se convirtio en una emulsion lechosa Se agregó DCM adicional y una cantidad de salmuera Los extractos organicos se secaron sobre $Na_2SO_4$, se filtraron y se concentraron hasta obtener un solido de color rosa, secado *in vacuo* (120 mg, al 61%) $^1H$ NMR ($CD_3OD$/ 400MHz) δ 7,66 (m, 2H), 7,44 (m, 2H), 7,04 (t, 2H, $J$ = 8,8 Hz), 6,64 (s, 1H), 5,36 (s, 2H), 2,04 (s, 3H), 2,01 (s, 3H) ESHRMS m/z 503,0415 y 505,0402 (M+H calculado para $C_{23}H_{18}BrF_2N_2O_4$ requiere 503,0413 y 505,0395)

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Ejemplo 713



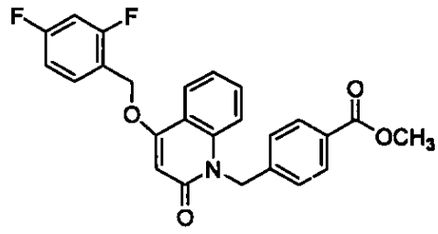
3-[4-{[2-({[(ciclopropilamino)carbonil]amino}metil)-4-fluorobencil]oxi}-6-metil-2-oxopiridin-1(2*H*)-il]-N,4-dimetilbenzamida

A una disolucion enfriada (-15 °C) de acido 3-[4-{[2-({[(ciclopropilamino)carbonil]amino}metil)-4-fluorobencil]oxi}-6-metil-2-oxopiridin-1(2*H*)-il]-4-metilbenzoico (vease Ejemplo 651) (0,30 g, 0,63 mmol) y cloroformato isobutilico (0,10 ml, 0,75 mmol) en DMF (3,00 ml) se agrego 4-metilmorfolina (0,08 ml, 0,75 mmol) La disolución instantaneamente se torno de un color amarillo y en apenas minutos tenia un color marrón oscuro Despues de 20 minutos, se agrego metilamina (0,47 ml de una disolución de 2,0 M en THF, 0,94 mmol) La reaccion se llevó a cabo a temperatura ambiente Despues de 2,5 horas, se agrego una cantidad catalitica de DMAP y metilamina adicional (0,47 ml, 0,94 mmol) Después de 2,5 horas adicionales, la reacción se concentró hasta obtener un aceite de color rojo oscuro El producto en crudo se purificó mediante HPLC preparatoria El acetonitrilo se evaporó y la disolucion se lavó con $NaHCO_3$ al 5% (20 ml) y se extrajo en DCM (3 x 15 ml) Los extractos organicos se secaron sobre $Na_2SO_4$, se filtraron y se concentraron hasta obtener un solido blanquecino, secado *in vacuo* (0,06 g, al 19%) $^1H$ NMR ($CD_3OD$/ 400MHz) δ7,85 (m, 1H), 7,58 (s, 1H), 7,48 (m, 2H),

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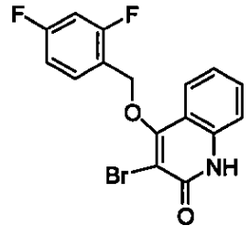
7,14 (m, 1H), 7,02 (m, 1H), 6,23 (s, 1H), 6,09 (s, 1H), 5,20 (s, 2H), 4,45 (s, 2H), 2,90 (s, 3H), 2,49 (m, 1H), 2,11 (s, 3H), 1,91 (s, 3H), 0,71 (m, 2H), 0,48 (m, 2H) ESHRMS m/z 493,2260 (M+H calculado para $C_{27}H_{30}N_4O_4F$ requiere 493,2246)

Ejemplo 714



4-{[4-[(2,4-difluorobencil)oxi]-2-oxoquinolin-1(2*H*)-il]metil}benzoato de metilo

Etapa 1 Preparacion de 3-bromo-4-[(2,4-difluorobencil)oxi]quinolin-2(1*H*)-ona

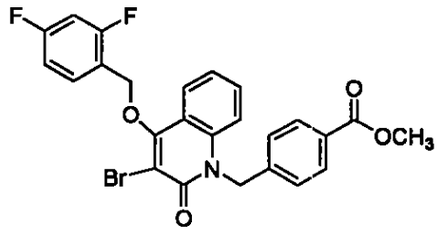


A una disolucion a temperatura ambiente de 4-hidroxi-1,2-dihidroquinolin-2-ona (500 mg, 3,10 mmol) en $CH_2Cl_2$ (10,0 ml) se agregó por porciones *N*-bromosuccinimida sólida (551,5 mg, 3,10 mmol) La reacción se agito energicamente durante 1,0 h, seguido de la adición secuencial de $K_2CO_3$ (540 mg, 3,90 mmol), DMF (4,0 ml), y 2,4 difluorobencil bromuro (0,430 ml, 3,30 mmol) La suspension resultante se agitó durante 4,5 horas hasta que la formación completa del producto deseado se observo por analisis LC/MS Después la reaccion se diluyó con acetato de etilo (400 ml) y se lavo con salmuera (3 X 200 ml) El extracto organico resultante se seco sobre $Na_2SO_4$, se filtro y se concentró *in vacuo*

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hasta obtener un residuo que se sometio a cromatografia sobre $SiO_2$ con acetato de etilo/hexanos/metanol (60 35 5) para formar un sólido (529 mg, al 47%) $^1H$ NMR (300 MHz, $d_6$-DMSO) δ 12,23 (s, 1H), 7,68 (*aprox* q, *J* = 7,5 Hz, 1H), 7,64 (*aprox* q, *J* = 8,5 Hz, 1H), 7,54 (*aprox* q, *J* = 8,3 Hz, 1H), 7,38-7,27 (m, 2H), 7,20 (*aprox* t, *J* = 7,4 Hz, 1H), 7,13 (*aprox* dt, *J* = 8,4, 2,6 Hz, 1H), 5,25 (s, 2H), LC/MS columna C-18, $t_r$ 2,64 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con deteccion a 254 nm, a 50 °C) ES-MS *m/z* 366 (M+H) ES-HRMS m/z 365,9967 (M+H calculado para $C_{16}H_{11}BrF_2NO_2$ requiere 365,9936)

Etapa 2 Preparación de 4-{[3-bromo-4-[(2,4-difluorobencil)oxi]-2-oxoquinolin-1(2*H*)-il]metil}benzoato de metilo




A una disolucion a temperatura ambiente de 3-bromo-4-[(2,4-difluorobencil)oxi]quinolin-2(1*H*)-ona (400 mg, 1,09 mmol) en THF (4,5 ml) se agregó por porciones hidruro de sodio sólido (95% libre de aceite, 60,0 mg, 2,49 mmol) La reaccion se agitó energicamente durante 30 minutos seguida por la adicion de metil-4-(bromometil)-benzoato (400 mg, 1,75 mmol) Esta suspensión resultante luego se calento a 60 °C durante 12,0 horas Despues la disolución resultante se trato con cloruro de amonio acuoso saturado (400 ml) y se extrajo con acetato de etilo (3 X 300 ml) Los extractos organicos resultantes fueron secados sobre $Na_2SO_4$, filtrados y concentrados *in vacuo* a un residuo que despues se sometio a cromatografia sobre $SiO_2$ con acetato de

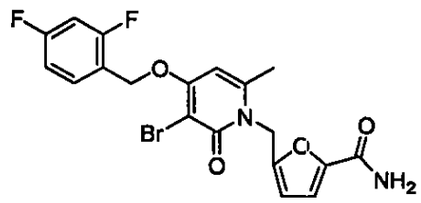
etilo/hexanos (60 40) para formar un solido (396 mg, al 71%) $^1$H NMR (400 MHz, $CDCl_3$) δ 7,97 (*aprox* d, *J* = 8,0 Hz, 2H), 7,87 (d, *J* = 7,5 Hz, 1H), 7,60 (*aprox* q, *J* = 8,4 Hz, 1H), 7,49-7,42 (m, 1H), 7,30-7,15 (m, 4H), 6,94 (*aprox* t, *J* = 6,3 Hz, 1H), 6,88 (*aprox* t, *J* = 9,4 Hz, 1H), 5,64 (s, 2H), 5,33 (s, 2H), 3,88 (s, 3H), LC/MS columna C-18, $t_r$ = 3,46 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con deteccion a 254 nm, a 50 °C) ES-MS *m/z* 514 (M+H) ES-HRMS m/z 514,0451 (M+H calculado para $C_{25}H_{19}BrF_2NO_4$ requiere 514,0460)

Etapa 3 Preparación del compuesto del titulo . En un matraz de fondo redondo de 25 ml se agrego, a temperatura ambiente, una disolución de 4-{[3-bromo-4-[(2,4-difluorobencil)oxi]-2-oxoquinolin-1(2H)-il]metil}benzoato de metilo (Etapa 2) (120 mg, 0,233 mmol) en MeOH (3,0 ml) A continuación, se agregó una combinación de Pd sobre carbono (Pd al 10%, peso por peso agua al 50%, 100 mg, 0 047 mmol) y $Pd(OAc)_2$ (15 mg, 0,067 mmol) al recipiente de reaccion que se purgó con argon y luego se equipo con un diafragma El recipiente luego se equipo con un balón de hidrogeno de 2,0 l (*c a* 20 libras por pulgada cuadrada) La suspension resultante se agitó durante 12,0 horas y luego se aplicó directamente a cromatografia sobre $SiO_2$ utilizando acetato de etilo/hexanos (3 7) para formar el compuesto del titulo deseado como un solido (52 mg, al 51%) $^1$H NMR (300 MHz, $CDCl_3$) δ 8,05-7,98 (m, 3H), 7,55 (aprox q, J = 8,3 Hz, 1H), 7,48 (aprox t, J = 7,5 Hz, 1H), 7,30 (d, J = 8,0 Hz, 2H), 7,19 (*aprox* q, *J* = 8,5, 2H), 7,05-6,90 (m, 2H), 6,28 (s, 1H), 5,60 (s, 2H), 5,26 (s, 2H), 3,91 (s, 3H), LC/MS columna C-18, $t_r$ = 3,71 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con deteccion a 254 nm, a

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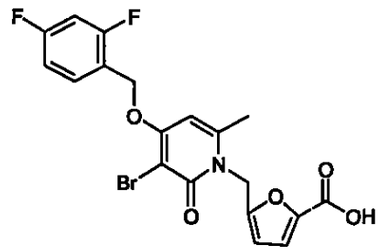
50 °C) ES-MS *m/z* 436 (M+H) ES-HRMS m/z 436,1371 (M+H calculado para $C_{22}H_{20}BrF_2NO_4$ requiere 436,1355)

Ejemplo 715



5-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]metil}-2-furamida

Etapa 1 Preparacion de acido 5-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]metil}-2-furoico



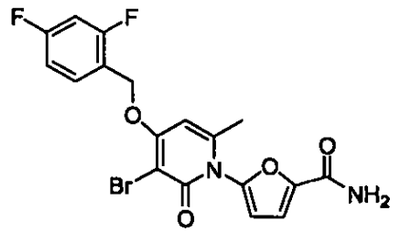
A una disolución de 5-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]metil}-2-furoato de metilo a temperatura ambiente (Ejemplo 660) ( (608 g, 1,30 mmol) en THF (8,0 ml) se agrego gota a gota una disolución acuosa de hidróxido de sodio (3,0 M, 0,50 ml, 1,50 mmol) La reaccion luego se calento a 60 °C durante 12,0 horas La suspension resultante despues se diluyó con 500 ml de acetato de etilo y se neutralizo con una disolución acuosa de ácido clorhidrico (1,0 N, 1,5 ml, 10 mmol) La disolucion bifasica resultante luego se concentró *in vacuo* hasta un volumen de 50 ml En este momento comenzo a formarse un solido de color blanco y la suspensión solida resultante se dejo reposar hasta que pareciera detenerse la precipitacion (aproximadamente 1,0 hora) El precipitado se recolecto y se secó *in vacuo* (1,0

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mm Hg) para formar el acido solido como un intermedio (500 mg, al 85%) $^1$H NMR (300 MHz, $d_4$-MeOH) δ 7,64 (*aprox* q, *J* = 8,3 Hz, 1H), 7,18 (d, *J* = 3,4 Hz, 1H), 7,10-7,02 (m, 2H), 6,54 (s, 1H), 6,50 (d, *J* = 3,5 Hz, 1H), 5,42 (s, 2H), 5,37 (s, 2H), 2,64 (s, 3H), LC/MS columna C-18, $t_r$ = 2,38 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con deteccion a 254 nm, a 50°C) ES-MS *m/z* 454 (M+H) ES-HRMS m/z 454,0070 (M+H calculado para $C_{19}H_{15}BrF_2NO_5$ requiere 454,0096)

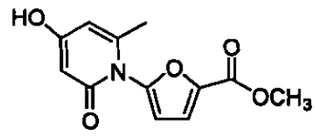
Etapa 2 Preparacion del compuesto del titulo A una suspension a temperatura ambiente de 5-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]metil}-2-furoico (500 mg, 1,10 mmol) en THF (6,0 ml) se agrego secuencialmente 2-cloro-4,6 dimetoxi-1,3,5 triazina (307 mg, 1,75 mmol) y N-metil morfolina (NMM, 184 mg, 1,82 mmol) La disolución resultante se maduro durante 2 horas y luego se le agregó una disolucion acuosa saturada de hidróxido de amonio (0,70 ml) Se dejó que la suspensión resultante continuara durante 1 hora adicional La mezcla de reacción se diluyo con 400 ml de salmuera y se extrajo con acetato de etilo (3 X 400 ml) Los extractos organicos se separaron, se secaron sobre $Na_2SO_4$ y se concentraron *in vacuo* y el residuo resultante se sometio a cromatografia sobre $SiO_2$ con acetato de etilo/hexanos/metanol (57 38 5) para proporcionar el compuesto del titulo (370 g, al 74%) $^1$H NMR (300 MHz, $d_4$-MeOH) δ 7,64 (*aprox* q, *J* = 8,1 Hz, 1H), 7,10-7,00 (m, 3H), 6,53 (s, 1H), 6,52 (d, *J* = 3,4 Hz, 1H), 5,43 (s, 2H), 5,32 (s, 2H), 2,61 (s, 3H), LC/MS columna C-18, $t_r$ = 2,15 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con deteccion a 254 nm, a 50 °C) ES-MS *m/z* 453 (M+H) ES-HRMS m/z 453,0249 (M+H calculado para $C_{19}H_{16}BrF_2N_2O_4$ requiere 453,0256)

Ejemplo 716



5-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-2-furamida

Etapa 1 Preparación de 5-(4-hidroxi-6-metil-2-oxopiridin-1(2*H*)-il)-2-furoato (PHA-816774)

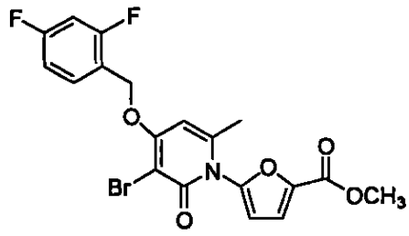


A una disolucion a temperatura ambiente de metil-2-amino-5-furoato (4,85 g, 34,4 mmol) en 1,4 dioxano (28,0 ml) se agrego 5-(1-h droxi-3-oxobutilideno)-2,2-dimetil-1,3-dioxano-4,6-diona (3,16 g, 44,3 mmol) La reaccion se agitó energicamente y se calento rápidamente (dentro de 8 minutos) a una temperatura interna de 98 °C Al alcanzar dicha temperatura, la reaccion se mantuvo durante 1 hora En este momento, la reaccion se enfrio a temperatura ambiente rápidamente utilizando un baño de hielo y se agregó acido metano sulfonico (3,30 g, 34,4 mmol) La mezcla de reaccion una vez más se llevo a una temperatura interna de aproximadamente 100 °C Después de 1,0 hora, la reaccion se diluyo con 10 ml de tolueno y se enfrió a temperatura ambiente por si sola Despues de 3,0 horas se formo un sólido que se recolecto y posteriormente se recristalizó a partir de metanol/acetato de etilo (1 1) Se formaron los cristales en desarrollo y reposaron durante 12,0 horas antes de ser recolectados para formar con ellos el producto deseado como un sólido (3,78 g, al 44%) $^1$H NMR

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(400 MHz, $d_7$-DMF) δ 11,34 (s, 1H), 7,43 (*aprox* d, *J* = 3,6 Hz, 1H), 6,79 (*aprox* d, *J* = 3,6 Hz, 1H), 6,01 (s, 1H), 5,63 (d, *J* = 2,0 Hz, 1H), 3,87 (s, 3H), 2,02 (s, 3H), LC/MS columna C-18, $t_r$ = 1,47 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con detección a 254 nm, a 50 °C) ES-MS *m/z* 250 (M+H) ES-HRMS m/z 250,0696 (M+H calculado para $C_{12}H_{12}NO_5$ requiere 250,0710)

Etapa 2 Preparación de 5-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-2-fuorato de metilo

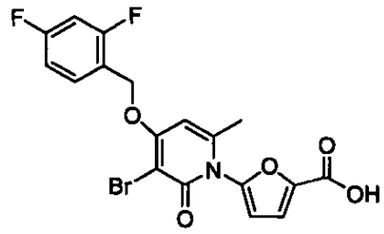



A una disolucion a temperatura ambiente de 5-(4-hidroxi-6-metil-2-oxopiridin-1(2*H*)-il)-2-fuorato (Etapa 1) (3,19 g, 12,8 mmol) en DMF (14 ml) se agrego por porciones *N*-bromosuccinimida solida (2,29 g, 12,9 mmol) La reacción se agitó enérgicamente durante 1,0 h, seguido de la adicion secuencial de $K_2CO_3$ (1,88 g, 13,6 mmol), DMF (4,0 mL), y 2,4 difluorobencil bromuro (2,00 mL, 15,55 mmol) La suspension resultante se agito durante 9,0 horas hasta que la formación completa del producto deseado se observo por analisis LC/MS Despues la reaccion se diluyó con salmuera saturada (300 ml) y se extrajo con acetato de etilo (3 X 300 ml) Los extractos organicos resultantes fueron secados sobre $Na_2SO_4$, filtrados y concentrados *in vacuo* a un residuo que se sometio a cromatografia sobre $SiO_2$ con un gradiente de elusión utilizando acetato de etilo/hexanos (40 60 a 60 40) para formar un sólido (3,20 mg, al 55%) $^1$H NMR (400 MHz, $d_7$-DMF) δ 7,78 (*arox* q, *J* = 8,6 Hz, 1H),

1394
1316

7,48 (*aprox* d, *J* = 3,6 Hz, 1H), 7,33 (*aprox* dt, *J* = 10,0, 2,4 Hz, 1H), 7,21 (*aprox* dt, *J* = 8,5, 1,8 Hz, 1H), 6,92 (d, *J* = 3,6 Hz, 1H), 6,81 (s, 1H), 5,47 (s, 2H), 3,88 (s, 3H), 2,15 (s, 3H), LC/MS columna C-18, $t_r$ = 3,11 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con deteccion a 254 nm, a 50 °C) ES-MS *m/z* 454 (M+H) ES-HRMS m/z 454,0117 (M+H calculado para $C_{19}H_{15}BrF_2N_2O_5$ requiere 454,0096)

Etapa 3 Ácido 5-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-2-furoico



A una disolucion de 5-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-2-furoato de metilo a temperatura ambiente (Etapa 2) ( (3,00 g, 6,61 mmol) en THF (20 ml) se agregó gota a gota una disolución acuosa de hidroxido de sodio (3,0 M, 4,00 ml, 12,0 mmol) La reaccion luego se calento a 60 °C durante 12,0 horas La suspension resultante después se diluyo con 800 ml de acetato de etilo y se neutralizo con una solución acuosa de ácido clorhidrico (3,0 N, 4,0 ml, 12 mmol) La disolucion bifasica resultante luego se concentro *in vacuo* hasta un volumen de 90 ml En este momento comenzo a formarse un solido de color blanco y la suspension sólida resultante se dejo repo ar hasta que pareciera detenerse la precipitación (aproximadamente 1,0 hora) El precipitado se recolecto y se secó *in vacuo* (1,0 mm Hg) para formar el acido solido como un intermedio (2,27 g, al 78%) $^1$H NMR

(400 MHz, $d_7$-DMF) δ 7,79 (*aprox* q, *J* = 8,0 Hz, 1H), 7,32 (t, *J* = 9,2 Hz, 1H), 7,20 (*aprox* t, *J* = 7,4 Hz, 1H), 6,88 (*aprox* d, *J* = 2,5 Hz, 1H), 6,74 (s, 1H), 6,51 (d, *J* = 2,5 Hz, 1H), 5,44 (s, 2H), 2,10 (s, 3H), LC/MS columna C-18, $t_r$ = 2,77 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con detección a 254 nm, a 50 °C) ES-MS *m/z* 440 (M+H) ES-HRMS m/z 439,9959 (M+H calculado para $C_{18}H_{13}BrF_2NO_5$ requiere 439,9940)

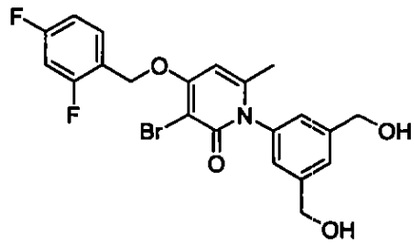
Etapa 4 Preparacion del compuesto del titulo (PHA-817443)

A una suspensión a temperatura ambiente de ácido 5-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-2-furoico (1,00 g, 2,27 mmol) en THF (8,0 ml) se agrego secuencialmente 2-cloro-4,6 dimetoxi-1,3,5 triazina (610 mg, 3,47 mmol) y N-metil morfolina (NMM, 368 mg, 3,62 mmol) La disolucion resultante se maduro durante 2 horas y luego se le agregó una solución acuosa saturada de hidroxido de amonio (1,5 ml) Se dejó que la suspensión resultante continuara durante 1 hora adicional La mezcla de reaccion se diluyo con 800 ml de salmuera y se extrajo con acetato de etilo (3 X 600 ml) Los extractos organicos se separaron, se secaron sobre $Na_2SO_4$ y se concentraron *in vacuo* y el residuo resultante se sometio a cromatografia sobre $SiO_2$ con acetato de etilo/hexanos/metanol (57 38 5) para formar el compuesto del titulo (710 mg, al 71%) $^1$H NMR (400 MHz, $d_7$-DMF) δ 8,07 (s, 1H), 7,79 (*aprox* q, *J* = 8,6 Hz, 1H), 7,50 (*br* s, 1H), 7,32 (*aprox* dt, *J* = 10,1, 2,2 Hz, 1H), 7,30 (*aprox* dd, *J* = 8,0, 3,3 Hz, 1H), 7,20 (*aprox* dt, *J* = 8,6, 2,0 Hz, 1H), 6,81 (s, 1H), 6,79 (d, *J* = 3,4 Hz, 1H), 5,47 (s, 2H), 2,14 (s, 3H), LC/MS columna C-18, $t_r$ = 2,60 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con deteccion a 254 nm, a 50 °C) ES-

1396
1398

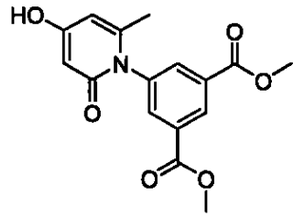
MS *m/z* 439 (M+H) ES-HRMS m/z 439,0088 (M+H calculado para $C_{18}H_{14}BrF_2N_2O_4$ requiere 439,0010)

Ejemplo 717



1-[3,5-bis(hidroximetil)fenil]-3-bromo-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona

Etapa 1 Preparacion de dimetil 5-(4-hidroxi-6-metil-2-oxopiridin-1(2H)-il)isoftalato

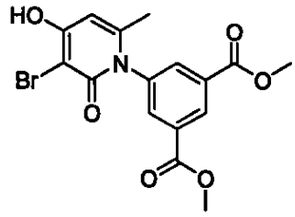


Se disolvio dimetil 5-aminoisoftalato (24,45 g, 117 mmol) en 500 ml de tolueno y se calento a reflujo Se agrego 5-(1-hidroxi-3-oxobutilideno)-2,2-dimetil-1,3-dioxano-4,6-diona (40,0 g, 175,3 mmol) y se sometio a reflujo durante 15 minutos La reaccion se evaporo Se agregaron 500 ml de acetonitrilo y acido p-toluenosulfonico (22,25 g, 117 mmol) y se sometió a reflujo durante 1 hora La reaccion se enfrió a temperatura ambiente y se dejo reposar durante toda la noche El precipitado resultante se filtró, se lavo tres veces con 250 ml de agua y 250 ml de acetonitrilo y se secó *in vacuo* para producir un sólido de color tostado (18,85 g, rendimiento 51%) $^1$H NMR (300 MHz, DMSO-$d_6$) δ 10,70 (br s, 1H), 8,47 (t, $J$ = 1,54 Hz, 1H), 7,99 (d, $J$ = 1,47 Hz, 2H), 5,90 (d, $J$ = 1,61 Hz, 1H), 5,55 (d, $J$ = 2,42 Hz, 1H), 3,87 (s, 6H), 1,82 (s, 3H), LC/MS, $t_r$ = 1,79 minutos (acetonitrilo/agua al 5 a 95%

1397
1399

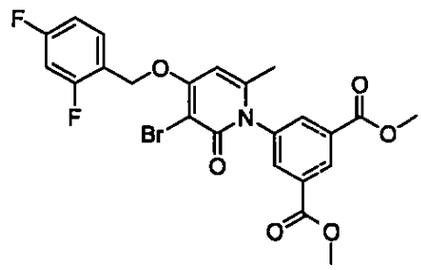
durante 5 minutos a 1 ml/min, a 254 nm, a 50 °C), ES-MS *m/z* 318 (M+H) ES-HRMS m/z 318,0994 (M+H calculado para $C_{16}H_{16}NO_6$ requiere 318,0972)

Etapa 2 Preparación de dimetil 5-(3-bromo-4-hidroxi-6-metil-2-oxopiridin-1(2H)-il)isoftalato



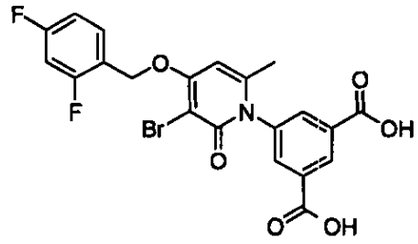
Dimetil 5-(4-hidroxi-6-metil-2-oxopiridin-1(2H)-il)isoftalato (de la Etapa 1) (18,0 g, 56,7 mmol) se agito a temperatura ambiente con N-Bromosuccinimida (10,6 g, 59,6 mmol) en 35 ml de *N,N*-dimetilformamida y 180 ml de cloruro de metileno Despues de 1 hora de agitación, se habia formado un precipitado de color blanco El precipitado se filtro, se lavo con acetonitrilo y se secó *in vacuo* para proporcionar un sólido de color blanco (11,55 g, al 51%) $^1$H NMR (400 MHz, DMSO-$d_6$) δ 11,49 (br s, 1H), 8,49 (t, *J* = 1,24 Hz, 1H), 8,06 (d, *J* = 1,47 Hz, 2H), 6,07 (s, 1H), 3,88 (s, 6H), 1,82 (s, 3H), LC/MS, $t_r$ = 1,81 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min, a 254 nm, a 50 °C), ES-MS *m/z* 396 (M+H) ES-HRMS m/z 396,0102 (M+H calculado para $C_{16}H_{15}NO_6$ requiere 396,0077)

Etapa 3 Preparación de 5-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]isoftalato de dimetilo



Se agitó energicamente 5-(3-bromo-4-hidroxi-6-metil-2-oxopiridin-1(2H)-il)isoftalato de dimetilo (de la Etapa 2) (11,3 g, 28,5 mmol) con 2,4-difluorobencilbromuro (3,66 ml, 28,5 mmol) y $K_2CO_3$ (5,91 g, 42,8 mmol) en 50 ml de *N,N*-dimetilformamida a temperatura ambiente durante 3 horas Luego se vertió la reaccion en 1 litro de agua fria y el precipitado resultante se filtro, se lavó con agua y éter dietilico y se secó *in vacuo* para proporcionar un solido de color blanco (13,8 g, al 93%) $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8,51 (t, *J* = 1,60 Hz, 1H), 8,12, (d, *J* = 1,60 Hz, 2H), 7,67 (*aprox* q, *J* = 7,92 Hz, 1H), 7,34 (*aprox* dt, *J* = 9,94, 2,19 Hz, 1H), 7,17 (dt, *J* = 8,53, 2,11 Hz, 1H), 6,68 (s, 1H), 5,33 (s, 2H), 3,88 (s, 6H), 1,93 (s, 3H), LC/MS, $t_r$ = 2,77 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min, a 254 nm, a 50 °C), ES-MS *m/z* 522 (M+H) ES-HR/MS *m/z* 522,0335 (M+H calculado para $C_{23}H_{19}BrF_2NO_6$ requiere 522,0358)

Etapa 4 Preparacion de ácido 5-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]isoftalico




Se agitó 5-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]isofthalato de dimetilo de la Etapa 3) (5,0 g, 9,57 mmol) a temperatura ambiente con 2,5 N NaOH (15,3 ml, 38,3 mmol) en 30 ml de 5 1 THF/agua durante 1 hora La reaccion se acidifico con 1 N HCl y el precipitante resultante se filtro, se lavo con agua y se seco *in vacuo* para producir un solido de color blanco (4,48

1399
(40)

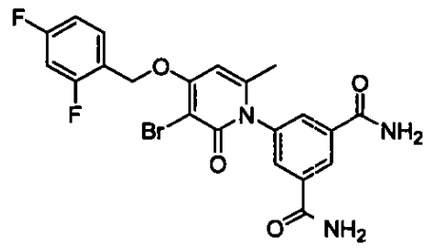
g, al 95%) $^1$H NMR (400 MHz, DMSO-$d_6$) δ 13,50 (br s, 2H), 8,51 (t, $J$ = 1,41 Hz, 1H), 8,02, (d, $J$ = 1,48 Hz, 2H), 7,67 (*aprox* q, $J$ = 7,88 Hz, 1H), 7,32 (dt, $J$ = 9,94, 2,19 Hz, 1H), 7,16 (dt, $J$ = 8,5', 1,99 Hz, 1H), 6,68 (s, 1H), 5,32 (s, 2H), 1,94 (s, 3H), LC/MS, $t_r$ = 2,27 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min, a 254 nm, a 50 °C), ES-MS *m/z* 494 (M+H) ES-HRMS m/z 494,0054 (M+H calculado para $C_{21}H_{15}BrF_2NO_6$ requiere 494,0045)

Etapa 5 Preparacion del compuesto del titulo Se agrego acido 5-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]isoftalico (de la Etapa 4 precedente) (500 mg, 1,01 mmol) a una solución de complejo 1M borano-dimetilsulfuro en tetrahidrofurano (9,0 ml, 9,00 mmol) en 2,5 ml de tetrahidrofurano a 0 °C Se dejo entibiar la reaccion hasta alcanzar la temperatura ambiente durante la agitación Despues de la agitación durante toda la noche, se agrego más complejo 1M borano-dimetilsulfuro en tetrahidrofurano (0,60 ml, 0,60 mmol) y se agito a temperatura ambiente Despues de 4 horas, se agregaron astillas de hielo para enfriar la reaccion repentinamente La reaccion se extrajo 2 veces con acetato de etilo y las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ y se evaporaron El sólido resultante se lavo con acetonitrilo y éter dietilico y se seco in vacuo para proporcionar un sólido de color blanco (281 mg, al 60%) $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7,66 (*aprox* q, $J$ = 7,92 Hz, 1H), 7,35 (s, 1H), 7,33 (dt, $J$ = 9,40, 2,24 Hz, 1H), 7,16 (dt, $J$ = 8,52, 1,88 Hz, 1H), 6,99 (s, 2H), 6,62 (s, 1H), 5,31 (s, 2H), 5,27 (br s, 2H), 4,51 (s, 4H), 1,93 (s, 3H) LC/MS, $t_r$ = 2,19 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutes a 1 ml/min, a 254 nm, a 50 °C), ES-MS

1.400
1402

*m/z* 466 (M+H) ES-HRMS m/z 466,0454 (M+H calculado para $C_{21}H_{19}BrF_2NO_4$ requiere 465,0460)

Ejemplo 718

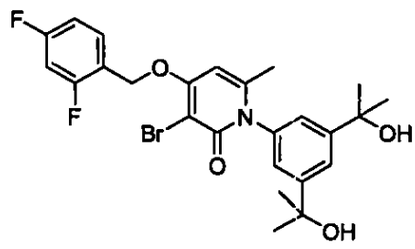


5-[3-bromo-4-[(2,4 difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]isoftalamida

Se disolvio ácido 5-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]isoftálico (Ejemplo 717, Etapa 4) (500 mg, 1,01 mmol) en 4 ml de tetrahidrofurano Se agregó amoniaco 0,5 M en 1,4-dioxano (12,12 ml, 6,06 mmol), seguida, en orden, por EDCI (494 mg, 2,53 mmcl), 1-hidroxibenzotriazol (342 mg, 2,53 mmol) y trietilamina (563 µl, 4,04 mmol) La reacción se agitó a temperatura ambiente durante toda la noche La reaccion se evaporo y se usó agua para triturar el producto El solido resultante se filtró y se lavo con agua, acetonitrilo, acetato de de etilo y éter dietilico y se seco *in* vacuo para proporcionar un sólido de color blanco (202 mg, al 41%) $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8,45 (s, 1H), 8,08 (br s, 2H), 7,86, (d, $J$ = 1,34 Hz, 2H), 7,67 (*aprox* q, $J$ = 7,92 Hz, 1H), 7,55 (br s, 2H), 7,33 (dt, $J$ = 9,94, 2,18 Hz, 1H), 7,17 (dt, $J$ = 8,59, 1,92 Hz, 1H), 6,70 (s, 1H), 5,34 (s, 2H) 1,96 (s, 3H), LC/MS, $t_r$ = 2,10 minutos (acetonitrilo/aqua al 5 a 95% durante 5 minutos a 1 ml/min, a 254 nm, a 50 °C), ES-MS *m/z* 492 (M+H) ES-HRMS m/z 492,0381 (M+H calculado para $C_{21}H_{17}BrF_2N_3O_4$ requiere 492,0365)

Ejemplo 719

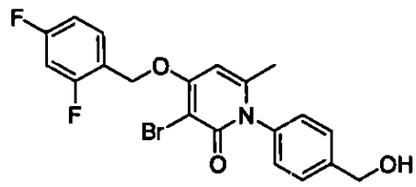
1401
1403



1-[3,5-bis(1-hidroxi-1-metiletil)fenil]-3-bromo-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona

Se agrego gota a gota 5-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]isoftalato de dimetilo (Ejemplo 717, Etapa 3) (500 mg, 0,96 mmol) a una disolucion de 3M MeMgBr en eter dietílico (1,6 ml, 4,79 mmol) en 15 ml de tetrahidrofurano a -5 °C y se agito a -5 °C La reaccion se torno de color rojo Despues de 2,5 horas, la reacción se enfrió repentinamente con una disolución de $NH_4Cl$ saturada y se extrajo 2 veces con acetato de etilo Las capas orgánicas combinadas se lavaron con una disolucion de $NaHCO_3$ y salmuera, se secaron sobre $MgSO_4$ y se evaporaron El sólido resultante se lavó con eter dietilico y se seco *in* vacuo para proporcionar un sólido de color blanco (329 mg, al 66%) $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 7,69 - 7,63 (m, 2H), 7,33 (dt, $J$ = 9,87, 2,41 Hz, 1H), 7,16 (dt, $J$ = 8,46, 1,75 Hz, 1H), 7,07 (d, $J$ = 1,48 Hz, 2H), 6,61 (s, 1H), 5,32 (s, 2H), 5,06 (s, 2H), 1,89 (s, 3H), 1,41 (s, 12H), LC/MS, $t_r$ = 2,45 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min, a 254 nm, a 50 °C), ES-MS *m/z* 522 (M+H) ES-HRMS m/z 522,1098 (M+H calculado para $C_{25}H_{27}BrF_2NO_4$ requiere 522,1086)

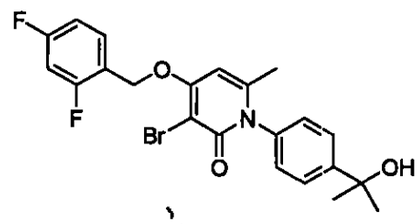
Ejemplo 720



3-bromo-4-[(2,4-difluorobencil)oxi]-1-[4-(hidroximetil)fenil]-6-metilpiridin-2(1H)-ona

Se agregó acido 4-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]benzoico (Ejemplo 203)( (500 mg, 1,11 mmol) a una disolucion de complejo 2M borano-dimetilsulfuro en tetrahidrofurano (3,33 ml, 6,66 mmol) en 2,5 ml de tetrahidrofurano a 0 °C Se dejo entibiar la reaccion hasta alcanzar la temperatura ambiente durante la agitación Despues de 2,5 horas, se agregaron astillas de hielo para enfriar la reaccion repentinamente El precipitado resultante se filtro, se lavó con eter dietilico y se secó *in vacuo* para proporcionar un solido de color blanco (160 mg, al 33%) $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7,66 (*aprox* q, *J* = 7,88 Hz, 1H), 7,42 (d, *J* = 8,19 Hz, 2H), 7,33 (dt, *J* = 9,87, 2,06 Hz, 1H), 7,19 - 7,14 (m, 3H), 6,62 (s, 1H), 5,31 (s, 2H), 5,30 (s, 1H), 4,54 (d, *J* = 5,24, 2H), 1,92 (s, 3H), LC/MS, $t_r$ = 2,36 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min, a 254 nm, a 50 °C), ES-MS *m/z* 436 (M+H) ES-HRMS m/z 436,0374 (M+H calculado para $C_{20}H_{17}BrF_2NO_3$ requiere 436,0354)

Ejemplo 721

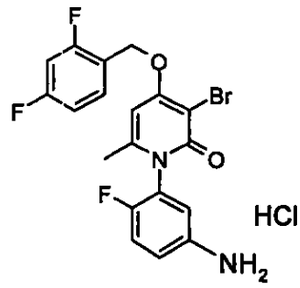


3-bromo-4-[(2,4-difluorobencil)oxi]-1-[4-(1-hidroxi-1-metiletil)fenil]-6-metilpiridin-2(1*H*)-ona

1403
1405

Se agrego gota a gota 4-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]benzoato de metilo (Ejemplo 202 de T Boehm)(500 mg, 1,08 mmol) a una disolucion de 3M MeMgBr en eter dietilico (0,90 ml, 2,69 mmol) en 15 ml de tetrahidrofurano a -5 °C y se agitó a -5 °C Despues de 2,75 horas, se agregó mas 3M MeMgBr en eter dietilico (0,45 ml, 1,35 mmol) y se agito a - 5 °C Despues de 4 horas, la reaccion se enfrio repentinamente con una disolucion de $NH_4Cl$ saturada y se extrajo 2 veces con acetato de etilo Las capas organicas combinadas se lavaron con una solucion de $NaHCO_3$ y salmuera, se secaron sobre $MgSO_4$ y se evaporaron El solido resultante se lavo con eter dietilico y se secó *in* vacuo para proporcionar un solido de color blanco (268 mg, al 53%) $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 7,66 (*aprox* q, *J* = 7,92 Hz, 1H), 7,57 (d, *J* = 8,46 Hz, 2H), 7,33 (dt, *J* = 9,87, 2,11 Hz, 1H), 7,16 (dt, *J* = 8,59, 2,24 Hz, 1H), 7,14 (d, *J* = 8,63 Hz, 2H), 6,62 (s, 1H), 5,31 (s, 2H), 5,12 (s, 1H), 1,91 (s, 3H), 1,44 (s, 6H), LC/MS, $t_r$ = 2,54 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min, a 254 nm, a 50 °C), ES-MS *m/z* 464 (M+H) ES-HRMS m/z 464,0604 (M+H calculado para $C_{22}H_{21}BrF_2NO_3$ requiere 464,0667)

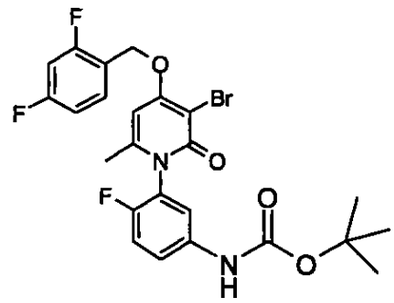
Ejemplo 722




1-(5-amino-2-fluorofenil)-3-bromo-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona hidrocloruro

1404
1406

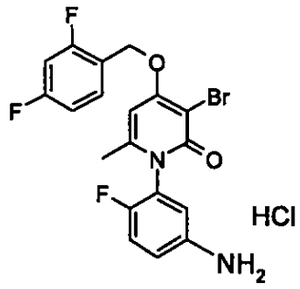
Etapa 1 Preparación de terc-butil 3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-fluorofenilcarbamato



Se lavo una disolucion del compuesto del Example 519 (4,3 g, 9,2 mmol) en *terc*-butanol (50 ml) con nitrogeno Se agregaron azida de fosforil difenilo (2 ml, 9,2 mmol) y trietilamina (1,3 ml, 9,2 mmol) Despues se calentó a 90 °C durante 20 horas, la mezcla de reaccion se concentró *in vacuo* El residuo se diluyo con cloruro de metileno y se lavó secuencialmente con cloruro de amonio acuoso y $NaHCO_3$ acuoso La capa orgánica se concentro *in vacuo*, los solidos resultantes se suspendieron en acetonitrilo y se filtraron para producir el compuesto del titulo (2,9 g, al 58%) $^1H$ NMR (400 MHz, $CD_3OD$) d 7,64 (q, $J$ = 7,2 y 14,4 Hz, 1H), 7,49 (m, 1H), 7,43 (m, 1H), 7,24 (t, $J$ = 9,6 Hz, 1H), 7,04 (t, $J$ = 8,4 Hz, 2H), 6,62 (s, 1H), 5,35 (s, 2H), 2,09 (s, 3H), 1,49 (s, 9H) ppm $^{19}$ F NMR (300 MHz, $CD_3OD$) δ -111,53 (1F), -115,93 (1 F), -132,58 ppm ES-HRMS *m/z* 540,0822 (M+H calculado para $C_{24}H_{23}BrF_3N_2O_4$ requiere 540,0820)

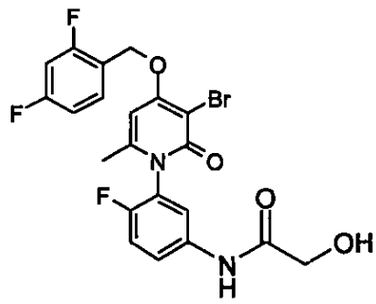
Etapa 2 Preparacion de hidrocloruro de 1-(5-amino-2-fluorofenil)-3-bromo-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1H)-ona

(818085A)



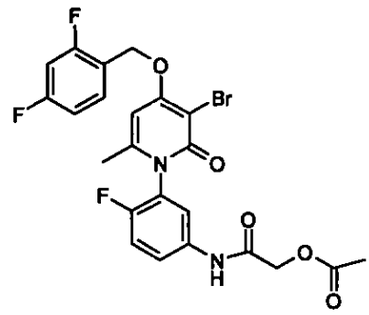
El producto de la Etapa 1, (2,9 g, 5,3 mmol) se disolvio en tetrahidrofurano (75 ml) y 6N HCl (10 ml) La mezcla de reaccion se calentó a 60 °C durante 18 horas y se concentro *in vacuo* para proporcionar el producto final (1,89 g, 75%) $^1$H NMR (400 MHz, $CD_3OD$) d 7,64 (q, $J$ = 8,4 y 152 Hz, 1H), 7,56 (m, 2H), 7,46 (m, 1H), 7,05 (m, 2H), 6,69 (s, 1H), 5,37 (s, 2H), 2,10 (s, 3H) ppm $^{19}$ F NMR (400 MHz, $CD_3OD$) δ -111,37 (1F), -115,86 (1 F), -123,16 ppm ES-HRMS m/z 440,0334 (M+H calculado para $C_{19}H_{15}BrFN_2O_2$ requiere 440,0295)

Ejemplo 723



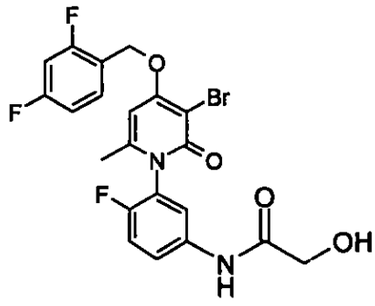
N-{3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-fluorofenil}-2- hidroxiacetamida

Etapa 1 Preparacion de 2-({3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-fluorofenil}amino)-2-oxoetil acetato



Una disolución del compuesto del Ejemplo 722 (0,5 g, 1,05 mmol) en tetrahidrofurano (20 ml) se trato con trietil amina (0,3 ml, 2,1 mmol) y acetoxi acetilcloruro (0,12 ml, 1,15 mmol) Después 2 horas de agitacion a temperatura ambiente, se completó la reaccion La mezcla de reacción se vertio en cloruro de amonio acuoso saturado Los solidos se filtraron y se lavaron con agua y eter dietilico El producto del titulo se aisló como un solido de color blanco (0,32 g, al 58%) $^{1}$H NMR (400 MHz, $CD_3OD$) d 7,65 (m, 3H), 7,32 (t, $J$ = 8,4 Hz, 1H), 7,04 (t, $J$ = 8,4 Hz, 2H), 6,64 (s, 1H), 5,35 (s, 2H), 4,68 (s, 2H), 2,15 (s, 3H), 2,10 (s, 3H) ppm $^{19}$ F NMR (400 MHz, $CD_3OD$) δ -111,56 (1F), -115,99 (1 F), -129,48 (1 F) ppm LC/MS, $t_r$ = 5,35 minutos (acetonitrilo/agua al 5 a 95% durante 8 minutos a 1 ml/min con detección de 254 nm, a 50 °C) ES-MS $m/z$ 540 (M+H)

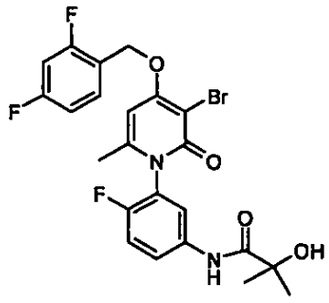
Paso 2 Preparación de N-{3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-fluorofenil}-2- hidroxiacetamida



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1409

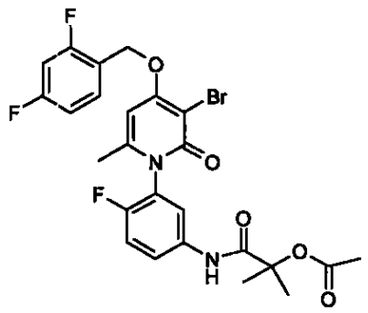
El producto de la Etapa 1, (0,1 g, 0,18 mmol) se suspendio en tetrahidrofurano (10 ml), metanol (2 ml), y 2, 5N NaOH (1 ml) Despues de 1 hora de agitacion a temperatura ambiente, se completó la reacción y los materiales orgánicos fueron retirados *in vacuo* La capa acuosa se acidifico a pH 1 con 6N HCl, los sólidos se suspendieron en agua, se filtraron y se lavaron con eter dietílico El compuesto del título se obtuvo como un polvo de color blanco (56,2 mg, al 61%) $^1$H NMR (400 MHz, $CD_3OD$) δ 7,75 (dq, J = 2,9, 4,8 y 9,2 Hz, 1H), 7,71 (dd, J = 2,4 y 6,8 Hz, 1H), 7,64 (q, *J* = 8 y 14,8 Hz, 1H), 7,32 (t, J = 9,6 Hz, 1H), 7,04 (t, J = 8,8 Hz, 2H), 6,64 (s, 1H), 5,36 (s, 2H), 4,10 (s, 2H), 2,10 (s,3H) ppm $^{19}$ F NMR (400 MHz, $CD_3OD$) δ -111,54 (1F), -115,99 (1 F), -129,71 (1 F) ppm LC/MS, $t_r$ = 5,04 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con detección de 254 nm, a 50 °C) ES-MS *m/z* 498 (M+H)

Ejemplo 724




N-{3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-fluorofenil}-2-hidroxi-2-metilpropanamida

Etapa 1 Preparacion de 2-({3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-fluorofenil}amino)-1,1-dimetil-2-oxoetil acetato

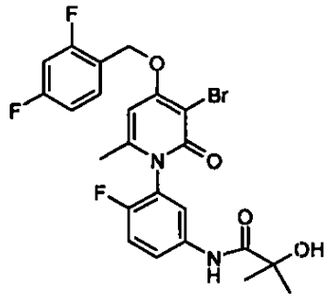


Una disolucion del compuesto del Ejemplo 722 (0,5 g, 1,05 mmol) en tetrahidrofurano (20 ml) se trató con trietilamina (0,3 ml, 2,1 mmol) y 1-clorocarbonil-1-metiletil acetato (0,16 ml, 1,15 mmol) Despues 2 horas de agitacion a temperatura ambiente, se completó la reacción La mezcla de reaccion se vertio en cloruro de amonio acuoso saturado Los solidos se filtraron y se lavaron con agua y éter dietilico El compuesto de la Etapa 1 se aislo como un solido de color blanco (0,23 g, al 39%) $^{1}$H NMR (400 MHz, $CD_3OD$) δ 7,64 (m, 2H), 7,54 (dd, J = 2,8 y 6,8 Hz, 1H), 7,30 (t, J = 9,2 Hz, 1H), 7,04 (t, J = 9,2 Hz, 2H), 6,64 (s, 1H), 5,35 (s, 2H), 2,11 (s, 3H), 2,08 (s, 3H), 1,61 (s, 6H) ppm $^{19}$ F NMR (400 MHz, $CD_3OD$) δ -111,57 (1F), -116,00 (1 F), -129,56 (1 F) ppm LC/MS, $t_r$ = 5,65 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con deteccion de 254 nm, a 50 °C) ES-MS *m/z* 568 (M+H)

Paso 2 Preparacion de N-{3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-4-fluorofenil}-2- hidroxi 2-metilpropanamida

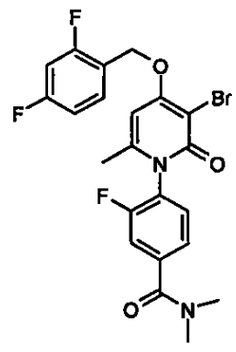
(PHA-819033)

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1411



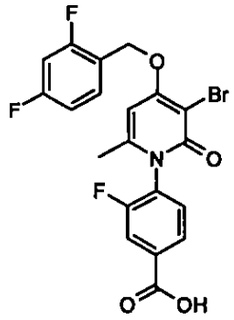
El producto de la Etapa 1, (0,1 g, 0,17 mmol) se suspendió en tetrahidrofurano (10 ml), metanol (2 ml), y 2,5 N NaOH (1 ml) Despues de 1 hora de agitacion a temperatura ambiente, se completo la reaccion y los materiales organicos fueron retirados *in vacuo* La capa acuosa se acidificó a pH 1 con 6N HCl, los solidos se suspendieron en agua, se filtraron y se lavaron con eter dietilico El compuesto del titulo se obtuvo como un polvo de color blanco (56 mg, al 61%) $^1$H NMR (400 MHz, $CD_3OD$) δ 7,75 (dq, J = 2,8, 4,4 y 9,2 Hz, 1H), 7,69 (dd, J = 2,8 y 6,8 Hz, 1H), 7,64 (q, *J* = 8 y 14,8 Hz, 1H), 7,31 (t, J = 9,2 Hz, 1H), 7,04 (t, J = 8,4 Hz, 2H), 6,64 (s, 1H), 5,35 (s, 2H), 2,10 (s, 3H), 1,43 (s,6H) ppm $^{19}$ F NMR (400 MHz, $CD_3OD$) δ -111,55 (1F), -115,95 (1 F), -129,80 (1 F) ppm LC/MS, $t_r$ = 5,34 minutos (acetonitrilo/agua al 5 a 95% durante 5 minutos a 1 ml/min con deteccion de 254 nm, a 50 °C) ES-MS *m/z* 526 (M+H)

Ejemplo 725



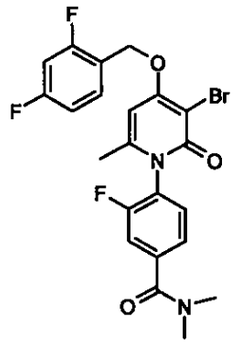
4-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-3-fluoro-N,N-dimetilbenzamida

Etapa 1 Preparación de acido 4-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-3-fluorobenzoico



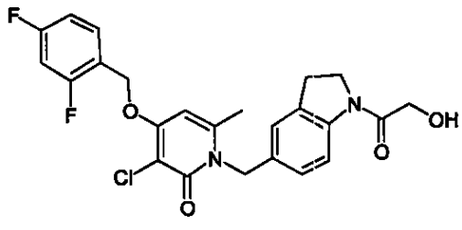
El compuesto del Ejemplo 604 ester (4,1 g, 8,5 mmol) se suspendio en tetrahidrofurano (30 ml), metanol (15 ml), agua (15 ml) y 2,5 N NaOH (6,8 mL, 17 mmol) Después de 2 horas de agitacion a temperatura ambiente, se completó la reaccion y los materiales organicos fueron retirados La capa acuosa se acidificó a pH 1 con 3N HCl, los sólidos se suspendieron en agua, se filtraron y se lavaron con éter dietilico El compuesto del titulo se obtuvo como un polvo de color blanco y se utilizó sin una purificación adicional (4,4 g) $^{1}$H NMR (400 MHz, $CD_3OD$) δ 8,00 (dd, J = 1,8 y 8,8 Hz, 1H), 7,93 (dd, J = 1,48 y 10 Hz, 1H), 7,64 (q, J = 8 y 14,8 Hz, 1H), 7,49 (t, J = 7,6 Hz, 1H), 7,05 (t, J = 10 Hz, 2H), 6,66 (s, 1H), 5,36 (s, 2H), 2,08 (s, 3H) ppm $^{19}$ F NMR (400 MHz, $CD_3OD$) δ -111,48 (1F), -115,96 (1 F), -123,35 (1 F) ppm ES-HRMS m/z 468,9987 (M+H calculado para $C_{20}H_{14}BrF_3NO_4$ requiere 469,0086)

Etapa 2 Preparación de 4-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]-3-fluoro-N,N-dimetilbenzamida



Una disolucion del producto de la Etapa 1, (0,5 g, 1,07 mmol) en *N,N*-dimetil formamida se enfrió a 0 °C y se agrego *Iso*-butil cloroformato (0,14 ml, 1,07 mmol) y *N*-metil morfolina (0,12 ml, 1,07 mmol) Despues de 20 minutos, se agrego *N,N*-dimetilamina (2,0 M, 1,1 ml, 2,14 mmol) y la mezcla de reaccion se entibio a temperatura ambiente superior a 18 horas La mezcla de reaccion se dividio entre acetato de etilo y una disolucion de $NaHCO_3$ acuosa saturada Los elementos organicos se lavaron con salmuera y se concentraron *in vacuo* El semisólido resultante se trato con acetato de etilo y acetona para precipitar el compuesto del titulo, (90 mg, al 17%) $^1H$ NMR (400 MHz, dmso-$d_6$) d 7,67 (q, $J$ = 8 y 14,8 Hz, 1H), 7,52 (m, 2H), 7,35 (m, 2H), 7,18 (td, $J$ = 2,8 y 8,8 Hz, 1H), 6,73 (s, 1H), 5,34 (s, 2H), 2,98 (s, 3H), 2,91 (s, 3H), 2,00 (s, 3H) ppm $^{19}$ F NMR (400 MHz, dmso-$d_6$) d-109,50 (1F), -113,63 (1 F), -122,09 (1 F) ppm ES-HRMS *m/z* 496,0570 (M+H calculado para $C_{22}H_{19}BrF_3N_2O_3$ requiere 496,0558)

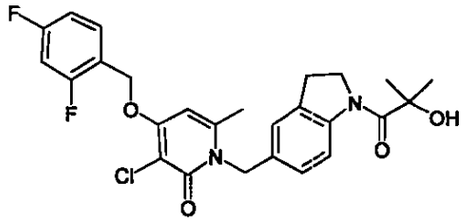
Ejemplo 726



3-cloro-4-[(2,4-difluorobencil)oxi]-1-(1-glicoloil-2,3-dihidro-1H-indol-5-il)metil-6-metilpiridin-2(1H)-ona

Un matraz de fondo redondo de 10 ml equipado con varilla para agitacion y entrada para nitrogeno se cargo con el compuesto del Ejemplo 633 (180 mg, 0,43 mmol), acetoxiacetil cloruro (51 µL, 0,47 mmol), trietilamina (119 µL, 0,86 mmol) y tetrahidrofurano (3,0 ml) Despues de agitar la reacción a 25 °C durante 20 minutos, esta se completo por LC/MS Se agregó NaOH (2,5M, 2,24 mmol, 1,0 ml) y MeOH (2,0 ml) y se agito durante 20 minutos para proporcionar el compuesto del titulo El compuesto se precipitó de la solucion El precipitado se filtro y se lavó con agua y éter dietilico para obtener el compuesto del titulo (130 mg, al 64%) como un sólido de color blanco $^1$H NMR (400 MHz, (DMSO) δ 7,9 (d, *J* = 8,2, 1H), 7,6 (q, *J* = 8,5 y 6,9 Hz, 1H), 7,3 (t, *J* = 8,7 Hz, 1H), 7,1 (t, *J* = 7,9 Hz, 1H), 6,9 (s, 2H), 6,5 (s, 1H), 5,25 (s, 2H), 4,1 (d, *J* = 5,5 Hz, 2H), 3,9 (t, *J* = 8,6 Hz, 2H), 3,42 (t, *J* = 5,4 Hz, 1H), 3,35 (t, *J* = 4,8 Hz, 1H), 3,2 (t, *J* = 8,5 Hz, 2H), 2,3 (s, 3H) ppm ES-HRMS *m/z* 475,1220 (M+H calculado para $C_{24}H_{22}ClF_2N_2O_4$ requiere 475,1231)

Ejemplo 727

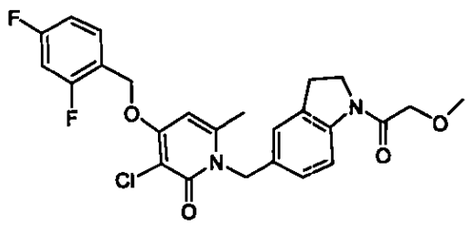



3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[1-(2-hidroxi-2-metilpropanoil)-2,3-dihidro-1*H*-indol-5-il]metil}-6-metilpiridin-2(1*H*)-ona

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Un matraz de fondo redondo de 10 ml equipado con varilla para agitacion y entrada para nitrógeno se cargó con el compuesto del Ejemplo 633 (200 mg, 0,48 mmol), 1-clorocarbonil-1-metiletil acetato (104,3 µL, 0,72 mmol), trietilamina (133 µL, 0,96 mmol) y tetrahidrofurano (4,0 ml) Despues de agitar la reaccion a 25 °C durante 20 minutos, ésta se completo por LC/MS Se agrego NaOH (2,5M, 2,24 mmol, 1,5 ml) y MeOH (2,0 ml) y se agito durante 20 minutos para proporcionar el compuesto del titulo El compuesto se precipito de la solucion El precipitado se filtro y se lavó con agua y éter dietilico para obtener un sólido de color blanco (240 mg, al 99%) $^1$H NMR (400 MHz, (DMSO) δ 8,0 (d, *J* = 8,3, 1H), 7,6 (q, *J* = 8,6 y 6,9 Hz, 1H), 7,3 (td, *J* = 2,5 y 7,8 Hz, 1H), 7,1 (td, *J* = 1,75 y 6,7 Hz, 1H), 6,95 (s, 1H), 6,89 (d, *J* = 8,5 Hz, 1H), 6,58 (s, 1H), 5,25 (s, 2H), 4,3 (t, *J* = 8,3 Hz, 2H), 3,42 (t, *J* = 5,4 Hz, 1H), 3,35 (t *J* = 5,2 Hz, 1H), 3,0 (t, *J* = 8,2 Hz, 2H), 2,3 (s, 3H), 1,3 (s, 6H) ppm ES-HRMS *m/z* 503,1561 (M+H calculado para $C_{26}H_{26}ClF_2N_2O_4$ requiere 503,1544)

Ejemplo 728

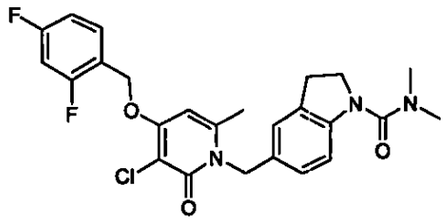



3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[1-(metoxiacetil)-2,3-dihidro-1H-indol-5-il]metil}-6-metilpiridin-2(1H)-ona

Un matraz de fondo redondo de 10 ml equipado con varilla para agitacion y entrada para nitrógeno se cargo con el compuesto del Ejemplo 633 (200 mg, 0,48 mmol), metoxiacetil cloruro (66 µL, 0,72 mmol), trietilamina (134

µL, 0,96 mmol) y tetrahidrofurano (4,0 ml) Despues de 20 minutos de agitación a 25 °C, la reaccion se completó mediante LC/MS El compuesto se precipito de la solucion El precipitado se filtro y se lavo con agua y éter dietilico para obtener un solido de color blanco (195 mg, al 83%) $^1$H NMR (400 MHz, (DMSO) δ 8,0 (d, *J* = 8,0, 1H), 7,6 (q, *J* = 8,6 y 6,7 Hz, 1H), 7,3 (td, *J* = 2,4 y 6,7 Hz, 1H), 7,1 (td, *J* = 1,88 y 6,6 Hz, 1H), 6,9 (s, 2H), 6,58 (s, 1H), 5,25 (s, 2H), 4,15 (s, 2H), 3,9 (t, *J* = 8,3 Hz, 2H), 3,45 (m, 1H), 3,4 (m, 1H), 3,32 (s, 3H), 3,0 (t, *J* = 8,5 Hz, 2H), 2,3 (s, 3H) ppm ES-HRMS *m/z* 489,1387 (M+H calculado para $C_{25}H_{24}ClF_2N_2O_4$ requiere 489,1387)

Ejemplo 729

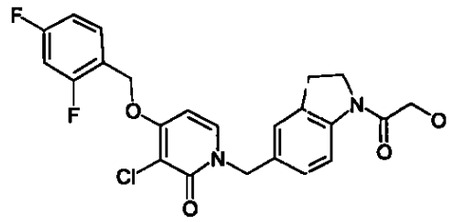


5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2H)-il]metil}-N,N-dimetilindolina-1-carboxamida

Un matraz de fondo redondo de 10 ml equipado con varilla para agitación y entrada para nitrógeno se cargo con el compuesto del Ejemplo 633 (200 mg, 0,48 mmol), dimetilcarbamil cloruro (66 µL, 0,72 mmol), trietilamina (133 µL, 0,96 mmol) y tetrahidrofurano (4,0 ml) Despues de 5 minutos de agitación a 25 °C, la reaccion se completó mediante LC/MS El compuesto se precipitó de la solucion El precipitado se filtro y se lavó con agua y eter dietilico para obtener un solido de color blanco (198 mg, al 85%) $^1$H NMR (400 MHz, (DMSO) d 7,6 (q, *J* = 7,4 Hz, 1H), 7,3 (t, *J* = 8,9 Hz, 1H), 7,1 (t, *J* = 8,5 Hz, 2H), 6,93 (s,

1H), 6,86 (s, 1H), 6,58 (s, 1H), 5,25 (s, 2H), 3,9 (t, *J* = 8,2 Hz, 2H), 3,45 (m, 1H), 3,4 (m, 1H), 2,9 (t, *J* = 8,3 Hz, 2H), 2,8 (s, 6H), 2,3 (s, 3H) ppm ES-HRMS *m/z* 488,1548 (M+H calculado para $C_{25}H_{24}ClF_2N_2O_4$ requiere 488,1547)

Ejemplo 730

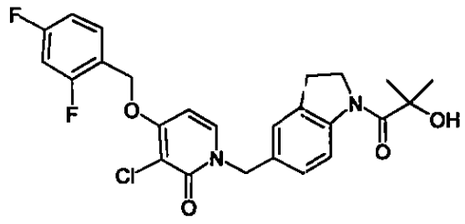


3-cloro-4-[(2,4-difluorobencil)oxi]-1-(1-glicoloil-2,3-dihidro-1H-indol-5-il)metil]piridin-2(1H)-ona

Un matraz de fondo redondo de 10 ml equipado con varilla para agitacion y entrada para nitrógeno se cargo con el compuesto del Ejemplo 88 (200 mg, 0,5 mmol), acetoxiacetil cloruro (59 µL, 0,55 mmol), trietilamina (140 µL, 1,0 mmol) y tetrahidrofurano (3,0 ml) Despues de agitar la reaccion a 25 °C durante 20 minutos, esta se completo por LC/MS Se agrego NaOH (2,5M, 2,24 mmol, 1,0 ml) y MeOH (2,0ml) y se agito durante 20 minutos para proporcionar el compuesto del titulo El compuesto se precipito de la solución El precipitado se filtro y se lavó con agua y eter dietilico para obtener el compuesto del titulo (200 mg, al 83%) como un solido de color blanco $^1$H NMR (400 MHz, (DMSO) δ 7,98 (d, *J* = 8,1, 1H), 7,9 (d, *J* = 7,8 Hz, 1H), 7,6 (q, *J* = 8,6 y 6,6 Hz, 1H), 7,3 (dt, *J* = 2,4 y 7,2 Hz, 1H), 7,1 (m, 2H), 6,56 (d, *J* =7,8 Hz, 1H), 5,25 (s, 2H), 5,1 (s, 2H), 4,8 (t, *J* = 5,8 Hz, 1H), 4,1 (d, *J* = 5,6 Hz 2H), 3,9 (t, *J* = 7,9 Hz, 2H), 3,1 (t, *J* = 7,9 Hz, 2H) ppm ES-HRMS m/z 461,1088 (M+H calculado para $C_{23}H_{20}ClF_2N_2O_4$ requiere 461,1074)

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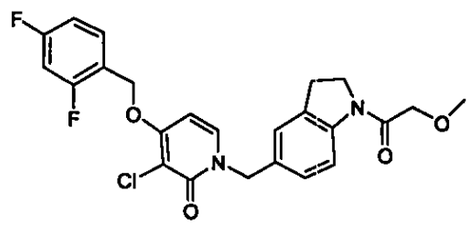
Ejemplo 731



Preparacion de 3-cloro-4-[(2,4-difluorobencil)oxi]-1-(1-glicoloil-2,3-dihidro-1H-indol-5-il)metil]piridin-2(1H)-ona

Un matraz de fondo redondo de 10 ml equipado con varilla para agitacion y entrada para nitrogeno se cargo con el compuesto del Ejemplo 88 (200 mg, 0,50 mmol), 1-clorocarbonil-1-metiletil acetato (80 µL, 0,55 mmol), trietilamina (140 µL, 1,0 mmol) y tetrahidrofurano (4,0 ml) Despues de agitar la reaccion a 25 °C durante 20 minutos, esta se completó por LC/MS Se agregó NaOH (2,5M, 2,24 mmol, 1,5 ml) y MeOH (2,0 ml) y se agito durante 20 minutos para proporcionar el compuesto del titulo El compuesto se precipito de la solucion El precipitado se filtró y se lavo con agua y eter dietílico para obtener el compuesto del titulo (136 mg, 55%) como un solido de color blanco $^1$H NMR (400 MHz, (DMSO) δ 7,98 (d, *J* = 8,1, 1H), 7,9 (d, *J* = 7,8 Hz, 1H), 7,6 (q, *J* = 8,6 y 6,6 Hz, 1H), 7,3 (m, 1H), 7,1 (m, 2H), 6,56 (d, *J* =7,8 Hz, 1H), 5,25 (s, 2H), 5,0 (s, 2H), 4,3 (t, *J* = 7,8 Hz, 2H), 3,0 (t, *J* = 7,9 Hz, 2H), 1,3 (s, 6H) ppm ES-HRMS *m/z* 489,1376 (M+H calculado para $C_{25}H_{24}ClF_2N_2O_4$ requiere 489,1387)

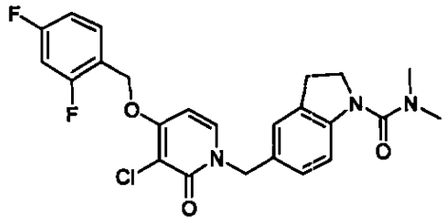
Ejemplo 732



3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[1-(metoxiacetil)-2,3-dihidro-1H-indol-5-il]metil}piridin-2(1H)-ona

Un matraz de fondo redondo de 10 ml equipado con varilla para agitación y entrada para nitrogeno se cargo con el compuesto del Ejemplo 88 (200 mg, 0,5 mmol), metoxiacetil cloruro (69 µL, 0,75 mmol), trietilamina (139 µL, 1,0 mmol) y tetrahidrofurano (4,0 ml) Después de 20 minutos de agitación a 25 °C, la reaccion se completo mediante LC/MS El compuesto se precipito de la solucion El precipitado se filtro y se lavo con agua y eter dietílico para obtener un solido de color blanco (195 mg, al 83%) $^1$H NMR (400 MHz, (DMSO) δ 7,98 (d, $J$ = 8,2, 1H), 7,9 (d, $J$ = 7,7 Hz, 1H) 7,6 (d, $J$ = 8,5 Hz, 1H), 7,3 (t, $J$ = 9,6 Hz, 1H), 7,1 (m, 3H), 6,56 (d, $J$ =7,8 Hz, 1H), 5,25 (s, 2H), 5,1 (s, 2H), 4,1 (s, 2H), 3,98 (t, $J$ = 7,9 Hz, 2H), 3,33 (s, 3H), 3,0 (t, $J$ = 7,9 Hz, 2H) ppm ES-HRMS m/z 461,1088 (M+H calculado para $C_{23}H_{20}ClF_2N_2O_4$ requiere 461,1074)

Ejemplo 733



5-{[3-cloro-4-[(2,4-difluorobencil)oxi]2-oxopiridin-1(2H)-il]metil}-N-N-dimetilindolina-1-carboxamida

Un matraz de fondo redondo de 10 ml equipado con varilla para agitacion y entrada para nitrógeno se cargó con el compuesto del Ejemplo 88 (200 mg, 0,5 mmol), dimetilcarbamil cloruro (69 µL, 0,75 mmol), trietilamina (139 µL, 1,0 mmol) y tetrahidrofurano (4,0 ml) Despues de

5 minutos de agitacion a 25 °C, la reacción se completo mediante LC/MS El compuesto se precipito de la solucion El precipitado se filtró y se lavo con agua y eter dietilico para obtener un sólido de color blanco (188 mg, al 58%) $^1$H NMR (400 MHz, (DMSO) δ 7,9 (d, $J$ = 8,1, 1H), 7,6 (q, $J$ = 8,6 and 6,6 Hz, 1H), 7,3 (t, $J$ = 9,3 Hz, 1H), 7,1 (m, 3H), 6,8 (d, $J$ =8,0 Hz, 1H), 6,5 (d, $J$ = 7,8 Hz, H), 5,25 (s, 2H), 5,0 (s, 2H), 3,7 (t, $J$ = 8,6 Hz, 2H), 2,9 (t, $J$ = 7,9 Hz, 2H), 2,3 (s, 6H) ppm ES-HRMS m/z 474,1387 (M+H calculado para $C_{24}H_{23}ClF_2N_3O_3$ requiere 474,1391)

EVALUACIÓN BIOLÓGICA

Estudio de la p38 quinasa

Clonacion de la p38a humana

La región codificadora de la p38a humana del cDNA se obtuvo por amplificacion por PCR del RNA aislado de la línea celular monocitica humana THP 1 La primera hebra de CDNA se sintetizo del RNA total como se describe a continuacion se templaron 2 µg de RNA a 100 ng de iniciadores hexameros aleatorios en 10 µl de reaccion por calentamiento a 70° C durante 10 minutos seguido por 2 minutos sobre hielo El cDNA luego se sintetizó mediante la adición de 1 µl de RNAsin (Promega, Madison Wis ), 2 µl de dNTP's 50 mM, 4 µl de tampon 5X, 2 µl de DTT 100 mM y 1 µl (200 U) de transcriptasa inversa Superscript II™ AMV El iniciador aleatorio, los reactivos dNTP's y Superscript II™ fueron comprados a Life-Technologies, Gaithersburg, Mass La reaccion se incubo a 42 °C durante 1 hora La amplificacion de la p38 del cDNA se realizó mediante alicuotas de 5 µl de la reaccion de transcriptasa inversa en 100 µl de una reaccion PCR que contenia lo siguiente 80 µl de dH sub 2 O, 2 de µl dNTP's 50 mM, 1 µl de cada uno de los iniciadores directos e inversos (50 pmol/µl), 10 µl de

tampon 10X y 1 µl de polimerasa Expand™ (Boehringer Mannheim) Los iniciadores de la PCR incorporaron sitios Bam HI en los extremos 5' y 3' del fragmento amplificado, y fueron comprados a Genosys Las secuencias de los iniciadores directos e inversos fueron 5'-GATCGAGGATTCATGTCTCAGGAGAGGCCCA-3' y 5'GATCGAGGATTCTCAGGACTCCATCTCTTC-3' respectivamente La amplificacion por PCR se llevo a cabo en un termociclador de DNA (Perkin Elmer) repitiendo 30 ciclos de 94 °C durante 1 minuto, 60 °C durante 1 minuto y 68 °C durante 2 minutos Despues de la amplificacion, los iniciadores sobrantes y el dNTP's no incorporado fueron eliminados del fragmento amplificado con una preparación Wizard™ PCR (Promega) y digeridos con Bam HI (New England Biolabs) El fragmento digerido por Bam HI se ligó en plásmido de DNA pGEX 2T digerido por Bam HI (PharmaciaBiotech) utilizando T-4 DNA ligasa (New England Biolabs) como lo describe T Maniatis, Molecular Cloning A Laboratory Manual, 2ª ed (1989) La reacción de ligación se transformo en celulas E Coli DH10B quimicamente competentes adquiridas en Life-Technologies siguiendo las instrucciones del fabricante El plásmido de DNA se aislo de las colonias bacterianas resultantes utilizando un kit Promega Wizard™ miniprep Los plasmidos que contenian el fragmento Bam HI apropiado fueron secuenciados en un termociclador de DNA (Perkin Elmer) con Prism™ (Applied Biosystems Inc ) Se identificaron los clones de DNA que codificaban ambas isoformas de p38a humanas (Lee et al Nature 372, 739) Uno de los clones que contenian el cDNA para p38a-2 (CBS-2) insertado en el sitio de clonacion del PGEX 2T, 3' de la region codificadora de GST fue designado pMON 35802 La secuencia obtenida para este clon es una combinacion exacta del clon de cDNA

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enunciado por Lee et al Este plasmido de expresion permite la producción de una proteina de fusión GST-p38a

Expresion de la p38a humana

La proteina de fusion GST/p38a fue expresada del plasmido pMON 35802 en E coli, cepa DH10B (Life Technologies, Gibco-BRL) Durante toda la noche los cultivos se desarrollaron en caldo Luria (LB) que contenia 100 mg/ml de ampicilina Al día siguiente, se inocularon 500 ml de LB nuevo con 10 ml de cultivo de la noche, y se cultivaron en un matra de 2 litros a 37 °C con agitación constante hasta que el cultivo alcanzo una absorbancia de 0,8 a 600 nm La expresión de la proteina de fusion fue inducida por la adicion de isopropil b-D-tiogalactosidasa (IPTG) hasta una concentración final de 0,05 mM Los cultivos se agitaron durante tres horas a temperatura ambiente, y las celulas se cosecharon por centrifugación Los granulos celulares se almacenaron congelados hasta la purificacion de la proteina

Purificación de P38 quinasa-alfa

Todos los elementos quimicos fueron de Sigma Chemical Co a menos que se indique de otro modo Se resuspendieron 20 gramos de gránulos celulares E coli recolectados de cinco fermentaciones en matraces de 1 litro con agitacion en un volumen de PBS (NaCl 140 mM, KCl 2,7 mM, Na sub 2 HPO sub 4 10 mM, KH sub 2 PO sub 4 1,8 mM, pH 7,3) hasta 200 ml La suspension cellular se ajusto a DTT 5mM con DTT 2 M y luego se dividió por igual en cinco tubos cónicos Falcon de 50 ml Las células se son_caron (Ultrasonics modelo W375) con una sonda de 1 cm (3 veces, 1 minuto)(pulsado) sobre hielo El material celular lisado fue eliminado por centrifugación (12 000 x g, 15 minutos) y el sobrenadante clarificado se aplicó a resina glutation/sepharosa (Pharmacia)

Cromatografía de afinidad en glutatión-sepharosa

Se agregaron 12 ml de una suspensión de glutatión sepharosa-PBS al 50% a 200 ml de sobrenadante clarificado y se incubó por lotes durante 30 minutos a temperatura ambiente La resina fue recolectada por centrifugación (600 veces x g , 5 min ) y se lavo con 2 veces x 150 ml de PBS/Triton X-100 al 1%, seguido de 4 veces x 40 ml de PBS Para clivar la p38 quinasa de la proteina de fusion GST-p38, la resina glutatión-sepharosa fue resuspendida en 6 ml de PBS que contenia 250 unidades de proteasa trombina (Pharmacia, actividad especifica >7500 unidades/mg) y se mezclo suavemente durante 4 horas a temperatura ambiente La resina glutatión-sepharosa se elimino por centrifugación (600 veces x g, 5 min ) y se lavo 2 veces x 6 ml con PBS Las fracciones de lavado con PBS y el sobrenadante de digestion que contenia proteina p38 quinasa fueron acumulados y ajustados a 0,3 mM PMSF

Cromatografía de intercambio aniónico en columnas Mono Q

La p38 quinasa clivada con trombina se purificó adicionalmente por cromatografía de intercambio anionico en sistema de FPLC La muestra clivada con trombina se diluyo al doble con Tampon A (HEPES 25 mM, pH 7,5, beta-glicerofosfato 25 mM, DTT 2 mM, glicerol al 5%) y se inyecto sobre una columna de intercambio anionico Mono Q HR 10/10 (Pharmacia) equilibrada con Tampon A La columna se eluyo con 160 ml de solucion de NaCl/Tampon A 0,1 M-0,6 M en gradiente (caudal 2 ml/minuto) El pico de p38 quinasa que se eluia a NaCL 200 mM se recolecto y se concentró a 3-4 ml con un concentrador Filtron 10 (Filtron Corp )

Cromatografía de filtración en gel Sephacryl S100

La muestra de p38 quinasa purificada en columnas Mono Q concentrada se purifico por cromatografía de filtración en gel (columna de Sephacryl S100 Pharmacia HiPrep 26/60 equilibrada con Tampon B (HEPES 50 mM, pH 7,5, NaCl 50 mM, DTT 2 mM, glicerol al 5%)) La proteína se eluyo de la columna con Tampon B a un caudal de 0,5 ml/minuto y se de detectó proteina por absorbancia a 280 nm Las fracciones que contenian p38 quinasa (detectada por electroforesis en gel de poliacrilamida en presencia de SDS) fueron acumuladas y congeladas a -80 °C Los rendimientos de la proteina purificada tipicos de fermentaciones en matraces de 5 litros de E coli con agitación fueron de 35 mg de p38 quinasa

Ensayo *in vitro*

Se evaluó la capacidad de los compuestos para inhibir la p38 quinasa alfa humana utilizando dos metodos de ensayo *in vitro* En el primer metodo, la p38 quinasa alfa humana activada fosforila un sustrato biotinilado, PHAS-I (proteina estable al acido y al calor fosforilada inducible por insulina), en presencia de $^{32}$P-ATP gamma ($^{32}$P-ATP) La PHAS-I fue biotinilada antes del ensayo y proporciona un medio para capturar el sustrato, el cual se fosforila durante el ensayo La p38 quinasa fue activada por MKK6 Los compuestos se probaron en diluciones seriales 10 veces mayores sobre el rango de 100 µM a 0,001 µM utilizando DMSO al 1% Cada concentracion de inhibidor se probo por triplicado

Todas las reacciones fueron ejecutadas en placas de polipropileno de 96 pozos Cada pozo de reacción contenia HEPES 25 mM pH 7,5, acetato de magnesio 10 mM y 50 µM de ATP no rotulado Fue necesaria la activacion de p38 para lograr una señal suficiente en el ensayo Se utilizó PHAS-I biotinilada a 1-2 µg por 50 µl de volumen de reaccion, con

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una concentración final de 1,5 µM La p38 quinasa alfa humana activada se utilizo a 1 µg por 50 µl de volumen de reaccion lo que represento una concentracion final de 0,3 µM La $^{32}$P-ATP gamma se utilizó para seguir la fosfoliracion de PHAS-I La $^{32}$P-ATP tiene una actividad especifica de 3000 Ci/mmol y se empleó a 1,2 µCi por 50 µl de volumen de reaccion La reaccion siguio su curso durante una hora o durante toda la noche a 30 °C

Despues de la incubacion, se transfirieron 20 µl de la mezcla de reaccion a una placa de filtro recubierta con estreptavidina de alta capacidad (matriz de estreptavidina SAM, Promega) prehumedecida con solución salina amortiguada con fosfato La mezcla de reacción transferida se puso en contacto con la membrana de estreptavidina de la placa Promega durante 1-2 minutos Después de la captura de la PHAS-I biotinilada con $^{32}$P incorporada, se lavo tres veces cada pozo para quitar la $^{32}$P-ATP no incorporada con NaCl 2M, tres lavados de NaCl 2M con fosfórico al 1%, tres lavados de agua destilada y finalmente un unico lavado de etanol al 95% Las placas de filtro se secaron con aire y se agrego 20 µl de escintilante Las placas se sellaron y contaron

También se empleo un segundo formato de ensayo basado en la fosforilacion de EGFRP (peptido receptor del factor de crecimiento epidérmico, 21 mer) inducida por p38 quinasa alfa en presencia de $^{33}$P-ATP Los compuestos se probaron en diluciones seriales 10 veces mayores sobre el rango de 100 µM a 0,001 µM en DMSO al 1% Cada concentracion de inhibidor se probo por triplicado Los compuestos fueron evaluados en volumenes de reaccion de 50 µl en presencia de Hepes 25 mM pH 7,5, acetato de magnesio 10 mM, glicerol al 4%, albumina de sueron bovino al 0,4%, DTT 0,4 mM, ATP no rotulado 50 µM, 25 µg de EGFRP (200 µM) y 0,05 µCi $^{33}$P-ATP

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Las reacciones se iniciaron mediante la adicion de 0,09 µg de GST-p38 quinasa alfa humana purificada, activada La activacion se llevó a cabo usando GST-MKK6 (5 1, p38 MKK6) durante una hora a 30 °C en presencia de ATP 50 µM Después de la incubacion durante 60 minutos a temperatura ambiente, la reaccion se detuvo mediante la adicion de 150 µl de AG 1 proporcion x 8 de resina en tampón formato de sodio 900 mM, pH 3,0 (1 volumen de resina a 2 volumenes de tampon) La mezcla se mezcló tres veces con pipeta y la resina se dejo asentar Un total de 50 µl del volumen principal de solución clarificada se transfirio desde los pozos de reacción a 2 placas de microtitulación Luego se agregaron 150 µl de Microscint 40 a cada pozo de la placa de microtitulacion, y la placa se selló, se mezclo y se conto

Los compuestos representativos que exhiben valores $IC_{50}$ de entre 1 y 25 µM (ensayo de p38 quinasa alfa) son Ejemplos N° 20, 22, 23, 39, 43, 44, 48, 50, 52, 53, 55, 57, 58, 62, 92, 115, 118, 136, 139, 141, 142, 149, 156, 157, 169, 174, 219, 220, 244, 245, 387, 288, 289, 291, 292, 293, 294, 295, 296, 298, 297, 300, 301, 302 304, 305, 309, 310, 311, 323, 360, 394 403, 414, 415, 416, 418, 420, 444, 447, 449, 451, 452, 471, 485, 486, 496, 498, 499, 503, 506, 561, 569, 574, 575 y 576

Los compuestos representativos que exhiben valores $IC_{50}$ de entre 25 y 100 µM (ensayo de p38 quinasa alfa) son Ejemplos N° 1, 25, 33, 35, 37, 42, 45, 47, 49, 119, 204, 308, 558, 560, 564, 565, 566, 568 y 577

Los compuestos representativos que exhiben valores $IC_{50}$ menores que 1 µM (ensayo de p38 quinasa alfa) son Ejemplos N° 6, 14, 8, 17, 10, 15, 4, 117, 161, 162, 165, 170, 171, 172, 173 176, 179, 217, 218, 219, 220, 221, 223, 225, 230, 231, 234, 235, 272, 273, 275, 276, 278, 280, 282,

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286, 285, 290, 312, 313, 314, 315, 316, 317, 318, 320, 321, 322, 364, 366, 400, 402, 405, 421, 422, 423, 446, 448, 450, 458, 466, 467, 468, 469, 470, 481, 482, 483, 484, 487, 489, 492, 493, 494, 495, 504, 521, 522, 523 557, 587, 589, 590, 591, 597, 609, 610, 613, 629, 642 y 643

Los compuestos representativos que exhiben valores $IC_{50}$ mayores que 100 µM (ensayo de p38 quinasa alfa) son Ejemplos N° 3, 11, 38, 56, 116, 121, 237, 236, 413, 497 y 578

Ensayos de células ante FNT

Metodo de aislación de celulas mononucleares de sangre periferica de seres humanos

Se recolecto sangre entera de seres humanos en tubos Vacutainer que contenian EDTA como anticoagulante Se formó cuidadosamente una capa de muestra de sangre (7 ml) sobre 5 ml de medio de aislamiento de células PMN (Robbins Scientific) en un tubo centrífugo de fondo redondo de 15 ml La muestra se centrifugo a 450-500 veces x g durante 30-35 minutos en un rotor oscilante a temperatura ambiente Después de la centifrugacion, la banda superior de celulas se quitó y se lavo 3 veces con PBS sin calcio ni magnesio Las celulas se centrifugaron a 400 veces x g durante 10 minutos a temperatura ambiente Las células se resuspendieron en medio libre de suero con macrofagos (Gibco BRL) a una concentración de 2 millones de células/ml

Estimulación por LPS de PBM humanas

Las celulas de PBM (0,1 ml, 2 millones/ml) se coincubaron con 0,1 ml de compuesto (10-0,41 µM, concentración final) durante 1 hora en placas de microtitulacion de 96 pozos de fondo plano Los compuestos se disolvieron en DMSO inicialmente y se diluyeron en TCM para obtener una

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concentracion final de DMSO al 0,1% Luego se agrego LPS (Calbiochem, 20 ng/ml, concentracion final) a un volumen de 0,010 ml Los cultivos se incubaron durante toda la noche a 37 °C Después se retiraron los sobrenadantes y se probaron mediante la tecnica de ELISA respecto del FNT-a e IL1-b La viabilidad se analizo utilizando MTS Despues de recolectar 0,1 ml de sobrenadante, se agregó 0,020 ml de MTS al 0,1 ml de celulas remanentes Las células se incubaron a 37 °C durante 2-4 horas, luego se midió la O D a 490-650 nM

Mantenimiento y diferenciacion de la linea celular de linfoma histiocitico humano U937

Las celulas U937 (ATCC) se propagaron en RPMI 1640 que contenia suero bovino fetal al 10%, 100 IU/ml de penicilina, 100 µg/ml de estreptomicina y glutamina 2 mM (Gibco) Cincuenta millones de céulas en 100 ml de medio fueron inducidas a diferenciacion monocitica terminal por 24 horas de incubación con 20 ng/ml de forbol 12-miristato 13-acetato (Sigma) Las celulas se lavaron por centrifugación (200 veces x g durante 5 min ) y se resuspendieron en 100 ml de medio nuevo Después de 24-48 horas, las celulas fueron cosechadas, centrifugadas y resuspendidas en medio de cultivo a 2 millones de células/ml

Estimulación por LPS de la producción de FNT por celulas U937

Las células U937 (0,1 ml, 2 millones/ml) se incubaron con 0,1 ml de compuesto (0,004-50 µM, concentración final) durante 1 hora en placas de microtitulación de 96 pozos Los compuestos se prepararon como soluciones madre 10 mM en DMSO y se diluyeron en medio de cultivo para producir una concentración final de DMSO de 0,1% en el ensayo celular

Luego se agrego LPS (E coli, 100 ng/ml, concentracion final) a un volumen de 0,02 ml Despues de 4 horas de incubacion a 37 °C, la cantidad de FNT-alfa liberado en el medio de cultivo se cuantificó mediante la tecnica de ELISA La potencia inhibidora se expresa como IC50 (µM)

Ensayo en ratas

La eficacia de los compuestos novedosos para bloquear la producción de FNT tambien se evaluó utilizando un modelo basado en ratas inducidas con LPS En este modelo se utilizaron ratas macho Harlen Lequis [Sprague Dawley Co ] Cada rata pesaba aproximadamente 300 g y se sometio a ayuno durante toda la noche anterior a la prueba La administracion del compuesto fue tipicamente por via oral (cebadura) (si bien en algunas ocasiones tambien se empleó administracion intraperitoneal, subcutánea e intravenosa) de 1 a 24 horas antes de la induccion con LPS A las ratas se les administró 30 µg/kg de LPS [salmonella tifosa, Sigma Co ] por via intravenosa a traves de la vena de la cola La sangre fue recolectada mediante puncion en el corazon 1 hora despues de la inducción con LPS Las muestras de suero se almacenaron a -20 °C hasta el analisis cuantitativo de FNT-alfa mediante un ensayo inmuno sorbente con enzima ligada ("ELISA") [Biosource] En Perretti, M , et al , Br J Pharmaco (1993), 110, 868-874, incorporado a la presente solicitud por referencia, se establecen detalles adicionales del ensayo

Ensayo en ratones

Modelo de produccion de FNT-alfa inducido con LPS en ratones

El FNT alfa fue inducido en ratones hembra BALB/c de 10-12 semanas de edad por inyección en la vena de la cola con 100 ng de lipopolisacárido (de S Tifosa) en 0,2 ml de

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solucion salina Una hora mas tarde los ratones sangraron desde el seno retroorbitario y las concentraciones de FNT en suero de sangre coagulada fueron cuantificadas mediante la tecnica de ELISA Tipicamente, los niveles pico de FNT en suero oscilaron entre 2-6 ng/ml una hora después de la inyeccion de LPS

Los compuestos probados fueron administrados a ratones en ayuno por via oral (cebadura) como suspension en 0,2 ml de metilcelulosa al 0,5% y Tween 20 al 0,025% en agua 1 hora o 6 horas antes de la inyeccion de LPS Mediante el protocolo de 1 hora se evaluó la potencia del compuesto en niveles de plasma Cmax mientras que con el protocolo de 6 horas se estimó la duracion de la acción del compuesto Se determinó la eficacia en cada punto de tiempo como la inhibicion porcentual de los niveles de FNT en suero en relacion con los ratones a los que se habia inyectado LPS que sólo recibieron el vehiculo

Induccion y evaluación de artritis inducida por colageno en ratones

Se indujo arthritis en ratones de acuerdo con el procedimiento establecido en J M Stuart, Collagen Autoimmune Arthritis, Annual Rev Immunol 2 199 (1984), el cual se incorpora a la presente por referencia Específicamente, se indujo artritis en ratones macho DBA/1 de 8 a 12 semanas de edad por inyección de 50 µg de colageno de pollo tipo II (CII) (provisto por Dr Marie Griffiths, Univ of UTA, Salt Lake City, Utah) en adyuvante completo de Freund (Sigma) el dia 0 en la base de la cola El volumen de inyeccion fue de 100 µl El dia 21 se inyectó a los animales con 50 µg de CII en adyuvante incompleto de Freund (volumen 100 µl) Cada semana se evaluo a los animales varias veces para detectar signos de

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artritis Los animales que presentaban enrojecimiento o hinchazon en las patas se consideraron artriticos Se llevo a cabo una puntuación de las patas artriticas de acuerdo con el procedimiento establecido en Wooley et al , Genetic Control of Type II Collagen Induced Arthritis in Mice Factors Influencing Disease Suspectibility and Evidence for Multiple MHC Associated Gene Control , Trans Proc , 15 180 (1983) La calificacion de la gravedad se efectuó utilizando un puntaje de 1 a 3 por cada pata (puntaje maximo de 12/raton) Los animales que mostraron cierto enrojecimiento o hinchazón de los dedos o de la pata recibieron un puntaje de 1 Una inflamación masiva de toda la pata o su deformidad se puntuo como 2 El anquilosamiento de las articulaciones recibió un puntaje de 3 Los animales fueron evaluados durante 8 semanas Se utilizaron de 8 a 10 animales por grupo

La invencion y el modo y proceso de hacerla y de utilizarla se describen ahora con términos tan comprehensivos, claros, concisos y exactos que permitan a un experto en esta tecnica realizar y utilizar dicha invención Se debe entender que lo precedente describe las realizaciones preferidas de la presente invención y que ellas pueden ser modif cadas sin apartarse del espiritu y alcance de la presente invencion segun se establece en las reivindicaciones A fin de señalar particularmente y de reivindicar univocamente el tema considerado como la invención, las reivindicaciones siguientes concluyen esta descripcion

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**REIVINDICACIONES**

Se reivindica lo siguiente

1 Un compuesto de la formula



o una sal farmacéuticamente aceptable del mismo, en la que

$R_1$ es H, halógeno, $NO_2$, alquilo, carboxaldehído, hidroxialquilo, dihidroxialquilo, arilalcoxi, arilalquilo, alquenilo, alquinilo, arilalquinilo, -CN, arilo, alcanoilo, alcoxi, alcoxialquilo, haloalquilo, haloalcoxi, carboxilo o arilalcanoilo,

en la que la porcion arilo del arilalcoxi, arilalquilo y arilalcanoilo no está sustituida o esta sustituida con 1, 2, 3, 4 o 5 grupos que son independientemente halogeno, alquilo $C_1$-$C_4$, nitro, CN, haloalquilo, haloalcoxi o $CO_2R$

en la que la porción alquilo de los grupos alquilo, hidroxialquilo, dihidroxialquilo, arilalcoxi, arilalquilo, alcanoilo, alcoxi, alcoxialquilo y arilalcanoilo no esta sustituida o está sustituida con 1, 2 o 3 grupos que son independientemente halogeno, alcoxi $C_1$-$C_4$, alcoxi $C_1$-$C_4$ carbonilo o cicloalquilo $C_3$-$C_7$,

$R_2$ es H, OH, halogeno, -$OSO_2$-alquilo ($C_1$-$C_6$), -$OSO_2$-arilo, ar_lalcoxi, ariloxi, ariltio, ariltioalcoxi, arilalquinilo, alcoxi, ariloxialquil($C_1$-$C_6$', alquilo, alquinilo, -OC(O)NH$(CH_2)_n$arilo, -OC(O)N(alquil)$(CH_2)_n$arilo, alcoxialcoxi, dialquilamino, alquilo, alcoxi, arilo, arilalquilo, heteroarilo, heteroarilalquilo,

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arilalquenilo, heterocicloalquilo, heterocicloalquilalquilo, alcoxialcoxi, $NR_8R_9$, dialquilamino o $CO_2R$, en la que

n es 0, 1, 2, 3, 4, 5 o 6,

cuyos grupos no se sustituyen o se sustituyen con 1, 2, 3, 4 o 5 grupos que son independientemente halógeno, -alquil($C_1$-$C_6$)-N(R)-$CO_2R_{30}$, haloalquilo, heteroarilo, heteroarilaquilo, $-NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, $-C(O)NR_6R_7$, -alquil($C_1$-$C_4$)-$C(O)NR_6R_7$, -(alquilo $C_1$-$C_4$)-$NRC(O)NR_{16}R_{17}$, haloalcoxi, alquilo, CN, hidroxialquilo, dihidroxialquilo, alcoxi, alcoxicarbonilo, fenilo, $-SO_2$-fenilo en los que los grupos fenilo y $-SO_2$-fenilo estan opcionalmente sustituidos con 1, 2 ó 3 grupos que son independientemente halógeno o $NO_2$ o $-OC(O)NR_6R_7$, en la que

$R_{16}$ y $R_1$ son independientemente H o alquilo $C_1$-$C_6$, o

$R_{16}$, $R_{17}$ y el nitrógeno al que estan acoplados forman un anillo morfolinilo,

$R_6$ y $R_7$ son independientemente en cada aparicion H, alquilo, hidroxialquilo, dihidroxialquilo, alcoxi, alcanoilo, arilalquilo, arilalcoxi, alcoxicarbonilo, $-SO_2$-alquilo, OH, alcoxi, alcoxialquilo, arilalcoxicarbonilo, -alquil($C_1$-$C_4$)-$CO_2$-alquilo, heteroarilalquilo o arilalcanoilo, en los que cada uno no esta sustituido o esta sustituido con 1, 2 ó 3 grupos que son independientemente halógeno, OH, SH, heterocicloalquilo, heterocicloalquilalquilo, cicloalquilo $C_3$-

$C_7$, alcoxi, $NH_2$, NH(alquilo), N(alquil)(alquilo), -O-alcanoilo, alquilo, haloalquilo, carboxaldehido o haloalcoxi, o

$R_6$, $R_7$ y el nitrogeno al cual se acoplan forman un anillo morfolinilo, pirrolidinilo, tiomorfolinilo, tiomorfolinilo S-oxido, tiomorfolinilo S,S-dióxido, piperidinilo, pirrolidinilo o piperazinilo que opcionalmente se sustituye con 1 o 2 grupos que son independientemente alquilo $C_1$-$C_4$, alcoxicarbonilo, alcoxi $C_1$-$C_4$, hidroxilo, hidroxialquilo, dihidroxialquilo o halógeno,

R, en cada aparicion, es independientemente hidrogeno o alquilo $C_1$-$C_6$ opcionalmente sustituido con 1 o 2 grupos que son independientemente OH, SH, halógeno, amino, monoalquilamino, dialquilamino o cicloalquilo $C_3$-$C_6$,

$R_{30}$ es alquilo $C_1$-$C_6$ opcionalmente sustituido con 1 ó 2 grupos que son independientemente OH, SH, halogeno, amino, monoalquilamino, dialquilamino o cicloalquilo $C_3$-$C_6$,

cada $R_8$ es independientemente hidrogeno, alquilo, alcanoilo, arilalquilo y arilalcanoilo, en el que cada uno de los anteriormente mencionados se sustituye opcionalmente con 1, 2, 3, 4 o 5 grupos que son independientemente alquilo, alcoxi, alcoxicarbonilo, halógeno o haloalquilo,

cada $R_9$ es hidrogeno, alquilo, alcanoilo, arilalquilo, cicloalquilo,

cicloalquilalquilo, alquenilo, heteroarilo, aminoalquilo, monoalquilaminoalquilo, dialquilaminoalquilo, arilalcanoilo, $-SO_2$-fenilo y arilo, en el que cada uno de los anteriormente mencionados se sustituye opcionalmente con 1, 2, 3, 4 o 5 grupos que son independientemente alquilo, alcoxi, alcoxicarbonilo, halógeno o haloalquilo,

$R_3$ es H, halogeno, alcoxicarbonilo, arilalcoxicarbonilo, ariloxicarbonilo, arilalquilo, $-OC(O)NH(CH_2)_n$arilo, arilalcoxi, $-OC(O)N(alquil)(CH_2)_n$arilo, ariloxi, ariltio, tioalcoxi, ariltioalcoxi, alquenilo, $-NR_6R_7$, $NR_6R_7$-alquil($C_1$-$C_6$) o alquilo, en el que

la porcion arilo del arilalcoxicarbonilo, ariloxicarbonilo, arilalquilo, $-OC(O)NH(CH_2)_n$arilo, arilalcoxi, $-OC(O)N(alquil)(CH_2)_n$arilo y ariltioalcoxi no está sustituida o esta sustituida con 1, 2, 3, 4 o 5 grupos que son independientemente halogeno, alcoxi, alquilo, haloalquilo o haloalcoxi,

en la que n es 0, 1, 2, 3, 4, 5 o 6, o

$R_4$ es hidrógeno o $R_4$ es alquilo no sustituido o sustituido con uno o dos grupos que son independientemente $CO_2R$, $-CO_2$-alquil($C_1$-$C_6$), $-C(O)NR_6R_7$, $-C(O)R_6$, $-N(R_{30})C(O)NR_{16}R_{17}$, $-N(R_{30})C(O)$-alcoxi($C_1$-$C_6$) o $-NR_6R_7$, arilalcoxi, arilalquilo, heteroarilo, heteroarilalquilo, hidroxialquilo, dihidroxialquilo, haloalquilo, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, $-NR_6R_7$, alcoxi, carboxaldehido, $C(O)NR_6R_7$, $CO_2R$, alcoxialquilo o alcoxialcoxi, en los que las porciones heteroarilo o arilo de los anteriormente mencionados no se sustituyen o se sustituyen con 1, 2, 3, 4 o 5 grupos

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que son independientemente halogeno, hidroxi, alcoxi, alquilo, $-CO_2$-alquil($C_1$-$C_6$), $-CONR_6R_7$, $NR_6R_7$, $R_6R_7N$-alquil($C_1$-$C_6$)-, nitro, haloalquilo o haloalcoxi, y

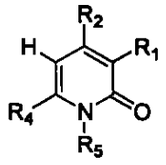
$R_5$ es H, arilo, arilalquilo, ariltioalquilo, alquilo opcionalmente sustituido con 1, 2 o 3 grupos que son independientemente arilalcoxicarbonilo, $-NR_8R_9$, halógeno, $-C(O)NR_8R_9$, alcoxicarbonilo, cicloalquilo $C_3$-$C_7$ o alcanoilo, alcoxi, alcoxialquilo opcionalmente sustituido con un grupo trimetilsililo, amino, alcoxicarbonilo, hidroxialquilo, dihidroxialquilo, alquinilo, $-SO_2$-alquilo, alcoxi opcionalmente sustituido con un grupo trimetilsililo, heterocicloalquilalquilo, cicloalquilo, cicloalquilalquilo, -alquil-S-arilo, -alquil-$SO_2$-arilo, heteroarilaquilo, heterocicloalquilo, heteroarilo o alquenilo opcionalmente sustituido con alcoxicarbonilo, en los que

cada uno de los anteriormente mencionados no esta sustituido o está sustituido con 1, 2, 3, 4 o 5 grupos que son independientemente alquilo, halógeno, alcoxi, hidroxialquilo, dihidroxialquilo, arilalcoxi, tioalcoxi, alcoxicarbonilo, arilalcoxicarbonilo, $CO_2R$, CN, OH, hidroxialquilo, dihidroxialquilo, amidino-oxima, $-NR_6R_7$, $-NR_8R_9$, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, carboxaldehido, $SO_2$alquilo, $-SO_2H$, $-SO_2NR_6R_7$, alcanoilo en el que la porción alquilo está opcionalmente sustituida con OH, halógeno o alcoxi, $-C(O)NR_6R_7$, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$ amidino, haloalquilo, -(alquilo $C_1$-$C_4$)-$NR_{15}C(O)NR_{16}R_{17}$, -(alquilo $C_1$-$C_4$)-$NR_{15}C(O)R_{18}$, $-O-CH_2-O$, $-O-CH_2CH_2-O$- o haloalcoxi, en la que

$R_{15}$ es H o alquilo $C_1$-$C_6$, y

$R_{18}$ es alquilo $C_1$-$C_6$ opcionalmente sustituido con -O-(alcanoilo $C_2$-$C_6$, hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-C6 alquilo, alcoxi $C_1$-$C_6$, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, aminoalquilo $C_1$-$C_6$, mono o dialquilaminoalquilo $C_1$-$C_6$

2 Un compuesto de acuerdo con la reivindicacion 1 de la formula




o una sal farmacéuticamente aceptable del mismo, en la que

$R_1$ es H, halogeno, alquilo, carboxaldehido, hidroxialquilo, dihidroxialquilo, arilalcoxi, arilalquilo, alquenilo, alquinilo, arilalquinilo, CN, alcanoilo, alcoxi, alcoxialquilo, haloalquilo, carboxilo o arilalcanoilo,

en la que la porcion arilo del arilalcoxi, arilalquilo y arilalcanoilo no esta sustituida o está sustituida con 1, 2, 3, 4 ó 5 grupos que son independientemente halógeno, alquilo $C_1$-$C_4$, nitro, CN, haloalquilo, haloalcoxi o $CO_2R$,

en la que la porcion alquilo de los grupos alquilo, hidroxialquilo, dihidroxialquilo, arilalcoxi, arilalquilo, alcanoilo, alcoxi, alcoxialquilo y arilalcanoilo no se sustituye o se sustituye con 1, 2 o 3 grupos que son independientemente halogeno, alcoxi $C_1$-$C_4$, alcoxi $C_1$-$C_4$ carbonilo o ciclopropilo,

$R_2$ es H, OH, halogeno, -$OSO_2$-alquilo ($C_1$-$C_6$), -$OSO_2$-arilo, arilalcoxi, ariloxi, ariltioalcoxi, arilalquinilo, alcoxi, feniloxialquil($C_1$-$C_6$),

$-OC(O)NH(CH_2)_n$arilo, $-OC(O)N$(alquil)$(CH_2)_n$arilo, alquilo, alquinilo, alcoxialcoxi, dialquilamino, heteroarilo, heterocicloalquilo, ariloxialquilo o $CO_2R$, en el que

cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2, 3, 4 ó 5 grupos que son independientemente halógeno, $-NR_6R_7$, haloalquilo, haloalcoxi, alquilo, heteroarilo, heteroarilalquilo, -alquil$(C_1-C_4)$-$C(O)NR_6R_7$, $R_6R_7N$-(alquilo $C_1-C_6$)-, $-C(O)NR_6R_7$, -(alquilo $C_1-C_4$)-$NRC(O)NR_{16}R_{17}$, CN, hidroxialquilo, dihidroxialquilo, $-OC(O)NR_6R_7$ o -alquil$(C_1-C_6)$-$N(R)-CO_2R_{30}$, en los que

$R_{16}$ y $R_{17}$ son independientemente H o alquilo $C_1-C_6$, o

$R_{16}$, $R_{17}$ y el nitrogeno al que estan acoplados forman un anillo morfolinilo,

$R_6$ y $R_7$ son independientemente, en cada aparición, H, alquilo, hidroxialquilo, dihidroxialquilo, alcoxi, alcoxialquilo, alcanoilo, arilalquilo, arilalcoxi, arilalcoxicarbonilo o arilalcanoilo, en los que cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2 ó 3 grupos que son independientemente halógeno, alcoxi, alquilo, OH, SH, carboxaldehido, haloalquilo o haloalcoxi, o

$R_6$, $R_7$ y el nitrogeno al cual se acoplan forman un anillo morfolinilo, tiomorfclinilo, tiomorfolinilo S-óxido, tiomorfclinilo S,S-dioxido, piperidinilo, pirrolidinilo o piperazinilo opcionalmente

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sustituido con 1 ó 2 grupos que son independientemente alquilo $C_1$-$C_4$, alcoxicarbonilo, hidroxilo, hidroxialquilo, dihidroxialquilo o halogeno,

n es 0, 1, 2, 3, 4, 5 ó 6,

R, en cada aparicion, es independientemente H o alquilo $C_1$-$C_6$ opcionalmente sustituido con 1 o 2 grupos que son independientemente OH, SH, halogeno, amino, monoalquilamino, dialquilamino o cicloalquilo $C_3$-$C_6$,

$R_{30}$ es alquilo $C_1$-$C_6$ opcionalmente sustituido con 1 ó 2 grupos que son independientemente OH, SH, halógeno, amino, monoalquilamino, dialquilamino o cicloalquilo $C_3$-$C_6$,

$R_4$ es H, alquilo opcionalmente sustituido con uno o dos grupos que son independientemente $CO_2R$, -$CO_2$alquilo, $-C(O)NR_6R_7$, $-C(O)R_6$, $-N(R_{30})C(O)NR_{16}R_{17}$, $-N(R_{30})C(O)$-alcoxi$(C_1$-$C_6)$ o $-NR_6R_7$, arilalcoxi, heteroarilo, arilalquilo, hidroxialquilo, dihidroxialquilo, haloalquilo, $-NR_6R_7$, $-C(O)NR_6R_7$, alcoxi, alcoxialquilo o alcoxialcoxi, en los que

las porciones heteroarilo o arilo de los anteriormente mencionados no se sustituyen o se sustituyen con 1, 2, 3, 4 o 5 grupos que son independientemente halogeno, hidroxi, alcoxi, alquilo, $-CO_2$-alquil$(C_1$-$C_6)$, $-CONR_6R_7$, $-NR_6R_7$, $R_6R_7N$-alquil$(C_1$-$C_6)$-, nitro, haloalquilo o haloalcoxi, y

$R_5$ es H, arilalquilo, alquilo opcionalmente sustituido con 1, 2 ó 3 grupos que son independientemente arilalcoxicarbonilo, $-NR_8R_9$, halogeno, $-C(O)NF_8R_9$, alcoxicarbonilo o alcanoilo,

alcoxialquilo opcionalmente sustituido con un grupo trimetilsililo, alcoxicarbonilo, amino, hidroxialquilo, dihidroxialquilo, alquenilo opcionalmente sustituido con alcoxicarbonilo, alquinilo, $-SO_2$-alquilo, arilo, alcoxi opcionalmente sustituido con un grupo trimetilsililo, heterocicloalquilalquilo, heteroarilalquilo, heterocicloalquilc o heteroarilo, en el que

cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2, 3, 4 ó 5 grupos que son independientemente alquilo, halogeno, alcoxi, arilalcoxi, hidroxialquilo, dihidroxialquilo, tioalcoxi, $-SO_2$alquilo, alcoxicarbonilo, arilalcoxicarbonilo, $CO_2R$, CN, OH, amidino-oxima $NR_8R_9$, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, $-C(O)NR_6R_7$, amidino, hidroxialquilo, dihidroxialquilo, carboxaldehido, $-NR_6R_7$, haloalquilo, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$, -(alquilo $C_1$-$C_4$)-$CO_2R$, -(alquilo $C_1$-$C_4$)-alcoxi $C_1$-$C_6$ carbonilo, -(alquilo $C_1$-$C_4$)-CN, -(alquilo $C_1$-$C_4$)-$NR_{15}C(O)R_{18}$, $-O-CH_2-O-$, $-O-CH_2CH_2-O-$, fenilo o haloalcoxi

$R_8$ es hidrógeno, alquilo, alcanoilo, arilalquilo y arilalcanoilo,

$R_9$ es alquilo, alcanoilo, arilalquilo, heteroarilo, aminoalquilo, monoalquilaminoalquilo, dialquilaminoalquilo y arila canoilo

3 Un compuesto de acuerdo con la reivindicación 2 en el que

$R_1$ es H, halogeno, alquilo opcionalmente sustituido con alcoxi $C_1$-$C_4$ carbonilo, carboxaldehido, hidroxialquilo, dihidroxialquilo, fenilalcoxi($C_1$-$C_6$),

fenilalquil($C_1$-$C_6$), CN, alcanoilo, alcoxi, alquinilo $C_2$-$C_4$, alquenilo $C_2$-$C_6$ opcionalmente sustituido con alcoxi $C_1$-$C_4$ carbonilo, alcoxialquilo, haloalquilo o fenilalcanoil($C_1$-$C_6$),

en la que los grupos fenilo no se sustituyen o se sustituyen con 1, 2, 3, 4 o 5 grupos que son independientemente halogeno, alquilo $C_1$-$C_4$, alcoxi $C_1$-$C_4$, nitro, CN, $CF_3$, $OCF_3$ o $CO_2R$,

en la que los grupos alquilo no se sustituyen o se sustituyen con 1, 2 ó 3 grupos que son independientemente halogeno, metoxi o etoxi,

$R_2$ es OH, fenilalcoxi($C_1$-$C_6$), feniloxi, feniloxialquil($C_1$-$C_6$), feniltioalcoxi ($C_1$-$C_4$), alcoxi $C_1$-$C_8$, alcoxialcoxi, -O-$SO_2$fenilo, alquinilo, fenilalquinilo ($C_2$-$C_4$), alquilo, -OC(O)NH$(CH_2)_n$fenilo, -OC(O)N(alquil)$(CH_2)_n$fenilo, dialquilamino, piridilo, pirimidilo, piridazilo, pirazolilo, imidazolilo, pirrolilo, tetrahidroquinolinilo, tetrahidroisoquinolinilo, tetrazolilo, pirazinilo, bencimidazolilo, triazinilo, tetrahidrofurilo, piperidinilo, hexahidropirimidinilo, tiazolilo, tienilo o $CO_2R$, en el que

n es 0, 1, 2, 3, 4, 5 ó 6,

cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2, 3, 4 o 5 grupos que son independientemente halogeno, $NR_6R_7$, haloalquilo, haloalcoxi, hidroxialquilo, dihidroxialquilo, alquilo, fenilo, piridilo, piperidinilo, piperazinilo, -alquil($C_1$-$C_6$)-N(R)-$CO_2R_{30}$, $R_6R_7$N-(alquilo $C_1$-$C_6$)-, -C(O)$NR_6R_7$, -alquil($C_1$-$C_4$)-C(O)$NR_6R_7$, -(alquilo $C_1$-$C_4$)-NRC(O)$NR_{16}R_{17}$, o -OC(O)$NR_6R_7$, en los que

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$R_6$ y $R_7$ son independientemente, en cada aparicion, H, alquilo, hidroxi ($C_1$-$C_4$) alquilo, dihidroxi ($C_1$-$C_4$) alquilo, alcoxi ($C_1$-$C_4$), alcoxi ($C_1$-$C_4$) alquilo ($C_1$-$C_4$), alcanoilo ($C_1$-$C_4$), fenilalquilo ($C_1$-$C_4$), fenilalcoxi ($C_1$-$C_4$), fenilalcoxi ($C_1$-$C_4$) carbonilo o fenilalcanoilo ($C_1$-$C_4$), en los que cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2 o 3 grupos que son independientemente halogeno, OH, SH, cicloalquilo $C_3$-$C_6$, alcoxi ($C_1$-$C_4$), alquilo ($C_1$-$C_4$), $CF_3$, carboxaldehido, $NH_2$, NHalquil($C_1$-$C_6$), Nalquil($C_1$-$C_6$) alquil($C_1$-$C_6$), $OCF_3$, o

$R_6$, $R_7$ y el nitrogeno al cual se acoplan forman un anillo morfolinilo, tiomorfolinilo, piperidinilo, pirrolidinilo o piperazinilo opcionalmente sustituido con 1 o 2 grupos que son independientemente alquilo $C_1$-$C_4$, hidroxi, hidroxialquilo $C_1$-$C_4$, dihidroxi $C_1$-$C_4$ alquilo, alcoxi $C_1$-$C_4$ carbonilo o halogeno, y

$R_4$ es H, alquilo opcionalmente sustituido con uno o dos grupos que son independientemente $CO_2R$, -$CO_2$alquilo, -C(O)$NR_6R_7$, -C(O)$R_6$, -N($R_{30}$)C(O)$NR_{16}R_{17}$, -N($R_{30}$)C(O)-alcoxi($C_1$-$C_6$), o -$NR_6R_7$, -C(O)$NR_6R_7$ fenilalcoxi($C_1$-$C_6$), fenilalquil($C_1$-$C_6$) hidroxialquilo, dihidroxialquilo, haloalquilo, alcoxi, alcoxialquilo o alcoxialcoxi, en los que

los grupos fenilo no se sustituyen o se sustituyen con 1, 2, 3, 4 o 5 grupos que son

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independientemente halógeno, hidroxi, alcoxi, alquilo, nitro, $CF_3$, $OCF_3$,

$R_5$ es fenilalquil($C_1$-$C_6$), alquil($C_1$-$C_6$) opcionalmente sustituido con 1, 2, 3, 4 o 5 grupos que son independientemente fenilalcoxi $C_1$-$C_4$ carbonilo, $-NR_8R_9$, halógeno, $-C(O)NR_8R_9$, alcoxicarbonilo o alcanoilo, fenilo, alcoxi, alquinilo $C_2$-$C_6$, alquenilo $C_2$-$C_6$ opcionalmente sustituido con alcoxicarbonilo, indolilo, quinolinilo, isoquinolinilo, isoindolilo, dihidroindolilo, pirazolilo, imidazolilo, dihidroisoindolilo, indolon-2-ilo, indazolilo, benzimidazolilo, piridilo, imidazolidina diona, pirazolil(alquilo $C_1$-$C_6$), imidazolil(alquilo $C_1$-$C_6$), piperidinilalquil($C_1$-$C_6$), pirrolidinilalquil($C_1$-$C_6$), imidazolidinilalquil($C_1$-$C_6$), tetrahidroisoquinolinilalquil($C_1$-$C_6$), 1H-indazolilalquil($C_1$-$C_6$), dihidroindolon-2-il(alquilo $C_1$-$C_6$), indolinil(alquilo $C_1$-$C_6$), dihidrobenzimidazolil(alquilo $C_1$-$C_6$) o dihidrobenzoimidazolonil(alquilo $C_1$-$C_6$), piridilalquilo ($C_1$-$C_6$), piridazinilalquilo ($C_1$-$C_6$), pirimidinilalquilo ($C_1$-$C_6$), pirazinilalquilo ($C_1$-$C_6$), tetrahidrofurilalquil($C_1$-$C_6$), naftilalquil($C_1$-$C_6$), morfolinilalquilo ($C_1$-$C_6$), tetrahidrofurilalquilo ($C_1$-$C_6$), tienilalquilo ($C_1$-$C_6$), piperazinilalquilo ($C_1$-$C_6$), indolilalquilo ($C_1$-$C_6$), quinolinilalquilo ($C_1$-$C_6$), isoquinolinilalquilo ($C_1$-$C_6$), isoindolilalquilo ($C_1$-$C_6$), dihidroindolilalquilo ($C_1$-$C_6$), pirazolilalquilo ($C_1$-$C_4$), imidazolilalquilo ($C_1$-$C_4$), dihidroisoindolilalquilo ($C_1$-$C_6$), indoon-2-ilalquilo ($C_1$-$C_6$), indolon-2-ilalquilo ($C_1$-$C_6$) o morfolinilalquilo $C_1$-$C_6$, en los que

cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2, 3, 4 o 5 grupos que son independientemente alquilo $C_1$-$C_6$, halogeno, alcoxi $C_1$-$C_6$, fenilalcoxi $C_1$-$C_6$, tioalcoxi $C_1$-$C_6$, alcoxi $C_1$-$C_6$ carbonilo, $CO_2R$, CN, $-SO_2$alquil($C_1$-$C_6$), amidino-oxima, $NR_8R_9$, $-NR_6R_7$, $NR_6R_7$ alquilo $C_1$-$C_6$, $-C(O)NR_6R_7$, $-$alquil($C_1$-$C_4$)$-C(O)NR_6R_7$, amidino, haloalquilo $C_1$-$C_4$, hidroxialquilo $C_1$-$C_6$, dihidroxi $C_1$-$C_6$ alquilo o haloalcoxi $C_1$-$C_4$, en los que

$R_8$ es hidrógeno, alquilo $C_1$-$C_6$, alcanoilo $C_1$-$C_6$, fenilalquilo $C_1$-$C_6$ y fenilalcanoilo $C_1$-$C_6$, y

$R_9$ es aminoalquilo, monoalquilo $C_1$-$C_6$ aminoalquilo $C_1$-$C_6$, dialquilo $C_1$-$C_6$ aminoalquilo $C_1$-$C_6$, alquilo $C_1$-$C_6$ alcanoilo $C_1$-$C_6$, fenilalquilo $C_1$-C6, indazolilo y fenilalcanoilo $C_1$-C6

4 Un compuesto de acuerdo con la reivindicacion 3 en el que

$R_1$ es H, halogeno, alquilo $C_1$-$C_4$ opcionalmente sustituido con alcoxi $C_1$-$C_4$ carbonilo, alquenilo $C_2$-$C_4$ opcionalmente sustituido con alcoxi $C_1$-$C_4$ carbonilo, alquinilo $C_2$-$C_4$ o carboxaldehido,

$R_2$ es benciloxi, OH, feniloxi, feniloxialquil($C_1$-$C_6$), feniltioalcoxi ($C_1$-$C_4$) o piridilo, en el que cada uno de los anteriormente mencionados se sustituye opcionalmente con 1, 2, 3, 4 o 5 grupos que son independientemente halógeno, $-$alquil($C_1$-$C_6$)$-N(R)-CO_2R_{30}$, $NR_6R_7$, $-$alquil($C_1$-$C_4$)$-C(O)NR_6R_7$, haloalquilo ($C_1$-$C_4$), $-C(O)NR_6R_7$, $-$(alquilo $C_1$-$C_4$)$-NRC(O)NR_{16}R_{17}$, haloalcoxi ($C_1$-$C_4$), hidroxialquilo, dihidroxi $C_1$-$C_6$ alquilo, alquilo ($C_1$-$C_6$), piridilo o $R_6R_7N-$(alquilo $C_1$-$C_6$)-

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5 Un compuesto de acuerdo con la reivindicación 4 en el que

$R_5$ es indolilo, piridilo, piridazinilo, pirimidinilo, ndazolilo, tetrahidroquinolilo, tetrahidroisoquino_ilo, pirazolilo, imidazolilo, furanilo, quinolinilo, isoquinolinilo, isoindolilo, dihidroindolilo, dihidroisoindolilo, indolon-2-ilo o pirazinilo, cada uno de los cuales no se sustituye o se sustituye con 1, 2, 3, 4 o 5 grupos que son independientemente alquilo $C_1$-$C_4$, halogeno, $CF_3$, $OCF_3$, $-CO_2CH_3$, hidroxi $C_1$-$C_4$ alquilo, dihidroxialquilo, alcoxi $C_1$-$C_4$, $-CO_2$(alquilo $C_1$-$C_5$), benciloxi, $-NR_6R_7$, -alquil($C_1$-$C_4$)-C(O)$NR_6R_7$, $-NR_8R_9$, $NR_6R_7$-(alquilo $C_1$-$C_4$), $-C(O)NR_6R_7$, o amidino-oxima, en los que

$R_6$ y $R_7$ son independientemente, en cada aparición, H, alquilo $C_1$-$C_4$, hidroxi $C_1$-$C_4$ alquilo, dihidroxi $C_1$-$C_4$ alquilo, alcoxi $C_1$-$C_4$, alcoxi $C_1$-$C_4$ alquilo $C_1$-$C_4$, alcanoilo $C_1$-$C_4$, fenilalquilo $C_1$-$C_4$, fenilalcoxi $C_1$-$C_4$ o fenilalcanoilo $C_1$-$C_4$, en los que cada uno no se sustituye o se sustituye con 1, 2 ó 3 grupos que son independientemente halogeno, OH, SH, cicloalquilo $C_3$-$C_6$, arilo, alcoxi $C_1$-$C_4$, alquilo $C_1$-$C_4$, OH, $CF_3$ u $OCF_3$, o

$R_6$, $R_7$ y el nitrogeno al cual se acoplan forman un anillo morfolinilo, tiomorfolinilo, pirrolidinilo o piperazinilo opcionalmente sustituido con 1 ó 2 grupos que son independientemente alquilo $C_1$-$C_4$, hidroxi, hidroxialquilo $C_1$-$C_4$, dihidroxi $C_1$-$C_4$ alquilo o halógeno

6 Un compuesto de acuerdo con la reivindicacion 5 en el que

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$R_5$ es incolilo, piridilo, pirimidinilo, pirazolilo, furanilo, indazolilo, dihidroindolilo, dihidroisoindolilo, indolon-2-il o pirazinilo, cada uno de los cuales no se sustituye o se sustituye con 1, 2, 3 o 4 grupos que son independientemente alquilo $C_1$-$C_4$, halogeno, $CF_3$, $OCF_3$, $-CO_2CH_3$, hidroxi $C_1$-$C_4$ alquilo, dihidroxi $C_1$-$C_4$ alquilo, alcoxi $C_1$-$C_4$, $-CO_2$(alquilo $C_1$-$C_5$), benciloxi, $-C(O)NR_6R_7$, $-NR_8R_9$, -alquil($C_1$-$C_4$)$-C(O)NR_6R_7$, $-NR_6R_7$, $NR_6R_7$-(alquilo $C_1$-$C_4$)- y amidino-oxima

7 Un compuesto de acuerdo con la reivindicacion 6 en el que

$R_5$ es incolilo, piridilo, pirimidinilo, dihidroindolilo, dihidroisoindolilo, pirazolilo o pirazinilo, cada uno de los cuales no se sustituye o se sustituye con 1, 2, 3 ó 4 grupos que son independientemente alquilo $C_1$-$C_4$, halogeno, $CF_3$, $OCF_3$, $-CO_2CH_3$, hidroxi $C_1$-$C_4$ alquilo, dihidroxi $C_1$-$C_4$ alquilo, alcoxi $C_1$-$C_4$, $-CO_2$(alquilo $C_1$-$C_5$), benciloxi, $-C(O)NR_6R_7$, $-NR_8R_9$, $-$alquil($C_1$-$C_4$)$-C(O)NR_6R_7$, $-NR_6R_7$, $NR_6R_7$-(alquilo $C_1$-$C_4$)- o amidino-oxima, en los que

$R_6$ y $R_7$ son independientemente, en cada aparición, H, alquilo $C_1$-$C_4$, hidroxi $C_1$-$C_4$ alquilo, dihidroxi $C_1$-$C_4$ alquilo, alcoxi $C_1$-$C_4$, alcanoilo $C_1$-$C_4$, alcoxi $C_1$-$C_4$ alquilo $C_1$-$C_4$ cada uno de los cuales se sustituye opcionalmente con 1, 2 ó 3 grupos que son independientemente halogeno, OH, SH, cicloalquilo $C_3$-$C_6$, alcoxi $C_1$-$C_4$, alquilo $C_1$-$C_4$, OH, $CF_3$ u $OCF_3$

8 Un compuesto de acuerdo con la reivindicacion 7 en el que

$R_5$ es indolilo, piridilo, pirimidinilo, dihidroindolilo, dihidroisoindolilo, pirazolilo o

pirazinilo, cada uno de los cuales no se sustituye o se sustituye con 1, 2 o 3 grupos que son independientemente alquilo $C_1$-$C_4$, halógeno, $CF_3$, $OCF_3$, hidroxi $C_1$-$C_4$ alquilo, dihidroxi $C_1$-$C_4$ alquilo, alcoxi $C_1$-$C_4$, $-C(O)NR_6R_7$, $-alquil(C_1-C_4)-C(O)NR_6R_7$, $NR_8R_9$, $-NR_6R_7$ o $NR_6R_7$-(alquilo $C_1$-$C_4$), en los que

$R_6$ y R son independientemente, en cada aparición, H, alquilo $C_1$-$C_4$, hidroxi $C_1$-$C_4$ alquilo, dihidroxi $C_1$-$C_4$ alquilo, alcanoilo $C_1$-$C_4$ o alcoxi $C_1$-$C_4$ cada uno de los cuales se sustituye opcionalmente con 1, 2 o 3 grupos que son independientemente halogeno, OH, SH, cicloalquilo $C_3$-$C_6$, alcoxi $C_1$-$C_4$, alquilo $C_1$-$C_4$, OH, $CF_3$ u $OCF_3$.

9 Un compuesto de acuerdo con la reivindicacion 4 en el que

$R_5$ es fenilo, fenilalquil($C_1$-$C_6$) o alquil($C_1$-$C_6$), en el que

cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2, 3, 4 o 5 grupos que son independientemente alquilo, halogeno, alcoxi, benciloxi, hidroxialquilo, dihidroxialquilo, tioalcoxi, $-CO_2$(alquilo $C_1$-$C_5$), $CO_2R$, CN, amidino-oxima, $-NR_8R_9$, $-NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, $-C(O)NR_6R_7$, $-alquil(C_1-C_4)-C(O)NR_6R_7$, amidino, $CF_3$ u $OCF_3$,

$R_8$ es hidrogeno, alquilo $C_1$-$C_6$, alcanoilo $C_1$-$C_6$, fenilalquilo $C_1$-$C_6$ y fenilalcanoilo $C_1$-$C_6$, y

$R_9$ es aminoalquilo, monoalquilo $C_1$-$C_6$ aminoalquilo $C_1$-$C_6$, dialquilo $C_1$-$C_6$ aminoalquilo $C_1$-$C_6$, alquilo $C_1$-$C_6$ alcanoilo $C_1$-$C_6$, fenilalquilo $C_1$-C4, indazolilo y fenilalcanoilo $C_1$-C4

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10 Un compuesto de acuerdo con la reivindicacion 4 en el que

$R_5$ es fenilo, fenilalquil($C_1$-$C_6$), que no se sustituye o se sustituye con 1, 2, 3, 4 ó 5 grupos que son independientemente alquilo, halógeno, alcoxi, benciloxi, tioalcoxi, -$CO_2$(alquilo $C_1$-$C_5$), $CO_2R$, CN, amidinooxima, -$NR_8R_9$, -$NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, -C(O)$NR_6R_7$ amidino, $CF_3$ u $OCF_3$, en los que

$R_6$ y $R_7$ son independientemente, en cada aparicion, H, alquilo $C_1$-$C_4$, hidroxi $C_1$-$C_4$ alquilo, dihidroxi $C_1$-$C_4$ alquilo, alcoxi $C_1$-$C_4$, alcoxi $C_1$-$C_4$ alquilo $C_1$-$C_4$, alcanoilo $C_1$-$C_4$, fenilalquilo $C_1$-$C_4$, fenilalcoxi $C_1$-$C_4$ o fenilalcanoilo $C_1$-$C_4$, en el que cada uno no está sustituido o esta sustituido con 1, 2 o 3 grupos que son independientemente halogeno, OH, SH, cicloalquilo $C_3$-$C_6$, alcoxi $C_1$-$C_4$, alquilo $C_1$-$C_4$, $CF_3$ u $OCF_3$, o

$R_6$, $R_7$ y el nitrogeno al cual se acoplan forman un arillo morfolinilo, tiomorfolinilo o piperazinilo opcionalmente sustituido con 1 o 2 grupos que son independientemente alquilo $C_1$-$C_4$, hidroxi, hidroxialquilo $C_1$-$C_4$, dihidroxi $C_1$-$C_4$ alquilo o halogeno,

$R_8$ es hidrógeno, alquilo $C_1$-$C_6$, alcanoilo $C_1$-$C_6$, fenilalquilo $C_1$-$C_6$ y fenilalcanoilo $C_1$-$C_6$, y

$R_9$ es aminoalquilo, monoalquilo $C_1$-$C_6$ aminoalquilo $C_1$-$C_6$, dialquilo $C_1$-$C_6$ aminoalquilo $C_1$-$C_6$, alquilo $C_1$-$C_6$ alcanoilo $C_1$-$C_6$, fenilalquilo $C_1$-C4, indazolilo y fenilalcanoilo $C_1$-C4

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11 Un compuesto de acuerdo con la reivindicación 10 en el que

$R_5$ es fenilo, bencilo o fenetilo, en el que cada uno se sustituye opcionalmente con 1, 2, 3, 4 ó 5 grupos que son independientemente alquilo $C_1$-$C_6$, -$NR_6R_7$, -$C(O)NR_6R_7$ -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$, -$NR_8R_9$, halogeno, alcoxi $C_1$-$C_6$, $CO_2R$, -(alquilo $C_1$-$C_4$)-$CO_2R$, tioalcoxi $C_1$-$C_6$, amidino-oxima, alcoxi $C_1$-$C_6$ carbonilo, -(alquilo $C_1$-$C_4$)-alcoxi $C_1$-$C_6$ carbonilo, hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-$C_6$ alquilo, -(alquilo $C_1$-$C_4$)-CN, CN, fenilalcoxi $C_1$-$C_6$, OH, haloalquilo $C_1$-$C_4$, haloalcoxi $C_1$-$C_4$, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, -(alquilo $C_1$-$C_4$)-$NR_{15}C(O)R_{18}$, amidino-oxima, -$SO_2$(alquilo $C_1$-$C_6$), -O-$CH_2$-O-, -O-$CH_2CH_2$-O-, fenilalcoxi $C_1$-$C_4$ o fenilo, en los que

$R_6$ y $R_7$ son independientemente, en cada aparición, H, alquilo $C_1$-$C_4$, hidroxi $C_1$-$C_4$ alquilo, dihidroxi $C_1$-$C_4$ alquilo, alcanoilo $C_1$-$C_4$ o alcoxi $C_1$ $C_4$ cada uno de los cuales se sustituye opcionalmente con 1, 2 o 3 grupos que son independientemente halogeno, OH, SH, cicloalquilo $C_3$-$C_6$, alcoxi $C_1$-$C_4$, alquilo $C_1$-$C_4$, OH, $CF_3$ u $OCF_3$

12 Un compuesto de acuerdo con la reivindicacion 11 en el que

$R_5$ es fenilo, bencilo o fenetilo, cada uno de los cuales no se sustituye o se sustituye con 1, 2, 3, 4 o 5 grupos que son independientemente CN, halogeno, alcoxi $C_1$-$C_4$, $CF_3$, $OCF_3$, alquilo $C_1$-$C_4$, -$NR_8R_9$, -$NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)- o -$C(O)NR_6R_7$, en los que

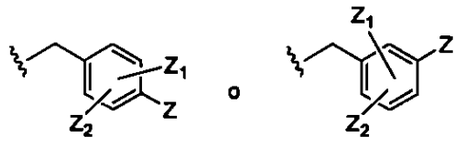
$R_6$ y $R_7$ son independientemente, en cada aparicion, H, alquilo $C_1$-$C_4$, hidroxi $C_1$-$C_4$ alquilo, dihidroxi $C_1$-$C_4$ alquilo, alcanoilo $C_1$-$C_4$

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o alcoxı $C_1$ $C_4$ cada uno de los cuales se sustıtuye opcıonalmente con 1, 2 o 3 grupos que son ındependıentemente halogeno, OH, SH, cıcloalquılo $C_3$-$C_6$, alcoxı $C_1$-$C_4$, alquılo $C_1$-$C_4$, OH, $CF_3$ u $OCF_3$

13 Un compuesto de acuerdo con la reıvındıcacıón 4 en el que

el grupo $R_5$ es de la fórmula



en la que

$Z_1$ y $Z_2$ sor ındependıentemente H, halogeno, alquılo $C_1$-$C_4$ o $CO_2R$, y

Z es $-C(O)NR_6R_7$ $-alquıl(C_1-C_4)-C(O)NR_6R_7$, $-(alquılo\ C_1-C_4)-NR_{15}C(O)R_{18}$, $-NR_6R_7$, $R_6R_7N-(alquılo\ C_1-C_6)-$, $-NR_8R_9$, hıdroxı $C_1$-$C_6$ alquılo, dıhıdroxı $C_1$-$C_6$ alquılo, alquılo $C_1$-$C_6$, $CO_2R$ o halógeno, en el que

$R_6$ y $R_7$ en cada aparıcıon, son ındependıentemente H, OH, alquılo $C_1$-$C_6$, amınoalquılo $C_1$-$C_4$, NH(alquılo $C_1$-$C_6$)alquılo, N(alquılo $C_1$-$C_6$)(alquılo $C_1$-$C_6$) alquılo $C_1$-$C_6$, hıdroxı $C_1$-$C_6$ alquılo, dıhıdroxı $C_1$-$C_6$ alquılo, alcoxı $C_1$-$C_6$ alquılo $C_1$-$C_6$ o $-SO_2$(alquılo $C_1$-$C_6$), cada uno de los cuales se sustıtuye opcıonalmente con 1, 2 ó 3 grupos que son ındependıentemente halogeno, OH, SH, cıcloalquılo $C_3$-$C_6$, alcoxı $C_1$-$C_4$, alquılo $C_1$-$C_4$, OH, $CF_3$ u $OCF_3$,

o

$R_6$, $R_7$ y el nıtrogeno al cual se acoplan forman un anıllo pıperıdınılo, pırrolıdınılo, pıperazınılo, morfolınılo, tıomorfolınılo

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opcionalmente sustituido con 1 ó 2 grupos que son independientemente alquilo, hidroxi, hidroxialquilo $C_1$-$C_4$, dihidroxi $C_1$-$C_4$ alquilo o halogeno, y

$R_{18}$ es alquilo $C_1$-$C_6$ opcionalmente sustituido con -O-(alcanoilo $C_2$-$C_6$, hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-C4 alquilo, alcoxi $C_1$-$C_6$, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, aminoalquilo $C_1$-$C_6$, mono o dialquilaminoalquilo $C_1$-$C_6$

14 Un compuesto de acuerdo con la reivindicacion 4 en el que

$R_5$ es pirazolil(alquilo $C_1$-$C_6$), imidazolil(alquilo $C_1$-$C_6$), tienil(alquilo $C_1$-$C_6$), furanil(alquilo $C_1$-$C_6$), piperidinilalquil($C_1$-$C_6$), pirrolidinialquilil($C_1$-$C_6$), imidazolidinilalquil($C_1$-$C_6$), piperazinilalquil($C_1$-$C_6$), piridilalquil($C_1$-$C_6$), pirimidilalquil($C_1$-$C_6$), piridazilalquil($C_1$-$C_6$), pirazinilalquil($C_1$-$C_6$), isoquinolinilalquil($C_1$-$C_6$), tetrahidroisoquinolinilalquil($C_1$-$C_6$), indolilalquil($C_1$-$C_6$), 1H-indazolilalquil($C_1$-$C_6$), dihidroindolil(alquilo $C_1$-$C_6$), dihidroindolon-2-il(alquilo $C_1$-$C_6$), indolinil(alquilo $C_1$-$C_6$), dihidroisoindolil(alquilo $C_1$-$C_6$), dihidrobencimdazolil(alquilo $C_1$-$C_6$) o dihidrobenzoimidazolonil(alquilo $C_1$-$C_6$), en el que

cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2, 3, 4 ó 5 grupos que scn independientemente alquil($C_1$-$C_6$), halogeno, alcoxi($C_1$-$C_6$), hidroxi($C_1$-$C_6$)alquilo, dihidroxi $C_1$-$C_6$ alquilo, fenilalcoxi($C_1$-$C_6$), tioalcoxi($C_1$-$C_6$), alcoxi($C_1$-$C_6$)carbonilo, fenilalcoxi($C_1$-$C_6$)carbonilo, OH, $CO_2R$, CN, amidino-oxima, $-NR_8R_9$, $-NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, $-C(O)NR_6R_7$, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$

amidino, piperazinilo, morfolinilo, $-SO_2$ alquilo ($C_1$-$C_6$), $-SO_2NH_2$, $-SO_2NH$alquil($C_1$-$C_6$), $-SO_2N$alquil($C_1$-$C_6$) alquil($C_1$-$C_6$), haloalquil($C_1$-$C_4$), -(alquilo $C_1$-$C_4$)-$NR_{15}C(O)NR_{16}R_{17}$, -(alquilo $C_1$-$C_4$)-$NR_{15}C(O)R_{18}$, $-O-CH_2-O$, $-O-CH_2CH_2-O-$, o haloalcoxi($C_1$-$C_4$), en los que

$R_6$ y $R_7$ son independientemente, en cada aparición, H, alquil($C_1$-$C_6$), alcoxi($C_1$-$C_6$), alcoxi($C_1$-$C_6$)alquil($C_1$-$C_6$), alcoxi($C_1$-$C_6$)carbonilo, hidroxi($C_1$-$C_6$)alquilo, dihidrox $C_1$-$C_6$ alquilo, -alquil($C_1$-$C_4$)-$CO_2$-alquil($C_1$-$C_6$), alcanoil($C_1$-$C_6$), fenilalquil($C_1$-$C_6$), fenilalcoxi($C_1$-$C_6$) o fenilalcanoil($C_1$-$C_6$), en los que cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2 ó 3 grupos que son independientemente halogeno, alcoxi($C_1$-$C_4$), OH, SH, cicloalquilo $C_3$-$C_6$, $NH_2$, NH(alquilo $C_1$-$C_6$), N(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$), alquil($C_1$-$C_4$), $CF_3$ u $OCF_3$, o

$R_6$, $R_7$ y el nitrogeno al cual se acoplan forman un anillo morfolinilo, tiomorfolinilo, piperidinilo, pirrolidinilo o piperazinilo opcionalmente sustituido con 1 o 2 grupos que son independientemente alquilo $C_1$-$C_4$, hidroxi, hidroxialquilo $C_1$-$C_4$, dihidroxi $C_1$-$C_4$ alquilo o halogeno, y

$R_{18}$ es alquilo $C_1$-$C_6$ opcionalmente sustituico con -O-(alcanoilo $C_2$-$C_6$, hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-C6 alquilo, alcoxi $C_1$-$C_6$, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$,

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aminoalcuilo $C_1$-$C_6$, mono o dialquilaminoalquilo $C_1$-$C_6$

15 Un compuesto de acuerdo con la reivindicacion 14 en el que

$R_5$ es pirazolil(alquilo $C_1$-$C_6$), imidazolil(alquilo $C_1$-$C_6$), bencimidazolil(alquilo $C_1$-$C_6$), tienil(alquilo $C_1$-$C_6$), pirimidilalquil($C_1$-$C_6$), indolil(alquilo $C_1$-$C_6$), dihidroindolil(alquilo $C_1$-$C_6$), dihidroisoindolil(alquilo $C_1$-$C_6$), dihidroindolon-2-il(alquilo $C_1$-$C_6$), piridinil(alquilo $C_1$-$C_6$), piperazinil(alquilo $C_1$-$C_6$), o pirazinil(alquilo $C_1$-$C_6$) cada uno de los cuales se sustituye opcionalmente con 1, 2 ó 3 grupos que son independientemente alquilo $C_1$-$C_4$, hidroxi $C_1$-$C_4$ alquilo, dihidroxi $C_1$-$C_4$ alquilo, halógeno, $-C(O)NR_6R_7$, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$ alcoxi $C_1$-$C_6$ carbonilo, $-NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, haloalquilo, alcanoilo $C_1$-$C_6$,

$R_6$ y $R_7$, en cada aparicion, son independientemente H, alquilo $C_1$-$C_6$ opcionalmente sustituido con 1, 2 ó 3 grupos que son independientemente alcoxi $C_1$-$C_4$ carbonilo, halógeno, cicloalquilo $C_3$-$C_6$, OH, SH o alcoxi $C_1$-$C_4$

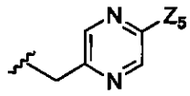
o

$R_6$, $R_7$ y el nitrogeno al cual se acoplan forman un anillo piperidinilo, pirrolidinilo, piperazinilo o morfolinilo opcionalmente sustituido con 1 ó 2 grupos que son independientemente alquilo, hidroxi, hidroxialquilc $C_1$-$C_4$, dihidroxi $C_1$-$C_4$ alquilo o halogeno

16 Un compuesto de acuerdo con la reivindicación 15 en el que

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$R_5$ es de la formula



en la que

$Z_5$ es alquilo $C_1$-$C_4$, hidroxi $C_1$-$C_4$ alquilo, dihidroxi $C_1$-$C_4$ alquilo, halógeno, $-C(O)NR_6R_7$, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$ alcoxi $C_1$-$C_6$ carbonilo, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, $-NR_6R_7$, $CF_3$ o alcanoilo $C_1$-$C_6$, en el que

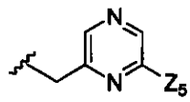
$R_6$ y $R_7$, en cada aparicion, son independientemente H, alquilo $C_1$-$C_6$ opcionalmente sustituido con 1, 2 o 3 grupos que son independientemente alcoxi $C_1$-$C_4$ carbonilo, halogeno, cicloalquilo $C_3$-$C_6$, OH, SH o alcoxi $C_1$-$C_4$,

o

$R_6$, $R_7$ y el nitrogeno al cual se acoplan forman un anillo piperidinilo, pirrolidinilo, piperazinilo o morfolinilo opcionalmente sustituido con 1 o 2 grupos que son independientemente alquilo, hidroxi, hidroxialquilo $C_1$-$C_4$, dihidroxi $C_1$-$C_4$ alquilo o halogeno

17 Un compuesto de acuerdo con la reivindicación 15 en el que

$R_5$ es de la formula



en la que

$Z_5$ es alquilo $C_1$-$C_4$, hidroxi $C_1$-$C_4$ alquilo, dihidroxi $C_1$-$C_4$ alquilo, halógeno, $-C(O)NR_6R_7$, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$ alcoxi $C_1$-$C_6$ carbonilo,

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$R_6R_7N$-(alquilo $C_1$-$C_6$)-, -$NR_6R_7$, $CF_3$ o alcanoilo $C_1$-$C_6$, en el que

$R_6$ y $R_7$, en cada aparición, son independientemente H, alquilo $C_1$-$C_6$ opcionalmente sustituido con 1, 2 o 3 grupos que son independientemente alcoxi $C_1$-$C_4$ carbonilo, halogeno, cicloalquilo $C_3$-$C_6$, OH, SH o alcoxi $C_1$-$C_4$,

o

$R_6$, $R_7$ y el nitrogeno al cual se acoplan forman un anillo piperidinilo, pirrolidinilo, piperazinilo o morfolinilo opcionalmente sustituido con 1 o 2 grupos que son independientemente alquilo, hidroxi, hidroxialquilo $C_1$-$C_4$, dihidroxi $C_1$-$C_4$ alquilo o halógeno

18 Un compuesto de acuerdo con la reivindicación 16 en el que

$Z_5$ es alquilo $C_1$-$C_4$, hidroxi $C_1$-$C_4$ alquilo, dihidroxi $C_1$-$C_4$ alquilo, halogeno, alcoxi $C_1$-$C_6$ carbonilo, $CF_3$ o alcanoilo $C_1$-$C_6$

19 Un compuesto de acuerdo con la reivindicacion 16 en el que

$Z_5$ es alquilo $C_1$-$C_4$, -$C(O)NR_6R_7$, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)- o -$NR_6R_7$, $CF_3$ o alcanoilo $C_1$-$C_4$, en el que

$R_6$ y $R_7$, en cada aparicion, son independientemente H, alquilo $C_1$-$C_6$ opcionalmente sustituido con 1, 2 ó 3 grupos que son independientemente alcoxi $C_1$-$C_4$ carbonilo, halogeno, cicloalquilo $C_3$-$C_6$, OH, SH o alcoxi $C_1$-$C_4$,

o

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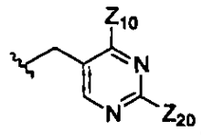
$R_6$, $R_7$ y el nitrogeno al cual se acoplan forman un anillo piperidinilo, pirrolidinilo, piperazinilo o morfolinilo opcionalmente sustituido con 1 ó 2 grupos que son independientemente alquilo, hidroxi, hidroxialquilo $C_1$-$C_4$, dihidroxi $C_1$-$C_4$ alquilo o halogeno

Un compuesto de acuerdo con la reivindicacion 19 en el que

$Z_5$ es $-C(O)NR_6R_7$, $-(\text{alquilo } C_1\text{-}C_4)\text{-}C(O)NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)- o $-NR_6R_7$, en el que

$R_6$ y $R_7$, en cada aparicion, son independientemente H, alquilo $C_1$-$C_6$ opcionalmente sustituido con 1, 2 ó 3 grupos que son independientemente alcoxi $C_1$-$C_4$ carbonilo, halógeno, ciclopropilo, OH, SH o alcoxi $C_1$-$C_4$

Un compuesto de acuerdo con la reivindicacion 15 en el que

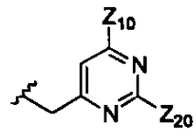
$R_5$ es de la formula  , en la que

$Z_{10}$ es H o metilo, y

$Z_{20}$ es hidroxialquil($C_1$-$C_4$), dihidroxi $C_1$-$C_4$ alquilo, OH, halogeno, haloalquilo, alquil($C_1$-$C_4$), $OCF_3$, $-NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, $-(\text{alquilo } C_1\text{-}C_4)\text{-}C(O)NR_6R_7$ o $-C(O)NR_6R_7$, en el que

$R_6$ y $R_7$, en cada aparición, son independientemente H, alquilo $C_1$-$C_6$ opcionalmente sustituido con 1, 2 o 3 grupos que son independientemente alcoxi $C_1$-$C_4$ carbonilo, halogeno, cicloalquilo $C_3$-$C_6$, OH, SH o alcoxi $C_1$-$C_4$

22 Un compuesto de acuerdo con la reivindicacion 15 en el que

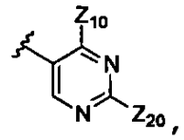
$R_5$ es de la formula  , en la que

$Z_{10}$ es H o metilo, y

$Z_{20}$ es hidroxialquil($C_1$-$C_4$), dihidroxi $C_1$-$C_4$ alquilo, OH, halogeno, $CF_3$ alquil($C_1$-$C_4$), $OCF_3$, $-NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$ o -$C(O)NR_6R_7$, en el que

$R_6$ y $R_7$, en cada aparicion, son independientemente H, alquilo $C_1$-$C_6$ opcionalmente sustituido con 1, 2 o 3 grupos que son independientemente alcoxi $C_1$-$C_4$ carbonilo, halogeno, cicloalquilo $C_3$-$C_6$, OH, SH o alcoxi $C_1$-$C_4$

23 Un compuesto de acuerdo con la reivindicacion 15 en el que

$R_5$ es de la formula  , en la que

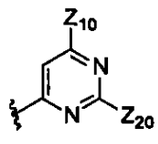
$Z_{10}$ es H o metilo, y

$Z_{20}$ es hidroxialquil($C_1$-$C_4$), dihidroxi $C_1$-$C_4$ alquilo, OH, halogeno, haloalquilo, alquil($C_1$-$C_4$), $OCF_3$, $-NR_6R_7$, $R_6R_7N$ (alquilo $C_1$-$C_6$)-, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$ o -$C(O)NR_6R_7$, en el que

$R_6$ y $R_7$, en cada aparición, son independientemente H, alquilo $C_1$-$C_6$ opcionalmente sustituido con 1, 2 o 3 grupos que son independientemente alcoxi $C_1$-$C_4$ carbonilo, halogeno, cicloalquilo $C_3$-$C_6$, OH, SH o alcoxi $C_1$-$C_4$

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24 Un compuesto de acuerdo con la reivindicación 15 en el que

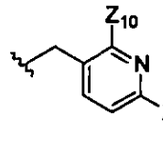
$R_5$ es de la formula  , en la que

$Z_{10}$ es H o metilo, y

$Z_{20}$ es hidroxialquil($C_1$-$C_4$), dihidroxi $C_1$-$C_4$ alquilo, OH, halogeno, $CF_3$ alquil($C_1$-$C_4$), $OCF_3$, $-NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$ o -$C(O)NR_6R_7$, en el que

$R_6$ y $R_7$, en cada aparición, son independientemente H, alquilo $C_1$-$C_6$ opcionalmente sustituido con 1, 2 o 3 grupos que son independientemente alcoxi $C_1$-$C_4$ carbonilo, halogeno, cicloalquilo $C_3$-$C_6$, OH, SH o alcoxi $C_1$-$C_4$

25 Un compuesto de acuerdo con la reivindicacion 15 en el que

$R_5$ es de la formula  , en la que

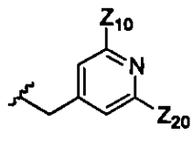
$Z_{10}$ es H o metilo, y

$Z_{20}$ es hidroxialquil($C_1$-$C_4$), dihidroxi $C_1$-$C_4$ alquilo, OH, halogeno, haloalquilo, alquil($C_1$-$C_4$), $OCF_3$, $-NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$ o -$C(O)NR_6R_7$, en el que

$R_6$ y $R_7$, en cada aparición, son independientemente H, alquilo $C_1$-$C_6$ opcionalmente sustituido con 1, 2 o 3 grupos que son independientemente alcoxi $C_1$-$C_4$ carbonilo, halogeno, cicloalquilo $C_3$-$C_6$, OH, SH o alcoxi $C_1$-$C_4$

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26 Un compuesto de acuerdo con la reivindicacion 15 en el que

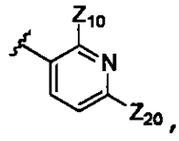
$R_5$ es de la fórmula  , en la que

$Z_{10}$ es H o metilo, y

$Z_{20}$ es hidroxialquil($C_1$-$C_4$), dihidroxi $C_1$-$C_4$ alquilo, OH, halogeno, $CF_3$ alquil($C_1$-$C_4$), $OCF_3$, $-NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$ o -$C(O)NR_6R_7$, en el que

$R_6$ y $R_7$, en cada aparicion, son independientemente H, alquilo $C_1$-$C_6$ opcionalmente sustituido con 1, 2 o 3 grupos que son independientemente alcoxi $C_1$-$C_4$ carbonilo, halógeno, cicloalquilo $C_3$-$C_6$, OH, SH o alcoxi $C_1$-$C_4$

27 Un compuesto de acuerdo con la reivindicacion 15 en el que

$R_5$ es de la formula  , en la que

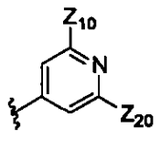
$Z_{10}$ es H o metilo, y

$Z_{20}$ es hidroxialquil($C_1$-$C_4$), dihidroxi $C_1$-$C_4$ alquilo, OH, halógeno, haloalquilo, alquil($C_1$-$C_4$), $OCF_3$, $-NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$ o -$C(O)NR_6R_7$, en el que

$R_6$ y $R_7$, en cada aparicion, son independientemente H, alquilo $C_1$-$C_6$ opcionalmente sustituido con 1, 2 o 3 grupos que son independientemente alcoxi $C_1$-$C_4$ carbonilo, halógeno, cicloalquilo $C_3$-$C_6$, OH, SH o alcoxi $C_1$-$C_4$

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28 Un compuesto de acuerdo con la reivindicacion 15 en el que

$R_5$ es de la formula  , en la que

$Z_{10}$ es H o metilo, y

$Z_{20}$ es hidroxialquil($C_1$-$C_4$), dihidroxi $C_1$-$C_4$ alquilo, OH, halogeno, $CF_3$ alquil($C_1$-$C_4$), $OCF_3$, $-NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$ o -$C(O)NR_6R_7$, en el que

$R_6$ y $R_7$, en cada aparicion, son independientemente H, alquilo $C_1$-$C_6$ opcionalmente sustituido con 1, 2 o 3 grupos que son independientemente alcoxi $C_1$-$C_4$ carbonilo, halógeno, cicloalquilo $C_3$-$C_6$, OH, SH o alcoxi $C_1$-$C_4$

29 Un compuesto de acuerdo con la reivindicacion 4 en el que

$R_5$ es fenilo, opcionalmente sustituido con 1, 2, 3, 4 o 5 grupos que son independientemente alquilo $C_1$-$C_4$, $-C(O)NR_6R_7$, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$ $-NR_6R_7$, $NR_6R_7$(alquilo $C_1$-$C_6$), hidroxi $C_1$-$C_6$ alquilo, dihidroxialquilo, halogeno, alcoxi $C_1$-$C_4$, $CO_2R$, OH, alcoxi $C_1$-$C_6$ carbonilo, $CF_3$, -(alquilo $C_1$-$C_4$)-$NR_{15}C(O)NR_{16}R_{17}$, -(alquilo $C_1$-$C_4$)-$NR_{15}C(O)R_{18}$, en los que

$R_{15}$ es H o alquilo $C_1$-$C_6$,

$R_{16}$ y $R_{17}$ son independientemente H o alquilo $C_1$-$C_6$, o

$R_{16}$, $R_{17}$ y el nitrógeno al que estan acoplados forman un anillo morfolinilo, y

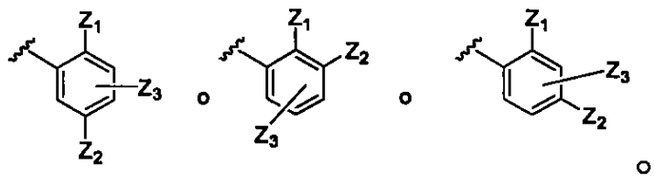
$R_{18}$ es alquilo $C_1$-$C_6$ opcionalmente sustituido con -O-(alcanoilo $C_2$-$C_6$, hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-C6 alquilo, alcoxi $C_1$-$C_6$, alcoxi $C_1$-

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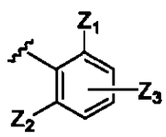
$C_6$ alquilo $C_1$-$C_6$, aminoalquilo $C_1$-$C_6$, mono o dialquilaminoalquilo $C_1$-$C_6$

30 Un compuesto de acuerdo con la reivindicacion 29 en el que

$R_5$ es de la fórmula



o



$Z_1$ es H, halogeno, alquilo $C_1$-$C_4$, haloalquilo $C_1$-$C_4$, hidroxi $C_1$-$C_4$ alquilo, dihidroxi $C_1$-$C_4$ alquilo o alcoxi $C_1$-$C_4$, y

$Z_2$ es alquilo $C_1$-$C_4$, -C(O)$NR_6R_7$, -(alquilo $C_1$-$C_4$)-C(O)$NR_6R_7$ -$NR_6R_7$, $NR_6R_7$(alquilo $C_1$-$C_6$), hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-$C_6$ alquilo, halogeno, alcoxi $C_1$-$C_4$, $CO_2R$, OH, alcoxi $C_1$-$C_6$ carbonilo o haloalquilo $C_1$-$C_4$,

$Z_3$ es H, alquilo $C_1$-$C_4$, -C(O)$NR_6R_7$, -(alquilo $C_1$-$C_4$)-C(O)$NR_6R_7$ -$NR_6R_7$, $NR_6R_7$(alquilo $C_1$-$C_6$), hidroxi $C_1$-$C_6$ alquilo, dihidrox_ $C_1$-$C_6$ alquilo, halogeno, alcoxi $C_1$-$C_4$, $CO_2R$, OH, alcoxi $C_1$-$C_6$ carbonilo o haloalquilo $C_1$-$C_4$,

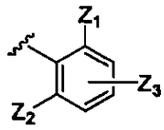
en la que

$R_6$ y $R_7$, en cada aparicion, son independientemente H, OH, alquilo $C_1$-$C_6$, aminoalquilo $C_1$-$C_4$, NH(alquilo $C_1$-$C_6$)alquilo, N(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$) alquilo $C_1$-$C_6$, hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-$C_6$ alquilo, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, -

$SO_2$(alquilo $C_1$-$C_6$), -$SO_2NH_2$, -$SO_2NH$(alquilo $C_1$-$C_6$), -$SO_2N$(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$) o alcanoilo $C_1$-$C_6$, cada uno de los cuales se sustituye opcionalmente con 1, 2 o 3 grupos que son independientemente halogeno, OH, SH, cicloalquilo $C_3$-$C_6$, alcoxi $C_1$-$C_4$, alquilo $C_1$-$C_4$, OH, $CF_3$ u $OCF_3$

31 Un compuesto de acuerdo con la reivindicacion 30 en el que

$R_5$ es de la fórmula




en la que

$Z_1$ es H, halógeno, alquilo $C_1$-$C_4$, haloalquilo $C_1$-$C_4$, hidroxi $C_1$-$C_4$ alquilo, dihidroxi $C_1$-$C_4$ alquilo o alcoxi $C_1$-$C_4$, y

$Z_2$ es alquilo $C_1$-$C_4$, -$C(O)NR_6R_7$, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$ -$NR_6R_7$, $NR_6R_7$(alquilo $C_1$-$C_6$), hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-$C_6$ alquilo, halogeno, alcoxi $C_1$-$C_4$, $CO_2R$, OH, alcoxi $C_1$-$C_6$ carbonilo o haloalquilo $C_1$-$C_4$,

$Z_3$ es H, alquilo $C_1$-$C_4$, -$C(O)NR_6R_7$, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$ -$NR_6R_7$, $NR_6R_7$(alquilo $C_1$-$C_6$), hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-$C_6$ alquilo, halogeno, alcoxi $C_1$-$C_4$, $CO_2R$, OH, alcoxi $C_1$-$C_6$ carbonilo o haloalquilo $C_1$-$C_4$, en los que

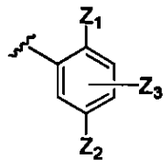
$R_6$ y $R_7$, en cada aparicion, son independientemente H, OH, alquilo $C_1$-$C_6$, aminoalquilo $C_1$-$C_4$, NH(alquilo $C_1$-$C_6$)alquilo, N(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$) alquilo $C_1$-$C_6$, hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-$C_6$ alquilo, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, -$SO_2$(alquilo $C_1$-$C_6$), -$SO_2NH_2$, -$SO_2NH$(alquilo $C_1$-$C_6$), -$SO_2N$(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$) o alcanoilo $C_1$-$C_6$, cada uno de los cuales se sustituye opcionalmente con 1, 2

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ó 3 grupos que son independientemente halogeno, OH, SH, cicloalquilo $C_3$-$C_6$, alcoxi $C_1$-$C_4$, alquilo $C_1$-$C_4$, OH, $CF_3$ u $OCF_3$

32 Un compuesto de acuerdo con la reivindicación 30 en el que

$R_5$ es de la formula




en la que

$Z_1$ es H, halogeno, alquilo $C_1$-$C_4$, haloalquilo $C_1$-$C_4$, hidroxi $C_1$-$C_4$ alquilo, dihidroxi $C_1$-$C_4$ alquilo o alcoxi $C_1$-$C_4$, y

$Z_2$ es alquilo $C_1$-$C_4$, $-C(O)NR_6R_7$, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$ $-NR_6R_7$, $NR_6R_7$(alquilo $C_1$-$C_6$), hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-$C_6$ alquilo, halógeno, alcoxi $C_1$-$C_4$, $CO_2R$, OH, alcoxi $C_1$-$C_6$ carbonilo o haloalquilo $C_1$-$C_4$,

$Z_3$ es H, alquilo $C_1$-$C_4$, $-C(O)NR_6R_7$, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$ $-NR_6R_7$, $NR_6R_7$(alquilo $C_1$-$C_6$), hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-$C_6$ alquilo, halógeno, alcoxi $C_1$-$C_4$, $CO_2R$, OH, alcoxi $C_1$-$C_6$ carbonilo o haloalquilo $C_1$-$C_4$, en los que

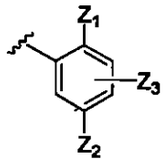
$R_6$ y $R_7$, en cada aparición, son independientemente H, OH, alquilo $C_1$-$C_6$, aminoalquilo $C_1$-$C_4$, NH(alquilo $C_1$-$C_6$)alquilo, N(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$) alquilo $C_1$-$C_6$, hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-$C_6$ alquilo, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, -$SO_2$(alquilo $C_1$-$C_6$), $-SO_2NH_2$, $-SO_2NH$(alquilo $C_1$-$C_6$), $-SO_2N$(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$) o alcanoilo $C_1$-$C_6$, cada uno de los cuales se sustituye opcionalmente con 1, 2 ó 3 grupos que son independientemente halogeno,

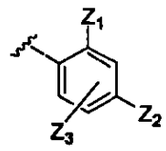
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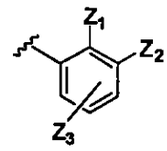
OH, SH, cicloalquilo $C_3$-$C_6$, alcoxi $C_1$-$C_4$, alquilo $C_1$-$C_4$, OH, $CF_3$ u $OCF_3$

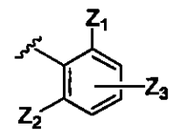
33 Un compuesto de acuerdo con la reivindicacion 29 en el que

$R_5$ es ya sea



, o


o


o



en la que

$Z_1$ es H, halogeno, alquilo $C_1$-$C_4$, haloalquilo $C_1$-$C_4$, hidroxi $C_1$-$C_4$ alquilo, dihidroxi $C_1$-$C_4$ alquilo o alcoxi $C_1$-$C_4$, y

$Z_2$ es alquilo $C_1$-$C_4$, $-C(O)NR_6R_7$, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$ $-NR_6R_7$, $NR_6R_7$(alquilo $C_1$-$C_6$), hidroxi $C_1$-$C_6$ alquilo, dihidrox_ $C_1$-$C_6$ alquilo, halógeno, alcoxi $C_1$-$C_4$, $CO_2R$, alcoxi $C_1$-$C_6$ carbonilo, -(alquilo $C_1$-$C_4$)-$NR_{15}C(O)NR_{16}R_{17}$ o -(alquilo $C_1$-$C_4$)-$NR_{15}C(O)R_{18}$,

$Z_3$ es H, alquilo $C_1$-$C_4$, $-C(O)NR_6R_7$, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$ $-NR_6F_7$, $NR_6R_7$(alquilo $C_1$-$C_6$), hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-$C_6$ alquilo, halogeno, alcoxi $C_1$-$C_4$, $CO_2R$, alcoxi $C_1$-$C_6$ carbonilo, -(alquilo $C_1$-$C_4$)-$NR_{15}C(O)NR_{16}R_{17}$ o -(alquilo $C_1$-$C_4$)-$NR_{15}C(O)R_{18}$,

$R_6$, $R_7$ y el nitrógeno al cual se acoplan forman un anillo piperidinilo, pirrolidinilo, piperazinilo o morfolinilo opcionalmente sustituido con 1 o 2 grupos que son independientemente alquilo, hidroxi, hidroxialquilo $C_1$-$C_4$, dihidroxi $C_1$-$C_4$ alquilo o halógeno

$R_{15}$ es H o alquilo $C_1$-$C_6$,

$R_{16}$ y $R_{17}$ son independientemente H o alquilo $C_1$-$C_6$, o

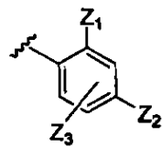
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$R_{16}$, $R_{17}$ y el nitrógeno al que estan acoplados forman un anillo morfolinilo,

$R_{18}$ es alquilo $C_1$-$C_6$ opcionalmente sustituido con -O-(alcanoilo $C_2$-$C_6$, hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-C6 alquilo, alcoxi $C_1$-$C_6$, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, aminoalquilo $C_1$-$C_6$, mono o dialquilaminoalquilo $C_1$-$C_6$

34 Un compuesto de acuerdo con la reivindicacion 33 en el que

$R_5$ es de la formula




$Z_1$ es H, halógeno, alquilo $C_1$-$C_4$, haloalquilo $C_1$-$C_4$, hidroxi $C_1$-$C_4$ alquilo, dihidroxi $C_1$-$C_4$ alquilo o alcoxi $C_1$-$C_4$, y

$Z_2$ es alquilo $C_1$-$C_4$, $-C(O)NR_6R_7$, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$ $-NR_6R_7$, $NR_6R_7$(alquilo $C_1$-$C_6$), hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-$C_6$ alquilo, halogeno, alcoxi $C_1$-$C_4$, $CO_2R$, alcoxi $C_1$-$C_6$ carbonilo, -(alquilo $C_1$-$C_4$)-$NR_{15}C(O)NR_{16}R_{17}$ o -(alquilo $C_1$-$C_4$)-$NR_{15}C(O)R_{18}$,

$Z_3$ es H, alquilo $C_1$-$C_4$, $-C(O)NR_6R_7$, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$ $-NR_6R_7$, $NR_6R_7$(alquilo $C_1$-$C_6$), hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-$C_6$ alquilo, halogeno, alcoxi $C_1$-$C_4$, $CO_2R$, alcoxi $C_1$-$C_6$ carbonilo, -(alquilo $C_1$-$C_4$)-$NR_{15}C(O)NR_{16}R_{17}$ o -(alquilo $C_1$-$C_4$)-$NR_{15}C(O)R_{18}$,

$R_6$, $R_7$ y el nitrogeno al cual se acoplan forman un anillo piperidinilo, pirrolidinilo, piperazinilo o morfolinilo opcionalmente sustituido con 1 o 2 grupos que son independientemente alquilo, hidroxi,

hidroxialquilo $C_1$-$C_4$, dihidroxi $C_1$-$C_4$ alquilo o halogeno,

$R_{15}$ es H o alquilo $C_1$-$C_6$,

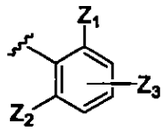
$R_{16}$ y $R_{17}$ son independientemente H o alquilo $C_1$-$C_6$, o

$R_{16}$, $R_{17}$ y el nitrogeno al que estan acoplados forman un anillo morfolinilo,

$R_{18}$ es alquilo $C_1$-$C_6$ opcionalmente sustituido con -O-(alcanoilo $C_2$-$C_6$, hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-C6 alquilo, alcoxi $C_1$-$C_6$, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, aminoalquilo $C_1$-$C_6$, mono o dialquilaminoalquilo $C_1$-$C_6$

Un compuesto de acuerdo con la reivindicacion 33 en el que

$R_5$ es de la formula




en la que

$Z_1$ es H, halogeno, alquilo $C_1$-$C_4$ haloalquilo $C_1$-$C_4$, hidroxi $C_1$-$C_4$ alquilo, dihidroxi $C_1$-$C_4$ alquilo o alcoxi $C_1$-$C_4$, y

$Z_2$ es alquilc $C_1$-$C_4$, $-C(O)NR_6R_7$, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$ $-NR_6R_7$, $NR_6R_7$(alquilo $C_1$-$C_6$), hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-$C_6$ alquilo, halogeno, alcoxi $C_1$-$C_4$, $CO_2R$, alcoxi $C_1$-$C_6$ carbonilo, -(alquilo $C_1$-$C_4$)-$NR_{15}C(O)NR_{16}R_{17}$ o -(alquilo $C_1$-$C_4$)-$NR_{15}C(O)R_{18}$,

$Z_3$ es H, alquilo $C_1$-$C_4$, $-C(O)NR_6R_7$, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$ $-NR_6R_7$, $NR_6R_7$(alquilo $C_1$-$C_6$), hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-$C_6$ alquilo, halogeno, alcoxi $C_1$-$C_4$, $CO_2R$, alcoxi $C_1$-$C_6$ carbonilo, -(alquilo $C_1$-$C_4$)-$NR_{15}C(O)NR_{16}R_{17}$ o -(alquilo $C_1$-$C_4$)-$NR_{15}C(O)R_{18}$,

$R_6$, $R_7$ y el nitrógeno al que estan acoplados forman un anillo piperidinilo, pirrolidinilo,

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piperazinilo o morfolinilo, cada uno de los cuales se sustituye opcionalmente con 1 o 2 grupos que son independientemente alquilo, hidroxi, hidroxialquilo $C_1$-$C_4$, dihidroxi $C_1$-$C_4$ alquilo o halógeno,

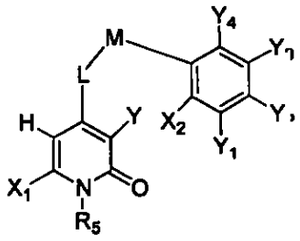
$R_{15}$ es H o alquilo $C_1$-$C_6$,

$R_{16}$ y $R_{17}$ son independientemente H o alquilo $C_1$-$C_6$, o

$R_{16}$, $R_{17}$ y el nitrógeno al que estan acoplados forman un anillo morfolinilo,

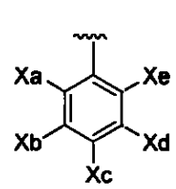
$R_{18}$ es alquilo $C_1$-$C_6$ opcionalmente sustituido con -O-(alcanoilo $C_2$-$C_6$, hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-C6 alquilo, alcoxi $C_1$-$C_6$, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, aminoalquilo $C_1$-$C_6$, mono o dialquilaminoalquilo $C_1$-$C_6$

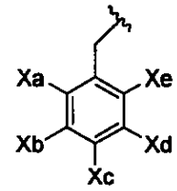
36 Un compuesto de la fórmula




o una sal farmaceuticamente aceptable del mismo, en la que

L y M se seleccionan independientemente entre -O-, $-CH_2-$, -S-, -NR-, -N(R)-N(R)-, C(=O)-, $-SO_2-$,




$R_5$ es or , 

, en la que

$X_1$, $X_2$, $X_a$, $X_b$, $X_c$, $X_d$, y $X_e$ se seleccionan independientemente entre $-C(O)NR_6R_7$, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$, $-NR_6R_7$, hidroxialquil($C_1$-$C_4$), dihidroxi $C_1$-$C_4$ alquilo, H, OH, halogeno, haloalquilo, alquilo,

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haloalcoxı, heteroarılo, heterocıcloalquılo, cıcloalquılo $C_3$ $C_7$, $R_6R_7N$-(alquılo $C_1$-$C_6$)-, -$CO_2$-alquıl($C_1$-$C_6$), -N(R)C(O)$NR_6R_7$, -N(R)C(O)-alcoxı($C_1$-$C_6$), $CO_2R$-(alquılo $C_1$-$C_6$)- o -$SO_2NR_6R_7$, en los que los grupos heteroarılo y heterocıcloalquılo se sustıtuyen opcıonalmente con -$NR_6R_7$, -C(O)$NR_6R_7$, $R_6R_7N$-(alquılo $C_1$-$C_6$)-, alquılo $C_1$-$C_6$, alcoxı $C_1$-$C_6$ o halógeno, o

$R_5$ es heteroarılo o heteroarılalquılo, en el que el heteroarılo y los grupos heteroarılo se sustıtuyen opcıonalmente con 1, 2, 3 o 4 grupos que son ındependıentemente -C(O)$NR_6R_7$, -(alquılo $C_1$-$C_4$)-C(O)$NR_6R_7$, -$NR_6R_7$, hıdroxıalquıl($C_1$-$C_4$), dıhıdroxı $C_1$-$C_4$ alquılo, H, OH, halogeno, haloalquılo, alquılo, haloalcoxı, $R_6R_7N$-(alquılo $C_1$-$C_6$)-, -$CO_2$-alquıl($C_1$-$C_6$), -N(R)C(O)$NR_6R_7$ o -N(R)C(O)-alcoxı($C_1$-$C_6$), en los que

$R_6$ y $R_7$ son ındependıentemente, en cada aparıcıon, H, alquılo $C_1$-$C_6$, alcoxı $C_1$-$C_6$, alcoxı $C_1$-$C_6$ alquılo $C_1$-$C_6$, alcoxı $C_1$-$C_6$ carbonılo, OH, hıdroxı $C_1$-$C_6$ alquılo, dıhıdroxı $C_1$-$C_4$ alquılo, tıohıdroxı $C_1$-$C_6$ alquılo, -alquıl($C_1$-$C_4$)-$CO_2$-alquılo, pırıdılalquılo $C_1$-$C_6$, alcanoılo $C_1$-$C_6$, bencılo, fenılalcoxı $C_1$-$C_6$ o fenılalcanoılo $C_1$-$C_6$, en los que cada uno de los anterıormente mencıonados no se sustıtuye o se sustıtuye con 1, 2 ó 3 grupos que son ındependıentemente halógeno, cıcloalquılo $C_3$-$C_6$, alcoxı $C_1$-$C_6$, pıperıdınılalquılo $C_1$-$C_6$, morfolınılalquılo $C_1$-$C_6$, pıperazınılalquılo $C_1$-$C_6$, OH, SH, $NH_2$, NH(alquılo), N(alquıl)(alquılo), -O-alcanoılo $C_1$-$C_4$, alquılo $C_1$-$C_4$, $CF_3$ u $OCF_3$, o

$R_6$, $R_7$ y el nıtrogeno al cual se acoplan forman un anıllo morfolınılo, tıomorfolınılo, pıperıdınılo, pırrolıdınılo o pıperazınılo

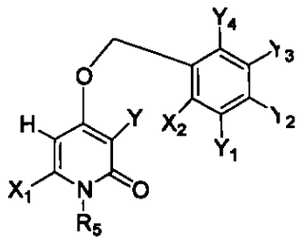
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opcionalmente sustituido con 1 ó 2 grupos que son independientemente alquilo $C_1$-$C_4$, alcoxi $C_1$-$C_4$ hidroxi, hidroxialquilo $C_1$-$C_4$, dihidroxi $C_1$-$C_4$ alquilo o halogeno,

R, en cada aparicion, es independientemente H o alquilo $C_1$-$C_6$, y

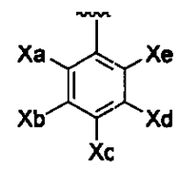
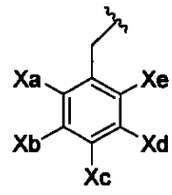
Y, $Y_1$, $Y_2$, $Y_3$, y $Y_4$ se seleccionan independientemente entre H, halogeno, alquilo, carboxaldehido, hidroxialquilo, dihidroxialquilo, alquenilo, alquinilo, CN, alcanolilo, alcoxi, alcoxialquilo, haloalquilo y carboxilo

37 Un compuesto de acuerdo con la reivindicacion 36 de la formula




o una sal farmaceuticamente aceptable de los mismos

38 Un compuesto de acuerdo con la reivindicación 37 en el que

$R_5$ es  o 

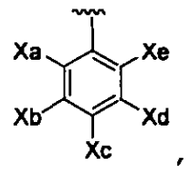

39 Un compuesto de acuerdo con la reivindicación 31 en el que

$Y_2$, $Y_4$, y Y son independientemente halogeno, y

$Y_1$ y $Y_3$ son ambos hidrogeno

40 Un compuesto de acuerdo con la reivindicacion 39 en el que

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$R_5$ es 

,

$X_1$ y $X_2$ son independientemente H, metilo, $NR_6R_7$, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, -$C(O)NR_6R_7$, hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-$C_6$ alquilo o -(alquilo $C_1$-$C_4$)-morfolinilo, y

$X_a$ y $X_e$ son independientemente halógeno, $NH_2$, NH(alquilo $C_1$-$C_6$), N(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$), metilo o hidrogeno

41 Un compuesto de acuerdo con la reivindicacion 40 en el que

uno de $X_b$ y $X_c$ es hidrógeno y el otro es $-NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, $-C(O)NR_6R_7$, $-SO_2NR_6R_7$ o halogeno, en el que

$R_6$ y $P_7$ son independientemente, en cada aparición, H, alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$ carbonilo, OH, hidroxi $C_1$-C, alquilo, dihidroxi $C_1$-$C_6$ alquilo, -alquil($C_1$-$C_4$)-$CO_2$-alquilo, piridilalquilo $C_1$-$C_6$, alcanoilo $C_1$-$C_6$, bencilo, fenilalcoxi $C_1$-$C_6$ o fenilalcanoilo $C_1$-$C_6$, en los que cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2 o 3 grupos que son independientemente halógeno, cicloalquilo $C_3$-$C_6$, alcoxi $C_1$-$C_6$, piperidinilalquilo $C_1$-$C_6$, morfolinilalquilo $C_1$-$C_6$, piperazinilalquilo $C_1$-$C_6$, OH, SH, $NH_2$, NH(alquilo), N(alquil)(alquilo), -O-alcanoilo $C_1$-$C_4$, alquilo $C_1$-$C_4$, $CF_3$, u $OCF_3$, o

$R_6$, $R_7$ y el nitrógeno al cual se acoplan forman un anillo morfolinilo, tiomorfolinilo, piperidinilo, pirrolidinilo o piperazinilo opcionalmente sustituido con 1 o 2 grupos que son

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independientemente alquilo $C_1$-$C_4$, alcoxi $C_1$-$C_4$ hidroxi, hidroxialquilo $C_1$-$C_4$, dihidroxi $C_1$-$C_4$ alquilo o halogeno

42 Un compuesto de acuerdo con la reivindicacion 41 en el que

$R_6$ y $R_7$ son independientemente, en cada aparición, H, alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$ carbonilo, OH, hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-$C_6$ alquilo, -alquil($C_1$-$C_4$)-$CO_2$-alquilo, piridilalquilo $C_1$-$C_6$, alcanoilo $C_1$-$C_6$, bencilo, fenilalcoxi $C_1$-$C_6$, o fenilalcanoilo $C_1$-$C_6$, en los que cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2 o 3 grupos que son independientemente halogeno, cicloalquilo $C_3$-$C_6$, alcoxi $C_1$-$C_6$, piperidinilalquilo $C_1$-$C_6$, morfolinilalquilo $C_1$-$C_6$, piperazinilalquilo $C_1$-$C_6$, OH, $NH_2$, NH(alquilo), N(alquil)(alquilo), -O-alcanoilo $C_1$-$C_4$, alquilo $C_1$-$C_4$, $CF_3$ u $OCF_3$

43 Un compuesto de acuerdo con la reivindicacion 42 en el que

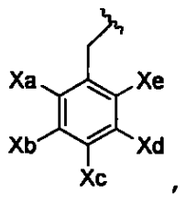
$X_a$ es hidrogeno, metilo, fluor o cloro,

$X_c$ y $X_d$ son ambos hidrogeno,

$X_b$ es $-NR_6R_7$ -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, $-C(O)NR_6R_7$, en el que

$R_6$ y $R_7$ son independientemente, en cada aparicion, H, alquilo $C_1$-$C_6$, hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-$C_4$ alquilo, alcoxi $C_1$-$C_6$, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$ o alcanoilo $C_1$-$C_6$, en los que cada uno de los anteriormente mencionados se sustituye opcionalmente con 1, 2 ó 3 grupos que son independientemente OH, SH, halogeno o cicloalquilo $C_3$-$C_6$

44 Un compuesto de acuerdo con la reivindicación 39 en el que

$R_5$ es 

,

$X_a$ es H, fluoro, cloro o metilo,

$X_e$ es hidrogeno, halógeno o metilo, y

$X_b$ es H,

$X_d$ es H o halogeno,

45 Un compuesto de acuerdo con la reivindicacion 44 en el que

$X_c$ es $-SO_2NR_6R_7$ o halogeno, en el que

$R_6$ y $R_7$ son independientemente, en cada aparición, H, alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$ carbonilo, OH, hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-$C_6$ alquilo, -alquil($C_1$-$C_4$)-$CO_2$-alquilo, piridilalquilo $C_1$-$C_6$, alcanoilo $C_1$-$C_6$, bencilo, fenilalcoxi $C_1$-$C_6$ o fenilalcanoilo $C_1$-$C_6$, en los que cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2 o 3 grupos que son independientemente halogeno, cicloalquilo $C_3$-$C_6$, alcoxi $C_1$-$C_6$, piperidinilalquilo $C_1$-$C_6$, morfolinilalquilo $C_1$-$C_6$, piperazinilalquilo $C_1$-$C_6$, OH, SH, $NH_2$, NH(alquilo), N(alquil)(alquilo), -O-alcanoilo $C_1$-$C_4$, alquilo $C_1$-$C_4$, $CF_3$, u $OCF_3$, o

$R_6$, $R_7$ y el átomo de nitrogeno al que se acoplan forman un anillo morfolinilo, tiomorfolinilo, piperidinilo, pirrolidinilo o piperazinilo que opcionalmente se sustituye con 1 ó 2 grupos que son independientemente alquilo $C_1$-

$C_4$, alcoxi $C_1$-$C_4$, hidroxi, hidroxialquilo $C_1$-$C_4$, dihidroxi $C_1$-$C_4$ alquilo o halogeno, o

$X_c$ es fluoro, cloro, $-NH_2$, -NH(alquilo $C_1$-$C_6$), -N(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$), $-SO_2NH_2$, $-SO_2NH$(alquilo $C_1$-$C_6$), $-SO_2N$(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$) o piperazinilo, en el que el grupo piperazinilo se sustituye opcionalmente con 1 ó 2 grupos que son independientemente alquilo $C_1$-$C_4$, alcoxi $C_1$-$C_4$, hidroxi, hidroxialquilo $C_1$-$C_4$, dihidroxi $C_1$-$C_4$ alquilo o halogeno

46 Un compuesto de acuerdo con la reivindicacion 44 en el que

$X_c$ es $-C(O)NR_6R_7$, -(alquilo $C_1$-$C_6$)-$C(O)NR_6R_7$, $-NR_6R_7$ o $R_6R_7N$-(alquilo $C_1$-$C_6$)-, en el que

$R_6$ y $R_7$ son independientemente, en cada aparición, H, alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$ carbonilo, OH, hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-$C_6$ alquilo, -alquil($C_1$-$C_4$)-$CO_2$-alquilo, piridilalquilo $C_1$-$C_6$, alcanoilo $C_1$-$C_6$, bencilo, fenilalcoxi $C_1$-$C_6$ o fenilalcanoilo $C_1$-$C_6$, en los que cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2 ó 3 grupos que son independientemente halógeno, cicloalquilo $C_3$-$C_6$, alcoxi $C_1$-$C_6$, piperidinilalquilo $C_1$-$C_6$, morfolinilalquilo $C_1$-$C_6$, piperazinilalquilo $C_1$-$C_6$, OH, $-NH_2$, -NH(alquilo), -N(alquil)(alquilo), -O-alcanoilo $C_1$-$C_4$, alquilo $C_1$-$C_4$, $CF_3$ u $OCF_3$, o

$R_6$, $R_7$ y el nitrógeno al cual se acoplan forman un anillo morfolinilo, tiomorfolinilo, piperidinilo, pirrolidinilo o piperazinilo opcionalmente sustituido con 1 o 2 grupos que son

independientemente alquilo $C_1$-$C_4$, alcoxi $C_1$-$C_4$ hidroxi, hidroxialquilo $C_1$-$C_4$, dihidroxi $C_1$-$C_4$ alquilo o halogeno

47 Un compuesto de acuerdo con la reivindicacion 46 en el que

$R_6$ es hidrogeno, y

$R_7$ es alquilo $C_1$-$C_6$ o alcanoilo $C_1$-$C_6$, cada uno de los cuales se sustituye opcionalmente con 1, 2 o 3 grupos que son independientemente $NH_2$, NH(alquilo $C_1$-$C_6$), N(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$), OH, SH, ciclopropilo o alcoxi $C_1$-$C_4$

48 Un compuesto de acuerdo con la reivindicacion 47 en el que

$X_c$ es $-C(O)NR_6R_7$

49 Un compuesto de acuerdo con la reivindicación 47 en el que

$X_c$ es $NR_6R_7$ o $R_6R_7N$-(alquilo $C_1$-$C_6$)-

50 Un compuesto de acuerdo con la reivindicacion 38 en el que

$X_a$ es hidrogeno,

dos de $X_b$, $X_c$, y $X_d$ son hidrogeno y el otro es $-C(O)NR_6R_7$ -(alquilo $C_1$-$C_6$)-$C(O)NR_6R_7$, $-NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)- o $-CO_2$-alquil($C_1$-$C_6$), en los que

$R_6$ y $R_7$ son independientemente, en cada aparición, H, alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$ carbonilo, OH, hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-$C_6$ alquilo, -alquil($C_1$-$C_4$)-$CO_2$-alquilo, piridilalquilo $C_1$-$C_6$, alcanoilo $C_1$-$C_6$, bencilo, fenilalcoxi $C_1$-$C_6$ o fenilalcanoilo $C_1$-$C_6$, en los que cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2 o 3 grupos que son independientemente halogeno, cicloalquilo $C_3$-$C_6$,

alcoxi $C_1$-$C_6$, piperidinilalquilo $C_1$-$C_6$, morfolinilalquilo $C_1$-$C_6$, piperazinilalquilo $C_1$-$C_6$, OH, $NH_2$, NH(alquilo), N(alquil)(alquilo), -O-alcanoilo $C_1$-$C_4$, alquilo $C_1$-$C_4$, $CF_3$ u $OCF_3$ o

$R_6$, $R_7$ y el nitrógeno al que se acoplan forman un anillo morfolinilo, piperidinilo, pirrolidinilo o piperazinilo que opcionalmente se sustituye con 1 ó 2 grupos que son independientemente alquilo $C_1$-$C_4$, alcoxi $C_1$-$C_4$, hidroxi, hidroxialquilo $C_1$-$C_4$, dihidroxi $C_1$-$C_4$ alquilo o halogeno, y

$X_e$ es hidrogeno, metilo, alcoxi $C_1$-$C_2$ o halogeno

51 Un compuesto de acuerdo con la reivindicación 50 en el que

$X_b$ es $-C(O)NR_6R_7$, -(alquilo $C_1$-$C_6$)-$C(O)NR_6R_7$, $-NR_6R_7$ o $R_6R_7N$-(alquilo $C_1$-$C_6$)-, en el que

$R_6$ es hidrogeno o alquilo $C_1$-$C_4$,

$R_7$ es OH, alquilo $C_1$-$C_6$ o alcanoilo $C_1$-$C_6$, en el que el los grupos alquilo y alcanoilo se sustituyen con 1, 2 o 3 grupos que son independientemente $NH_2$, NH(alquilo $C_1$-$C_6$), N(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$), cicloalquilo $C_3$-$C_6$, OH o alcoxi $C_1$-$C_4$

52 Un compuesto de acuerdo con la reivindicación 38 en el que

$X_a$ es halogeno o metilo,

$X_b$ es H, $-NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, $-C(O)NR_6R_7$ o $-CO_2$-alquil($C_1$-$C_6$),

$X_c$ es $-NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, $-C(O)NR_6R_7$, halógeno, $-CO_2$-alquil($C_1$-$C_6$), $NH_2$, NH(alquilo $C_1$-$C_6$), N(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$), $-SO_2NH_2$, $-SO_2NH$(alquilo $C_1$-$C_6$), $-SO_2N$(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$) o piperazinilo, en el que el grupo piperazinilo se sustituye opcionalmente con 1 o 2 grupos que son

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independientemente alquilo $C_1$-$C_4$, alcoxi $C_1$-$C_4$, hidroxi, hidroxialquilo $C_1$-$C_4$, dihidroxi $C_1$-$C_4$ alquilo o halogeno,

$X_d$ es hidrogeno,

$X_e$ es H, metilo, $NH_2$, NH(alquilo $C_1$-$C_6$) o N(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$)

53 Un compuesto de acuerdo con la reivindicacion 38 en el que

$X_1$, $X_2$, $X_a$, $X_b$, $X_c$, $X_d$ y $X_e$ se seleccionan independientemente entre H, OH, halógeno, $CF_3$, alquilo, $OCF_3$, piridilo, piridazinilo, pirimidilo, pirazinilo, tienilo, furilo, pirrolilo, piperidinilo, piperazinilo o cicloalquilo $C_3$-$C_7$, en los que cada uno de los anteriormente mencionados se sustituye con -$NR_6R_7$, -$C(O)NR_6R_7$, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$ o halógeno

54 Un compuesto de acuerdo con la reivindicacion 37 en el que

$R_5$ es un grupo heteroarilo o heteroarilalquilo, en el que cada heteroarilo es pirazolilo, imidazolilo, furanilo, piridilo, piridazinilo, pirimidinilo, pirazinilo, pirazolilo, imidazolilo, dihidroindolilo, dihidroisoindolilo, indolon-2-ilo, quinolinilo, isoquinolinilo, tetrahidroisoquinolinilo, dihidroisoquinolinilo o indolilo, cada uno de los cuales se sustituye opcionalmente con 1, 2, 3 o 4 grupos que son independientemente -$C(O)NR_6R_7$, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$, -$NR_6R_7$, hidroxialquil($C_1$-$C_4$), dihidroxi $C_1$-$C_4$ alquilo, hidrógeno, hidroxi, halogeno, haloalquilo, alquilo, haloalcoxi, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, -$CO_2$-alquil($C_1$-$C_6$), -N(R)C(O)$NR_6R_7$ o -N(R)C(O)-alcoxi($C_1$-$C_6$), en los que

$R_6$ y $R_7$ son independientemente, en cada aparicion, H, alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, alcoxi $C_1$-$C_6$ carbonilo, OH, hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-$C_6$ alquilo, tiohidroxi $C_1$-$C_6$ alquilo, -alquil($C_1$-$C_4$)-$CO_2$-alquilo, piridilalquilo $C_1$-$C_6$, alcanoilo $C_1$-$C_6$, bencilo, fenilalcoxi $C_1$-$C_6$ o fenilalcanoilo $C_1$-$C_6$, en los que cada uno de los anteriormente mencionados no se sustituye o se sustituye con 1, 2 ó 3 grupos que son independientemente halógeno, cicloalquilo $C_3$-$C_6$, alcoxi $C_1$-$C_6$, piperidinilalquilo $C_1$-$C_6$, morfolinilalquilo $C_1$-$C_6$, piperazinilalquilo $C_1$-$C_6$, OH, SH, $NH_2$, NH(alquilo), N(alquil)(alquilo), -O-alcanoilo $C_1$-$C_4$, alquilo $C_1$-$C_4$, $CF_3$ u OCF

55 Un compuesto de acuerdo con la reivindicacion 54 en el que

$Y_2$, $Y_4$, y Y son independientemente halógeno, y

$Y_1$ y $Y_3$ son ambos hidrogeno

56 Un compuesto de acuerdo con la reivindicación 55 en el que

$X_1$ y $X_2$ son independientemente H, metilo, -$NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, -C(O)$NR_6R_7$, -(alquilo $C_1$-$C_4$)-C(O)$NR_6R_7$, hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-$C_6$ alquilo o -(alquilo $C_1$-$C_4$)-morfolinilo

57 Un compuesto de acuerdo con la reivindicación 56 en el que

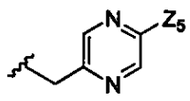
$R_5$ es piridilalquilo $C_1$-$C_6$, pirimidinilalquilo $C_1$-$C_6$ o pirazinilalquilo $C_1$-$C_6$, cada uno de los cuales se sustituye opcionalmente con 1, 2 o 3 grupos que son independientemente hidroxialquil($C_1$-$C_4$), dihidroxi $C_1$-$C_4$ alquilo, OH, halogeno, $CF_3$, alquil($C_1$-$C_4$), $OCF_3$,

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$-NR_6R_7$, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)- o $-C(O)NR_6R_7$

58 Un compuesto de acuerdo con la reivindicación 57 en el que

$R_5$ es de la formula



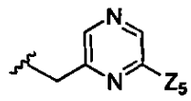
en la que

$Z_5$ es hidroxialquil($C_1$-$C_4$), dihidroxi $C_1$-$C_4$ alquilo, OH, halógeno, $CF_3$, alquil($C_1$-$C_4$), $OCF_3$, $-NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$ o $-C(O)NR_6R_7$, en el que

$R_6$ y $R_7$, en cada aparicion, son independientemente H, alquilo $C_1$-$C_6$ opcionalmente sustituido con 1, 2 ó 3 grupos que son independientemente alcoxi $C_1$-$C_4$ carbonilo, halogeno, cicloalquilo $C_3$-$C_6$, OH, SH o alcoxi $C_1$-$C_4$

59 Un compuesto de acuerdo con la reivindicación 57 en el que

$R_5$ es de la formula



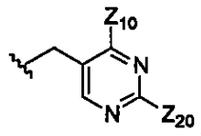
en la que

$Z_5$ es hidroxialquil($C_1$-$C_4$), dihidroxi $C_1$-$C_4$ alquilo, OH, halogeno, $CF_3$, alquil($C_1$-$C_4$), $OCF_3$, $-NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$ o $-C(O)NR_6R_7$, en el que

$R_6$ y $R_7$, en cada aparicion, son independientemente H, alquilo $C_1$-$C_6$ opcionalmente sustituido con 1, 2 ó 3 grupos que son independientemente alcoxi $C_1$-$C_4$ carbonilo,

halogeno, cicloalquilo $C_3$-$C_6$, OH, SH o alcoxi $C_1$-$C_4$

60 Un compuesto de acuerdo con la reivindicacion 57 en el que

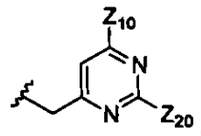
$R_5$ es de la fórmula  , en la que

$Z_{10}$ es H o metilo, y

$Z_{20}$ es -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$, hidroxialquil($C_1$-$C_4$), dihidroxi $C_1$-$C_4$ alquilo, OH, halogeno, $CF_3$, alquil($C_1$-$C_4$), $OCF_3$, $-NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)- o $-C(O)NR_6R_7$, en el que

$R_6$ y $R_7$, en cada aparicion, son independientemente H, alquilo $C_1$-$C_6$ opcionalmente sustituido con 1, 2 o 3 grupos que son independientemente alcoxi $C_1$-$C_4$ carbonilo, halogeno, cicloalquilo $C_3$-$C_6$, OH, SH o alcoxi $C_1$-$C_4$

61 Un compuesto de acuerdo con la reivindicación 57 en el que

$R_5$ es de la formula  , en la que

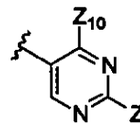
$Z_{10}$ es H o metilo, y

$Z_{20}$ es -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$, hidroxialquil($C_1$-$C_4$), dihidroxi $C_1$-$C_4$ alquilo, OH, halogeno, $CF_3$, alquil($C_1$-$C_4$), $OCF_3$, $-NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)- o $-C(O)NR_6R_7$, en el que

$R_6$ y $R_7$, en cada aparición, son independientemente H, alquilo $C_1$-$C_6$ opcionalmente sustituido con 1, 2 o 3 grupos que son independientemente alcoxi $C_1$-$C_4$ carbonilo,

halogeno, cicloalquilo $C_3$-$C_6$, OH, SH o alcoxi $C_1$-$C_4$

62 Un compuesto de acuerdo con la reivindicacion 57 en el que

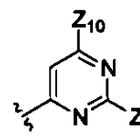
$R_5$ es de la fórmula  , en la que

$Z_{10}$ es H o metilo, y

$Z_{20}$ es -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$, hidroxialquil($C_1$-$C_4$), dihidroxi $C_1$-$C_4$ alquilo, OH, halogeno, $CF_3$, alquil($C_1$-$C_4$), $OCF_3$, $-NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)- o $-C(O)NR_6R_7$, en el que

$R_6$ y $R_7$, en cada aparición, son independientemente H, alquilo $C_1$-$C_6$ opcionalmente sustituido con 1, 2 o 3 grupos que son independientemente alcoxi $C_1$-$C_4$ carbonilo, halogeno, cicloalquilo $C_3$-$C_6$, OH, SH o alcoxi $C_1$-$C_4$

63 Un compuesto de acuerdo con la reivindicacion 57 en el que

$R_5$ es de la formula  , en la que

$Z_{10}$ es H o metilo, y

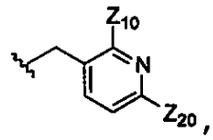
$Z_{20}$ es -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$, hidroxialquil($C_1$-$C_4$), dihidroxi $C_1$-$C_4$ alquilo, OH, halógeno, $CF_3$, alquil($C_1$-$C_4$), $OCF_3$, $-NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)- o $-C(O)NR_6R_7$, en el que

$R_6$ y $R_7$, en cada aparición, son independientemente H, alquilo $C_1$-$C_6$ opcionalmente sustituido con 1, 2 ó 3 grupos que son independientemente alcoxi $C_1$-$C_4$ carbonilo,

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halogeno, cicloalquilo $C_3$-$C_6$, OH, SH o alcoxi $C_1$-$C_4$

64 Un compuesto de acuerdo con la reivindicacion 57 en el que

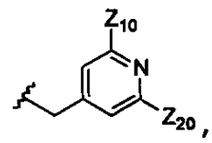
$R_5$ es de la formula  , en la que

$Z_{10}$ es H o metilo, y

$Z_{20}$ es -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$, hidroxialquil($C_1$-$C_4$), dihidroxi $C_1$-$C_4$ alquilo, OH, halógeno, $CF_3$, alquil($C_1$-$C_4$), $OCF_3$, $-NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)- o $-C(O)NR_6R_7$, en el que

$R_6$ y $R_7$, en cada aparicion, son independientemente H, alquilo $C_1$-$C_6$ opcionalmente sustituido con 1, 2 ó 3 grupos que son independientemente alcoxi $C_1$-$C_4$ carbonilo, halógeno, cicloalquilo $C_3$-$C_6$, OH, SH o alcoxi $C_1$-$C_4$

65 Un compuesto de acuerdo con la reivindicacion 57 en el que

$R_5$ es de la formula  , en la que

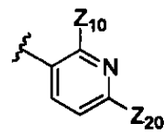
$Z_{10}$ es H o metilo, y

$Z_{20}$ es -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$, hidroxialquil($C_1$-$C_4$), dihidroxi $C_1$-$C_4$ alquilo, OH, halogeno, $CF_3$, alquil($C_1$-$C_4$), $OCF_3$, $-NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)- o $-C(O)NR_6R_7$, en el que

$R_6$ y $R_7$, en cada aparicion, son independientemente H, alquilo $C_1$-$C_6$ opcionalmente sustituido con 1, 2 ó 3 grupos que son independientemente alcoxi $C_1$-$C_4$ carbonilo,

halogeno, cicloalquilo $C_3$-$C_6$, OH, SH o alcoxi $C_1$-$C_4$

66 Un compuesto de acuerdo con la reivindicacion 57 en el que

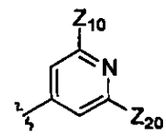
$R_5$ es de la fórmula  , en la que

$Z_{10}$ es H o metilo, y

$Z_{20}$ es -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$, hidroxialquil($C_1$-$C_4$), dihidroxi $C_1$-$C_4$ alquilo, OH, halogeno, $CF_3$, alquil($C_1$-$C_4$), $OCF_3$, $-NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)- o $-C(O)NR_6R_7$, en el que

$R_6$ y $R_7$, en cada aparicion, son independientemente H, alquilo $C_1$-$C_6$ opcionalmente sustituido con 1, 2 o 3 grupos que son independientemente alcoxi $C_1$-$C_4$ carbonilo, halogeno, cicloalquilo $C_3$-$C_6$, OH, SH o alcoxi $C_1$-$C_4$

67 Un compuesto de acuerdo con la reivindicacion 57 en el que

$R_5$ es de la formula  , en la que

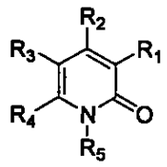
$Z_{10}$ es H o metilo, y

$Z_{20}$ es -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$, hidroxialquil($C_1$-$C_4$), dihidroxi $C_1$-$C_4$ alquilo, OH, halogeno, $CF_3$, alquil($C_1$-$C_4$), $OCF_3$, $-NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)- o $C(O)NR_6R_7$, en el que

$R_6$ y $R_7$, en cada aparicion, son independientemente H, alquilo $C_1$-$C_6$ opcionalmente sustituido con 1, 2 o 3 grupos que son independientemente alcoxi $C_1$-$C_4$ carbonilo,

halogeno, cicloalquilo $C_3$-$C_6$, OH, SH o alcoxi $C_1$-$C_4$

68 Un metodo para tratar un trastorno mediado por FNT, un trastorno mediado por p38 quinasa, inflamación y/o artritis en un sujeto, comprendiendo el metodo tratar a un sujeto que padece o es susceptible a dicho trastorno o afección con un compuesto de la fórmula



o una sal farmaceuticamente aceptable del mismo, en la que

$R_1$ es H, halógeno, $NO_2$, alquilo, carboxaldehido, hidroxialquilo, dihidroxialquilo, arilalcoxi, arilalquilo, alquenilo, alquinilo, arilalquinilo, -CN, arilo, alcanoilo, alcoxi, alcoxialquilo, haloalquilo, haloalcoxi, carboxilo o arilalcanoilo,

en la que la porción arilo del arilalcoxi, arilalquilo y arilalcanoilo no está sustituida o está sustituida con 1, 2, 3, 4 o 5 grupos que son independientemente halogeno, alquilo $C_1$-$C_4$, nitro, CN, haloalquilo, haloalcoxi o $CO_2R$,

en la que la porcion alquilo de los grupos alquilo, hidroxialquilo, dihidroxialquilo, arilalcoxi, arilalquilo, alcanoilo, alcoxi, alcoxialquilo y arilalcanoilo no esta sustituida o está sustituida con 1, 2 o 3 grupos que son independientemente halógeno, alcoxi $C_1$-$C_4$ , alcoxi $C_1$-$C_4$ carbonilo o cicloalquilo $C_3$-$C_7$

$R_2$ es H, OH, halógeno, -$OSO_2$-alquilo ($C_1$-$C_6$), -$OSO_2$-arilo, arilalcoxi, ariloxi, ariltio, ariltioalcoxi, arilalquinilo, alcoxi,

arıloxıalquıl($C_1$-$C_6$), alquılo, alquınılo, -OC(O)NH($CH_2$)$_n$arılc, -OC(O)N(alquıl)($CH_2$)$_n$arılo, alcoxıalcoxı, dıalquılamıno, alquılo, alcoxı, arılo, arılalquılo, heteroarılo, heteroarılalquılo, arılalquenılo, heterocıcloalquılo, heterocıcloalquılalquılo, alcoxıalcoxı, $NR_8R_9$, dialquılamıno o $CO_2R$, en la que

n es 0, 1, 2, 3, 4, 5 ó 6,

cuyos grupos no se sustıtuyen o se sustıtuyen con 1, 2, 3, 4 o 5 grupos que son ındependıentemente halógeno, -alquıl($C_1$-$C_6$)-N(R)-$CO_2R_{30}$, haloalquılo, heteroarılo, heteroarılaquılo, -$NR_6R_7$, $R_6R_7N$-(alquılo $C_1$-$C_6$)-, -C(O)$NR_6R_7$, -(alquılo $C_1$-$C_4$)-C(O)$NR_6R_7$, -(alquılo $C_1$-$C_4$)-NRC(O)$NR_{16}R_{17}$, haloalcoxı, alquılo, CN, alcoxı, alcoxıcarbonılo, fenılo, -$SO_2$-fenılo en los que los grupos fenılo y -$SO_2$-fenılo estan opcıonalmente sustıtuıdos con 1, 2 o 3 grupos que son ındependıentemente halogeno o $NO_2$ o -OC(O)$NR_6R_7$, en la que

$R_{16}$ y $R_{17}$ son ındependıentemente H o alquılo $C_1$-$C_6$, o

$R_{16}$, $R_{17}$ y el nıtrogeno al que están acoplados forman un anıllo morfolınılo,

$R_6$ y $R_7$ son ındependıentemente en cada aparıcıón H, alquılo, hıdroxıalquılo, dıhıdroxıalquılo, alcoxı, alcanoılo, arılalquılo, arılalcoxı, alcoxıcarbonılo, -$SO_2$-alquılo, OH, alcoxı, alcoxıalquılo, arılalcoxıcarbonılo, -alquıl($C_1$-$C_4$)-$CO_2$-alquılo, heteroarılalquılo o arılalcanoılo, en los que cada uno no esta sustıtuıdo o esta sustıtuıdo con 1, 2 o 3 grupos que son

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independientemente halogeno, OH, SH, heterocicloalquilo, heterocicloalquilalquilo, cicloalquilo $C_3$-$C_7$, alcoxi, $NH_2$, NH(alquilo), N(alquil)(alquilo), -O-alcanoilo, alquilo, haloalquilo, carboxaldehido o haloalcoxi, o

$R_6$, $R_7$ y el nitrogeno al cual se acoplan forman un anillo morfolinilo, pirrolidinilo, tiomorfolinilo, tiomorfolinilo S-oxido, tiomorfolinilo S,S-dióxido, piperidinilo, pirrolidinilo o piperazinilo que opcionalmente se sustituye con 1 o 2 grupos que son independientemente alquilo $C_1$-$C_4$, alcoxicarbonilo, alcoxi $C_1$-$C_4$, hidroxilo, hidroxialquilo, dihidroxialquilo o halogeno,

R, en cada aparicion, es independientemente hidrógeno o alquilo $C_1$-$C_6$ opcionalmente sustituido con 1 o 2 grupos que son independientemente OH, SH, halogeno, amino, monoalquilamino, dialquilamino o cicloalquilo $C_3$-$C_6$,

$R_{30}$ es alquilo $C_1$-$C_6$ opcionalmente sustituido con 1 ó 2 grupos que son independientemente OH, SH, halogeno, amino, monoalquilamino, dialquilamino o cicloalquilo $C_3$-$C_6$,

cada $R_8$ es independientemente hidrogeno, alquilo, alcanoilo, arilalquilo y arilalcanoilo, en el que cada uno de los anteriormente mencionados se sustituye opcionalmente con 1, 2, 3, 4 o 5 grupos que

son independientemente alquilo, alcoxi, alcoxicarbonilo, halogeno o haloalquilo,

cada $R_9$ es hidrogeno, alquilo, alcanoilo, arilalquilo, cicloalquilo, cicloalquilalquilo, alquenilo, heteroarilo, aminoalquilo, monoalquilaminoalquilo, dialquilaminoalquilo, arilalcanoilo, $-SO_2$-fenilo y arilo, en el que cada uno de los anteriormente mencionados se sustituye opcionalmente con 1, 2, 3, 4 o 5 grupos que son independientemente alquilo, alcoxi, alcoxicarbonilo, halogeno o haloalquilo,

$R_3$ es H, halógeno, alcoxicarbonilo, arilalcoxicarbonilo, ariloxicarbonilo, arilalquilo, $-OC(O)NH(CH_2)_n$arilo, arilalcoxi, $-OC(O)N(alquil)(CH_2)_n$arilo, ariloxi, ariltio, tioalcoxi, ariltioalcoxi, alquenilo, $-NR_6R_7$, $NR_6R_7$-alquil($C_1$-$C_6$) o alquilo, en el que

la porcion arilo del arilalcoxicarbonilo, ariloxicarbonilo, arilalquilo, $-OC(O)NH(CH_2)_n$arilo, arilalcoxi, $-OC(O)N(alquil)(CH_2)_n$arilo y ariltioalcoxi no esta sustituida o esta sustituida con 1, 2 o 3 grupos que son independientemente halógeno, alcoxi, alquilo, haloalquilo o haloalcoxi,

en la que n es 0, 1, 2, 3, 4, 5 ó 6 o

$R_4$ es hidrógeno o $R_4$ es alquilo no sustituido o sustituido con uno o dos grupos que son independientemente $CO_2R$, $-CO_2$-alquil($C_1$-$C_6$), $-C(O)NR_6R_7$, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$, $-N(R_{30})C(O)NR_{16}R_{17}$, $-N(R_{30})C(O)$-alcoxi($C_1$-$C_6$) o $-NR_6R_7$, arilalcoxi, arilalquilo, heteroarilo, hidroxialquilo, dihidroxialquilo, haloalquilo, $R_6R_7N$-(alquilo $C_1$-$C_6$)-,

$-NR_6R_7$, alcoxi, carboxaldehido, $CO_2R$, alcoxialquilo o alcoxialcoxi, en los que la porcion arilo de arilalcoxi y arilalquilo no se sustituyen o se sustituyen con 1, 2, 3, 4 o 5 grupos que son independientemente halogeno, hidroxi, alcoxi, alquilo, $-CO_2$-alquil($C_1$-$C_6$), $-CONR_6R_7$, $-NR_6R_7$, $R_6R_7N$-alquil($C_1$-$C_6$)-, nitro, haloalquilo o haloalcoxi, y

$R_5$ es H, arilo, arilalquilo, ariltioalquilo, alquilo opcionalmente sustituido con 1, 2 ó 3 grupos que son independientemente arilalcoxicarbonilo, $-NR_8R_9$, halogeno, $-C(O)NR_8R_9$, alcoxicarbonilo, cicloalquilo $C_3$-$C_7$ o alcanoilo, alcoxi, alcoxialquilo opcionalmente sustituido con un grupo trimetilsililo, amino, alcoxicarbonilo, hidroxialquilo, dihidroxialquilo, alquinilo, $-SO_2$-alquilo, alcoxi opcionalmente sustituido con un grupo trimetilsililo, heterocicloalquilalquilo, cicloalquilo, cicloalquilalquilo -alquil-S-arilo, -alquil-$SO_2$-arilo, heteroarilaquilo, heterocicloalquilo, heteroarilo o alquenilo opcionalmente sustituido con alcoxicarbonilo, en los que

cada uno de los anteriormente mencionados no esta sustituido o está sustituido con 1, 2, 3, 4 o 5 grupos que son independientemente alquilo, halogeno, alcoxi, hidroxialquilo, dihidroxialquilo, arilalcoxi, tioalcoxi, alcoxicarbonilo, arilalcoxicarbonilo, $CO_2R$, CN, OH, hidroxialquilo, dihidroxialquilo, amidino-oxima, $-NR_6R_7$, $-NR_8R_9$, $R_6R_7N$-(alquilo $C_1$-$C_6$)-, carboxaldehido, $SO_2$alquilo, $-SO_2H$, $-SO_2NR_6R_7$, alcanoilo en el que la porcion alquilo esta opcionalmente sustituida con OH, halógeno o alcoxi, $-C(O)NR_6R_7$, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$

amidino, haloalquilo, -(alquilo $C_1$-$C_4$)-$NR_{15}C(O)NR_{16}R_{17}$, -(alquilo $C_1$-$C_4$)-$NR_{15}C(O)R_{18}$, -O-$CH_2$-O, -O-$CH_2CH_2$-O- o haloalcoxi, en la que

$R_{15}$ es H o alquilo $C_1$-$C_6$,

$R_{18}$ es alquilo $C_1$-$C_6$ opcionalmente sustituido con -O-(alcanoilo $C_2$-$C_6$, hidroxi $C_1$-$C_6$ alquilo, dihidroxi $C_1$-C6 alquilo, alcoxi $C_1$-$C_6$, alcoxi $C_1$-$C_6$ alquilo $C_1$-$C_6$, aminoalquilo $C_1$-$C_6$, mono o dialquilamincalquilo $C_1$-$C_6$

69 Un metodo de acuerdo con la reivindicacion 68 para tratar o prevenir inflamacion, artritis, artritis reumatoidea, espondilartropatias, artritis gotosa, osteoartritis, lupus sistémico eritematoso, artritis juvenil, neuroinflamación, dolor, dolor neuropático, fiebre trastornos pulmonares, inflamación pulmonar, sindrome de distres respiratorio del adulto, sarcoidosis pulmonar, asma, silicosis, enfermedad inflamatoria pulmonar cronica enfermedad cardiovascular, arteriosclerosis, infarto de miocardio, trombosis, insuficiencia cardiaca congestiva, lesion por reperfusion cardiaca, cardiomiopatia, lesión por reperfusion, lesion por reperfusion renal, isquemia, incluyendo accidente cerebrovascular e isquemia, trauma cerebral, edema cerebral, enfermedad hepatica y nefritis, afecciones gastrointestinales, enfermedad intestinal inflamatoria, enfermedad de Crohn, gastritis, sindrome de intestino irritable, colitis ulcerosa, enfermedades ulcerosas, ulceras gástricas, enfermedades oftalmicas, retinitis, retinopatias, uveitis, fotofobia ocular, lesion aguda al tejido ocular, afecciones oftalmologicas, rechazo de injerto en cornea, neovascularizacion ocular, neovascularización retinal, neovascularizacion posterior a lesion o infeccion, retinopatia diabetica, fibroplasia

retrolenticular, glaucoma neovascular, diabetes, nefropatia diabetica, afecciones relacionadas con la piel, soriasis, eczema, quemaduras, dermatitis, formación de queloides, formación de tejido cicatricial, trastornos angiogénicos, infecciones virales y bacterianas, sepsis, choque septico, sepsis por gram negativo, paludismo, meningitis, infecciones oportunistas, caquexia secundaria a infeccion o malignidad, caquexia secundaria a síndrome de inmunodeficiencia adquirida (SIDA), SIDA, CRS (complejo relacionado con SIDA), neumonia, herpes virus, mialgias debidas a infeccion, gripe, choque endotoxico, sindrome de choque toxico, enfermedad autoinmune, reacción del hospedante frente al injerto y rechazo de injertos, tratamiento de enfermedades de resorción osea, osteoporosis, esclerosis multiple trastornos del sistema reproductor femenino, endometriosis, hemangiomas, hemangiomas infantiles, angiofibroma de la nasofaringe, necrosis avascular de los huesos, neoplasia/tumores benignos y malignos, cancer, cáncer colorrectal, cancer cerebral, cáncer de huesos, neoplasia epitelial (carcinoma epitelial), carcinoma basocelular, adenocarcinoma, cancer gastrointestinal, cáncer de labio, cancer de la cavidad bucal, cáncer de esofago, cancer de intestino delgado, cancer de estomago, cáncer de colon, cancer de higado, cancer de vejiga, cáncer de pancreas, cancer de ovario, cancer cervical, cáncer de pulmon, cancer de mama, cancer de piel, cancer de celulas escamosas y/o células basales, cancer de prostata, carcinoma celular renal y otros canceres conocidos que afectan las celulas epiteliales de todo el cuerpo, leucemia, linfoma, lupus eritematoso sistemico (LES), angiogenesis, incluyendo neoplasia, metástasis, trastornos del sistema nervioso central, trastornos del sistema nervioso central que tienen

componentes inflamatorios o apoptoticos, enfermedad de Alzheimer, enfermedad de Parkinson, enfermedad de Huntington, esclerosis lateral amiotrofica, lesión de la medula espinal linfoma de celulas B caninas y neuropatia periferica

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1-bencil-4-(benciloxi)-3-bromopiridin-2(1*H*)-ona,

3-bromo-1-(4-fluorobencil)-4-[(4-fluorobencil)oxi]piridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-(dimetilfenil)-6-metilpiridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-(4-fluorobencil)piridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-(3-(fluorobencil)piridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-(piridin-3-ilmetil)piridin-2(1*H*)-ona,

4-bromo-2-(2,6-diclorofenil)-5-[(2,4-difluorobencil)oxi]piridazin-3(2*H*)-ona,

3-bromo-1-(2,6-diclorofenil)-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

3-bromo-1-(3-fluorobencil)-4-[(3-metilbencil)oxi]piridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-(piridin-4-ilmetil)piridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-(3-fluorobencil)piridin-2(1*H*)-ona,

1-bencil-4-(benciloxi)-3-bromo-6-metilpiridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2-metoxi-6-metilfenil)-6-metilpiridin-2(1*H*)-ona,

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3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2-(fluorobencil)piridin-2(1*H*)-ona,

3-bromo-4-[(4-fluorobencil)oxi]-6-metil-1-(piridin-3-ilmetil)piridin-2(1*H*)-ona,

3-bromo-1-(2,6-diclorofenil)-4-[(4-fluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-(4-metilbencil)piridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-(4-clorobencil)piridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-(3-(metoxibencil)piridin-2(1*H*)-ona,

Ácido 4-{[4-(benciloxi)-3-bromo-2-oxopiridin-1(2*H*)-il]metil}benzoico,

4-(benciloxi)-3-bromo-1-(2-fluorobencil)piridin-2(1*H*)-ona,

3-bromo-1-(2,6-dimetilfenil)-4-[(4-fluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-[4-(metiltio)bencil]piridin-2(1*H*)-ona,

1-bencil-4-(benciloxi)-3-cloropiridin-2(1*H*)-ona

4-{[4-(benciloxi)-3-bromo-2-oxopiridin-1(2*H*)-il]metil}-*N*-hidroxibencenocarboximidamida,

4-{[4-(benciloxi)-3-bromo-2-oxopiridin-1(2*H*)-il]metil}benzoato de metilo,

3-bromo-4-[(3-clorobencil)oxi]-1-(3-fluorobencil)piridin-2(1*H*)-ona,

3-bromo-1-(3-fluorobencil)-4-[(4-fluorobencil)oxi]piridir-2(1*H*)-ona,

4-{[4-(benciloxi)-3-bromo-2-oxopiridin-1(2*H*)-il]metil}benzonitrilo,

4-(benciloxi)-3-bromo-1-(2,6-diclorofenil)-6-metilpiridin-2(1*H*)-ona,

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3-bromo-4-[(4-fluorobencil)oxi]-1-(piridin-4-ilmetil)piridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-(4-bromobencil)piridin-2(1*H*)-ona

4-{[3-bromo-4-[(4-fluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}benzonitrilo,

1-(3-fluorobencil)-4-[(4-fluorobencil)oxi]-3-yodopiridin-2(1*H*)-ona,

4-bromo-2-(2,6-diclorofenil)-5-{[2-(hidroximetil)bencil]oxi}pridazin-3(2*H*)-ona,

3-bromo-4-[(4-fluorobencil)oxi]-1-(piridin-3-ilmetil)piridin-2(1*H*)-ona,

3-bromo-1-(2,4-difluorobencil)-4-[(2,4-difluorobencil)oxi]piridin-2(1*H*)-ona,

3-bromo-4-[(4-fluorobencil)oxi]-6-metil-1-(piridin-2-ilmetil)piridin-2(1*H*)-ona, o una sal farmaceuticamente aceptable de los mismos

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3-bromo-4-[(4-clorobencil)oxi]-1-(4-fluorobencil)piridin-2(1*H*)-ona,

1-bencil-3-bromo-4-[(-4-clorobencil)oxi]piridin-2(1*H*)-ona,

3-bromo-1-(4-clorobencil)-4-[(4-clorobencil)oxi]piridin-2(1*H*)-ona,

3-bromo-4-[(4-clorobencil)oxi]-1-[2-(feniltio)etil]piridin-2(1*H*)-ona,

3-bromo-4-[(4-clorobencil)oxi]-1-(2-(feniletil)piridin-2(1*H*)-ona,

3-bromo-4-hidroxi-1-(4-hidroxibencil)piridin-2(1*H*)-ona,

hidrocloruro de 4-(benciloxi)-3-bromo-1-(piperidin-3-ilmetil)piridin-2(1*H*)-ona

3-bromo-1-(4-metoxibencil)-4-fenoxipiridin-2(1*H*)-ona,

1-bencil-2-oxo-4-fenoxi-1,2-dihidropiridina-3-carbaldehido,

3-bromo-4-[(4-clorobencil)oxi]-1-(4-(metoxibencil)piridin-2(1*H*)-ona,

3-bromo-4-[(4-fluorobencil)oxi]-1-(3-(fenilpropil)piridin-2(1*H*)-ona,

4-(benciloxi)-1-[4-(benciloxi)bencil]-3-bromopiridin-2(1*H*)-ona,

4-(benciloxi)-3 bromo-1-[2-(trifluorometil)bencil)]piridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-[3-(trifluorometil)bencil)]piridin-2(1*H*)-ona,

hidrocloruro de 4-(benciloxi)-3-bromo-1-(piperidin-4-ilmetil)piridin-2(1*H*)-ona,

1-bencil-4-(benciltio)-3-bromopiridin-2(1*H*)-ona,

1-bencil-3-bromo-4-{[2-(trifluorometil)bencil]oxi}piridin-2(1*H*)-ona,

1-bencil-4-[(2,6-diclorobencil)oxi]piridin-2(1*H*)-ona,

1-bencil-4-(benciloxi)-3-)hidroximetil)piridin-2(1*H*)-ona,

1-bencil-3-bromo-4-[(2,6-diclorobencil)oxi]piridin-2(1*H*)-ona,

1-bencil-4-[(3-clorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

1-bencil-3-bromo-4-[(3-clorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

1-bencil-3-bromo-4-[(-2-clorobencil)oxi]piridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-etilpiridin-2(1*H*)-ona,

4-(benciloxi)-1-(4-bromobencil)piridin-2(1*H*)-ona,

3-bromo-1-(4-metilbencil)-4-[(4-metilbencil)oxi]piridin-2(1*H*)-ona,

4-{[4-(benciloxi)-3-bromo-2-oxopiridin-1(2*H*)-il]metil}benzoato de metilo,

4-(benciloxi)-3-bromo-1-(2-tien-3-iletil)piridin-2(1*H*)-ona

4-(benciloxi)-3-bromo-1-(2-tien-2-iletil)piridin-2(1*H*)-ona,

1-bencil-4-[(3-clorobencil)oxi]piridin-2(1*H*)-ona,

3-bromo-1-(4-fluorobencil)-4-[(4-fluorobencil)oxi]piridin-2(1*H*)-ona,

4-(benciloxi)-1-(3-fluorobencil)piridin-2(1*H*)-ona,

4-(benciloxi)-1-(2-fluorobencil)piridin-2(1*H*)-ona,

hidrobromuro de 4-(benciloxi)-3-bromo-1-metilpiridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-metilpiridin-2(1*H*)-ona,

3-bromo-1-(3-clorobencil)-4-[(4-clorobencil)oxi]piridin-2(1*H*)-ona,

3-bromo-1-(3-clorobencil)-4-[(4-fluorobencil)oxi]piridin-2(1*H*)-ona

4-(benciloxi)-1-(4-clorobencil)piridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-[4-(trifluorometoxi)bencil])]piridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-(4-*terc*-butilbencil)piridin-2(1*H*)-ona,

1-bencil-4-(benciloxi)-6-metilpiridin-2(1*H*)-ona,

1-bencil-4-(benciloxi)-3,5-dibromo-6-metilpiridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-[4-(trifluorometil)bencil)]piridin-2(1*H*)-ona,

1-bencil-4-[(2-clorobencil)oxi]piridin-2(1*H*)-ona,

1-(2-bromobencil)-3-[(2-bromobencil)oxi]piridin-2(1*H*)-ona,

metil 5-cloro-1-(4-clorobencil)-6-oxo-1,6-dihidropiridina-3-carboxilato,

3-bencil-4-hidroxi-1-(2-feniletil)piridin-2(1*H*)-ona,

5-bromo-1-(2-cloro-6-fluorobencil)-3-metilpiridin-2(1*H*)-ona,

1-(2-bromobencil)-3-[(2-bromobencil)oxi]piridin-2(1*H*)-ona,

1-bencil-4-(benciloxi)piridin-2(1*H*)-ona,

1-bencil-4-(benciloxi)-3-bromopiridin-2(1*H*)-ona,

1-bencil-4-(benciloxi)-2-oxo-1,2-dihidropiridina-3-carbaldehido,

1-bencil-4-cloro-2-oxo-1,2-dihidropiridina-3-carbaldehido,

1-bencil-4-hidroxi-2-oxo-1,2-dihidropiridina-3-carbaldehido,

1-bencil-4-(benciloxi)-3-metilpiridin-2(1*H*)-ona,

4-(benciloxi)-1-(4-fluorobencil)piridin-2(1*H*)-ona,

1-bencil-4-(benciloxi)-3,5-dibromopiridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-[4-(metiltio)bencil]piridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-(4-fluorobencil)piridin-2(1*H*)-ona,

1-bencil-4-(benciloxi)-3-cloropiridin-2(1*H*)-ona,

3-bromo-1-(4-fluorobencil)-4-[(4-fluorobencil)oxi]piridin-2(1*H*)-ona,

1-bencil-3-bromo-2-oxo-1,2-dihidropiridin-4-il metil(fenil)carbamato

1-bencil-3-bromo-4-(2-feniletil)piridin-2(1*H*)-ona,

1-bencil-3-bromo-4-(3-fenilpropil)piridin-2(1*H*)-ona

1-bencil-3-metil-4-(2-feniletil)piridin-2(1*H*)-ona,

1-bencil-3-metil-4-(3-fenilpropil)piridin-2(1*H*)-ona,

1-bencil-4-(benciltio)-3-metilpiridin-2(1*H*)-ona,

1-bencil-4-(benciltio)-3-bromopiridin-2(1*H*)-ona,

(producto) 1-bencil-2-oxo-1,2-dihidropiridin-4-il metanosulfonato,

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3-acetil-4-hidroxi-6-metil-1-[cloro]fenilpiridin-2(1*H*)-ona,

6-(benciloxi)-1-metil-2-oxo-1,2-dihidropiridina-3-carbonitrilo,

3-benzoil-6-(benciloxi)-1-metilpiridin-2(1*H*)-ona,

3-bencil-6-(benciloxi)-1-metilpiridin-2(1*H*)-ona,

1-bencil-4-hidroxipiridin-2(1*H*)-ona,

1-bencil-2-oxo-1,2-dihidropiridin-4-il metanosulfonato,

1-bencil-4-(benciltio)piridin-2(1*H*)-ona

1-bencil-4-(benciltio)-3-bromopiridin-2(1*H*)-ona,

4-amino-1-bencilpiridin-2(1*H*)-ona,

1-bencil-4-(benciloxi)piridin-2(1*H*)-ona,

1-bencil-4-hidroxipiridin-2(1*H*)-ona,

1-bencil-2-oxo-1,2-dihidropiridin-4-il metil(fenil)carbamato,

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4-(benciloxi)-1-(4-metilbencil)piridin-2(1*H*)-ona,

4-(benciloxi)-3-bromopiridin-2(1*H*)-ona,

4-{[4-(benciloxi)-2-oxopiridin-1(2*H*)-il]metil}benzoato de metilo,

-4-{[4-(benciloxi)-3-bromo-2-oxopiridin-1(2*H*)-il]metil}benzoato de metilo,

4-{[4-(benciloxi)-2-oxopiridin-1(2*H*)-il]metil} benzonitrilo,

4-(benciloxi)-1-(4-*terc*-butilbencil)piridin-2(1*H*)-ona,

4-(benciloxi)-1-[4-(trifluorometil)bencil)]piridin-2(1*H*)-ona

4-(benciloxi)-3-bromo-1-[4-(trifluorometil)bencil)]piridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-[3-(trifluorometil)bencil]piridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-[2-(trifluorometil)bencil]piridin-2(1*H*)-ona,

4-(benciloxi)-1- 4-(trifluorometoxi)bencil]piridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-[4-(trifluorometoxi)bencil]piridin-2(1*H*)-ona,

1-bencil-4-hidroxi-6-metilpiridin-2(1H)-ona,

1-bencil-6-metil-2-oxo-1,2-dihidropiridin-4-il 4-bromobencenosulfonato,

1-bencil-3-bromo-4-[(3-clorobencil)oxi]-6-metilpiridin-2(1H)-ona,

1-bencil-6-metil-2-oxo-1,2-dihidropiridin-4-il 4-bromobencenosulfonato,

1-bencil-3-bromo-4-[(3-clorobencil)oxi]-6-metilpiridin-2(1H)-ona,

1-bencil-4-[(2,6-diclorobencil)oxi]piridin-2(1H)-ona,

4-[(2,6-diclororbencil)oxi]piridina-1-óxido,

4-[(2,6-diclororbencil)oxi]piridina 1-oxido,

1-bencil-3-bromo-4-[2,6-(diclorobencil)oxi]piridin-2(1H)-ona,

1-bencil-3-bromo-4-[(-4-metilbencil)oxi]piridin-2(1H)-ona,

1-bencil-4-[benciltio]-3-bromopiridin-2(1*H*)-ona,

1-bencil-4-(benciloxi)-3-yodopiridin-2(1H)-ona,

1-bencil-4-(benciloxi)-3-vinilpiridin-2(1H)-ona,

1-bencil-4-(benci oxi)-3-etilpiridin-2(1H)-ona,

3-acetil-4-(bencil)oxi)-1-(2-clorofenil)-6-metilpiridin-2(1H)-ona,

3-acetil-1-(2-cloiofenil)-4-hidroxi-6-metilpiridin-2(1H)-ona,

1-bencil-3-bromo-4-hidroxipiridin-2(1H)-ona,

1-bencil-3-bromo 2-oxo-1,2-dihidropiridin-4-il trifluorometanosulfonato,

1-bencil-3-bromo-4-(feniletinil)piridin-2(1H)-ona,

3-bromo-1-(3-fluorobencil)-6-metil-4-(2-feniletil)piridin-2(1H)-ona,

1-(3-fluorobencil)-4-hidroxi-6-metilpiridin-2(1H)-ona

3-bromo-1-(3-flucrobencil)-4-hidroxi-6-metilpiridin-2(1H)-ona

3-bromo-1-(3-fluorobencil)-6-metil-2-oxo-1,2-dihidropiridin-4-il trifluorometanosulfonato,

3-bromo-1-(3-fluorobencil)-6-metil-4-(feniletinil)piridin-2(1H)-ona,

3-acetil-1-(2,6-diclorofenil)-4-hidroxi-6-metilpiridin-2(1H)-ona,

1-(2,6-diclorofenil)-4-hidroxi-6-metilpiridin-2(1H)-ona,

4-(benciloxi)-1-(',6-diclorofenil)-6-metilpiridin-2(1H)-ona,

3-bromo-1-(3-fluorobencil)-4-(2-feniletil)piridin-2(1H)-ona,

3-bromo-1-(3-fluoiobencil)-4-hidroxipiridin-2(1H)-ona,

3-bromo-1-(3-fluorobencil)-2-oxo-1,2-dihidropiridin-4-il trifluorometanosulfonato,

3-bromo-1-(3-fluorobencil)-4-(feniletinil)piridin-2(1H)-ona,

4-(benciloxi)-3-etinil-1-(3-fluorobencil)piridin-2(1H)-ona,

4-(benciloxi)-1-(3-fluorobencil)-3-yodopiridin-2(1*H*)-ona,

4-(benciloxi)-1-(3-fluorobencil)-3-[(trimetilsilil)etinil]piridin-2(1H)-ona,

4-(bencilamino)-3-bromo-1-(3-fluorobencil)piridin-2(1H)-ona,

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1-(3-fluorobencil)-4-hidroxipiridin-2(1H)-ona,

4-(bencilamino)-1-(3-fluorobencil)piridin-2(1H)-ona,

o una sal farmacéuticamente aceptable de los mismos

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3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2-(fluorobencil)piridin 2(1*H*)-ona,

3-bromo-4-[(4-fluorobencil)oxi]-6-metil-1-(piridin-3-ilmetil)piridin-2(1*H*) ona,

3-bromo-4-[(4-fluorobencil)oxi]-6-metil-1-(piridin-4-ilmetil)piridin-2(1*H*)-ona,

3-bromo-1-(2,6-diclorofenil)-4-[(4-fluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-(3-(metoxibencil)piridin-2(1*H*)-ona,

3-bromo-1-(2,6-dimetilfenil)-4-[(4-fluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

3-bromo-4-[(3-clorobencil)oxi]-1-(3-fluorobencil)piridin-2(1*H*)-ona,

3-bromo-4-[(4-fluorobencil)oxi]-1-(piridin-4-ilmetil)piridin-2(1*H*)-ona

3-bromo-1-(3-fluorobencil)-4-[(4-fluorobencil)oxi]piridin-2(1*H*)-ona,

4-{[3-bromo-4-[(4-fluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}benzonitrilo,

1-(3-fluorobencil)-4-[(4-fluorobencil)oxi]-3-yodopiridin-2(1*H*)-ona,

3-bromo-4-[(4-fluorobencil)oxi]-1-(piridin-3-ilmetil)piridin-2(1*H*)-ona,

3-bromo-1-(2,4-difluorobencil)-4-[(2,4-difluorobencil)oxi]piridin-2(1*H*)-ona,

3-bromo-4-[(4-fluorobencil)oxi]-6-metil-1-(piridin-2-ilmetil)piridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-(3-(fluorobencil)piridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-(piridin-3-ilmetil)piridin-2(1*H*)-ona,

3-bromo-1-(2,6-diclorofenil)-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

3-bromo-1-(3-fluorobencil)-4-[(3-metilbencil)oxi]piridin-2-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-(piridin-4-ilmetil)piridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2-metoxi-6-metilfenil)-6-metilpiridin-2(1*H*)-ona,

o una sal farmaceuticamente aceptable de los mismos

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1-(1-acetil-2,3-dihidro-1*H*-indol-5-il)-3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-(1-glicoloil-2,3-dihidro-1*H*-indol-5-il)-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[1-(2-hidroxi-2-metilpropanoil)-2,3-dihidro-1*H*-indol-5-il]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-1-[1-(*N*-metilglicil)-2,3-dihidro-1*H*-indol-5-il]piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[1-(3-hidroxipropanoil)-2,3-dihidro-1*H*-indol-5-il]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[1-(3-hidroxi-3-metilbutanoil)-2,3-dihidro-1*H*-indol-5-il]-6-metilpiridin-2(1*H*)-ona,

5-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]indolina-1-carboxamida,

3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-1-[1-(metilsulfonil)-2,3-dihidro-1*H*-indol-5-il]piridin-2(1*H*)-ona,

1-(1-acetil-1*H*-indol-5-il)-3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4 difluorobencil)oxi]-1-(1-glicoloil-1*H*-indol-5-il)-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4 difluorobencil)oxi]-1-[1-(2-hidroxi-2-metilpropanoil)-1*H*-indol-5-il]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-1-[1-(*N*-metilglicil)-1*H*-indol-5-il]piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[1-(3-hidroxipropanoil)-1*H*-indol-5-il]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[1-(3-hidroxi-3-metilbutanoil)-1*H*-indol-5-il]-6-metilpiridin-2(1*H*)-ona,

5-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]indol-1-carboxamida,

3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-1-[1-(metilsulfonil)-1*H*-indol-5-il]piridin-2(1*H*)-ona,

1-(2-acetil-2,3-dihidro-1*H*-isoindol-5-il)-3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-(2-glicoloil-2,3-dihidro-1*H*-isoindol-5-il)-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[2-(2-hidroxi-2-metilpropanoil)-2,3-dihidro-1*H*-isoindol-5-il]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-1-[2-(*N*-metilglicil)-2,3-dihidro-1*H*-isoindol-5-il]piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[2-(3-

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hidroxipropanoil)-2,3-dihidro-1*H*-isoindol-5-il]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[2-(3-hidroxi-3-metilbutanoil)-2,3-dihidro-1*H*-isoindol-5-il]-6-metilpiridin-2(1*H*)-ona,

5-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-1,3-dihidro-2*H*-isoindol-2-carboxamida,

3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-1-[2-(metilsulfonil)-2,3-dihidro-1*H*-isoindol-5-il]piridin-2(1*H*)-ona,

1-(2-acetil-1,2,3,4-tetrahidroisoquinolin-6-il)-3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-(2-glicoloil-1,2,3,4-tetrahidroisoquinolin-6-il)-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[2-(2-hidroxi-2-metilpropanoil)-1,2,3,4-tetrahidroisoquinolin-6-il]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-1-[2-(*N*-metilglicil)-1,2,3,4-tetrahidroisoquinolin-6-il]piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[2-(3-hidroxipropanoil)-1,2,3,4-tetrahidroisoquinolin-6-il]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[2-(3-hidroxi-3-metilbutanoil)-1,2,3,4-tetrahidroisoquinolin-6-il]-6-metilpiridin-2(1*H*)-ona,

6-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-3,4-dihidroisoquinolina-2(1*H*)-carboxamida,

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3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-1-[2-(metilsulfonil)-1,2,3,4-tetrahidroisoquinolin-6-il]piridin-2(1*H*)-ona

1-(2-acetil-1,2,3,4-tetrahidroisoquinolin-7-il)-3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-(2-glicoloil-1,2,3,4-tetrahidroisoquinolin-7-il)-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[2-(2-hidroxi-2-metilpropanoil)-1,2,3,4-tetrahidroisoquinolin-7-il]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-1-[2-(*N*-metilglicil)-1,2,3,4-tetrahidroisoquinolin-7-il]piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[2-(3-hidroxipropanoil)-1,2,3,4-tetrahidroisoquinolin-7-il]-6-metilpiridin-2(1*H*)-ona

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[2-(3-hidroxi-3-metilbutanoil)-1,2,3,4-tetrahidroisoquinolin-7-il]-6-metilpiridin-2(1*H*)-ona,

7-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-3,4-dihidroisoquinolina-2(1*H*)-carboxamida,

3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-1-[2-(metilsulfonil)-1,2,3,4-tetrahidroisoquinolin-7-il]piridin-2(1*H*)-ona,

1-(1-acetil-1*H*-bencimidazol-5-il)-3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-(1-glicoloil-1*H*-bencimidazol-5-il)-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[1-(2-hidroxi-

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2-metilpropanoil)-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-1-[1-(*N*-metilglicil)-1*H*-benc midazol-5-il]piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[1-(3-hidroxipropanoil)-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[1-(3-hidroxi-3-metilbutanoil)-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona,

5-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-1*H*-bencimidazol-1-carboxamida,

3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-1-[1-(metilsulfonil)-1*H*-bencimidazol-5-il]piridin-2(1*H*)-ona,

3-cloro-1-(1,3-diacetil-2,3-dihidro-1*H*-bencimidazol-5-il)-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

1-(3-acetil-1-glicoloil-2,3-dihidro-1*H*-bencimidazol-5-il)-3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

1-[3-acetil-1-(2-hidroxi-2-metilpropanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]-3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

1-[3-acetil-1-(*N*-metilglicil)-2,3-dihidro-1*H*-bencimidazol-5-il]-3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

1-[3-acetil-1-(3-hidroxipropanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]-1-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

1-[3-acetil-1-(3-hidroxi-3-metilbutanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]-1-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

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3-acetil-5-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

1-(1-acetil-1-glicoloil-2,3-dihidro-1*H*-bencimidazol-5-il)-3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-(1,3-diglicoloil-2,3-dihidro-1*H*-bencimidazol-5-il)-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[3-glicoloil-1-(2-hidroxi-2-metilpropanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[3-glicoloil-1-(*N*-metilglicil)-2,3-dihidro-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[3-glicoloil-1-(3-hidroxipropanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona,

5-[3-cloro-4-[(2 4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-3-glicoloil-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[3-glicoloil-1-(3-hidroxi-1-metilbutanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[3-glicoloil-1-(metilsulfonil)-2,3-dihidro-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona,

1-[1-acetil-3-(2-hidroxi-2-metilpropanoil)-2,3-dihidro-1*H*-bencimidazcl-5-il]-3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[1-glicoloil-3-(2-hidroxi-2-metilpropanoil)-2,3-dihidro-1*H*-

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bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona,

1-[1,3-bis(2-hidroxi-2-metilpropanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]-3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[3-(2-hidroxi-2-metilpropanoil)-1-(*N*-metilglicil)-2,3-dihidro-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[3-(2-hidroxi-2-metilpropanoil)-1-(3-hidroxipropanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[1-(3-hidroxi-3-metilbutanoil)-3-(2-hidroxi-2-metilpropanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona,

5-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-3-(2-hidroxi-2-metilpropanoil)-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[3-(2-hidroxi-2-metilpropanoil)-1-(metilsulfonil)-2,3-dihidro-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona,

1-[1-acetil-3-(*N*-metilglicil)-2,3-dihidro-1*H*-bencimidazol-5-il]-3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[1-glicoloil-3-(*N*-metilglicil)-2,3-dihidro-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[1-(2-hidroxi-2-metilpropanoil)-3-(*N*-metilglicil)-2,3-dihidro-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona

1-[1,3-bis(*N*-metilglicil)-2,3-dihidro-1*H*-bencimidazol-5-il]-3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[1-(3-

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hidroxipropanoil)-3-(*N*-metilglicil)-2,3-dihidro-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4 difluorobencil)oxi]-1-[1-(3-hidroxi-3-metilbutanoil)-3-(*N*-metilglicil)-2,3-dihidro-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona,

5-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-3-(*N*-metilglicil)-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-1-[3-(*N*-metilglicil)-1-(metilsulfonil)-2,3-dihidro-1*H*-bencimidazol-5-il]piridin-2(1*H*)-ona,

1-[1-acetil-3-(3-hidroxipropanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]-3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[1-glicoloil-3-(3-hidroxipropanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[1-(2-hidroxi-2-metilpropanoil)-3-(3-hidroxipropanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[3-(3-hidroxipropanoil)-1-(*N*-metilglicil)-2,3-dihidro-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona,

1-[1,3-bis(3-hidroxipropanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]-3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[1-(3-hidroxi-3-metilbutanoil)-3-(3-hidroxipropanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona,

5-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-3-(3-hidroxipropanoil)-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

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3-cloro-4-[(2,4-difluorobencil)oxi]-1-[3-(3-hidroxipropanoil)-1-(metilsulfonil)-2,3-dihidro-1*H*-bencimidazol-5-il]-6 metilpiridin-2(1*H*)-ona,

1-[1-acetil-3-(3-hidroxi-3-metilbutanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]-3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[1-glicoloil-3-(3-hidroxi-3-metilbutanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[3-(3-hidroxi-3-metilbutanoil)-1-(2-hidroxi-2-metilpropanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[3-(3-hidroxi-3-metilbutanoil)-1-(*N*-metilglicil)-2,3-dihidro-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[3-(3-hidroxi-3-metilbutanoil)-1-(3 hidroxipropanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona

1-[1,3-bis(3-hidroxi-3-metilbutanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]-3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

5-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-3-(3-hidroxi-3-metilbutanoil)-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[3-(3-hidroxi-3-metilbutanoil)-1-(metilsulfonil)-2,3-dihidro-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona,

3-acetil-6-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

6-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-3-glicoloil-2,3-dihidro-1*H*-

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bencımıdazol-1-carboxamıda,

6-[3-cloro-4-[(2,4-dıfluorobencıl)oxı]-6-metıl-2-oxopırıdın-1(2*H*)-ıl]-3-(2-hıdroxı-2-metılpropanoıl)-2,3-dıhıdro-1*H*-bencımıdazol-1-carboxamıda,

6-[3-cloro-4-[(2,4-dıfluorobencıl)oxı]-6-metıl-2-oxopırıdın-1(2*H*)-ıl] 3-(*N*-metılglıcıl)-2,3-dıhıdro-1*H*-bencımıdazol-1-carboxamıda,

6-[3-cloro-4-[(2,4-dıfluorobencıl)oxı]-6-metıl-2-oxopırıdın-1(2*H*)-ıl]-3-(3-hıdroxıpropanoıl)-2,3-dıhıdro-1*H*-bencımıdazol-1-carboxamıda,

6-[3-cloro-4-[(2,4-dıfluorobencıl)oxı]-6-metıl-2-oxopırıdın-1(2*H*)-ıl]-3-(3-hıdroxı-3-metılbutanoıl)-2,3-dıhıdro-1*H*-bencımıdazol-1-carboxamıda,

5-[3-cloro-4-[(2,4-dıfluorobencıl)oxı]-6-metıl-2-oxopırıdın-1(2*H*)-ıl]-1*H*-bencımıdazol-1,3(2*H*)-dıcarboxamıda,

6-[3-cloro-4-[(2 4-dıfluorobencıl)oxı]-6-metıl-2-oxopırıdın-1(2*H*)-ıl]-3-(metılsulfonıl)-2,3-dıhıdro-1*H*-bencımıdazol-1-carboxamıda,

1-(1-acetıl-3-(metılsulfonıl)-2,3-dıhıdro-1*H*-bencımıdazol-5-ıl)-3-cloro-4-[(2,4-dıfluorobencıl)oxı]-6-metılpırıdın-2(1*H*)-ona

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-[1-glıcoloıl-3-(metılsulfonıl)-2,3-dıhıdro-1*H*-bencımıdazol-5-ıl]-6-metılpırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-[1-(2-hıdroxı-2-metılpropanoıl)-3-(metılsulfonıl)-2,3-dıhıdro-1*H*-bencımıdazol-5-ıl]-6-metılpırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-6-metıl-1-[1-(*N*-metılglıcıl)-3-(metılsulfonıl)-2,3-dıhıdro-1*H*-bencımıdazol-5-ıl]pırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-[1-(3-

hidroxipropanoil)-3 (metilsulfonil)-2,3-dihidro-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[1-(3-hidroxi-3-metilbutanoil)-3-(metilsulfonil)-2,3-dihidro-1*H*-bencimidazol-5-il]-6-metilpiridin-2(1*H*)-ona,

5-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-3-(metilsulfonil)-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

1-[1,3-bis(metilsulfonil)-2,3-dihidro-1*H*-bencimidazol-5-il]-3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

1-(3-acetil-1-(metilsulfonil)-2,3-dihidro-1*H*-bencimidazol-5-il)-3 cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

1-(1-acetil-1*H*-pirrol-3-il)-3-cloro-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-(1-glicoloil-1*H*-pirrol-3-il)-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[1-(2-hidroxi-2-metilpropanoil)-1*H*-pirrol-3-il]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-1-[1-(*N*-metilglicil)-1*H*-pirrol-3-il]piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[1-(3-hidroxipropanoil)-1*H*-pirrol-3-il]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[1-(3-hidroxi-3-metilbutanoil)-1*H*-pirrol-3-il]-6-metilpiridin-2(1*H*)-ona,

3-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-1*H*-pirrol-1-carboxamida,

3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-1-[1-

(metılsulfonıl)-1*H*-pırrol-3-ıl]pırıdın-2(1*H*)-ona,

1-(1-acetıl-1*H*-ımıdazol-4-ıl)-3-cloro-4-[(2,4-dıfluorobencıl)oxı]-6-metılpırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-(1-glıcoloıl-1*H*-ımıdazol-4-ıl)-6-metılpırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-[1-(2-hıdroxı-2-metılpropanoıl)-1*H*-ımıdazol-4-ıl]-6-metılpırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-6-metıl-1-[1-(*N*-metılglıcıl)-1*H*-ımıdazol-4-ıl]pırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-[1-(3-hıdroxıpropanoıl)-1*H*-ımıdazol-4-ıl]-6-metılpırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-[1-(3-hıdroxı-3-metılbutanoıl)-1*H*-ımıdazol-4-ıl]-6-metılpırıdın-2(1*H*)-ona

4-[3-cloro-4-[(2,4-dıfluorobencıl)oxı]-6-metıl-2-oxopırıdın-1(2*H*)-ıl]-1*H*-ımıdazol-1-carboxamıda,

3-cloro-4-[(2,4-cıfluorobencıl)oxı]-6-metıl-1-[1-(metılsulfonıl)-1*H*-ımıdazol-4-ıl]pırıdın-2(1*H*)-ona,

1-(1-acetıl-1*H*-pırazol-4-ıl)-3-cloro-4-[(2,4-dıfluorobencıl)oxı]-6-metılpırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-(1-glıcoloıl-1*H*-pırazol-4-ıl)-6-metılpırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-[1-(2-hıdroxı-2-metılpropanoıl)-1*H*-pırazol-4-ıl]-6-metılpırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-6-metıl-1-[1-(*N*-metılglıcıl)-1*H*-pırazol-4-ıl]pırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-[1-(3-hıdroxıpropanoıl)-1*H*-pırazol-4-ıl]-6-metılpırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[1-(3-hidroxi-3-metilbutanoil)-1*H*-pirazol-4-il]-6-metilpiridin-2(1*H*)-ona,

4-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-1*H*-pirazol-1-carboxamida,

3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-1-[1-(metilsulfonil)-1*H*-pirazol-4-il]piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-isoquinolin-7-il-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-(isoquinolin-6-ilmetil)piridin-2(1*H*)-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1,3-dihidro-2*H*-indol-2-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-(2,3-dihidro-1*H*-indol-5-ilmetil)piridin-2(1*H*)-ona,

1-[(1-acetil-2,3-dihidro-1*H*-indol-5-il)metil]-3-cloro-4-[(2,4-difluorobencil)oxi]piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-(1-glicoloil-2,3-dihidro-1*H*-indol-5-il)metil]piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[1-(2-hidroxi-2-metilpropanoil)-2,3-dihidro-1*H*-indol-5-il]metil}piridin-2(1*H*)-ona

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[1-(*N*-metilglicil)-2,3-dihidro-1*H*-indol-5-il]metil}piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[1-(3-hidroxipropanoil)-2,3-dihidro-1*H*-indol-5-il]metil}piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[1-(3-hidroxi-3-metilbutanoil)-2,3-dihidro-1*H*-indol-5-il]metil}piridin-2(1*H*)-ona,

5-[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-

1(2*H*)-il]metil}indolina-1-carboxamida,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[1-(metilsulfonil)-2,3-dihidro-1*H*-indol-5-il]metil}piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-(2,3-dihidro-1*H*-isoindol-5-ilmetil)piridin-2(1*H*)-ona,

1-[(2-acetil-2,3-dihidro-1*H*-isoindol-5-il)metil]-3-cloro-4-[(2,4-difluorobencil)oxi]piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[(2-glicoloil-2,3-dihidro-1*H*-indol-5-il)metil]piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[2-(2-hidroxi-2-metilpropanoil)-2,3-dihidro-1*H*-isoindol-5-il]metil}piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-d fluorobencil)oxi]-1-{[2-(*N*-metilglicil)-2,3-dihidro-1*H*-isoindol-5-il]metil}piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[2-(3-hidroxipropanoil)-2,3-dihidro-1*H*-isoindol-5-il]metil}piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[2-(3-hidroxi-3-metilbutanoil)-2,3-dihidro-1*H*-isoindol-5-il]metil}piridin-2(1*H*)-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1,3-dihidro-2*H*-isoindol-2-carboxamida

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[2-(metilsulfonil)-2,3-dihidro-1*H*-isoindol-5-il]metil}piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-(1,2,3,4-tetrahidroisoquinolin-6-ilmetil)piridin-2(1*H*)-ona,

1-[(2-acetil-1,2,3 4-tetrahidroisoquinolin-6-il)metil]-3-cloro-4-[(2,4-difluorobencil)oxi]-piridin-

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2(1*H*)-ona,

3-cloro-4-[(2,4 difluorobencil)oxi]-1-[(2-glicoloil-1,2,3,4-tetrahidroisoquinolin-6-il)metil]piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[2-(2-hidroxi-2-metilpropanoil)-1,2,3,4-tetrahidroisoquinolin-6-il]metil}piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[2-(*N*-metilglicil)-1,2,3,4-tetrahidroisoquinolin-6-il]metil}piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[2-(3-hidroxipropanoil)-1,2,3,4-tetrahidroisoquinolin-6-il]metil}piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[2-(3-hidroxi-3-metilbutanoil)-1,2,3,4-tetrahidroisoquinolin-6-il]metil}piridin-2(1*H*)-ona,

6-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3,4-dihidroisoquinolina-2(1*H*)-carboxamida,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[2-(metilsulfonil)-1,2,3,4-tetrahidroisoquinolin-6-il]metil}piridin-2(1*H*) ona,

3-cloro-4-[(2,4-d fluorobencil)oxi]-1-(1,2,3,4-tetrahidroisoquinolin-5-ilmetil)piridin-2(1*H*)-ona,

1-[(2-acetil-1,2,3,4-tetrahidroisoquinolin-5-il)metil]-3-cloro-4-[(2,4-difluorobencil)oxi]-piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[(2-glicoloil-1,2,3,4-tetrahidroisoquinolin-5-il)metil]piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[2-(2-hidroxi-2-metilpropanoil)-1,2,3,4-tetrahidroisoquinolin-

5-il]metil}piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[2-(*N*-metilglicil)-1,2,3,4-tetrahidroisoquinolin-5-il]metil}piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[2-(3-hidroxipropanoil)-1,2,3,4-tetrahidroisoquinolin-5-il]metil}piridin-2(1*H*)-ona,

3-cloro-4-[(2,4 difluorobencil)oxi]-1-{[2-(3-hidroxi-3-metilbutanoil)-1,2,3,4-tetrahidroisoquinolin-5-il]metil}piridin-2(1*H*)-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3,4-dihidroisoquinolina-2(1*H*)-carboxamida,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[2-(metilsulfonil)-1,2,3,4-tetrahidroisoquinolin-5-il]metil}piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-(2,3-dihidro-1*H*-bencimidazol-5-ilmetil)piridin-2(1*H*)-ona,

1-[(1-acetil-2,3-dihidro-1*H*-bencimidazol-5-il)metil]-3-cloro-4-[(2,4-difluorobencil)oxi]piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-(1-glicoloil-2,3-dihidro-1*H*-bencimidazol-5-il)metil]piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[1-(2-hidroxi-2-metilpropano 1)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[1-(*N*-metilglicil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[1-(3-hidroxipropanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[1-(3-hidroxi-3-metilbutaroil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}piridin-2(1*H*)-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[1-(metilsulfonil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}piridin-2(1*H*)-ona,

1-[(3-acetil-2,3-dihidro-1*H*-bencimidazol-5-il)metil]-3-cloro-4-[(2,4-difluorobencil)oxi]piridin-2(1*H*)-ona,

3-cloro-1-[(1,3-diacetil-2,3-dihidro-1*H*-bencimidazol-5-il)metil]-4-[(2,4-difluorobencil)oxi]piridin-2(1*H*)-ona,

1-[(3-acetil-1-glicoloil-2,3-dihidro-1*H*-bencimidazol-5-il)metil]-3-cloro-4-[(2,4-difluorobencil)oxi]piridin-2(1*H*)-ona,

1-{[3-acetil-1-(2-hidroxi-2-metilpropanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}-3-cloro-4-[(2,4-difluorobencil)oxi]piridin-2(1*H*)-ona,

1-{[3-acetil-1-(*N*-metilglicil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}-3-cloro-4-[(2,4-difluorobencil)oxi]piridin-2(1*H*)-ona,

1-{[3-acetil-1-(3-hidroxipropanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}-1-cloro-4-[(2,4-difluorobencil)oxi]piridin-2(1*H*)-ona,

1-{[3-acetil-1-(3-hidroxi-3-metilbutanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}-1-cloro-4-[(2,4-difluorobencil)oxi]piridin-2(1*H*)-ona,

3-acetil-5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-2,3-dihidro-1*H*-bencimidazol-1-

carboxamıda,

1-{[3-acetıl-1-(metılsulfonıl)-2,3-dıhıdro-1*H*-bencımıdazol-5-ıl]metıl}-3-cloro-4-[(2,4-dıfluorobencıl)oxı]pırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-(3-glıcoloıl-2,3-dıhıdro-1*H*-bencımıdazol-5-ıl)metıl]pırıdın-2(1*H*)-ona,

1-[(1-acetıl-3-glıcoloıl-2,3-dıhıdro-1*H*-bencımıdazol-5-ıl)metıl]-3-cloro-4-[(2,4-dıfluorobencıl)oxı]pırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-(1,3-dıglıcoloıl-2,3-dıhıcro-1*H*-bencımıdazol-5-ıl)metıl]pırıdın-2(1*h*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-{[3-glıcoloıl-1-(2-hıdroxı-2-metılpropanoıl)-2,3-dıhıdro-1*H*-bencımıdazol-5-ıl]metıl}pırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-{[3-glıcoloıl-1-(*N*-metılglıcıl)-2,3 dıhıdro-1*H*-bencımıdazol-5-ıl]metıl}pırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-{[3-glıcoloıl-1-(3-hıdroxıpropanoıl)-2,3-dıhıdro-1*H*-bencımıdazol-5-ıl]metıl}pırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-{[3-glıcoloıl-1-(3-hıdroxı-1-metılbutanoıl)-2,3-dıhıdro-1*H*-bencımıdazol-5-ıl]metıl}pırıdın-2(1*H*)-ona,

5-{[3-cloro-4-[(2,4-dıfluorobencıl)oxı]-2-oxopırıdın-1(2*H*)-ıl]metıl}-3-glıcoloıl-2,3-dıhıdro-1*H*-bencımıdazol-1-carboxamıda,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-{[3-glıcoloıl-1-(metılsulfonıl)-2,3-dıhıdro-1*H*-bencımıdazol-5-ıl]metıl}pırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-{[3-(2-hıdroxı-2-metılpropanoıl)-2,3-dıhıdro-1*H*-bencımıdazol-5-

ıl]metıl}pırıdın-2(1*H*)-ona,

1-{[1-acetıl-3-(2-hıdroxı-2-metılpropanoıl)-2,3-dıhıdro-1*H*-bencımıdazol-5-ıl]metıl}-3-cloro-4-[(2,4-dıfluorobencıl)oxı]pırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-{[1-glıcoloıl-3-(2-hıdroxı-2-metılpropanoıl)-2,3-dıhıdro-1*H*-bencımıdazol-5-ıl]metıl}pırıdın-2(1*H*)-ona,

1-{[1,3-bıs(2-hıdroxı-2-metılpropanoıl)-2,3-dıhıdro-1*H*-bencımıdazol-5-ıl]metıl}-3-cloro-4-[(2,4-dıfluorobencıl)oxı]pırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-{[3-(2-hıdroxı-2-metılpropanoıl)-1-(*N*-metılglıcıl)-2,3-dıhıdro-1*H*-bencımıdazol-5-ıl]metıl}pırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-{[3-(2-hıdroxı-2-metılpropanoıl)-1-(3-hıdroxıpropanoıl)-2,3-dıhıdro-1*H*-bencımıdazol-5-ıl]metıl}pırıdın-2(1*H*)-ona

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-{[1-(3-hıdroxı-3-metılbutanoıl)-3-(2-hıdroxı-2-metılpropanoıl)-2,3-dıhıdro-1*H*-bencımıdazol-5-ıl]metıl}pırıdın-2(1*H*)-ona,

5-{[3-cloro-4-[(2,4-dıfluorobencıl)oxı]-2-oxopırıdın-1(2*H*)-ıl]metıl}-3-(2-hıdroxı-2-metılpropanoıl)-2,3-dıhıdro-1*H*-bencımıdazol-1-carboxamıda,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-{[3-(2-hıdroxı-2-metılpropanoıl)-1-(metılsulfonıl)-2,3-dıhıdro-1*H*-bencımıdazol-5-ıl]metıl}pırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-{[3-(*N*-metılglıcıl)-2,3-dıhıdro-1*H*-bencımıdazol-5-ıl]metıl}pırıdın-2(1*H*)-ona,

1-{[1-acetıl-1-(*N*-metılglıcıl)-2,3-dıhıdro-1*H*-bencımıdazol-5-ıl]metıl}-3-cloro-4-[(2,4-dıfluorobencıl)oxı]pırıdın-2(1*H*)-ona,

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3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[1-glicoloil-3-(*N*-metilglicil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[1-(2-hidroxi-2-metilpropanoil)-3-(*N*-metilglicil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}piridin-2(1*H*)-ona,

1-{[1,3-bis(*N*-metilglicil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}-3-cloro-4-[(2,4-difluorobencil)oxi]piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[1-(3-hidroxipropanoil)-3-(*N*-metilglicil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[1-(3-hidroxi-3-metilbutanoil)-3-(*N*-metilglicil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}piridin-2(1*H*)-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(*N*-metilglicil)-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[3-(*N*-metilglicil)-1-(metilsulfonil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[3-(3-hidroxipropanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}piridin-2(1*H*)-ona,

1-{[1-acetil-3-(3-hidroxipropanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}-3-cloro-4-[(2,4-difluorobencil)oxi]piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[1-glicoloil-3-(3-hidroxipropanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[1-(2-hidroxi-2-metilpropanoil)-3-(3-hidroxipropanoil)-2,3-

dihidro-1*H*-bencimidazol-5-il]metil}piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[3-(3-hidroxipropanoil)-1-(*N*-metilglicil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}piridin-2(1*H*)-ona

1-{[1,3-bis(3-hidroxipropanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}-3-cloro-4-[(2,4-difluorobencil)oxi]piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[1-(3-hidroxi-3-metilbutanoil)-3-(3-hidroxipropanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}piridin-2(1*H*)-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(3-hidroxipropanoil)-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[3-(3-hidroxipropanoil)-1-(metilsulfonil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[3-(3-hidroxi-3-metilbutanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}piridin-2(1*H*)-ona,

1-{[1-acetil-3-(3-hidroxi-3-metilbutanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}-3-cloro-4-[(2,4-difluorobencil)oxi]piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[1-glicoloil-3-(3-hidroxi-3-metilbutanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[3-(3-hidroxi-3-metilbutanoil)-1-(2-hidroxi-2-metilpropanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[3-(3-hidroxi-3-metilbutanoil)-1-(*N*-metilglicil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[3-(3-

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hidroxi-3-metilbutanoil)-1-(metilsulfonil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}piridin-2(1*H*)-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(3-hidroxi-3-metilbutanoil)-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

1-{[1,3-bis(3-hidroxi-3-metilbutanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}-3-cloro-4-[(2,4-difluorobencil)oxi]piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[3-(3-hidroxi-3-metilbutanoil)-1-(3-hidroxipropanoil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}piridin-2(1*H*)-ona,

6-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

3-acetil-6-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

6-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-glicoloil-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

6-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(2-hidroxi-2-metilpropanoil)-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

6-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(*N*-metilglicil)-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

6-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(3-hidroxipropanoil)-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

6-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(3-hidroxi-3-metilbutanoil)-

2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

5-{[3-cloro-4-[(2 4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1*H*-bencimidazol-1,3(2*H*)-dicarboxamida,

6-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(metilsulfonil)-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[3-(metilsulfonil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}piridin-2(1*H*) ona,

1-{[1-acetil-3-(metilsulfonil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}-3-cloro-4-[(2,4-difluorobencil)oxi]piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[1-glicoloil-3-(metilsulfonil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}piridin-2(1*H*) ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[1-(2-hidroxi-2-metilpropanoil)-3-(metilsulfonil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[1-(*N*-metilglicil)-3-(metilsulfonil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[1-(3-hidroxipropanoil)-3-(metilsulfonil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[1-(3-hidroxi-3-metilbutanoil)-3-(metilsulfonil)-2,3-dihidro-1*H*-bencimidazol-5-il]metil}piridin-2(1*H*)-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(metilsulfonil)-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

1-{[1,3-bis(metilsulfonil)-2,3-dihidro-1*H*-

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bencımıdazol-5-ıl]metıl}-3-cloro-4-[(2,4-dıfluorobencıl)oxı]pırıdın-2(1*H*)-ona,

5-{[3-cloro-4-[(2,4-dıfluorobencıl)oxı]-2-oxopırıdın-1(2*H*)-ıl]metıl}-1,3-dıhıdro-2*H*-bencımıdazol-2-ona,

1-acetıl-5-{[3-cloro-4-[(2,4-dıfluorobencıl)oxı]-2-oxopırıdın-1(2*H*)-ıl]metıl}-1,3-dıhıdro-2*H*-bencımıdazol-2-ona,

5-{[3-cloro-4-[(2,4-dıfluorobencıl)oxı]-2-oxopırıdın-1(2*H*)-ıl]metıl}-1-glıcoloıl-1,3-dıhıdro-2*H*-bencımıdazol-2-ona

5-{[3-cloro-4-[(2,4-dıfluorobencıl)oxı]-2-oxopırıdın-1(2*H*)-ıl]metıl}-1-(2-hıdroxı-2-metılpropanoıl)-1,3-dıhıdro-2*H*-bencımıdazol-2-ona,

5-{[3-cloro-4-[(2,4-dıfluorobencıl)oxı]-2-oxopırıdın-1(2*H*)-ıl]metıl}-1-(*N*-metılglıcıl)-1,3-dıhıdro-2*H*-bencımıdazol-2-ona,

5-{[3-cloro-4-[(2,4-dıfluorobencıl)oxı]-2-oxopırıdın-1(2*H*)-ıl]metıl}-1-(3-hıdroxıpropanoıl)-1,3-dıhıdro-2*H*-bencımıdazol-2-ona,

5-{[3-cloro-4-[(2,4-dıfluorobencıl)oxı]-2-oxopırıdın-1(2*H*)-ıl]metıl}-1-(3-hıdroxı-3-metılbutanoıl)-1,3-dıhıdro-2*H*-bencımıdazol-2-ona,

5-{[3-cloro-4-[(2,4-dıfluorobencıl)oxı]-2-oxopırıdın-1(2*H*)-ıl]metıl}-2-oxo-2,3-dıhıdro-1*H*-bencımıdazol-1-carboxamıda,

5-{[3-cloro-4-[(2,4-dıfluorobencıl)oxı]-2-oxopırıdın-1(2*H*)-ıl]metıl}-1-(metılsulfonıl)-1,3-dıhıdro-2*H*-bencımıdazol-2-ona,

1-acetıl-6-{[3-cloro-4-[(2,4-dıfluorobencıl)oxı]-2-oxopırıdın-1(2*H*)-ıl]metıl}-1,3-dıhıdro-2*H*-bencımıdazol-2-ona,

1,3-diacetil-5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1,3-dihidro-2*H*-bencimidazol-2-ona,

3-acetil-5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1-glicoloil-1,3-dihidro-2*H*-bencimidazol-2-ona,

3-acetil-5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1-(2-hidroxi-2-metilpropanoil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

3-acetil-5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1-(*N*-metilglicil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

3-acetil-5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1-(3-hidroxipropanoil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

3-acetil-5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1-(3-hidroxi-3-metilbutanoil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

3-acetil-5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-2-oxo-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

3-acetil-5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1-(metilsulfonil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

6-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1-glicoloil-1,3-dihidro-2*H*-bencimidazol-2-ona,

1-acetil-5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-glicoloil-1,3-dihidro-2*H*-bencimidazol-2-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1,3-diglicoloil-1,3-dihidro-

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2*H*-bencımıdazol-2-ona,

5-{[3-cloro-4-[(2,4-dıfluorobencıl)oxı]-2-oxopırıdın-1(2*H*)-ıl]metıl}-3-glıcoloıl-1-(2-hıdroxı-2-metılpropanoıl)-1,3-dıhıdro-2*H*-bencımıdazol-2-ona,

5-{[3-cloro-4-[(2 4-dıfluorobencıl)oxı]-2-oxopırıdın-1(2*H*)-ıl]metıl}-3-glıcoloıl-1-(*N*-metılglıcıl)-1,3-dıhıdro-2*H*-bencımıdazol-2-ona,

5-{[3-cloro-4-[(2,4-dıfluorobencıl)oxı]-2-oxopırıdın-1(2*H*)-ıl]metıl}-3-glıcoloıl-1-(3-hıdroxıpropanoıl)-1,3-dıhıdro-2*H*-bencımıdazol-2-ona,

5-{[3-cloro-4-[(2,4-dıfluorobencıl)oxı]-2-oxopırıdın-1(2*H*)-ıl]metıl}-3-glıcoloıl-1-(3-hıdroxı-3-metılbutanoıl)-1,3-dıhıdro-2*H*-bencımıdazol-2-ona,

5-{[3-cloro-4-[(2,4-dıfluorobencıl)oxı]-2-oxopırıdın-1(2*H*)-ıl]metıl}-3-glıcoloıl-2-oxo-2,3-dıhıdro-1*H*-bencımıdazol-1-carboxamıda,

5-{[3-cloro-4-[(2,4-dıfluorobencıl)oxı]-2-oxopırıdın-1(2*H*)-ıl]metıl}-3-glıcoloıl-1-(metılsulfonıl)-1,3-dıhıdro-2*H*-bencımıdazol-2-ona,

6-{[3-cloro-4-[(2,4-dıfluorobencıl)oxı]-2-oxopırıdın-1(2*H*)-ıl]metıl}-1-(2-hıdroxı-2-metılpropanoıl)-1,3-dıhıdro-2*H*-bencımıdazol-2-ona,

1-acetıl-5-{[3-cloro-4-[(2,4-dıfluorobencıl)oxı]-2-oxopırıdın-1(2*H*)-ıl]metıl}-3-(2-hıdroxı-2-metılpropanoıl)-1,3-dıhıdro-2*H*-bencımıdazol-2-ona,

5-{[3-cloro-4-[(2,4-dıfluorobencıl)oxı]-2-oxopırıdın-1(2*H*)-ıl]metıl}-1-glıcoloıl-3-(2-hıdroxı-2-metılpropanoıl)-1,3-dıhıdro-2*H*-bencımıdazol-2-ona,

5-{[3-cloro-4-[(2,4-dıfluorobencıl)oxı]-2-oxopırıdın-1(2*H*)-ıl]metıl}-1,3-bıs(2-hıdroxı-2-metılpropanoıl)-1,3-dıhıdro-2*H*-bencımıdazol-2-ona,

5-{[3-cloro-4-[(2,4-dıfluorobencıl)oxı]-2-

oxopiridin-1(2*H*)-il]metil}-3-(2-hidroxi-2-metilpropanoil)-1-(N-metilglicil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(2-hidroxi-2-metilpropanoil)-1-(3-hidroxipropanoil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1-(3-hidroxi-3-metilbutanoil)-3-(2-hidroxi-2-metilpropanoil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(2-hidroxi-2-metilpropanoil)-2-oxo-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(2-hidroxi-2-metilpropanoil)-1-(metilsulfonil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

6-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1-(*N*-metilglicil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

1-acetil-5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(*N*-metilglicil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1-glicoloil-3-(*N*-metilglicil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1-(2-hidroxi-2-metilpropanoil)-3-(N-metilglicil)-1,3-dihidro-2*H*-bencimidazol-2-ona

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1,3-bis(*N*-metilglicil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1-(3-hidroxipropanoil)-3-(*N*-metilglicil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1-(3-hidroxi-3-metilbutanoil)-3-(*N*-metilglicil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(*N*-metilglicil)-2-oxo-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(*N*-metilglicil)-1-(metilsulfonil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

6-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1-(3-hidroxipropanoil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

1-acetil-5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(3-hidroxipropanoil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1-glicoloil-3-(3-hidroxipropanoil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1-(2-hidroxi-2-metilpropanoil)-3-(3-hidroxipropanoil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(3-hidroxipropanoil)-1-(*N*-metilglicil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-

oxopirıdın-1(2*H*)-ıl]metıl}-1,3-bıs(3-hıdroxıpropanoıl)-1,3-dıhıdro-2*H*-bencımıdazol-2-ona,

5-{[3-cloro-4-[(2 4-dıfluorobencıl)oxı]-2-oxopırıdın-1(2*H*)-ıl]meıl}-1-(3-hıdroxı-3-metılbutanoıl)-3-(3-hıdroxıpropanoıl)-1,3-dıhıdro-2*H*-bencımıdazol-2-ona,

5-{[3-cloro-4-[(2 4-dıfluorobencıl)oxı]-2-oxopırıdın-1(2*H*)-ıl]meıl}-3-(3-hıdroxıpropanoıl)-2-oxo-2,3-dıhıdro-1*H*-bencımıdazol-1-carboxamıda,

5-{[3-cloro-4-[(2,4-dıfluorobencıl)oxı]-2-oxopırıdın-1(2*H*)-ıl]metıl}-3-(3-hıdroxıpropanoıl)-1-(metılsulfonıl)-1,3-dıhıdro-2*H*-bencımıdazol-2-ona,

6-{[3-cloro-4-[(2,4-dıfluorobencıl)oxı]-2-oxopırıdın-1(2*H*)-ıl]meıl}-1-(3-hıdroxı-3-metılbutanoıl)-1,3-dıhıdro-2*H*-bencımıdazol-2-ona

1-acetıl-5-{[3-cloro-4-[(2,4-dıfluorobencıl)oxı]-2-oxopırıdın-1(2*H*)-ıl]metıl}-3-(3-hıdroxı-3-metılbutanoıl)-1,3-dıhıdro-2*H*-bencımıdazol-2-ona,

5-{[3-cloro-4-[(2,4-dıfluorobencıl)oxı]-2-oxopırıdın-1(2*H*)-ıl]metıl}-1-glıcoloıl-3-(3-hıdroxı-3-metılbutanoıl)-1,3-dıhıdro-2*H*-bencımıdazol-2-ona,

5-{[3-cloro-4-[(2,4-dıfluorobencıl)oxı]-2-oxopırıdın-1(2*H*)-ıl]metıl}-3-(3-hıdroxı-3-metılbutanoıl)-1-(2-hıdroxı-2-metılprcpanoıl)-1,3-dıhıdro-2*H*-bencımıdazol-2-ona,

5-{[3-cloro-4-[(2,4-dıfluorobencıl)oxı]-2-oxopırıdın-1(2*H*)-ıl]metıl}-3-(3-hıdroxı-3-metılbutanoıl)-1-(*N*-metılglıcıl)-1,3-dıhıdro-2*H*-bencımıdazol-2-ona,

5-{[3-cloro-4-[(2,4-dıfluorobencıl)oxı]-2-oxopırıdın-1(2*H*)-ıl]metıl}-3-(3-hıdroxı-3-metılbutanoıl)-1-(3-hıdroxıpropanoıl)-1,3-dıhıdro-2*H*-bencımıdazol-2-ona,

5-{[3-cloro-4-[(2,4-dıfluorobencıl)oxı]-2-oxopırıdın-1(2*H*)-ıl]metıl}-1,3-bıs(3-hıdroxı-3-

metilbutanoil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(3-hidroxi-3-metilbutanoil)-2-oxo-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(3-hidroxi-3-metilbutanoil)-1-(metilsulfonil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

6-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-2-oxo-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

3-acetil-6-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-2-oxo-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

6-{[3-cloro-4-[(2 4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-glicoloil-2-oxo-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

6-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(2-hidroxi-2-metilpropanoil)-2-oxo-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

6-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(*N*-metilglicil)-2-oxo-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

6-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(3-hidroxipropanoil)-2-oxo-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

6-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(3-hidroxi-3-metilbutanoil)-2-oxo-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi}-2-oxopiridin-1(2*H*)-il]metil}-2-oxo-2,3-dihidro-1*H*-bencimidazol-1,3-dicarboxamida,

6-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(metilsulfonil)-2-oxo-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

6-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1-(metilsulfonil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

1-acetil-5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(metilsulfonil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1-glicoloil-3-(metilsulfonil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1-(2-hidroxi-2-metilpropanoil)-3-(metilsulfonil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1-(*N*-metilglicil)-3-(metilsulfonil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1-(3-hidroxipropanoil)-3-(metilsulfonil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1-(3-hidroxi-3-metilbutanoil)-3-(metilsulfonil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-3-(metilsulfonil)-2-oxo-2,3-dihidro-1*H*-bencimidazol-1-carboxamida,

5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}-1,3-bis(metilsulfonil)-1,3-dihidro-2*H*-bencimidazol-2-ona,

3-bencil-4-hidroxi-1-(2-feniletil)piridin-2(1*H*)-ona,

1-bencil-4-hidrox -2-oxo-1,2-dihidropiridina-3-carbaldehido,

1-bencil-4-cloro-?-oxo-1,2-dihidropiridina-3-carbaldehido,

metil 5-cloro-1-(4-clorobencil)-6-oxo-1,6-dihidropiridina-3-carboxilato,

5-bromo-1-(2-cloro-6-fluorobencil)-3-metilpiridin-2(1*H*)-ona,

3-bromo-1-(2,6-diclorofenil)-4-[(4-fluorofenil)etinil]-6-metilpiridin-2(1*H*)-ona,

3-bromo-1-(2,6-diclorofenil)-4-[(4-fluorofenil)etinil]-6-metilpiridin-2(1*H*)-ona,

3-cloro-4-[4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]benzoato de metilo,

4-[(2,4-difluorobencil)oxi]-1-(3-fluorobencil)-2-oxo-1,2-dihidropiridina-3-carbonitrilo

4-[(2,4-difluorobencil)oxi]-6-(hidroximetil)-1-(2,4,6-trifluorofenil)piridin-2(1*H*)-ona,

4-[(2,4-difluorobencil)oxi]-6-metil-1-[2-(trifluorometil)fenil]piridin-2(1*H*)-ona,

3-[4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]benzaldehido,

4-[(2,4-difluorobencil)oxi]-1-(2,6-difluoro-4-morfolina-4-ilfenil)-6-metilpiridin-2(1*H*)-ona,

4-[(2,4-difluorobencil)oxi]-1-[2,6-difluoro-4-(4-metilpiperazin-1-il)fenil]-6-metilpiridin-2(1*H*)-ona,

acido 3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il] benzoico,

4-[(2,4-difluorobencil)oxi]-1-[4-(dimetilamino)-2,6-difluorofenil]-6-metilpiridin-2(1*H*)-ona,

4-[(2,4-difluorobencil)oxi]-1-{2,6-difluoro-4-[(2-hidroxietil)(metil)amino]fenil}-6-metilpiridina-2(1*H*)-

ona,

3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]benzoato de metilo,

acido 3-[4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-4-metilbenzoico,

4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorofenil)-6-(hidroximetil)piridin-2(1*H*)-ona,

3-bromo-1-{[5-(clorometil)pirazin-2-il]metil}-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

1-[2-cloro-5-(hidroximetil)fenil]-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

4-[(2,4-difluorobencil)oxi]-1-(2,6-difluoro-4-hidroxifenil)-6-metilpiridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-[4-(hidroximetil)-2-metoxifenil]-6-metilpiridin-2(1*H*)-ona,

metil 3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]4-metilbenzoato,

3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-{3-[(4-(metilpiperazin-1-il)carbonil]fenil}piridin-2(1*H*)-ona,

3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-*N*-[2-dimetilamino)etil]benzamida,

3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-*N*-(2-metoxietil)benzamida,

3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-*N*-[2-dimetilamino)etil]-*N*-metilbenzamida,

3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-*N*-(2-hidroxietil)-*N*-metilbenzamida,

3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-*N*-(2-metoxietil)-*N*-metilbenzamida,

4-[3-bromo-4-[(2 4-difluorobencil)oxi]-6-metil-2-

oxopiridin-1(2*H*)-il]benzamida,

metil 3-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-4-fluorobenzoato,

ácido 4-[4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-3-metilbenzoico,

1-(4-bromo-2-metilfenil)-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

1-[(1-acetil-1*H*-indol-5-il)metil]-3-cloro-4-[(2,4-difluorobencil)oxi]piridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-[(5-metilpirazin-2-il)metil]piridin-2(1*H*)-ona,

2-({[3-bromo-1-(2 6-difluorofenil)-6-metil-2-oxo-1,2-dihidropiridin-4-il]oxy}metil)-3,5-difluorobencilcarbamato de metilo,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-{[5-(hidroximetil)pirazin-2-il]metil}-6-metilpiridin-2(1*H*)-ona,

4-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]metil}-*N*,*N*-dimetilbenzamida,

3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-*N*-(2-hidroxietil)-4-metilbenzamida,

3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-{4-[(4-(metilpiperazin-1-il)carbonil]bencil}piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-(1*H*-indol-5-ilmetil)piridin-2(1*H*)-ona,

3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-*N*-metilbenzamida,

3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]benzamida,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-{[5-(hidroximetil)pirazin-2-il]metil}-6-metilpiridin-2(1*H*)-

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ona,

3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-*N* (2-metoxietil)-4-metilbenzamida,

3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-*N* 4-dimetilbenzamida,

3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-*N* *N*,4-trimetilbenzamida

3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-[2-metil-5-(morfolin-4-ilcarbonil)fenil]piridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-[5-(1-hidroxi-1-metiletil)-2-metilfenil]-6-metilpiridin-2(1*H*)-ona,

1-(2-bromobencil)-3-[(2-bromobencil)oxi]piridin-2(1*H*)-ona,

1-(2-bromobencil)-3-[(2-bromobencil)oxi]piridin-2(1*H*)-ona,

3-bromo-1-(4-metoxibencil)-4-fenoxipiridin-2(1*H*)-ona,

1-bencil-2-oxo-4-fenoxi-1,2-dihidropiridina-3-carbaldehido,

3-Bromo-4-(2,4-difluoro-benciloxi)-1-(3-dimetilaminometil-bencil)-6-metil-1H-piridin-2-ona,

N-{3-[3-Bromo-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-ilmetil]-bencil}-2-hidroxi-acetamida,

3-Bromo-4-(2,4-difluoro-benciloxi)-6-metil-1-[4-(piperidina-1-carbonil)-bencil]-1H-piridin-2-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorofenil)-6-[(etoxiamino)metil]piridin-2(1*H*)-ona,

4-[3-Bromo-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-ilmetil]-N-isopropil-benzamida,

hidrocloruro de *N*-(3-aminopropil)-4-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]metil}benzamida,

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3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-*N*,4-dimetilbenzamida,

4-[3-Bromo-4-(2,4 difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-ilmetil]-N-N-bis-(2-hidroxi-etil)-benzamida,

3-Bromo-4-(2,4-difluoro-benciloxi)-6-metil-1-[4-(pirrolidina-1-carbonil)-bencil]-1H-piridin-2-ona,

4-[3-Bromo-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-ilmetil]-N-hidroxi-benzamida,

4-[3-Bromo-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-ilmetil]-N-metil-benzamida,

4-[3-Bromo-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-ilmetil]-N-(2-dimetilamino-etil)-benzamida,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-(1*H*-indazol-5-ilmetil)piridin-2(1*H*)-ona,

3-Bromo-4-(2,4-difluoro-benciloxi)-6-metil-1-[4-(4-metil-piperazina-1-carbonil)-bencil]-1H-piridin-2-ona,

3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-4-metilbenzaldehido,

3-Bromo-4-(2,4-difluoro-benciloxi)-1-(4-dimetilaminometil-bencil)-6-metil-1H-piridin-2-ona,

3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-*N*-(2-metoxietil)-4-metilbenzamida,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-[2-(dimetilamino)-4,6-difluorofenil]-6-metilpiridin-2(1*H*)-ona,

hidrocloruro de *N*-(2-aminoetil)-4-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]metil}benzamida,

4-[3-Bromo-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-ilmetil]-N-(2-hidroxi-etil)-benzamida,

3-Bromo-4-(2,4-difluoro-benciloxi)-1-(4-hidroximetil-bencil)-6-metil-1H-piridin-2-ona,

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3-cloro-4-[(2,4-difluorobencil)oxi]-1-[2,6-difluoro-4-(4-metilpiperazin-1-il)fenil]-6-metilpiridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-[2-(dimetilamino)-4,6-difluorofenil]-6-metilpiridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-[2,6-difluoro-4-(4-metilpiperazin-1-il)fenil]-6-metilpiridin-2(1*H*)-ona,

4-[3-Bromo-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-ilmetil]-N-(2-metoxi-etil)-benzamida,

3-Bromo-4-(2,4-difluoro-benciloxi)-1-{4-[(2-hidroxi-etilamino)-metil]-bencil}-6-metil-1H-piridin-2-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorofenil)-6-[(dimetilamino)metil]piridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-[2-metil-5-(morfolin-4-ilcarbonil)fenil]piridin-2(1*H*)-ona,

3-Bromo-4-(2,4-difluoro-benciloxi)-6-metil-1-(4-metilaminometil-bencil)-1H-piridin-2-ona,

3-Bromo-4-(2,4-difluoro-benciloxi)-6-metil-1-[4-(morfolina-4-carbonil)-bencil]-1H-piridin-2-ona,

*N*-(2-aminoetil)-3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il] benzamida,

hidrocloruro de *N*-(3-aminopropil)-3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il] benzamida,

4-[3-Bromo-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-ilmetil]-N-(2-metoxi-etil)-N-metil-benzamida,

1-(4-Aminometil-bencil)-3-bromo-4-(2,4-difluoro-benciloxi)-6-metil-1H-piridin-2-ona,

hidrocloruro de 3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-[4-(piperazin-1-ilcarbonil)bencil]piridin-

2(1*H*)-ona,

3-Bromo-4-(2,4-difluoro-benciloxi)-1-[4-(isopropilamino-metil)bencil]-6-metil-1H-piridin-2-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-(dimetilfenil)-6-metilpiridin-2(1*H*)-ona,

3-Bromo-4-(2,4-difluoro-benciloxi)-1-{3-[(2-hidroxi-etilamino)-metil]-bencil}-6-metil-1H-piridin-2-ona,

1-(3-Aminometil-bencil)-3-bromo-4-(2,4-difluoro-benciloxi)-6-metil-1H-piridin-2-ona,

3-Bromo-4-(2,4-difluoro-benciloxi)-1-(4-hidroxi-bencil)-6-metil-1H-piridin-2-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorofenil)-6-[(dimetilamino)metil]piridin-2(1*H*)-ona,

N-{3-[3-Bromo-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-ilmetil]-bencil}-acetamida,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-{2,6-difluoro-4-[(2-hidroxietil) (metil)amino]fenil]-6-metilpiridin-2(1*H*)-ona,

3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]benzoato de etilo

trifluoroacetato de 1-[3-(aminometil)bencil]-3-bromo-4-[(2,4-difluorobencil)oxi]piridin-2(1*H*)-ona ,

1-(3-{[Bis(2-hidroxi-etil)-amino]-metil}-bencil)-3-bromo-4-(2,4-difluoro-benciloxi)-6-metil-1H-piridin-2-ona,

3-Bromo-4-(2,4-difluoro-benciloxi)-1-[3-(isopropilamino-metil)bencil]-6-metil-1H-piridin-2-ona,

Ester terc-butílico de acido {3-[3-bromo-4-(2,4-difluoro-benciloxi)-2-oxo-2H-piridin-1-ilmetil]-bencil}-carbamico,

3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]benzamida,

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3-Bromo-4-(2,4-difluoro-benciloxi)-1-[4-(1-hidroxi-1-metil-etil)-bencil]-6-metil-1H-piridin-2-ona,

3-Bromo-4-(2,4-difluoro-benciloxi)-1-(3-dimetilaminometil-bencil)-1H-piridin-2-ona,

3-Bromo-4-(2,4-difluoro-benciloxi)-6-metil-1-(3-piperidin-1-ilmetil-bencil)-1H-piridin-2-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorofenil)-6-{[(2-metoxietil)amino]metil}piridin-2(1*H*)-ona,

3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-*N*-metilbenzamida,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-{2,4-difluoro-6-[(2-hidroxietil) (metil)amino]fenil]-6-metilpiridin-2(1*H*)-ona,

3-Bromo-4-(2,4-difluoro-benciloxi)-6-metil-1-(3-morfolin-4-ilmetil-bencil)-1H-piridin-2-ona,

3-bromo-1-(2,6-dimetilfenil)-6-metil-4-[(2,4,6-trifluorobencil)oxi]piridin-2(1*H*)-ona,

3-bromo-1-(2,6-dimetilfenil)-6-metil-4-[(2,4,6-trifluorobencil)oxi]piridin-2(1*H*)-ona,

1-(4-{[Bis(2-hidroxi-etil)-amino]-metil}-bencil)-3-bromo-4-(2,4-difluoro-benciloxi)-6-metil-1H-piridin-2-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-difluoro-4-morfolin-4-ilfenil)-6-metilpiridin-2(1*H*)-ona,

4-Benciloxi-3-bromo-1-(4-fluoro-bencil)-1H-piridin-2-ona,

4-[3-Cloro-4-(2,4-difluoro-benciloxi)-2-oxo-2H-piridin-1-ilmetil]-benzamida,

3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-*N*,*N*,4-trimetilbenzamida,

3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-

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oxopirıdın-1(2*H*)-ıl]-*N*-ısopropılbenzamıda,

4-[3-Bromo-4-(2,4-dıfluoro-bencıloxı)-6-metıl-2-oxo-2H-pırıdın-1-ılmetıl]-benzamıda,

4-[3-Bromo-4-(2,4-dıfluoro-bencıloxı)-6-metıl-2-oxo-2H-pırıdın-1-ılmetıl]-benzonıtrılo,

3-Bromo-4-(2,4-dıfluoro-bencıloxı)-6-metıl-1-(3-pıperazın-1-ılmetıl-bencıl)-1H-pırıdın-2-ona,

4-[3-Bromo-4-(2,4-dıfluoro-bencıloxı)-6-metıl-2-oxo-2H-pırıdın-1-ılmetıl]-N-(2-hıdroxı-etıl)-N-metıl-benzamıda,

4-[3-bromo-4-[(2,4-dıfluorobencıl)oxı]-6-metıl-2-oxopırıdın-1(2*H*)-ıl]-3-clorobenzoato de metılo,

3-Bromo-4-(2,4-dıfluoro-bencıloxı)-6-metıl-1-[3-(morfolına-4-carbonıl)-bencıl]-1H-pırıdın-2-ona,

3-[3-Bromo-4-(2,4-dıfluoro-bencıloxı)-6-metıl-2-oxo-2H-pırıdın-1-ılmetıl]-N-N-bıs-(2-hıdroxı-etıl)-benzamıda,

Éster metılıco de acıdo 4-[3-bromo-4-(2,4-dıfluoro-bencıloxı)-6-metıl-2-oxo-2H-pırıdın-1-ılmetıl]-benzoıco,

3-[3-Bromo-4-(2,4-dıfluoro-bencıloxı)-6-metıl-2-oxo-2H-pırıdın-1-ılmetıl]-N-hıdroxı-benzamıda,

3-Bromo-4-(2,4-dıfluoro-bencıloxı)-1-(3-hıdroxımetıl-bencıl)-6 metıl-1H-pırıdın-2-ona,

3-bromo-4-[(2,4-dıfluorobencıl)oxı]-1-(3-(fluorobencıl)pırıdın-’(1*H*)-ona,

3-Bromo-4-(2,4-dıfluoro-bencıloxı)-1-(3-fluoro-bencıl)-1H-pırıdın-2-ona,

N-{3-[3-Bromo-4-(’,4-dıfluoro-bencıloxı)-6-metıl-2-oxo-2H-pırıdın-1-ılmetıl]-bencıl}-metanosulfonamıda,

3-Bromo-4-(2,4-dıfluoro-bencıloxı)-6-metıl-1-[3-(pırrolıdına-1-carbonıl)-bencıl]-1H-pırıdın-2-ona,

3-bromo-4-[(2,4-dıfluorobencıl)oxı]-6-metıl-1-(pırıdın-3-ılmetıl)pırıdın-2(1*H*)-ona,

hidrocloruro de *N*-(3-aminopropil)-3-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]metil}benzamida,

3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-(piridin-3-ilmetil)piridin-2(1*H*)-ona,

3-Bromo-4-(2,4-difluoro-benciloxi)-1-(3-metilaminometil-bencil)-1H-piridin-2-ona,

4-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-3,5-diclorobencenosulfonamida,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-[4-(dimetilamino)-2,6-difluorofenil]-6-metilpiridin-2(1*H*)-ona,

3-Bromo-4-(2,4-difluoro-benciloxi)-6-metil-1-(4-piperidin-1-ilmetil-bencil)-1H-piridin-2-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-(piridin-4-ilmetil)piridin-2(1*H*)-ona,

hidrocloruro de *N*-(2-aminoetil)-3-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]metil}benzamida,

3-bromo-1-[2-cloro-5-(hidroximetil)fenil]-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-(difluorofenil)-6-metilpiridin-2(1*H*)-ona

3-cloro-1-[2-cloro-5-(hidroximetil)fenil]-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona

3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-*N*-(2-hidroxietil)-4-metilbenzamida,

2-{3-[3-Bromo-4-(2,4-difluoro-benciloxi)-2-oxo-2H-piridin-1-ilmetil]-fenil}-acetamida,

hidrocloruro de 3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-[3-(piperazir-1-ilcarbonil)bencil]piridin-2(1*H*)-ona,

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3-cloro-4-[(2,4-difluorobencil)oxi]-1-(2,6-(difluorofenil)-6-metilpiridin-2(1*H*)-ona,

Ester metílico de ácido 4-[3-bromo-4-(2,4-difluoro-benciloxi)-2-oxo-2H-piridin-1-ilmetil]-benzoico,

1-(3-Aminometil-2-fluoro-bencil)-3-bromo-4-(2,4-difluoro-benciloxi)-1H-piridin-2-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorofenil)-6-(morfolin-4-ilmetil)piridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-(4-fluorobencil)piridin-2(1*H*)-ona,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-(1*H*-indol-5-ilmetil)piridin-2(1*H*) ona,

trifluoroacetato de 1-[3-(aminometil)bencil]-3-bromo-4-[(4-fluorobencil)oxi]piridin-2(1*H*)-ona,

trifluoroacetato de 1-[3-(2-aminoetil)bencil]-3-bromo-4-[(2,4-difluorobencil)oxi]piridin-2(1*H*)-ona,

1-[3-(aminometil)bencil]-3-bromo-4-[(4-fluorobencil)oxi]piridin-2(1*H*)-ona,

3-bromo-1-(2,6-diclorofenil)-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-*N*-(2-hidroxietil)benzamida,

3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-(piridin-4-ilmetil)piridin-2(1*H*)-ona,

3-Bromo-4-(2,4-difluoro-benciloxi)-1-(4-metoxi-bencil)-6-metil-1H-piridin-2-ona,

4-[3-Bromo-4-(2 4-difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-ilmetil]-N,N-dimetil-benzamida,

3-bromo-6-metil-1-(piridin-4-ilmetil)-4-[(2,4,6-trifluorobencil)oxi]piridin-2(1*H*)-ona,

4-[3-Bromo-4-(2,4-difluoro-benciloxi)-2-oxo-2H-piridin-1-ilmetil]-benzamida,

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3-[3-Bromo-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-ilmetil]-N-metil-benzamida,

Ester metílico de ácido {3-[3-bromo-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-ilmetil]-bencil}-carbamico,

3-bromo-4-[(2,6-difluorobencil)oxi]-1-(2,6-(dimetilfenil)-6-metilpiridin-2(1*H*)-ona,

4-[3-Bromo-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-ilmetil]-benzonitrilo,

3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-(piridin-4-ilmetil)piridin-2(1*H*)-ona,

1-bencil-4-(benciloxi)-3-bromo-6-metilpiridin-2(1*H*)-ona,

1-Bencil-4-benciloxi-3-bromo-6-metil-1H-piridin-2-ona,

1-bencil-4-(benciloxi)-3-bromo-6-metilpiridin-2(1*H*)-ona,

1-Bencil-3-brono-4-(2,4-difluoro-benciloxi)-6-metil-1H-piridin-2-ona

{3-[3-Bromo-4-(2,4-difluoro-benciloxi)-2-oxo-2H-piridin-1-ilmetil]-fenil}-acetonitrilo

3-[3-Bromo-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-ilmetil]-N-(2-hidroxi-etil)-benzamida,

3-Cloro-4-(2,4-difluoro-benciloxi)-1-(3-fluoro-bencil)-1H-piridin-2-ona,

1-Alil-3-cloro-4-(2,4-difluoro-benciloxi)-6-metil-1H-piridin-2-ona,

3-Cloro-4-(2,4-difluoro-benciloxi)-1-[4-isopropilamino-metil)bencil]-1H-piridin-2-ona,

3-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]4-metilbenzoato de metilo,

3-bromo-4-[(2,4-difluorobencil)oxi]-6-

(hıdroxımetıl)-1-(2 4,6-trıfluorofenıl)pırıdın-2(1*H*)-ona,

3-Bromo-4-(2,4-dıfluoro-bencıloxı)-6-metıl-1-(4-pıperazın-1-ılmetıl-bencıl)-1H-pırıdın-2-ona,

3-bromo-4-[(2,4-dıfluorobencıl)oxı]-1-(2,6-(dıfluorofenıl)-6-(hıdroxımetıl)pırıdın-2(1*H*)-ona,

3-[3-Bromo-4-(',4-dıfluoro-bencıloxı)-6-metıl-2-oxo-2H-pırıdın-1-ılmetı ]-N,N-dımetıl-benzamıda,

3-bromo-1-(3-fluorobencıl)-4-[(3-metılbencıl)oxı]pırıdın-2(1*H*)-ona,

3-Bromo-1-(3-fluoro-bencıl)-4-(3-metıl-bencıloxı)-1H-pırıdın-2-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-(1,2,3,4-tetrahıdroısoquınolın-5-ılmetıl)pırıdın-2(1*H*)-ona,

3-bromo-1-(3-fluorobencıl)-4-[(3-metılbencıl)oxı]pırıdın-2(1*H*)-ona,

trıfluoroacetato de 3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-(ısoquınolın-5-ılmetıl)pırıdın-2(1*H*)-ona

3-[3-Bromo-4-(2,4-dıfluoro-bencıloxı)-6-metıl-2-oxo-2H-pırıdın-1-ılmetıl]-benzamıda,

3-bromo-4-[(2,4-dıfluorobencıl)oxı]-6-metıl-1-({5-[(4-(metılpıperazın-1-ıl)carbonıl]pırazın-2-ıl}metıl)pırıdın-2(1*H*)-ona trıfluoroacetato,

3-bromo-4-[(2,4-dıfluorobencıl)oxı]-1-[5-(hıdroxımetıl)-2-metılfenıl]-6-metılpırıdın-2(1*H*)-ona,

1-alıl-3-bromo-4-[(2,4-dıfluorobencıl)oxı]-6-metılpırıdın-2(1*H*)-ona,

3-bromo-4-[(2,4-dıfluorobencıl)oxı]-1-(pırıdın-3-ılmetıl)pırıdın-2(1*H*)-ona,

3-bromo-4-[(2,4-dıfluorobencıl)oxı]-1-(2-metoxı-6-metılfenıl)-6-metılpırıdın-2(1*H*)-ona,

3-bromo-4-[(2,4-dıfluorobencıl)oxı]-1-(2-metoxı-6-

metilfenil)-6-metilpiridin-2(1*H*)-ona,

3-[3-Bromo-4-(2,4-difluoro-benciloxi)-2-oxo-2H-piridin-1-ilmetil]-benzamida,

3-cloro-4-[(2,4-difluorobencil)oxi]-6-(hidroximetil)-1-(2,4,6-trifluorofenil)piridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-[2-(trifluorometil)fenil]piridin-2(1*H*)-ona,

Ácido 4-[3-bromo-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-ilmetil]-benzoico,

3-Bromo-4-(2,4-difluoro-benciloxi)-6-metil-1-(4-morfolin-4-ilmetil-bencil)-1H-piridin-2-ona,

4-(2,4-Difluoro-benciloxi)-1-(3-fluoro-bencil)-3-yodo-1H-piridin-2-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-(2,4,6-trifluorofenil)piridin-2(1*H*)-ona,

3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-*N*-hidroxibenzamida,

3-bromo-1-(2,6-diclorofenil)-4-[(2,6-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

3-(4-Benciloxi-3-bromo-2-oxo-2H-piridin-1-ilmethil)-benzonitrilo,

3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-[3-(pirrolidin-1-ilcarbonil)fenil]piridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2-(fluorobencil)piridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-(4-metilbencil)piridin-2(1*H*)-ona,

3-{[3-cloro-4-[ 2,4-difluorobencil)amino]-6-metil-2-oxopiridin-1(2*H*)-il]metil}benzonitrilo,

3-[3-Bromo-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-ilmetil]-N-isopropil-benzamida,

3-bromo-1-(4-bromo-2,6-difluorofenil)-4-[(2,4-

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difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

3-bromo-4-[(4-fluorobencil)oxi]-6-metil-1-(piridin-3-ilmetil)piridin-2(1*H*)-ona,

3-bromo-4-[(4-fluorobencil)oxi]-6-metil-1-(piridin-4-ilmetil)piridin-2(1*H*)-ona,

3-bromo-4-[(4-fluorobencil)oxi]-6-metil-1-(piridin-4-ilmetil)piridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-(4-clorobencil)piridin-2(1*H*)-ona,

4-Benciloxi-3-bromo-1-(4-cloro-bencil)-1H-piridin-2-ona,

3-bromo-1-(4-fluorobencil)-4-[(4-fluorobencil)oxi]piridin-2(1*H*)-ona,

3-bromo-1-(2,6-diclorofenil)-4-[(4-fluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

3-Bromo-1-(4-fluoro-bencil)-4-(4-fluoro-benciloxi)-1H-piridin-2-ona,

4-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]benzoato de metilo,

Ácido 4-(4-benciloxi-3-bromo-2-oxo-2H-piridin-1-ilmethil)-benzoico,

Ácido 4-{[4-(benciloxi)-3-bromo-2-oxopiridin-1(2*H*)-il]metil}benzoico,

3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-1-(2,4,6-trifluorofenil)piridin-2(1*H*)-ona,

4-(benciloxi)-3 bromo-1-(2-fluorobencil)piridin-2(1*H*)-ona

3-cloro-4-[(2,4 difluorobencil)oxi]-1-(2,6-(difluorofenil)-6-(hidroximetil)piridin-2(1*H*)-ona,

hidrocloruro de *N*-(2-aminoetil)-4-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]benzamida,

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4-Benciloxi-3-bromo-1-(4-metilsulfanil-bencil)-1H-piridin-2-ona,

1-Bencil-4-benciloxi-3-cloro-1H-piridin-2-ona,

4-(benciloxi)-3-bromo-1-[4-(metiltio)bencil)]piridin-2(1*H*)-ona,

1-bencil-4-(benciloxi)-3-cloropiridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-{[5-(hidroximetil)pirazin-2-il]metil}-6-metilpiridin-2(1*H*)-ona,

3-bromo-1-(2,6-dimetilfenil)-4-[(4-fluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

3-bromo-1-(2,6-dimetilfenil)-4-[(4-fluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

3-Bromo-4-(2,4-difluoro-benciloxi)-1-[3-isopropilamino-metil)bencil]-1H-piridin-2-ona,

3-[3-Cloro-4-(2,4-difluoro-benciloxi)-2-oxo-2H-piridin-1-ilmetil]-2-fluoro-benzamida,

5-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]metil}-*N*-(2,3-hidroxipropil)pirazina-2-carboxamida,

Éster etílico de ácido {3-[3-bromo-4-(2,4-difluoro-benciloxi)-2-oxo-2H-piridin-1-ilmetil]-fenil}-acetico,

4-(4-Benciloxi-3-bromo-2-oxo-2H-piridin-1-ilmethil)-N-hidroxi-benzamidina,

4-{[4-(benciloxi)-3-bromo-2-oxopiridin-1(2*H*)-il]metil}-*N*-hidroxibencenocarboximidamida,

etil 5-{[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]metil}pirazina-2-carboxilato,

3-Bromo-4-(2,4-difluoro-benciloxi)-1-(3-metoxi-bencil)-1H-piridin-2-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-[(5-metilpirazin-2-il)metil]piridin-2(1*H*)-ona

3-bromo-4-[(2,4-difluorobencil)oxi]-1-(3-(metoxibencil)piridin-2(1*H*)-ona,

Éster metílico de ácido 4-(4-benciloxi-3-bromo-2-oxo-2H-piridin-1-ilmethil)-benzoico,

3-Bromo-4-(2,4-difluoro-benciloxi)-1-(4-dimetilaminometil-bencil)-1H-piridin-2-ona,

3-Cloro-4-(2,4-difluoro-benciloxi)-1-(3-metanosulfonil-benci_)-1H-piridin-2-ona,

Éster metílico de ácido 4-(4-benciloxi-3-bromo-2-oxo-2H-piridin-1-ilmethil)-benzoico,

4-{[4-(benciloxi)-3-bromo-2-oxopiridin-1(2*H*)-il]metil}benzoato de metilo,

5-{[3-bromo-4-[ 2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]metil}pirazina-2-carboxilato de etilo,

4-{[4-(benciloxi)-3-bromo-2-oxopiridin-1(2*H*)-il]metil}benzonitrilo,

4-(4-Benciloxi-3-bromo-2-oxo-2H-piridin-1-ilmethil)-benzonitrilo,

Ester terc-butílico de acido {3-[3-bromo-4-(4-fluoro-benciloxi)-2-oxo-2H-piridin-1-ilmetil]-bencil}-carbámico,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-[5-(1-hidroxi-1-metiletil)-2-metilfenil]-6-metilpiridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-(2,6-diclorofenil)-6-metilpiridin-2(1*H*)-ona,

1-(3-Aminometil-bencil)-4-benciloxi-3-bromo-1H-piridin-2-ona,

3-bromo-4-[(4-fluorobencil)oxi]-1-(piridin-4-ilmetil)piridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-(4-bromobencil)piridin-2(1*H*)-ona,

4-Bencıloxı-3-bromo-1-(4-bromo-bencıl)-1H-pırıdın-2-ona,

5-bromo-4-[(2,4-dıfluorobencıl)oxı]-1-(2,6-(dıfluorofenıl)-6-oxo-1,6-dıhıdropırıdına-2-carbaldehıdo,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-{[5-(hıdroxımetıl)pırazın-2-ıl]metıl}-6-metılpırıdın-2(1*H*)-ona,

4-(4-Bencıloxı-3-bromo-2-oxo-2H-pırıdın-1-ılmethıl)-benzamıda,

hıdrocloruro de 3-bromo-4-[(2,4-dıfluorobencıl)oxı]-6-metıl-1-[3-(pıperazın-1-ılcarbonıl)fenıl]pırıdın-2(1*H*)-ona,

3-bromo-4-[(2,4-dıfluorobencıl)amino]-1-(3-(fluorobencıl)pırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-6-metıl-1-[(5-metılpırazın-2-ıl)metıl]pırıdın-2(1*H*)-ona,

3-cloro-4-[(2,4-dıfluorobencıl)oxı]-1-[5-(hıdroxımetıl)-2-metılfenıl]-6-metılpırıdın-2(1*H*)-ona,

3-bromo-1-(3-fluorobencıl)-4-[(4-fluorobencıl)oxı]pırıdın-2(1*H*)-ona,

3-Bromo-1-(3-fluoro-bencıl)-4-(4-fluoro-bencıloxı)-1H-pırıdın-2-ona,

3-bromo-4-[(2,4-dıfluorobencıl)oxı]-6-metıl-1-[3-(morfolın-4-ılcarbonıl)fenıl]pırıdın-2(1*H*)-ona,

Éster metılıco de acıdo 3-(4-bencıloxı-3-bromo-2-oxo-2H-pırıdın-1-ılmethıl)-benzoıco,

3-bromo-1-(3-fluorobencıl)-4-{[2-(hıdroxımetıl)bencıl]oxı}pırıdın-2(1*H*)-ona,

3-Bromo-1-(3-fluoro-bencıl)-4-(2-hıdroxımetıl-bencıloxı)-1H-pırıdın-2-ona,

1-Benzo[1,3]dıoxol-5-ılmetıl-3-bromo-4-(2,4-dıfluoro-bencıloxı)-1H-pırıdın-2-ona,

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3-bromo-4-[(2,6-difluorobencil)oxi]-6-metil-1-(piridin-4-ilmetil)piridin-2(1*H*)-ona,

3-bromo-4-[(3-clorobencil)oxi]-1-(3-fluorobencil)piridin-2(1*H*)-ona,

3-bromo-4-[(3-clorobencil)oxi]-1-(3-fluorobencil)piridin-2(1*H*)-ona,

3-Bromo-4-(3-cloro-benciloxi)-1-(3-fluoro-bencil)-1H-piridin-2-ona,

4-(benciloxi)-3-bromo-1-(3-fluorobencil)piridin-2(1*H*)-ona

4-Benciloxi-3-biomo-1-(3-fluoro-bencil)-1H-piridin-2-ona,

3-Bromo-4-(2,4-difluoro-benciloxi)-6-metil-1-[3-(piperidina-1-carbonil)-bencil]-1H-piridin-2-ona,

3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-*N*,*N*-dimetilbenzamida,

Éster metílico de ácido 3-[3-cloro-4-(2,4-difluoro-benciloxi)-2-oxo-2H-piridin-1-ilmetil]-2-fluoro-benzoico,

1-(3-fluorobencil)-4-[(4-fluorobencil)oxi]-3-yodopiridin-2(1*H*)-ona,

1-(3-Fluoro-bencil)-4-(4-fluoro-benciloxi)-3-yodo-1H-piridin-2-ona

hidrocloruro de *N*-(3-aminopropil)-4-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il] benzamida,

4-{[3-bromo-4-[(4-fluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}benzonitrilo,

4-[3-Bromo-4-(4-fluoro-benciloxi)-2-oxo-2H-piridin-1-ilmetil]-benzonitrilo,

3-Bromo-1-(3-fluoro-bencil)-4-(2,3,4-trifluoro-benciloxi)-1H-piridin 2-ona,

1-bencil-4-(benciloxi)-3-bromopiridin-2(1*H*)-ona,

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5-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]metil}-*N*-(2-hidroxietil)-*N*-metilpirazina-2-carboxamida,

4-(4-Benciloxi-3-bromo-2-oxo-2H-piridin-1-ilmethil)-benzonitrilo,

3-bromo-1-(2,4-difluorobencil)-4-[(2,4-difluorobencil)oxi]piridin-2(1*H*)-ona,

3-Bromo-1-(2,4-difluoro-bencil)-4-(2,4-difluoro-benciloxi)-1H-piridin-2-ona,

4-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-*N*-(2-hidroxietil)benzamida,

3-bromo-4-[(4-fluorobencil)oxi]-1-(piridin-3-ilmetil)piridin-2(1*H*)-ona,

1-Bencil-4-benciloxi-3-bromo-1H-piridin-2-ona,

3-bromo-1-(ciclcpropilmetil)-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

1-(4-Aminometil-bencil)-4-benciloxi-3-bromo-1H-piridin-2-ona

3-bromo-1-(4-fluorobencil)-4-[(4-fluorobencil)amino]-6-metilpiridin-2(1*H*)-ona,

Éster metílico de ácido 3-[3-bromo-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-ilmetil]-benzoico,

5-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]metil}-*N*,*N*-dimetilpirazina-2-carboxamida,

3-bromo-4-[(4-fluorobencil)oxi]-6-metil-1-(piridin-2-ilmetil)piridin-2(1*H*)-ona

3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-(dimetilfenil)-6-metilpiridin-2(1*H*)-ona,

3-bromo-1-(2,6-diclorofenil)-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

4-(benciloxi)-1-(4-bromobencil)piridin-2(1*H*)-ona,

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3-bromo-4-hidroxi-1-(4-hidroxibencil)piridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-[2-(trifluorometil)bencil)]piridin-2(1*H*)-ona,

1-bencil-4-[(3-clorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

hidrocloruro de 4-(benciloxi)-3-bromo-1-(piperidin-3-ilmetil)piridin-2(_*H*)-ona,

1-bencil-3-bromo-2-oxo-1,2-dihidropiridin-4-il metil(fenil)carbamato,

4-(bencilamino)-1-(3-fluorobencil)-6-metil-3-nitropiridin-2(1*H*)-ona,

4-[3-bromo-1-(3-fluorobencil)-2-oxo-1,2-dihidropiridin-4-il]piperazina-1-carboxilato *terc*-butílico ,

[4-(benciloxi)-3-bromo-2-oxopiridin-1(2*H*)-il]metil)acetato de etilo,

*N*-[3-bromo-1-(3-fluorobencil)-2-oxo-1,2-dihidropiridin-4-il]bencenosulfonamida,

3-bromo-4-[(4-*terc*-butilbencil)oxi]-1-(3-(fluorobencil)piridir-2(1*H*)-ona,

*N*-[3-bromo-1-(3-fluorobencil)-2-oxo-1,2-dihidropiridin-4-il]-1-fenilmetilmetanosulfonamida

1-(bifenil-2-ilmetil)-3-bromo-4-[(4-fluorobencil)oxi]piridin-2(1*H*)-ona,

4-(bifenil-2-ilmetoxi)-3-bromo-1-(3-fluorobencil)piridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorofenil)amino]-1-(3-(fluorobencil)piridin-2(1*H*)-ona,

4-(anilino)-3-bromo-1-(3-fluorobencil)piridin-2(1*H*)-ona

4-{[3-bromo-1-(3-fluorobencil)-2-oxo-1,2-

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dihidropiridin-4-il]-1-amino}benzoato de metilo,

3-bromo-1-(3-fluorobencil)-4-[(3,4,5trimetoxifenil)amino]piridin-2(1*H*)-ona,

3-bromo-1-(3-fluorobencil)-4-[4-(4-fluorofenil)piperazin-1-il]piridin-2(1*H*)-ona,

3-bromo-1-(3-fluorobencil)-4-(4-metilpiperazin-1-il)piridin-2(1*H*)-ona trifluoroacetato,

*N*-[3-bromo-1-(3-fluorobencil)-2-oxo-1,2-dihidropiridin-4-il]-2,5-difluorobenzamida,

*N*-[3-bromo-1-(3-fluorobencil)-2-oxo-1,2-dihidropiridin-4-il]-2,4-difluorobenzamida,

3-bromo-1-(ciclchexilmetil)-4-[(4-fluorobencil)oxi]piridin-2(1*H*)-ona,

acido 3-[4-(benciloxi)-3-bromo-2-oxopiridin-1(2*H*)-il]propanoico,

*N*-[3-bromo-1-(3-fluorobencil)-2-oxo-1,2-dihidropiridin-4-il]-*N*-(2,4-difluorofenil)urea,

3-[4-(benciloxi)-3-bromo-2-oxopiridin-1(2*H*)-il]propanamida

4-(benciloxi)-3-bromo-1-(3-morfolin-4-il-3-oxopropyl)piridin-2(1*H*)-ona,

hidrocloruro de *N*-(3-aminopropil)-3-[4-(benciloxi)-3-bromo-2-oxopiridin-1(2*H*)-il]propanamida,

hidrocloruro de 4-(benciloxi)-3-bromo-1-(3-oxo-3-piperazin-1-ilpropil)piridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-(2-morfolin-4-iletil)piridin-2(1*H*)-ona,

3-bromo-1-(3-fluorobencil)-4-{[4-fluoro-2-(trifluorometil)bencil]amino}piridin-2(1*H*)-ona,

hidrocloruro de *N*-(2-aminoetil)-3-[4-(benciloxi)-3-bromo-2-oxopiridin-1(2*H*)-il]propanamida,

acido [3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-

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2-oxopiridin-1(2*H*)-il]acetico,

3-bromo-4-[(2,4 difluorobencil)oxi]-6-metil-1-(tetrahidrofuran-2-ilmetil)piridin-2(1*H*)-ona,

4-[(2,4-difluorobencil)oxi]-6-metil-1-(tetrahidrofuran-2-il)metil)piridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridina-1(2*H*)-carboxilato de metilo,

1-alil-3-(2,4-difluorobencil)-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

4-(benciloxi)-1-(2,2-dietoxietil)piridin-2(1*H*)-ona,

*N*-acetil-3-[4-(benciloxi)-2-oxopiridin-1(2*H*)-il]alaninato de metilo,

*N*-acetil-3-[4-(benciloxi)-2-oxopiridin-1(2*H*)-il]alaninato de bencilo,

*N*-[(benciloxi)carbonil]-3[4-(benciloxi)-2-oxopiridin-1(2*H*)-il]alaninato de bencilo,

4-(benciloxi)-1-(2-oxopropil)piridin-2(1*H*)-ona,

5-{[4-(benciloxi)-2-oxopiridin-1(2*H*)-il]metil}-5-metilimidazolina-2,4-diona,

[4-(benciloxi)-2-oxopiridin-1(2*H*)-il] acetato de etilo,

2- [4-(benciloxi)-2-oxopiridin-1(2*H*)-il] acetamida,

1-bencil-4-(benciloxi)-3,5-dibromopiridin-2(1*H*)-ona,

4-(benciloxi)-1-etilpiridin-2(1*H*)-ona,

4-(benciloxi)-1-(4-*terc*-butilbencil)piridin-2(1*H*)-ona

4-{[4-(benciloxi)-2-oxopiridin-1(2*H*)-il]metil} benzonitrilo,

3-{[4-(benciloxi)-2-oxopiridin-1(2*H*)-il]metil}piperidina-1-carboxilato *terc*-butilico,

1,3-dibencil-4-hidroxi-6-metilpiridin-2(1*H*)-ona,

1-bencil-6-metil-2-oxo-1,2-dihidropiridin-4-il

metanosulfonato,

4-(benciloxi)-1-(4-bromobencil)piridin-2(1*H*)-ona,

4-(benciloxi)-3-bromopiridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-[2-(trifluorometil)bencil)]piridin-2(1*H*)-ona,

1-bencil-4-(1-naftilmetoxi)piridin-2(1*H*)-ona,

1-bencil-4-(benciltio)-3,5-dibromopiridin-2(1*H*)-ona,

1-bencil-4-[(2,6-diclorobencil)oxi]piridin-2(1*H*)-ona,

1-bencil-3-[(bencilamino)metil]-4-(benciloxiy)piridin-2(1*H*)-ona,

1-bencil-4-(benciloxi)-3-{[(2-ciclohexiletil)amino]metil}piridin-2(1*H*)-ona,

1-bencil-4-(benciltio)-5-metilpiridin-2(1*H*)-ona,

1-bencil-3-bromo-6-metil-2-oxo-1,2-dihidropiridin-4-il metanosulfonato,

1-bencil-3-bromo-6-metil-4-{[2-(trifluorometil)bencil]oxi}piridin-2(1*H*)-ona,

1-bencil-6-metil-2-oxo-1,2-dihidropiridin-4-il 4-bromobencenosulfonato,

1-bencil-4-[(3-clorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

1-bencil-3-bromo-6-metil-2-oxo-1,2-dihidropiridin-4-il 4-bromobencenosulfonato,

4-fenoxi-1-{[2-(trimetilsililo)etoxi]metil}piridin-2(1*H*)-ona,

1-bencil-4-fenoxipiridin-2(1*H*)-ona,

1-(4-metoxibencil)-4-fenoxipiridin-2(1*H*)-ona

hidrocloruro de 3-bromo-4-hidroxi-1-(4-hidroxibencil)piridin-2(1*H*)-ona,

hidrocloruro de 4-(benciloxi)-3-bromo-1-(piperidin-3-ilmetil)piridin-2(1*H*)-ona,

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1-bencil-4-[(2,6-diclorobencil)oxi]piridin-2(1*H*)-ona,

1-bencil-4-(benciloxi)-3,5-dibromopiridin-2(1*H*)-ona,

3-bromo-1-(3-fluorobencil)-4-[(*E*)-2-(4-fluorofenil)vinil]piridin-2(1*H*)-ona,

1-bencil-4-(benciloxi)-2-oxo-1,2-dihidropiridina-3-carbaldehido,

1-bencil-4-(benciloxi)piridin-2(1*H*)-ona,

1-bencil-4-(benciloxi)piridin-2(1*H*)-ona,

1-bencil-4-(benciltio)piridin-2(1*H*)-ona,

4-[3-cloro-4-[(2,4-difluorobencil)oxi] -2-oxopiridin-1(2*H*)-il]benzoato de metilo,

(5-nitro-2,6-dioxo-3,6-dihidropirimidin-1(2*H*)-il)acetato de bencilo,

3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxo-2*H*-1,2'-bipiridina-5'-carboxilato de etilo,

4-(benciloxi)-1-(4-metilbencil)piridin-2(1*H*)-ona,

[5-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorofenil)-2-metil-6-oxo-1,6-dihidropiridin-3-il]carbamato de metilo,

4-(benciloxi)-1-(4-clorobencil)piridin-2(1*H*)-ona,

(2*E*)-4-[4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]but-2-enoato de metilo,

4-(benciloxi)-1-(2-fluorobencil)piridin-2(1*H*)-ona,

4-{[4-(benciloxi)-3-bromo-2-oxopiridin-1(2*H*)-il]metil}piperidina-1-carboxilato *terc*-butílico,

4-(benciloxi)-1-(3-fluorobencil)piridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-(difluorofenil)-5-(1,2-dihidroxietil)-6-metilpiridin-2(1*H*)-ona,

1-bencil-4-hidrcxi-6-metilpiridin-2(1*H*)-ona,

4-({[3-bromo-1-(3-fluorobencil)-2-oxo-1,2-

dihidropiridin-4-il]oxi}metil)benzonitrilo,

1-bencil-4-(benciloxi)-6-metilpiridin-2(1*H*)-ona,

5-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-(difluorofenil)-2-metil-6-oxo-1,6-dihidropiridina-3-carbaldehido oxima,

1-bencil-4-(benciltio)-3-metilpiridin-2(1*H*)-ona,

1-bencil-4-[(4-metilbencil)oxi]piridin-2(1*H*)-ona,

1-bencil-4-(benciloxi)-3,5-dibromo-6-metilpiridin-2(1*H*)-ona,

1-bencil-4-(benciloxi)-3,5-dibromo-6-metilpiridin-2(1*H*)-ona,

3-bromo-1-(3-fluorobencil)-4-(1-feniletoxi)piridin-2(1*H*)-ona,

4-(benciloxi)-1-[4-(trifluorometil)bencil)]piridin-2(1*H*)-ona,

2-({[3-bromo-2-oxo-1-(piridin-3-ilmetil)-1,2-dihidropiridin-4-il]oxi}metil)-5-fluorobenzonitrilo,

5-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-(difluorofenil)-2-metil-6-oxo-1,6-dihidropiridina-3-carbonitrilo,

4-(benciloxi)-1-(3-fluorobencil)-3-(trifluorometil)piridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorofenil-6-metil-5-oxiran-2-ilpiridin-2(1*H*)-ona,

1-bencil-4-[(3-clorobencil)oxi]piridin-2(1*H*)-ona,

1-bencil-4-[(3-clorobencil)oxi]piridin-2(1*H*)-ona,

5-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-(difluorofenil)-2-metil-6-oxo-1,6-dihidropiridina-3-carbaldehido,

3-{[4-(benciloxi)-3-bromo-2-oxopiridin-1(2*H*)-il]metil}piperidina-1-carboxilato *terc*-butílico,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-

(difluorofenil)-6-metil-5-vinilpiridin-2(1*H*)-ona,

4-(benciloxi)-1 [4-(trifluorometoxi)bencil]piridin-2(1*H*)-ona,

3-bromo-4-[(4-clorobencil)oxi]-1-[2-(feniltio)etil]piridin-2(1*H*)-ona,

3-Bromo-4-(4-cloro-benciloxi)-1-(2-fenilsulfanil-etil)-1H-piridin-2-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-(2-morfolin-4-iletil)piridin-2(1*H*)-ona,

4-[(2,4-difluorobencil)oxi]-6-(hidroximetil)-1-(piridin-3-ilmetil)piridin-2(1*H*)-ona,

Trifluoroacetato de 4-{[2-(aminometil)-4-fluorobencil]oxi}-3-bromo-1-(2,6-difluorofenil)-6-metilpiridin-2(1H)-ona,

4-(benciloxi)-1-(4-fluorobencil)piridin-2(1*H*)-ona,

4-(benciloxi)-1-(4-fluorobencil)piridin-2(1*H*)-ona,

4-Benciloxi-3-bromo-1-metanosulfonil-1H-piridin-2-ona,

4-[4-(benciloxi)-3-bromo-2-oxopiridin-1(2*H*)-il] piperidina-1-carboxilato *terc*-butílico,

1-bencil-4-(benciloxi)-3-vinilpiridin-2(1*H*)-ona,

4-(benciloxi)-1-[4-(metiltio)bencil]piridin-2(1*H*)-ona,

3-Bromo-4-(2,4-difluoro-benciloxi)-1-(2-metil-4-metilamino-pirimidin-5-ilmetil)-1H-piridin-2-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

1-bencil-3-bromo-4-{[2-(trifluorometil)bencil]oxi}piridin-2(1*H*)-ona,

1-bencil-3-bromo-4-{[2-(trifluorometil)bencil]oxi}piridin-2(1*H*)-ona,

4-[(2,4-difluorobencil)oxi]-1-[5-(hidroximetil)-2-

metilfenil]-6-metilp_ridin-2(1*H*)-ona,

4-(benciloxi)-1 [4-(metilsulfonil)bencil]piridin-2(1*H*)-ona,

4-Fenoxi-1H-piridin-2-ona,

1-bencil-4-[(2-clorobencil)oxi]piridin-2(1*H*)-ona,

1-bencil-4-[(2-clorobencil)oxi]piridin-2(1*H*)-ona,

4-{[4-(benciloxi)-2-oxopiridin-1(2*H*)-il]metil}benzoato de metilo,

4-[(2,4-difluorobencil)oxi]-1-(2,6-difluorofenil)-6-metilpiridin-2(1*H*)-ona,

1-(3-fluorobencil)-4-(feniletinil)piridin-2(1*H*)-ona,

hidrocloruro de 4-(benciloxi)-3-bromo-1-(piperidin-4-ilmetil)piridin-2(1*H*)-ona,

hidrocloruro de 4-(benciloxi)-3-bromo-1-(piperidin-4-ilmetil)piridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-[2-(metilito)pirimidin-4-il]piridin-2(1*H*)-ona

hidrocloruro de 4-(benciloxi)-3-bromo-1-piperidin-4-ilpiridin-2(1*H*)-ona,

4-Benciloxi-1-difluorometil-1H-piridin-2-ona,

4-Benciloxi-3-bromo-1-(2-cloro-fenil)-6-metil-1H-piridin-2-ona,

3-Bromo-6-metil-1-piridin-3-ilmetil-4-[(piridin-3-ilmetil)-amino-]-1H-piridin-2-ona,

Acido 1-(3,4-dicloro-bencil)-6-oxo-1,6-dihidro-piridina-3-carboxilico (2,4-difluoro-fenil)-amida,

Ácido 1-(2 6-dicloro-bencil)-6-oxo-1,6-dihidro-piridina-3-carboxilico (2,4-difluoro-fenil)-amida

Acido 5-cloro-1-(2,6-dicloro-bencil)-6-oxo-1,6-dihidro-piridina-3-carboxilico (2,4-difluoro-fenil)-amida,

Acido 5-cloro-1-(2,6-dicloro-bencil)-6-oxo-1,6-

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dihidro-piridina-3-carboxílico metil-fenil-amida,

Acido 1-(2,6-dicloro-bencil)-6-oxo-1,6-dihidro-piridina-3-carboxílico bencilamida,

Acido 1-(2 6-dicloro-bencil)-6-oxo-1,6-dihidro-piridina-3-carboxílico (3-dimetilamino-propil)-amida,

Ácido 1-(2 6-dicloro-bencil)-6-oxo-1,6-dihidro-piridina-3-carboxílico (2-morfolin-4-il-etil)-amida,

N-[5-Acetil-1-(4-cloro-bencil)-6-metil-2-oxo-1,2-dihidro-piridin-3-il]-4-cloro-benzamida,

ácido 1-(2 6-Dicloro-bencil)-6-oxo-1,6-dihidro-piridina-3-carboxílico N'-(3-cloro-5-trifluorometil-piridin-2-il)-hidracida,

*N*-alil-2-[(1-bencil-6-oxo-1,6-dihidropiridin-3-il)carbonil]hidracinacarbotioamida,

*1-Bencil-5-[5-(3,4-dicloro-bencilsulfanil)-[1,3,4]oxadiazol-2-il]-1H-piridin-2-ona,*

*N'*-{[(1-bencil-6-oxo-1,6-dihidropiridin-3-il)carbonil]oxi}piridina-4-carboximidamida,

Ácido 1-(,6-dicloro-bencil)-6-oxo-1,6-dihidro-piridina-3-carboxílico 3-trifluorometil-bencilamida,

Acido 1-bencil-6-oxo-1,6-dihidro-piridina-3-carboxílico (2-morfolin-4-il-etil)-amida,

5-[4-(3-Cloro-fenil)-piperazina-1-carbonil]-1-(3,4-dicloro-bencil)-1H-piridin-2-ona,

Ácido 5-cloro-1-(2,6-dicloro-bencil)-6-oxo-1,6-dihidro-piridina-3-carboxílico bencilamida,

1-(4-Cloro-bencil)-5-[3-(4-cloro-fenil)-[1,2,4]oxadiazol-5-il]-1H-piridin-2-ona,

1-(4-Cloro-bencil)-5-[3-(4-cloro-fenil)-[1,2,4]oxadiazol-5-il]-1H-piridin-2-ona,

2-Cloro-N-[1-(2,6-dicloro-bencil)-6-oxo-5-trifluorometil-1,6-dihidro-piridin-3-il]-4-fluoro-

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benzamida,

N-[1-(2,6-Dicloro-benzil)-6-oxo-5-trifluorometil-1,6-dihidro-piridin-3-il]-4-isopropoxi-benzamida,

Ácido 1-(2,6-dicloro-benzil)-6-oxo-1,6-dihidro-piridina-3-carboxílico (4-trifluorometoxi-fenil)-amida,

Acido 1-(2,6-dicloro-benzil)-6-oxo-1,6-dihidro-piridina-3-carboxílico (3-trifluorometil-fenil)-amida,

Acido 5-cloro-1-(2,6-dicloro-benzil)-6-oxo-1,6-dihidro-piridina-3-carboxílico (3-trifluorometil-fenil)-amida,

Ácido 1-(2 6-dicloro-benzil)-6-oxo-1,6-dihidro-piridina-3-carboxílico (4-cloro-fenil)-amida,

Ácido 1-(2 6-dicloro-benzil)-6-oxo-1,6-dihidro-piridina-3-carboxílico (2-dimetilamino-etil)-amida,

5-Metil-1-fenil-1H-piridin-2-ona,

3-Bromo-1-(3-fluoro-benzil)-4-(3-metoxi-fenil)-1H-piridin-2-ona,

3-Bromo-1-(3-fluoro-benzil)-4-(3-isopropil-fenil)-1H-piridin-2-ona,

3'-Bromo-1'-(3-fluoro-benzil)-6-metoxi-1'H-[3,4']bipiridinil-2'-ona,

4-Benzo[1,3]dioxol-5-il-3-bromo-1-(3-fluoro-benzil)-1H-piridin-2-ona,

3-Bromo-1-(3-fluoro-benzil)-4-tiofen-3-il-1H-piridin-2-ona,

3-Bromo-1-(3-fluoro-benzil)-4-(3-trifluorometil-fenil)-1H-piridin-2-ona,

3-Bromo-1-(3-fluoro-benzil)-4-naftalen-2-il-1H-piridin-2-ona,

3-Bromo-1-(3-fluoro-benzil)-4-(4-fluoro-fenil)-1H-piridin-2-ona,

1-Bencenosulfonil-4-benciloxi-3-bromo-1H-piridin-2-

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ona,

4-[3-Amino-1-(2,4-difluoro-fenil)-propoxi]-3-bromo-6-metil-1-piridin-3-ilmetil-1H-piridin-2-ona,

1-(4-Bromo-2,6-difluoro-fenil)-4-(2,4-difluoro-benciloxi)-6-metil-1H-piridin-2-ona,

2-[1-(4-Amino-2-metil-pirimidin-5-ilmetil)-3-bromo-6-metil-2-oxo-1,2-dihidro-piridin-4-iloximetil]-5-fluoro-benzonitrilo,

4-(2,4-Difluoro-benciloxi)-6-metil-1-(2,4,6-trifluoro-fenil)-1H-piridin-2-ona,

1-(2-Cloro-4-hidroxi-fenil)-4-(2,4-difluoro-benciloxi)-6-metil-1H-piridin-2-ona,

Éster metílico de acido 3-[4-(2,4-Difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-il]-benzoico,

3-Bromo-1-(2,6-difluoro-fenil)-4-metoxi-6-metil-5-vinil-1H-piridin-2-ona,

3-Bromo-1-(2,6-difluoro-fenil)-4-metoxi-6-metil-5-estiril-1H-piridin-2-ona,

1-(2,6-Difluoro-fenil)-4-metoxi-6-metil-5-fenetil-1H-piridin-2-ona,

3-Bromo-1-(2,6-difluoro-fenil)-4-metoxi-6-metil-5-fenetil-1H-piridin-2-ona,

1-(1*H*-indazol-5-il)-4-(1*H*-indazol-5-ilamino)-6-metilpiridin-2(1*H*)-ona,

5-Bromo-4-(2,4-difluoro-benciloxi)-1-(2,6-difluoro-fenil)-2-[2-(2,4-difluoro-fenil)-etil]-6-oxo-1,6-dihidro-piridina-3-carbaldehido,

4-[3-Bromo-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-ilmetil]-pirimidine-2-cabonitrilo,

Acido 3-bromo-1-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-[1,2']bipiridinil-5'-carboxilico,

Ácido 3-bromo-4 (5-carboxi-piridin-2-iloxi)-6-metil-

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2-oxo-2H-[1,2']bipir_dinil-5'-carboxílico,

3-Bromo-4-(2,4-difluoro-benciloxi)-6,6-dimetil-2-oxo-2H-[1,2']bipirid_nil-3'-carbonitrilo,

Ácido 3-bromo-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-[1,2']bipiridinil-5'-carboxílico metilamida,

Acido 3-bromo-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-[1,2']bipiridinil-5'-carboxílico (2-hidroxi-etil)-amida,

Ácido 3-Bromo-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-[1,2']bipiridinil-5'-carboxílico (2-metoxi-etil)-amida,

3-Bromo-1-(2,6-difluoro-fenil)-4-metoxi-6-metil-5-)4-metil-bencil)-1H-piridin-2-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-(difluorofenil)-5-(1,2-dihidroxi-2-feniletil)-6-metilpiridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-5'-(1-hidroxi-1-metiletil)-6-metil-2H-1,2'-bipiridin-2-ona,

4-Benciloxi-1H-piridin-2-ona,

4-Benciloxi-3-metil-1H-piridin-2-ona,

2-Oxo-6-fenetil-1,2-dihidro-piridina-3-carbonitrilo,

2-Oxo-6-fenil-1,2-dihidro-piridina-3-carbonitrilo,

6-Oxo-1,6-dihidro-[2,3']bipiridinil-5-carbonitrilo,

Ácido 6-Oxo-1,6-dihidro-[2,3']bipiridinil-5-carboxílico,

3-{[4-(benciloxi)-3-bromo-2-oxopiridin-1(2*H*)-il]metil}benzamida,

3-bromo-4-[(4-fluorobencil)oxi]-1-(4-(metoxibencil)piridin-2(1*H*)-ona,

3-bromo-4-[(4-fluorobencil)oxi]-1-(4-(metoxibencil)piridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-[2-fluoro-5-

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(hidroximetil)fenil]-6-metilpiridin-2(1*H*)-ona,

3-cloro-1-(4-flucrobencil)-4-[(4-fluorobencil)oxi]piridin-2(1*H*)-ona,

3-cloro-1-(4-flucrobencil)-4-[(4-fluorobencil)oxi]piricin-2(1*H*)-ona,

3-bromo-1-(3-clorobencil)-4-[(4-fluorobencil)oxi]piricin-2(1*H*)-ona,

3-bromo-4-[(3,4-difluorobencil)oxi]-1-(3-(fluorobencil)piridin-2(1*H*)-ona,

acido 3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-4-metilbenzoico,

3-bromo-1-(3-cloiobencil)-4-[(4-fluorobencil)oxi]piridin-2(1*H*)-ona,

3-bromo-1-(3-cloiobencil)-4-[(4-fluorobencil)oxi]piridin-2(1*H*)-ona,

trifluoroacetato de 4-{[3-cloro-4-[(2,4-difluorobencil)amino] 6-metil-2-oxopiridin-1(2*H*)-il]metil}benzonitrilo,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-{[5-(1-hidroxi-1-metiletil)p razin-2-il]metil}-6-metilpiridin-2(1*H*)-ona,

4-(bencilamino)-3-bromo-1-(3-fluorobencil)piridin-2(1*H*)-ona,

4-(bencilamino)-3-bromo-1-(3-fluorobencil)piridin-2(1*H*)-ona,

2-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]metil}benzonitrilo,

trifluoroacetato de 3-bromo-4-[(2,4-difluorobencil)oxi]-1-[2-fluoro-6-(4-metilpiperazin-1-il)fenil]-6-metilpiridin-2(1*H*)-ona,

4-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-*N*-metilbenzamida

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1-[2-(aminometil)bencil]-3-bromo-4-[(2,4-difluorobencil)oxi]piridin-2(1*H*)-ona,

3-bromo-1-(4-fluorobencil)-4-[(4-fluorobencil)oxi]piridin-2(1*H*)-ona,

1-[2-(aminometil)bencil]-3-bromo-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-[3-(piperidin-1-ilcarbonil)fenil]piridin-2(1*H*)-ona,

1-bencil-3-bromo-4-[(-4-clorobencil)oxi]piridin-2(1*H*)-ona,

4-[(2,4-difluorobencil)oxi]-1-(3-fluorobencil)-3-metilpiridin-2(1*H*)-ona,

4-(benciloxi)-1-[4-(benciloxi)bencil]-3-bromopiridin-2(1*H*)-ona,

4-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-*N*-hidroxibenzamida,

4-(benciloxi)-1-[4-(benciloxi)bencil]-3-bromopiridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-[4-(trifluorometil)bencil)]piridin-2(1*H*)-ona,

3-bromo-1-(ciclopropilmetil)-4-[(4-fluorobencil)oxi]piricin-2(1*H*)-ona,

3-bromo-1-(ciclopropilmetil)-4-[(4-fluorobencil)oxi]piricin-2(1*H*)-ona,

1-bencil-3-bromo-4-[(3-clorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

1-bencil-3-bromo-4-[(3-clorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

1-bencil-3-bromo-4-[(3-clorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

2-{[3-bromo-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}benzonitrilo,

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trifluoroacetato de 3-bromo-4-[(2,4-difluorobencil)oxi]-6 metil-1-({5-[(metilamino)metil]piazin-2-il}metil)piridin-2(1*H*)-ona,

3-bromo-1-(3-fluorobencil)-4-[(2-metilbencil)oxi]pirid_n-2(1*H*)-ona,

3-bromo-1-(3-fluorobencil)-4-[(2-metilbencil)oxi]piridin-2(1*H*)-ona,

3-{[3-bromo-4-[(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}benzoato de metilo,

3-bromo-1-(3-fluorobencil)-6-metil-4-(2-feniletil)piridin-2(1*H*)-ona,

3-bromo-1-(3-fluorobencil)-6-metil-4-(2-feniletil)piridin-2(1*H*)-ona,

1-bencil-3-bromo-4-[(-4-metilbencil)oxi]piridin-2(1*H*)-ona,

1-bencil-3-bromo-4-[(-4-metilbencil)oxi]piridin-2(1*H*)-ona,

1-bencil-3-bromo-4-[(-4-metilbencil)oxi]piridin-2(1*H*)-ona

4-(benciloxi)-1-(3-fluorobencil)-3-yodopiridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-[3-(hidroximetil)fenil]-6-metilpiridin-2(1*H*)-ona,

4-(benciloxi)-1-(3-fluorobencil)-3-yodopiridin-2(1*H*)-ona,

ácido 3-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]metil}benzoico,

3-bromo-4-[(4-fluorobencil)oxi]-1-[2-(hidroximetil)bencil]piridin-2(1*H*)-ona

trifluoroacetato de 3-bromo-4-[(2,4-difluorobencil)oxi]-1-[(5-{[(2-hidroxietil)(metil)amino]metil}pirazin-2-il)metil]-6-

metilpiridin-2(1*H*)-ona (sal),

4-(benciloxi)-3-bromo-1-[(6-fluoropiridin-3-il)metil]piridin-2(1*H* -ona,

3-bromo-4-[(4-clorobencil)oxi]-1-(4-fluorobencil)piridin-'(1*H*)-ona,

3-bromo-4-[(4-cloro-2-fluorobencil)amino]-1-(3-(fluorobencil)piridin 2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-etilpiridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-etilpiridin-2(1*H*)-ona

4-(benciloxi)-3-bromo-1-etilpiridin-2(1*H*)-ona,

2-(2-{[3-bromo-4 [(2,4-difluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}fenil) acetamida,

1-bencil-3-bromo-4-[(-2-clorobencil)oxi]piridin-2(1*H*)-ona,

1-bencil-3-bromo-4-[(-2-clorobencil)oxi]piridin-2(1*H*)-ona,

2-{[3-bromo-4-[(4-fluorobencil)oxi]-2-oxopiridin-1(2*H*)-il]metil}benzoato de metilo,

3-bromo-1-(2,6-diclorofenil)-4-[2-(4-fluorofenil)etil]-6-metilpiridin-2(1*H*)-ona,

3-bromo-1-(2,6-diclorofenil)-4-[2-(4-fluorofenil)etil]-6-metilpiridin-2(1*H*)-ona,

hidrocloruro de 3-bromo-4-[(2,4-difluorobencil)oxi]-1-{5-[(isopropilamino)metil]-2-metilfenil}-6-metilpiridin-2(1*H*)-ona,

3-bromo-1-(3-fluorobencil)-4-(2-feniletil)piridin-2(1*H*)-ona

*N*-{3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-yl]bencil}-*N*'-metilurea,

3-cloro-4-[(2,4-difluorobencil)oxi]-1-[3-(hidroximetil)fenil]-6-metilpiridin-2(1*H*)-ona,

3-bromo-1-(3-fluorobencil)-4-[(3-

fluorobencil)oxi]piridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-[2-(2-tienil)etil]piridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-[2-(2-tienil)etil]piridin-2(1*H*)-ona,

trifluoroacetato de 3-bromo-4-[(2,4-difluorobencil)oxi]-1 (2,6-(difluorofenil)-6-metilpiridin-2(1*H*)-ona,

trifluoroacetato de 3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-(difluorofenil)-6-metilpiridin-2(1*H*)-ona

3-bromo-4-[(4-clorobencil)oxi]-1-(4-(metoxibencil)piridin-2(1*H*)-ona,

3-bromo-4-[(4-clorobencil)oxi]-1-(4-(metoxibencil)piridin-2(1*H*)-ona,

3-bromo-1-(4-cloiobencil)-4-[(4-clorobencil)oxi]piridin-2(1*H*)-ona,

3-bromo-1-(3-fluorobencil)-4-[(4-metoxibencil)oxi]piridin-2(1*H*)-ona,

3-bromo-1-(3,5-dibromo-2,6 difluoro-4-hidroxifenil)-4-[(2,4-difluorobencil)oxi]-6-metilpiridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-[4-(trifluorometoxi)bencil)]piridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-[4-(trifluorometoxi)bencil)]piridin-2(1*H*)-ona

*N*'-{3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]bencil}-*N*,*N*-dimetilurea,

3-bromo-4-[(4-fluorobencil)oxi]-1-[4-(trifluorometil)bencil]piridin-2(1*H*)-ona,

2-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]metil} benzamida,

*N*-{3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-

oxopirıdın-1(2*H*)-ıl]bencıl}morfolına-4-carboxamıda,

*N*-{3-[3-bromo-4-ı(2,4-dıfluorobencıl)oxı]-6-metıl-2-oxopırıdın-1(2*H*)-ıl]bencıl} metanosulfonamıda,

4-[3-bromo-4-[(2,4-dıfluorobencıl)oxı]-6-metıl-2-oxopırıdın-1(2*H*)-ıl]-*N*-ısopropılbenzamıda,

4-(alılamıno)-3-bromo-1-(2,6-dıfluorofenıl)-5-yodo-6-metılpırıdın-2(1*H*)-ona,

4-(alılamıno)-3-bromo-1-(2,6-dıfluorofenıl)-5-yodo-6-metılpırıdın-2(1*H*)-ona,

acıdo (4-{[4-(bencıloxı)-3-bromo-2-oxopırıdın-1(2*H*)-ıl]metıl}fenıl)acetıco,

3-bromo-4-[(2,4-dıfluorobencıl)oxı]-6-metıl-1-[4-(pırrolıdın-1-ılcarbonıl)fenıl]pırıdın-2(1*H*)-ona,

1-bencıl-4-(bencıloxı)-3-yodopırıdın-2(1*H*)-ona,

1-(bıfenıl-4-ılmetıl)-3-bromo-4-[(4-fluorobencıl)oxı]pırıdın-2(1*H*)-ona,

acıdo 4-[3-bromo-4-[(2,4-dıfluorobencıl)oxı]-6-metıl-2-oxopırıdın-1(2*H*)-ıl] benzoıco,

4-(bencıloxı)-3-bromo-1-[2-(3-tıenıl)etıl]pırıdın-2(1*H*)-ona,

4-(bencıloxı)-3-bromo-1-[2-(3-tıenıl)etıl]pırıdın-2(1*H*)-ona,

3-bromo-4-[(4-fluorobencıl)oxı]-1-[3-(trıfluorometıl)bencıl]pırıdın-2(1*H*)-ona,

*N*- [3-bromo-1-(3-fluorobencıl)-2-oxo-1,2-dıhıdropırıdın-4-ıl]-4-fluorobenzamıda,

3-[3-bromo-4-[(2,4-dıfluorobencıl)oxı]-6-metıl-2-oxopırıdın-1(2*H*)-ıl]bencılcarbamato de metılo,

1-bencıl-4-(bencıltıo)-3-bromopırıdın-2(1*H*)-ona,

4-(bencıloxı)-3-bromo-1-(4-*terc*-butılbencıl)pırıdın-2(1*H*)-ona,

4-(bencıloxı)-3-bromo-1-(4-*terc*-butılbencıl)pırıdın-

2(1*H*)-ona,

*N*-{3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]bencil}-2- metoxiacetamida,

trifluoroacetato de 3-bromo-4-[(2,4-difluorobencil)oxi]-1-({5-[(dimetilamino)metil]pirazin-2-il}metil)-6-metilpiridin-2(1*H*)-ona,

hidrocloruro de 3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-[4-(piperazin-1-ilcarbonil)fenil]piridin-2(1*H*)-ona,

4-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-*N*,*N*-bis(2-hidroxietil)benzamida,

hidrocloruro de 3-bromo-4-[(2,4-difluorobencil)oxi]-1-{5-[(dimetilamino)metil]-2-metilfenil}-6-metilpiridin-2(1*H*)-ona,

1-bencil-3-bromo-4-(2-feniletil)piridin-2(1*H*)-ona,

1-(3-fluorobencil)-4-[(4-fluorobencil)oxi]-3-metilpiridin-2(1*H*)-ona,

trifluorocaetato de 4-(benciloxi)-1-(piperidin-3-ilmetil)piridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-[4-(morfolin-4-ilcarbonil)fenil]piridin-2(1*H*)-ona,

4-(benciloxi)-1-(3-fluorobencil)-3-metilpiridin-2(1*H*)-ona,

hidrocloruro de $N^1$-{3-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]bencil}glicinamida,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-(difluorofenil)-5-yodo-6-metilpiridin-2(1*H*)-ona

3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-1-[4-(piperidin-1-ilcarbonil)fenil]piridin-2(1*H*)-ona

*N*- [3-bromo-1-(3-fluorobencil)-2-oxo-1,2-dihidropiridin-4-il]-2,6-difluorobenzamida,

2-{[4-(benciloxi)-3-bromo-2-oksopiridin-1(2*H*)-il]metil}benzonitrilo,

5-{[3-bromo-4-[(2,4-difluorobencil)oksi]-6-metil-2-oksopiridin-1(2*H*)-il]metil}-*N*-metilpirazina-2-karboksamida,

3-kloro-4-[(2,4-difluorobencil)amino]-1-(2,6-(difluorofenil)-6-metilpiridin-2(1*H*)-ona,

acido 3-[3-kloro-4-[(2,4-difluorobencil)oksi]-6-metil-2-oksopiridin-1(2*H*)-il]benzoico,

3-bromo-1-(3-fluorobencil)-4-[(3-fluorobencil)amino]piridin-2(1*H*)-ona,

3-bromo-1-(3-fluorobencil)-4-[(3-metoksibencil)oksi]piridin-2(1*H*)-ona,

3-bromo-1-(2,4-*terc*-butilbencil)-4-[(2,4-difluorobencil)oksi]piridin-2(1*H*)-ona,

*N*-{3-[3-bromo-4-[(2,4-difluorobencil)oksi]-6-metil-2-oksopiridin-1(2*H*)-il]bencil} acetamida,

2-({3-[3-bromo-4-[(2,4-difluorobencil)oksi]-6-metil-2-oksopiridin-1(2*H*)-il]bencil}amino)-2-oksoetil acetato,

1-bencil-4-(benciloksi)-3-metilpiridin-2(1*H*)-ona,

*N*-{3-[3-bromo-4-[(2,4-difluorobencil)oksi]-6-metil-2-oksopiridin-1(2*H*)-il]bencil}urea,

1-bencil-4-(benciloksi)-3-etilpiridin-2(1*H*)-ona,

*N*-{3-[3-bromo-4-[(2,4-difluorobencil)oksi]-6-metil-2-oksopiridin-1(2*H*)-il]bencil}-2- hidroksiacetamida,

3-bromo-4-[(4-clorobencil)oksi]-1-(2-(feniletil)piridin-2(1*H*)-ona,

3-bromo-1-(3-clorobencil)-4-[(4-clorobencil)oksi]piridin-2(1*H*)-ona,

1-[3-(aminometil)fenil]-3-bromo-4-[(2,4-difluorobencil)oksi]-6-metilpiridin-2(1*H*)-ona,

2-{[4-(benciloksi)-3-bromo-2-oksopiridin-1(2*H*)-il]metil}benzamida,

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1-(4-fluorobencil)-4-[(4-fluorobencil)oxi]piridin-2(1*H*)-ona,

1-[2-(aminoetil)bencil]-4-(benciloxi)-3-bromopiridin-2(1*H*)-ona,

metil 3-[4-(benciloxi)-3-bromo-2-oxopiridin-1(2*H*)-il]propanoato,

1-bencil-4-(benciloxi)-3-metilpiridin-2(1*H*)-ona,

4-(alilamino)-1-(2,6-difluorofenil)-5-yodo-6-metilpiridin-2(1*H*)-ona,

4-(alilamino)-1-(2,6-difluorofenil)-5-yodo-6-metilpiridin-2(1*H*)-ona,

3-bromo-1-(3-flucrobencil)-4-(feniletinil)piridin-2(1*H*)-ona,

4-[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]-*N*,*N*-dimetilbenzamida

ácido {4-[({4-(benciloxi)-3-bromo-1-[4-(carboximetil)bencil]-1,2-dihidropiridin-2-il}oxi)metil]fenil}acetico,

4-(benciloxi)-3-bromo-1-[3-(trifluorometil)bencil)]piridin-2(1*H*)-ona,

4-(benciloxi)-3-etinil-1-(3-fluorobencil)piridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-{3-[(dimetilamino)metil]fenil}-6-metilpiridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-metilpiridin-2(1*H*)-ona,

1-bencil-3-bromo-4-(feniletinil)piridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-metilpiridin-2(1*H*)-ona,

3-bromo-1-(3-fluorobencil)-4-{[4-(trifluorometil)bencil]oxi}piridin-2(1*H*)-ona,

4-(bencilamino)-3-bromo-1-(2,6-difluorofenil)-5-yodo-6-metilpiridin-2(1*H*)-ona,

4-[(2,4-difluorobencil)oxi]-1-(4-metoxibencil)-6-

metilpiridin-2(1*H*)-ona,

hidrobromuro de 4-(benciloxi)-3-bromo-1-metilpiridin-2(1*H*)-ona,

4-(benciloxi)-3-bromo-1-[4-morfolin-4-ilcarbonil)fenil]piridin-2(1*H*)-ona,

acido 5-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-(difluorofenil)-6-oxo-1,6-dihidropiridina-2-carboxilico,

1-bencil-3-bromo-4-[(2,6-diclorobencil)oxi]piridin-2(1*H*)-ona,

acido 3-[3-cloro-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(?*H*)-il]-2-metilbenzoico,

acido 4-[4-(benciloxi)-3-bromo-2-oxopiridin-1(2*H*)-il]benzoico,

*N*-(5-{[3-bromo-4-[(2,4-difluorobencil)oxi]-6-metil-2-oxopiridin-1(2*H*)-il]metil}-2-metilpirimidin-4-il)glicinato trifluoroacetato de etilo,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-(difluorofenil)-6-metil-5-[(*E*)-2-fenilvinil]piridin-2(1*H*)-ona,

3-bromo-1-(3-fluorobencil)-4-{[3-(trifluorometil)benci ]amino}piridin-2(1*H*)-ona,

3-bromo-4-[(4-fluorobencil)oxi]-1-(3-(fenilpropil)piridin-'(1*H*)-ona,

3-bromo-1-(4-*terc*-butilbencil)-4-[(2,4-fluorobencil)oxi]piridin-2(1*H*)-ona,

4-(alilamino)-3-bromo-1-(2,6-difluorofenil)-6-metilpiridin-2(1*H*)-ona,

1-ciclohexil-4-[ 2,4-difluorobencil)oxi]-3,6-dimetilpiridin-2(1*H*)-ona,

3-bromo-4-[(2,4-difluorobencil)oxi]-1-(2,6-(difluorofenil)-5-(hidroximetil)-6-metilpiridin-2(1*H*)-ona,

1-bencil-4-(benciloxi)-2-oxo-1,2-dihidropiridina-3-carbaldehído,

4-[(2,4-difluorobencil)oxi]-6-metil-1-prop-2-in-1-ilpiridin-2(1*H*)-ona,

3-[4-(benciloxi)-3-bromo-2-oxopiridin-1(2*H*)-il]propanoato de etilo,

1-bencil-4-(benciloxi)-3-)hidroximetil)piridin-2(1*H*)-ona,

3-Cloro-4-(2,4-difluoro-benciloxi)-6-metil-1-(5-metil-pirazin-2-ilmetil)-1H-piridin-2-ona,

3-Cloro-4-(2,4-difluoro-benciloxi)-1-(5-hidroximetil-pirazin-2-ilmetil)-6-metil-1H-piridin-2-ona,

3-Bromo-4-(2,4-difluoro-benciloxi)-1-(2,3-dihidro-1H-indol-5-ilmetil)-1H-piridin-2-ona,

3-Bromo-4-(2,4-difluoro-benciloxi)-1-[1-(2-hidroxi-acetil)-2,3-dihidro-1H-indol-5-ilmetil]-6-metil-1H-piridin-2-ona,

3-Bromo-4-(2,4-difluoro-benciloxi)-6-metil-1-(1H-pirazol-3-ilmetil)-1H-piridin-2-ona,

3-[3-Cloro-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-il]-4,N-dimetil-benzamida,

3-[3-Cloro-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-il]-4-metil-benzamida,

3-[3-Cloro-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-il]-4-fluoro-N-metil-benzamida,

4-Cloro-3-[3-cloro-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-il]-N-metil-benzamida,

3-[3-Cloro-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-il]-4-fluoro-benzamida,

4-[3-Cloro-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-il]-3,N-dimetil-benzamida,

3-Cloro-4-(2,4-difluoro-benciloxi)-1-[4-(1,2-

dihidroxi-etil)-2-metil-fenil]-6-metil-1H-piridin-2-ona,

N-{4-[3-Cloro-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-ilmetil]-fenil}-2-hidroxi-acetamida,

Ácido 1-hidroxi ciclopropanocarboxílico 4-[3-cloro-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-ilmetil]-bencilamida,

N-{4-[3-Cloro-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-ilmetil]-bencil}-2-hidroxi-acetamida,

N-{4-[3-Cloro-4-(2,4-difluoro-benciloxi)-6-metil-2-oxo-2H-piridin-1-ilmetil]-fenil}-acetamida,

Éster etílico de acido {2-[3-Bromo-1-(2,6-difluoro-fenil)-6-metil-2-oxo-1,2-dihidro-piridin-4-iloximetil]-5-fluoro-bencil}-carbamico, o una sal farmacéuticamente aceptable

75 Un compuesto de acuerdo con la reivindicacion 17 en el que $Z_5$ es alquilo $C_1$-$C_4$, hidroxi $C_1$-$C_4$ alquilo, dihidroxi $C_1$-$C_4$ alquilo, halógeno, alcoxi $C_1$-$C_6$ carbonilo, $CF_3$ o alcanoilo $C_1$-$C_6$

76 Un compuesto de acuerdo con la reivindicacion 17 en el que

$Z_5$ es alquilo $C_1$-$C_4$, $-C(O)NR_6R_7$, -(alquilo $C_1$-$C_4$)-$C(O)NR_6R_7$, $R_6R_7N$-(alquilo $C_1$-$C_6$)- o $-NR_6R_7$, $CF_3$ o alcanoilo $C_1$-$C_4$, en el que

$R_6$ y $R_7$, en cada aparición, son independientemente H, alquilo $C_1$-$C_6$ opcionalmente sustituido con 1, 2 o 3 grupos que son independientemente alcoxi $C_1$-$C_4$ carbonilo, halógeno, cicloalquilo $C_3$-$C_6$, OH, SH o alcoxi $C_1$-$C_4$,

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Resumen

Se describen compuestos de la Fórmula I



I

y sus sales farmaceuticamente aceptables, en los que $R_1$, $R_2$, $R_3$, $R_4$, y $R_5$ se definen en la presente Estos compuestos son utiles para tratar enfermedades y afecciones causadas o exacerbadas por la acvididad de p38 MAP quinasa desregulada y/o FNT Tambien se describen composiciones farmaceuticas que contienen los compuestos, metodos para preparar los compuestos y métodos de tratamiento que utilizan los compuestos

# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| | | |
|---|---|---|
| Applicant s or agent s file reference<br>01 1077-C | **FOR FURTHER ACTION** | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
| International application No<br>PCT/US 03/04634 | International filing date *(day/month/year)*<br>14 02 2003 | Priority date *(day/month/year)*<br>14 02 2002 |
| International Patent Classification (IPC) or both national classification and IPC<br>A61K31/4412 A61K31/4412 | | |
| Applicant<br>PHARMACIA CORPORATION | | |

1 This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36

2 This REPORT consists of a total of 6 sheets including this cover sheet

☒ This report is also accompanied by ANNEXES i e sheets of the description claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70 16 and Section 607 of the Administrative Instructions under the PCT)

These annexes consist of a total of 13 sheets

3 This report contains indications relating to the following items

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☒ Non establishment of opinion with regard to novelty inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66 2(a)(ii) with regard to novelty inventive step or industrial applicability citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

| | |
|---|---|
| Date of submission of the demand<br>15 09 2003 | Date of completion of this report<br>06 05 2004 |
| Name and mailing address of the international preliminary examining authority<br>European Patent Office<br>D-80298 Munich<br>Tel +49 89 2399 0 Tx 523656 epmu d<br>Fax +49 89 2399 4465 | Authorized Officer<br>Seymour, L<br>Telephone No +49 89 2399 8694 |

Form PCT/IPEA/409 (Cover Sheet) (January 2004)

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# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No PCT/US 03/04634

## I Basis of the report

1 With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70 16 and 70 17))*

**Description, Pages**

1 912 as originally filed

**Claims, Numbers**

4 (part) 5 34, 35 (part), 37 74 as originally filed

1 3 4 (part) 35 (part) 36 filed with telefax on 22 03 2004

2 With regard to the **language** all the elements marked above were available or furnished to this Authority in the language in which the international application was filed unless otherwise indicated under this item

These elements were available or furnished to this Authority in the following language which is

☐ the language of a translation furnished for the purposes of the international search (under Rule 23 1(b))

☐ the language of publication of the international application (under Rule 48 3(b))

☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55 2 and/or 55 3)

3 With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application the international preliminary examination was carried out on the basis of the sequence listing

☐ contained in the international application in written form

☐ filed together with the international application in computer readable form

☐ furnished subsequently to this Authority in written form

☐ furnished subsequently to this Authority in computer readable form

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

4 The amendments have resulted in the cancellation of

☐ the description pages

☐ the claims Nos

☐ the drawings sheets

5 ☒ This report has been established as if (some of) the amendments had not been made since they have been considered to go beyond the disclosure as filed (Rule 70 2(c))

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report )*

**see separate sheet**

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**INTERNATIONAL PRELIMINARY EXAMINATION REPORT** International application No PCT/US 03/04634

6 Additional observations if necessary

**III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1 The questions whether the claimed invention appears to be novel to involve an inventive step (to be non obvious) or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos 1 35 68 74 (all partially), 68 and 69 with respect to industrial applicability

because

☒ the said international application or the said claims Nos 68 and 69 relate to the following subject matter which does not require an international preliminary examination (specify)

**see separate sheet**

☐ the description claims or drawings *(indicate particular elements below)* or said claims Nos are so unclear that no meaningful opinion could be formed *(specify)*

☐ the claims or said claims Nos are so inadequately supported by the description that no meaningful opinion could be formed

☒ no international search report has been established for the said claims Nos 1 35 68 74 (all partially)

2 A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/ or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions

☐ the written form has not been furnished or does not comply with the Standard

☐ the computer readable form has not been furnished or does not comply with the Standard

**V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability, citations and explanations supporting such statement**

1 Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes | Claims | |
| | No | Claims | 1 74 |
| Inventive step (IS) | Yes | Claims | |
| | No | Claims | 1 74 |
| Industrial applicability (IA) | Yes | Claims | 1 67 70 74 |
| | No | Claims | |

2 Citations and explanations

**see separate sheet**

**INTERNATIONAL PRELIMINARY EXAMINATION REPORT - SEPARATE SHEET** International application No PCT/US 03/04634

**Re Item I**

The amendments filed with the fax dated 22 03 04 introduce subject-matter which extends beyond the content of the application as filed, contrary to Article 34(2)(b) PCT The amendments concerned are the addition of provisos to claims 1 and 36 The applicant has not indicated on which passages of the original application these amendments are based or explained the precise reasons for the amendments (Rule 66 8 PCT), i e which particular prior art is intended to be excluded by each proviso (it is noted that newly introduced disclaimers must have a precise basis in the prior art, i e the disclaimer should not be more comprehensive than the disclosure of the excluded prior art) Furthermore, it appears that these provisos may be intended to exclude documents D1-D6 The introduction of such disclaimers is not admissible under Article 34(2)(b) PCT since they exclude documents which are relevant to the assessment of inventive step Disclaimers may only be used to exclude accidentally novelty-destroying documents, i e which have no relevance for any further examination

**This report has therefore been established without taking into account said provisos**

It is also noted that, although "alkoxy" and "alkyl" have been deleted from one position in the definition of $R_2$, these substituents are nevertheless present further down in the list

**Re Item III**

For reasoning with regards to unsearched subject-matter, see Form PCT/ISA/210 of the International Search Report **No international Preliminary Examinati n will be carried out with respect to subject-matter which is not covered by the search report** (Rule 66 1(e) PCT)

Claims 68 and 69 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67 1(iv) PCT Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT)

**Re Item V**

1 Reference is made to the following documents

D1 WO-A-97 10712 D2 US-A-3 715 358 D3 US-A-3 654 291
D4 GB-A-1 289 187 D5 US-A-3 644 626 D6 WO-A-00 31063
D7 Beilstein [Online], database accession no 5069110 (BRN) (XP002243098) & J Chem Soc , Perkin Trans 1, 1986, pages 1289-1296,
D8 Beilstein [Online], database accession no 5587856 (BRN) (XP002243099) & Liebigs Ann Recl , vol 8, 1997, pages 1777-1782
D9 Beilstein [Online], database accession no 6347000 (BRN) (XP002243100) & Collect Czech Chem Commun , vol 58, no 4, 1993, pages 947-953
D10 Beilstein [Online], database accession no 255148 (BRN) XP002243101 & Chem Ber , vol 89, 1956, pages 876-879,
D11 WO-A-86 01815

2 Novelty (Article 33(2) PCT)

The subject-matter of the present claims is not new (see D1 - D11 and corresponding citations in search report) In several instances, the applicant has attempted to reestablish novelty by simply deleting particular exemplified meanings of substituents However, for a region of overlap with a known group to be considered novel, it must provide a technical teaching not contained in the prior art (e g a particular substituent at a selected position of the molecule) In the present case it is not apparent what might constitute said novel technical teaching

3 Inventive step (Article 33(3) PCT)

Pyridinones of the type claimed are well known to be useful in the treatment of conditions falling within the scope of TNF mediated disorders and p38 kinase mediated disorders, such as inflammation (see D1-D6, cf present claims 68 and 69) The present compounds cannot therefore be viewed as being an inventive solution to the problem of providing further compounds for the treatment of TNF and p38 kinase mediated disorders, in the absence of comparative data showing that substantially all the claimed compounds have an unexpected property or improved activity with respect to the structurally closest prior art compounds, which is attributable to the distinguishing feature of the invention

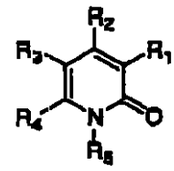
4 Industrial applicability (Article 33(4) PCT)

For the assessment of the present claims 68 and 69 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States The patentability can also be dependent upon the formulation of the claims The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment

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What is claimed is

1 A compound of the formula



or a pharmaceutically acceptable salt thereof, wherein

$R_1$ is H, halogen, $NO_2$, alkyl, carboxaldehyde, hydroxyalkyl, dihydroxyalkyl arylalkoxy, arylalkyl, alkenyl, alkynyl arylalkynyl, -CN, aryl, alkanoyl alkoxy, alkoxyalkyl, haloalkyl, haloalkoxy, carboxyl, or arylalkanoyl,

wherein the aryl portion of arylalkoxy, arylalkyl, and arylalkanoyl is unsubstituted or substituted with 1 2, 3, 4 or 5 groups that are independently halogen, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, nitro, CN, haloalkyl, haloalkoxy or $CO_2R$,

wherein the alkyl portion of the alkyl, hydroxyalkyl, dihydroxyalkyl, arylalkoxy, arylalkyl, alkanoyl, alkoxy, alkoxyalkyl and arylalkanoyl groups is unsubstituted or substituted with 1 2 or 3 groups that are independently halogen $C_1$-$C_4$ alkoxy $C_1$-$C_4$ alkoxycarbonyl, or $C_3$-$C_7$ cycloalkyl

$R_2$ is OH, halogen, $-OSO_2-(C_1-C_6)$ alkyl $-OSO_2$-aryl, arylalkoxy, aryloxy, arylthio, arylthioalkoxy, arylalkynyl, aryloxy($C_1$-$C_6$)alkyl, alkynyl, $-OC(O)NH(CH_2)_n$aryl, $-OC(O)N(alkyl)(CH_2)_n$aryl, alkoxyalkoxy, dialkylamino, alkyl alkoxy, aryl, arylalkyl heteroaryl, heteroarylalkyl, arylalkenyl, heterocycloalkyl heterocycloalkylalkyl, alkoxyalkoxy, $NR_8R_9$, dialkylamino, or $CO_2R$, wherein

n is 0, 1, 2, 3, 4, 5 or 6,

each of which groups is unsubstituted or substituted with 1, 2 3, 4 or 5 groups that are independently halogen,





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$-(C_1-C_6)$alkyl-N(R)-$CO_2R_{30}$, haloalkyl, heteroaryl, heteroarylalkyl, $-NR_6R_7$, $R_6R_7N-(C_1-C_6$ alkyl)-, $-C(O)NR_6R_7$ $-(C_1-C_4)$alkyl-$C(O)NR_6R_7$, $-(C_1-C_4$ alkyl)-$NRC(O)NR_{16}R_{17}$, haloalkoxy, alkyl, CN hydroxyalkyl, dihydroxyalkyl, alkoxy, alkoxycarbonyl, phenyl $-SO_2$-phenyl wherein the phenyl and $-SO_2$-phenyl groups are optionally substituted with 1, 2, or 3 groups that are independently halogen or $NO_2$, or $-OC(O)NR_6R_7$, wherein

$R_{16}$ and $R_{17}$ are independently H or $C_1-C_6$ alkyl, or

$R_{16}$, $R_{17}$ and the nitrogen to which they are attached form a morpholinyl ring,

$R_6$ and $R_7$ are independently at each occurrence H, alkyl, hydroxyalkyl dihydroxyalkyl alkoxy, alkanoyl arylalkyl, arylalkoxy, alkoxycarbonyl, $-SO_2$-alkyl, OH, alkoxy, alkoxyalkyl, arylalkoxycarbonyl, $-(C_1-C_4)$alkyl-$CO_2$-alkyl, heteroarylalkyl, or arylalkanoyl, wherein each is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, OH, SH heterocycloalkyl, heterocycloalkylalkyl $C_3-C_7$ cycloalkyl, alkoxy, $NH_2$, NH(alkyl), N(alkyl)(alkyl) -O-alkanoyl, alkyl, haloalkyl, carboxaldehyde, or haloalkoxy, or

$R_6$, $R_7$, and the nitrogen to which they are attached form a morpholinyl, pyrrolidinyl, thiomorpholinyl, thiomorpholinyl S-oxide, thiomorpholinyl S,S-dioxide, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently $C_1-C_4$ alkyl, alkoxycarbonyl $C_1-C_4$ alkoxy, hydroxyl, hydroxyalkyl dihydroxyalkyl, or halogen,





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R at each occurrence is independently hydrogen or $C_1$-$C_6$ alkyl optionally substituted with 1 or 2 groups that are independently OH, SH, halogen, amino, monoalkylamino, dialkylamino or $C_3$-$C_6$ cycloalkyl,

$R_{30}$ is $C_1$-$C_6$ alkyl optionally substituted with 1 or 2 groups that are independently OH, SH, halogen, amino, monoalkylamino, dialkylamino or $C_3$-$C_6$ cycloalkyl,

each $R_8$ is independently hydrogen, alkyl, alkanoyl, arylalkyl and arylalkanoyl, wherein each of the above is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, alkoxy, alkoxycarbonyl, halogen, or haloalkyl,

each $R_9$ is hydrogen, alkyl, alkanoyl, arylalkyl, cycloalkyl, cycloalkylalkyl, alkenyl, heteroaryl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, arylalkanoyl $-SO_2$-phenyl, and aryl wherein each of the above is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, alkoxy, alkoxycarbonyl, halogen, or haloalkyl,

$R_3$ is H, halogen alkoxycarbonyl, arylalkoxycarbonyl, aryloxycarbonyl, arylalkyl, $-OC(O)NH(CH_2)_n$aryl, arylalkoxy $-OC(O)N(alkyl)(CH_2)_n$aryl, aryloxy, arylthio, thioalkoxy, arylthioalkoxy alkenyl, $-NR_6R_7$, $NR_6R_7$-$(C_1$-$C_6)$alkyl or alkyl, wherein

the aryl portion of arylalkoxycarbonyl, aryloxycarbonyl, arylalkyl, $-OC(O)NH(CH_2)_n$aryl arylalkoxy, $-OC(O)N(alkyl)(CH_2)_n$aryl, and arylthioalkoxy, is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, alkoxy, alkyl, haloalkyl, or haloalkoxy,



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wherein n is 0, 1, 2, 3, 4, 5, or 6, or

$R_4$ is hydrogen or $R_4$ is alkyl unsubstituted or substituted with one or two groups that are independently $CO_2R$, $-CO_2-(C_1-C_6)$alkyl, $-C(O)NR_6R_7$, $-C(O)R_6$, $-N(R_{30})C(O)NR_{16}R_{17}$, $-N(R_{30})C(O)-(C_1-C_6)$alkoxy, or $-NR_6R_7$, arylalkoxy, arylalkyl, heteroaryl, heteroarylalkyl, hydroxyalkyl, dihydroxyalkyl haloalkyl, $R_6R_7N-(C_1-C_6$ alkyl)-, $-NR_6R_7$, alkoxy, carboxaldehyde, $-C(O)NR_6R_7$, $CO_2R$, alkoxyalkyl, or alkoxyalkoxy, wherein the heteroaryl or aryl portions of is the above are unsubstituted or substituted with 1 2, 3, 4, or 5 groups that are independently halogen, hydroxy, alkoxy, alkyl $-CO_2-(C_1-C_6)$alkyl, $-CONR_6R_7$, $-NR_6R_7$, $R_8R_7N-(C_1-C_6)$alkyl-, nitro, haloalkyl, or haloalkoxy, and

$R_5$ is aryl, arylalkyl, arylthioalkyl, alkyl substituted with at least one 1, or optionally 2 or 3 groups that are independently arylalkoxycarbonyl, $-NR_8R_9$, halogen, $-C(O)NR_8R_9$, alkoxycarbonyl, $C_3-C_7$ cycloalkyl, or alkanoyl, alkoxy, alkoxyalkyl optionally substituted with one trimethylsilyl group, amino alkoxycarbonyl hydroxyalkyl dihydroxyalkyl, alkynyl, $-SO_2$-alkyl, alkoxy optionally substituted with one trimethylsilyl group, heterocycloalkylalkyl, cycloalkyl, cycloalkylalkyl, -alkyl-S-aryl, -alkyl-$SO_2$-aryl, heteroarylalkyl, heterocycloalkyl, heteroaryl, or alkenyl optionally substituted with alkoxycarbonyl, wherein

each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, halogen, alkoxy, hydroxyalkyl, dihydroxyalkyl, arylalkoxy, thioalkoxy, alkoxycarbonyl, arylalkoxycarbonyl, $CO_2R$, CN, OH, hydroxyalkyl, dihydroxyalkyl, amidinooxime, $-NR_6R_7$, $-NR_8R_9$, $R_6R_7N-(C_1-C_8$ alkyl)-, carboxaldehyde, $SO_2$alkyl, $-SO_2H$ $-SO_2NR_6R_7$, alkanoyl wherein the alkyl portion is





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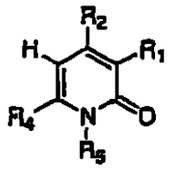
optionally substituted with OH, halogen or alkoxy, -C(O)$NR_6R_7$, -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$ amidino, haloalkyl, -($C_1$-$C_4$ alkyl)-$NR_{15}$C(O)$NR_{16}R_{17}$, -($C_1$-$C_4$ alkyl)-$NR_{15}$C(O)$R_{18}$, -O-$CH_2$-O, -O-$CH_2CH_2$-O- or haloalkoxy wherein

$R_{15}$ is H or $C_1$-$C_6$ alkyl, and

$R_{18}$ is $C_1$-$C_6$ alkyl optionally substituted with -O-($C_2$-$C_6$ alkanoyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_6$ dihydroxyalkyl, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, amino $C_1$-$C_6$ alkyl, mono or dialkylamino $C_1$ $C_6$ alkyl,

provided that (a) at least one of $R_1$ $R_3$, and $R_4$ is not hydrogen, (b) when $R_2$ is benzyloxy and $R_5$ is benzyl, at least one of the benzyl portions carries a non-hydrogen substituent, or (c) when $R_2$ is benzylamino and $R_5$ is benzyl, $R_4$ is not methyl

2 A compound according to claim 1, of the formula




or a pharmaceutically acceptable salt thereof, wherein

$R_1$ is H, halogen, alkyl, carboxaldehyde, hydroxyalkyl, dihydroxyalkyl, arylalkoxy, arylalkyl, alkenyl, alkynyl, arylalkynyl, CN, alkanoyl, alkoxy, alkoxyalkyl, haloalkyl, carboxyl, or arylalkanoyl

wherein the aryl portion of arylalkoxy, arylalkyl, and arylalkanoyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, $C_1$-$C_8$ alkyl, $C_1$-$C_4$ alkoxy, nitro CN, haloalkyl, haloalkoxy or $CO_2R$,

wherein the alkyl portion of the alkyl, hydroxyalkyl, dihydroxyalkyl, arylalkoxy, arylalkyl, alkanoyl, alkoxy,





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alkoxyalkyl and arylalkanoyl groups is unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkoxycarbonyl, or cyclopropyl,

$R_2$ is OH, halogen, $-OSO_2-(C_1-C_6)$ alkyl, $-OSO_2$-aryl, arylalkoxy, aryloxy, arylthioalkoxy, arylalkynyl, phenyloxy$(C_1-C_6)$alkyl, $-OC(O)NH(CH_2)_n$aryl, $-OC(O)N(alkyl)(CH_2)_n$aryl, alkynyl, alkoxyalkoxy, dialkylamino, heteroaryl, heterocycloalkyl, aryloxyalkyl, or $CO_2R$, wherein

each of the above is unsubstituted or substituted with 1 2 3, 4 or 5 groups that are independently halogen, $-NR_6R_7$, haloalkyl, haloalkoxy, alkyl, heteroaryl, heteroarylalkyl $-(C_1-C_4)$alkyl-$C(O)NR_6R_7$ $R_6R_7N-(C_1-C_6$ alkyl)-, $-C(O)NR_6R_7$, $-(C_1-C_4$ alkyl)$-NRC(O)NR_{16}R_{17}$ CN, hydroxyalkyl, dihydroxyalkyl, $-OC(O)NR_6R_7$, or $-(C_1-C_6)$alkyl-N(R)-$CO_2R_{30}$, wherein

$R_{16}$ and $R_{17}$ are independently H or $C_1$-$C_6$ alkyl, or

$R_{16}$, $R_{17}$ and the nitrogen to which they are attached form a morpholinyl ring,

$R_6$ and $R_7$ are independently at each occurrence H, alkyl, hydroxyalkyl, dihydroxyalkyl, alkoxy, alkoxyalkyl, alkanoyl, arylalkyl, arylalkoxy, arylalkoxycarbonyl, or arylalkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, alkoxy, alkyl, OH, SH, carboxaldehyde, haloalkyl or haloalkoxy, or

$R_6$, $R_7$ and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, thiomorpholinyl S-oxide, thiomorpholinyl S,S-dioxide, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are





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independently $C_1$-$C_4$ alkyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl dihydroxyalkyl, or halogen,

n is 0, 1, 2, 3, 4, 5 or 6,

R at each occurrence is independently H or $C_1$-$C_6$ alkyl optionally substituted with 1 or 2 groups that are independently OH, SH, halogen, amino, monoalkylamino, dialkylamino or C -$C_6$ cycloalkyl,

$R_{30}$ is $C_1$-$C_6$ alkyl optionally substituted with 1 or 2 groups that are independently OH, SH, halogen, amino, monoalkylamino, dialkylamino or $C_3$-$C_6$ cycloalkyl,

$R_4$ is H, alkyl optionally substituted with one or two groups that are independently $CO_2R$, -$CO_2$alkyl -$C(O)NR_6R_7$, -$C(O)R_6$, -$N(R_{30})C(O)NR_{16}R_{17}$, -$N(R_{30})C(O)$-($C_1$-$C_6$)alkoxy, or -$NR_6R_7$ arylalkoxy, heteroaryl, arylalkyl, hydroxyalkyl, dihydroxyalkyl, haloalkyl, -$NR_6R_7$, -$C(O)NR_6R_7$, alkoxy, alkoxyalkyl, or alkoxyalkoxy, wherein

the heteroaryl or aryl portions of the above are unsubstituted or substituted with 1, 2, 3, 4 or 5 groups that are independently halogen, hydroxy alkoxy, alkyl, -$CO_2$-($C_1$-$C_6$)alkyl, -$CONR_6R_7$, -$NR_6R_7$, $R_6R_7N$-($C_1$-$C_6$)alkyl-, nitro, haloalkyl, or haloalkoxy, and

$R_5$ is arylalkyl, alkyl substituted with at least one 1, or optionally 2 or 3 groups that are independently arylalkoxycarbonyl, -$NR_8R_9$, halogen, -$C(O)NR_8R_9$, alkoxycarbonyl, or alkanoyl, alkoxyalkyl optionally substituted with one trimethylsilyl group, alkoxycarbonyl, amino, hydroxyalkyl, dihydroxyalkyl, alkenyl optionally substituted with alkoxycarbonyl, alkynyl, -$SO_2$-alkyl, aryl, alkoxy optionally substituted with one trimethylsilyl group, heterocycloalkylalkyl, heteroarylalkyl, heterocycloalkyl, or heteroaryl, wherein





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each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, halogen, alkoxy, arylalkoxy, hydroxyalkyl, dihydroxyalkyl, thioalkoxy, $-SO_2$alkyl, alkoxycarbonyl arylalkoxycarbonyl, $CO_2R$, CN, OH, amidinooxime, $NR_8R_9$, $R_6R_7N-(C_1-C_6$ alkyl)-, $-C(O)NR_6R_7$ amidino, hydroxyalkyl, dihydroxyalkyl, carboxaldehyde, $-NR_6R_7$, haloalkyl, $-(C_1-C_4$ alkyl)$-C(O)NR_6R_7$ $-(C_1-C_4$ alkyl)$-CO_2R$, $-(C_1-C_4$ alkyl)$-C_1-C_6$ alkoxycarbonyl, $-(C_1-C_4$ alkyl)$-CN$ $-(C_1-C_4$ alkyl)$-NR_{15}C(O)R_{18}$, $-O-CH_2-O-$, $-O-CH_2CH_2-O-$, phenyl or haloalkoxy,

$R_8$ is hydrogen, alkyl, alkanoyl, arylalkyl and arylalkanoyl

$R_9$ is alkyl, alkanoyl, arylalkyl, heteroaryl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, and arylalkanoyl

3 A compound according to claim 2 wherein

$R_1$ is H, halogen, alkyl optionally substituted with $C_1-C_4$ alkoxycarbonyl, carboxaldehyde hydroxyalkyl, dihydroxyalkyl, phenyl$(C_1-C_6)$alkoxy, phenyl$(C_1-C_6)$alkyl CN, alkanoyl, alkoxy, $C_2-C_4$ alkynyl $C_2-C_6$ alkenyl optionally substituted with $C_1-C_4$ alkoxycarbonyl, alkoxyalkyl, haloalkyl or phenyl$(C_1-C_6)$alkanoyl,

wherein the phenyl groups are unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, $C_1-C_4$ alkyl, $C_1-C_4$ alkoxy, nitro CN, $CF_3$, $OCF_3$ or $CO_2R$,

wherein the alkyl groups are unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, methoxy, or ethoxy





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$R_2$ is OH, phenyl($C_1$-$C_6$)alkoxy, phenyloxy, phenyloxy($C_1$-$C_6$)alkyl phenyl ($C_1$-$C_4$) thioalkoxy, alkoxyalkoxy, -O-$SO_2$phenyl alkynyl, phenyl ($C_2$-$C_4$) alkynyl, -OC(O)NH$(CH_2)_n$phenyl, -OC(O)N(alkyl)$(CH_2)_n$phenyl, dialkylamino, pyridyl, pyrimidyl, pyridazyl, pyrazolyl, imidazolyl, pyrrolyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, tetrazolyl, pyrazinyl benzimidazolyl, triazinyl, tetrahydrofuryl, piperidinyl, hexahydropyrimidinyl, thiazolyl, thienyl, or $CO_2R$, wherein

n is 0, 1, 2, 3, 4, 5 or 6,

each of the above is unsubstituted or substituted with 1 2, 3, 4, or 5 groups that are independently halogen, $NR_6R_7$, haloalkyl, haloalkoxy, hydroxyalkyl, dihydroxyalkyl alkyl, phenyl, pyridyl, piperidinyl, piperazinyl, -($C_1$-$C_6$)alkyl-N(R)-$CO_2R_{30}$ $R_6R_7N$-($C_1$-$C_6$ alkyl)-, -C(O)$NR_6R_7$, -($C_1$-$C_4$)alkyl-C(O)$NR_6R_7$, -($C_1$-$C_4$ alkyl)-NRC(O)$NR_{16}R_{17}$, or -OC(O)$NR_6R_7$, wherein

$R_6$ and $R_7$ are independently at each occurrence H, alkyl, ($C_1$-$C_4$) hydroxyalkyl, ($C_1$-$C_4$) dihydroxyalkyl, ($C_1$-$C_4$) alkoxy, ($C_1$-$C_4$) alkoxy ($C_1$-$C_4$) alkyl, ($C_1$-$C_4$) alkanoyl phenyl ($C_1$-$C_4$) alkyl, phenyl ($C_1$-$C_4$) alkoxy, phenyl ($C_1$-$C_4$) alkoxycarbonyl, or phenyl ($C_1$-$C_4$) alkanoyl, wherein each of the above is unsubstituted or substituted with 1 2, or 3 groups that are independently, halogen, OH, SH, $C_3$-$C_6$ cycloalkyl, ($C_1$-$C_4$) alkoxy, ($C_1$-$C_4$) alkyl, $CF_3$, carboxaldehyde, $NH_2$, NH($C_1$-$C_6$)alkyl, N($C_1$-$C_6$)alkyl ($C_1$-$C_6$)alkyl, $OCF_3$, or

$R_6$, $R_7$, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is



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optionally substituted with 1 or 2 groups that are independently $C_1$-$C_4$ alkyl, hydroxy, hydroxy $C_1$-$C_4$ alkyl, $C_1$-$C_4$ dihydroxyalkyl, $C_1$-$C_4$ alkoxycarbonyl, or halogen, and

$R_4$ is H, alkyl optionally substituted with one or two groups that are independently $CO_2R$, $-CO_2$alkyl, $-C(O)NR_6R_7$, $-C(O)R_6$, $-N(R_{30})C(O)NR_{16}R_{17}$, $-N(R_{30})C(O)-(C_1-C_6)$alkoxy, or $-NR_6R_7$, $-C(O)NR_6R_7$, phenyl$(C_1-C_6)$alkoxy, phenyl$(C_1-C_6)$alkyl, hydroxyalkyl, dihydroxyalkyl, haloalkyl, alkoxy, alkoxyalkyl or alkoxyalkoxy, wherein

the phenyl groups are unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen hydroxy, alkoxy, alkyl, nitro, $CF_3$, $OCF_3$,

$R_5$ is phenyl$(C_1-C_6)$alkyl, $(C_1-C_6)$alkyl substituted with at least one 1, or optionally 2, 3, 4, or 5 groups that are independently phenyl $C_1$-$C_4$ alkoxycarbonyl, $-NR_8R_9$, halogen, $-C(O)NR_8R_9$, alkoxycarbonyl, or alkanoyl, phenyl, alkoxy, $C_2$-$C_6$ alkynyl $C_2$-$C_6$ alkenyl optionally substituted with alkoxycarbonyl, indolyl, quinolinyl, isoquinolinyl, isoindolyl, dihydroindolyl, pyrazolyl, imidazolyl, dihydroisoindolyl, indolon-2-yl, indazolyl, benzimidazolyl, pyridyl, imidazolidine dione pyrazolyl$(C_1-C_6$ alkyl), imidazolyl$(C_1-C_6$ alkyl), piperidinyl$(C_1-C_6)$alkyl, pyrrolidinyl$(C_1-C_6)$alkyl imidazolidinyl$(C_1-C_6)$alkyl, tetrahydroisoquinolinyl$(C_1-C_6)$alkyl, 1H-indazolyl$(C_1-C_6)$alkyl, dihydroindolon-2-yl$(C_1-C_6$ alkyl), indolinyl$(C_1-C_6$ alkyl), dihydrobenzimidazolyl$(C_1-C_6$ alkyl), or dihydrobenzoimidazolonyl$(C_1-C_6$ alkyl), pyridyl $(C_1-C_6)$ alkyl, pyridazinyl $(C_1-C_6)$ alkyl, pyrimidinyl $(C_1-C_6)$ alkyl, pyrazinyl $(C_1-C_6)$ alkyl, tetrahydrofuryl$(C_1-C_6)$alkyl, naphthyl$(C_1-C_6)$alkyl, morpholinyl $(C_1-C_6)$ alkyl,



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tetrahydrofuryl $(C_1-C_6)$ alkyl, thienyl $(C_1-C_6)$ alkyl piperazinyl $(C_1-C_6)$ alkyl, indolyl $(C_1-C_6)$ alkyl, quinolinyl$(C_1-C_6)$ alkyl, isoquinolinyl$(C_1-C_6)$ alkyl, isoindolyl$(C_1-C_6)$ alkyl, dihydroindolyl$(C_1-C_6)$ alkyl, pyrazolyl$(C_1-C_4)$ alkyl, imidazolyl$(C_1-C_4)$ alkyl, dihydroisoindolyl$(C_1-C_6)$ alkyl, indoon-2-yl$(C_1-C_6)$ alkyl, indolon-2-yl$(C_1-C_6)$ alkyl, or morpholinyl $C_1-C_6$ alkyl, wherein each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently $C_1-C_6$ alkyl, halogen, $C_1-C_6$ alkoxy, phenyl $C_1-C_6$ alkoxy, $C_1-C_6$ thioalkoxy, $C_1-C_6$ alkoxycarbonyl, $CO_2R$, CN, $-SO_2(C_1-C_6)$alkyl, amidinooxime, $NR_8R_9$ $-NR_6R_7$, $NR_6R_7$ $C_1-C_6$ alkyl, $-C(O)NR_6R_7$, $-(C_1-C_4)$alkyl-$C(O)NR_6R_7$, amidino, $C_1-C_4$ haloalkyl, hydroxy $C_1-C_6$ alkyl, $C_1-C_6$ dihydroxyalkyl, or $C_1-C_4$ haloalkoxy, wherein

$R_8$ is hydrogen, $C_1-C_6$ alkyl, $C_1-C_6$ alkanoyl, phenyl $C_1-C_6$ alkyl and phenyl $C_1-C_6$ alkanoyl, and

$R_9$ is aminoalkyl, mono $C_1-C_6$ alkylamino $C_1-C_6$ alkyl, di $C_1-C_6$ alkylamino $C_1-C_6$ alkyl, $C_1-C_6$ alkyl, $C_1-C_6$ alkanoyl, phenyl $C_1-C_6$ alkyl, indazolyl, and phenyl $C_1-C_6$ alkanoyl

4 A compound according to claim 3, wherein

$R_1$ is H, halogen, $C_1-C_4$ alkyl optionally substituted with $C_1-C_4$ alkoxycarbonyl, $C_2-C_4$ alkenyl optionally substituted with $C_1-C_4$ alkoxycarbonyl, $C_2-C_4$ alkynyl, or carboxaldehyde,

$R_2$ is benzyloxy OH, phenyloxy, phenyloxy$(C_1-C_6)$alkyl, phenyl $(C_1-C_4)$ thioalkoxy, or pyridyl wherein each of the above is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen $-(C_1-C_6)$alkyl-$N(R)-CO_2R_{38}$, $NR_6R_7$ $-(C_1-C_4)$alkyl-$C(O)NR_6R_7$, $(C_1-C_4)$ haloalkyl, $-C(O)NR_6R_7$, $-(C_1-C_4$ alkyl)$-NRC(O)NR_{16}R_{17}$, $(C_1-C_4)$ haloalkoxy,



Empf zeit 22/03/2004 23 24 Empf.nr. 077 P 016

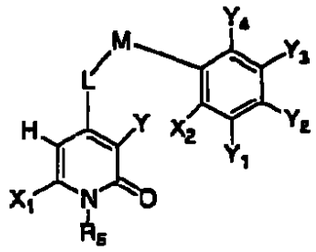
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$R_{16}$ and $R_{17}$ are independently H or $C_1$-$C_6$ alkyl, or

$R_{16}$, $R_{17}$, and the nitrogen to which they are attached form a morpholinyl ring,

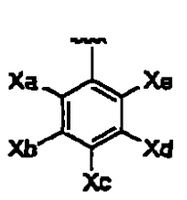
$R_{18}$ is $C_1$-$C_6$ alkyl optionally substituted with -O-($C_2$-$C_5$ alkanoyl, $C_1$-$C_6$ hydroxyalkyl, $C_1$-$C_8$ dihydroxyalkyl $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ alkoxy $C_1$-$C_6$ alkyl, amino $C_1$-$C_6$ alkyl, mono or dialkylamino $C_1$-$C_5$ alkyl

36 A compound of the formula

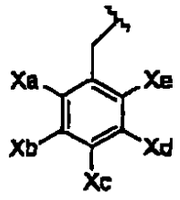


or a pharmaceutically acceptable salt thereof wherein

L and M are indepedently selected from -O-, -$CH_2$-, -S-,-NR-, -N(R)-N(R)- C(=O)-, -$SO_2$-,



$R_5$ is or , wherein



$X_1$ $X_2$, $X_a$, $X_b$, $X_c$, $X_d$ and $X_e$ are independently selected from -C(O)$NR_6R_7$, -($C_1$-$C_4$ alkyl)-C(O)$NR_6R_7$, -$NR_6R_7$, hydroxy($C_1$-$C_4$)alkyl, $C_1$-$C_6$ dihydroxyalkyl, H OH, halogen, haloalkyl alkyl haloalkoxy heteroaryl, heterocycloalkyl, $C_3$-$C_7$ cycloalkyl, $R_6R_7N$-($C_1$-$C_6$ alkyl)-, -$CO_2$-($C_1$-$C_6$)alkyl -N(R)C(O)$NR_6R_7$, -N(R)C(O)-($C_1$-$C_5$)alkoxy, $CO_2$R-($C_1$-$C_5$ alkyl)-, or -$SO_2NR_6R_7$, where at least one of $X_a$, $X_b$, $X_c$, $X_d$, and $X_e$ is not hydrogen and wherein the heteroaryl and heterocycloalkyl groups are optionally substituted with -$NR_6R_7$, -C(O)$NR_6R_7$, $R_6R_7N$-($C_1$-$C_5$ alkyl)-, $C_1$-$C_5$ alkyl, $C_1$-$C_5$ alkoxy, or halogen, or



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$R_3$ is heteroaryl or heteroarylalkyl, wherein the heteroaryl and heteroaryl groups are optionally substituted with at least 1, and optionally 2, 3, or 4 groups that are independently $-C(O)NR_6R_7$, $-(C_1-C_4$ alkyl$)-C(O)NR_6R_7$, $-NR_6R_7$, hydroxy$(C_1-C_4)$alkyl, $C_1-C_6$ dihydroxyalkyl, H, OH, halogen, haloalkyl, alkyl, haloalkoxy, $R_6R_7N-(C_1-C_6$ alkyl$)-$, $-CO_2-(C_1-C_6)$alkyl $-N(R)C(O)NR_6R_7$, or $-N(R)C(O)-(C_1-C_6)$alkoxy, wherein

$R_6$ and $R_7$ are independently at each occurrence H $C_1-C_6$ alkyl, $C_1-C_6$ alkoxy $C_1-C_6$ alkoxy $C_1-C_6$ alkyl, $C_1-C_6$ alkoxycarbonyl, OH, $C_1-C_8$ hydroxyalkyl, $C_1-C_4$ dihydroxyalkyl $C_1-C_6$ thiohydroxyalkyl, $-(C_1-C_4)$alkyl$-CO_2-$alkyl, pyridyl $C_1-C_6$ alkyl, $C_1-C_6$ alkanoyl benzyl, phenyl $C_1-C_6$ alkoxy, or phenyl $C_1-C_6$ alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2 or 3 groups that are independently, halogen, $C_3-C_6$ cycloalkyl, $C_1-C_6$ alkoxy, piperidinyl $C_1-C_6$ alkyl, morpholinyl $C_1-C_6$ alkyl, piperazinyl $C_1-C_6$ alkyl OH, SH, $NH_2$, NH(alkyl), N(alkyl)(alkyl), $-O-C_1-C_4$ alkanoyl, $C_1-C_4$ alkyl, $CF_3$, or $OCF_3$ or

$R_6$, $R_7$, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently $C_1-C_6$ alkyl, $C_1-C_4$ alkoxy, hydroxy, hydroxy $C_1-C_4$ alkyl, $C_1-C_4$ dihydroxyalkyl, or halogen,

R at each occurrence is independently H or $C_1-C_6$ alkyl, and

Y, $Y_1$, $Y_2$, $Y_3$, and $Y_4$ are independently selected from H, halogen, alkyl, carboxaldehyde, hydroxyalkyl, dihydroxyalkyl, alkenyl, alkynyl, CN, alkanoyl, alkoxy, alkoxyalkyl haloalkyl, and carboxyl



Empf zeit 22/03/2004 23:25 Empf nr 077 P 018

AMENDED SHEET

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# INTERNATIONAL SEARCH REPORT

Interna application No
PCT/US 03/04634

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4412 A61P29/00 C07D213/69 C07D401/06 C07D409/06
C07D213/70 C07D213/64 C07D213/74 C07D405/06 C07D213/84
C07D401/10 C07D405/12 C07D401/12 C07D213/75 C07D401/14

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 A61K

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)
BEILSTEIN Data, EPO-Internal, WPI Data PAJ 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 |
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[X] Further documents are listed in the continuation of box C

[X] Patent family members are listed in annex.

Special categories of cited documents

A document defining the general state of the art which is not considered to be of particular relevance
E earlier document but published on or after the international filing date
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
O document referring to an oral disclosure use, exhibition or other means
P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
X document of particular relevance the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
Y document of particular relevance the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents such combination being obvious to a person skilled in the art
& document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 5 June 2003 | 23/06/2003 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office P B 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel (+31-70) 340-2040, Tx 31 651 epo nl<br>Fax (+31-70) 340-3016 | Seymour, L |

Form PCT/ISA/210 (second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/US 03/04634

A CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D213/79 C07D401/04 C07D405/04 C07D413/10 C07D25/22
C07D405/14 C07D409/14 C07D213/85

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)

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)

C DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document with indication where appropriate of the relevant passages | Relevant to claim No |
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[X] Further documents are listed in the continuation of box C

[X] Patent family members are listed in annex.

Special categories of cited documents

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure use exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents such combination being obvious to a person skilled in the art.

& document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 5 June 2003 | |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office P B. 5818 Patentlaan 2<br>NL – 2280 HV Rijswijk<br>Tel (+3 –70) 340–2040 Tx 31 651 epo nl<br>Fax (+31–70) 340–3016 | Seymour, L |

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT International Application No PCT/US 03 04634

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I 2

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT) For these reasons, a meaningful search over the whole breadth of the claims is impossible Consequently the search has been restricted to compounds according to claim 36

The applicant s attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66 1(e) PCT) The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern Application No
PCT/US 03/04634

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C (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document with indication where appropriate of the relevant passages | Relevant to claim No |
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| X | DATABASE CROSSFIRE BEILSTEIN 'Online' Beilstein Institut zur Forderung der Chemischen Wissenschaften Frankfurt am Main, DE, Database accession no 5069110 (BRN) XP002243098 & JOURNAL OF THE CHEMICAL SOCIETY PERKIN TRANSACTIONS 1 1986 pages 1289-1296 --- | 1 36 |
| X | DATABASE CROSSFIRE BEILSTEIN 'Online' Beilstein Institut zur Förderung der Chemischen Wissenschafter, Frankfurt am Main DE Database accession no 5587856 (BRN) XP002243099 see also Product BRN 7719203 & LIEBIGS ANN , RECL , vol 8, 1997 pages 1777-1782, --- | 1 36 |
| X | DATABASE CROSSFIRE BEILSTEIN 'Online' Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE, Database accession no 6347000 (BRN) XP002243100 & COLLECT CZECH CHEM COMMUN , vol 58, no 4, 1993, pages 947-953, --- | 1 36 |
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# INTERNATIONAL SEARCH REPORT

International application No
PCT/US 03/04634

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons

1 [X] Claims Nos
because they relate to subject matter not required to be searched by this Authority namely

Although claims 68 and 69 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 [X] 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

see FURTHER INFORMATION sheet PCT/ISA/210

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 II Observations where unity of invention is lacking (Continuation of item 2 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

Interna Application No
PCT/US C3/04634

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| Patent document cited in search report | | Publication date | Patent family member(s) | | Publication date |
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# REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

| | USUARIO | RADICADOR |
|---|---|---|
| PATENTE DE INVENCIÓN MODELO DE UTILIDAD | ( ) | ( ) |
| - Indicacion de que se solicita la concesion de una patente | ( ) | ( ) |
| - Datos de identificacion del solicitante o de la persona que se presenta la solicitud | ( ) | ( ) |
| - Descripcion de la invencion | ( ) | ( ) |
| Dibujos de ser estos pertinentes. | ( ) | ( ) |
| Comprobante de Pago de las tasas establecidas | | |
| COMPLETA ( ) INCOMPLETA | ( ) | ( ) |
| DISEÑO INDUSTRIAL ( ) | | |
| - Indicacion de que se solicita el registro de Diseño Industrial | ( ) | ( ) |
| - Datos de identificación del solicitante o de la persona que presenta | ( ) | ( ) |
| - la solicitud | | |
| - Representacion gráfica o fotografica del Diseño Industrial o muestra del | | |
| Material que incorpora el diseño | ( ) | ( ) |
| Comprobante de pago de las tasas establecidas | ( ) | ( ) |
| COMPLETA ( ) INCOMPLETA | ( ) | ( ) |
| ESQUEMA DE TRAZADO ( ) | | |
| - Indicacion de que solicita el registro de un Esquema de trazado | ( ) | ( ) |
| - Datos de identificación del solicitante o de la persona que presenta | | |
| La solicitud | ( ) | ( ) |
| Representacion grafica del esquema de trazado | ( ) | ( ) |
| Comprobante de pago de las tasas establecidas | ( ) | ( ) |
| COMPLETA ( ) INCOMPLETA | ( ) | ( ) |

Firma Responsable

Fecha

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Radicacion 04076760 00000000 Folios 1595
Fecha (AMD) 2004-08-06 17 00 00
Tramite 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia 2020 DIVISION DE NUEVAS CREACIONES

Extracto publicación
fólios 1597 a 1602

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Bogota D C

Doctor(a)
CARLOS R OLARTE
Apoderado
PHARMACIA CORPORATION

Oficio N° 08438

**ASUNTO**

| | |
|---|---|
| Radicación N° | 04-76760 |
| Solicitud internacional | PCT/US03/04634 |
| Fecha inicio fase nacional | 14/09/2004 |
| Tramite | 011 |
| Evento | 379 |
| Actuacion | 416 |
| Folios | 001 |

Como resultado del examen de forma, realizado con fundamento en el articulo 38 de la Decision 486 de la Comisión de la Comunidad Andina articulo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Unica de la Superintendencia de Industria y Comercio, se le comunica que

- La solicitud no contiene copia del documento en que consta la cesión del derecho de patente del inventor al solicitante o a su causante (Art 26-k) Decisión 486)
- El solicitante debe presentar un nuevo titulo, que permita identificar la materia de la cual trata la solicitud ya que el relacionado no se encuentra con la precision necesaria para identificar claramente el objeto de la solicitud de patente (Regla 4 3 PCT, Art 27, 27 Decision 486 Circular Unica 5 2 9)

En cumplimiento de lo dispuesto por el articulo 39 de la Decisión 486, se le requiere para que dentro del termino de dos meses siguientes a la fecha de notificacion del presente oficio, complete los requisitos anteriormente enunciados En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerara abandonada y perderá su prelación

Notifiquese el presente oficio conforme a lo dispuesto en el numeral 5 2, literal e) del capitulo quinto del titulo primero de la Circular Unica N° 10 de 2001

**ALIX CARMENZA CESPEDES DE VERGEL**
Jefe de la Division de Nuevas Créaciones

El anterior requerimiento fue notificado por fijación en lista de fecha

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